Dr. McGILL. At our own expense we are doing this, and I wonder if it serves any additional purpose, but perhaps I am not the one to judge that.

Senator NELSON. We haven't adequately explored this question. I introduced legislation to create a compendium for the purpose of having extensive hearings on that specific proposal so that we could get the viewpoint of everybody who might in any way be involved and see whether or not a consensus could be reached. If, in the meantime, however, a compendium were developed that was adequate to serve this purpose—I don't know that I would see any point in involving the Government. I have an open mind in this regard.

Dr. McGILL. Fine.

I would like to make just this final statement.

As doctors, our primary consideration must always be the welfare of our patients. We have many medical problems yet to solve, most of which will depend on the discovery of new chemical agents. We are very concerned that nothing interfere with the research and development of these new agents. We are acutely aware of what delay means in terms of human suffering. These are values which cannot be measured by cost-benefit ratios.

Any fair appraisal of our pharmaceutical industry would have to credit it with a remarkable record of achievement. Our system of providing medicines may not be perfect but it has achieved excellence. The industry has earned our respect where it counts the most—at the patient's bedside. I am certain the doctors of this country will continue to place quality and reliability ahead of price in their choice of therapeutic agents, not that cost can be ignored, but it should never be the primary factor. For the instrument of government to recommend we do otherwise is unthinkable.

Senator NELSON. Thank you, Doctor. Senator Hatfield, I have to leave in a few minutes because I am directly involved in a matter pending on the floor. But I would like to make an inquiry or two before I leave.

In a widely circulated, widely publicized speech [1] which you gave on December 3, 1968, at the Pharmaceutical Manufacturers Association conference in the New York Hilton you stated in part—I would like to quote from the copy I have here:

> For the past 18 months I have watched with increasing alarm the proceedings of Senator Nelson's subcommittee. It was evident from the very beginning that the hearings were slanted and the facts were being distorted. We have been exposed to a steady stream of handpicked witnesses whose testimony became as predictable as the rising sun. Over and over again we heard the same tired charges of excess profits, price gouging, unreasonable patent protection, and the like, without even the pretense of fairness or objectivity.
>
> Not that I was surprised by the tenor of the hearings. I am aware that Senator Nelson is not one of our admirers.
>
> Then, too, none of us in the health industry has been treated gently in the Halls of Congress these past several years, but I kept expecting to hear testimony from the other side. I though surely they would call witnesses from the various specialty groups, the Academy of General Practice, the AMA, the individual practitioner like myself, but when none was forthcoming, I decided to have a try at it.
>
> As it happens, one member of the Subcommittee is Senator Mark Hatfield from my own State. Last spring I had occasion to visit the Senator in Washington

[1] See information beginning at p. 4138, infra.

and we discussed the Nelson hearings at some length. He was sympathetic to my point of view that the hearings were being used to malign the drug industry and the medical profession for political purposes. He agreed to help me get called as a witness.

Since that time I have had a series of polite but noncommittal letters from Senator Nelson. I discussed this situation again with Senator Hatfield just 10 days ago and he expressed his frustration in the selection of witnesses before the Committee.

It seems very clear that Senator Nelson does not want anyone to tell the story from the private practitioner's point of view or even to allow us to defend ourselves against the scurrilous attacks that are now a part of the public record.

Fortunately Joe Stetler learned of my dilemma and invited me here today to express my views. I am indebted to Joe for finally giving me a platform. I think it is about time that somebody speaks out against this travesty of justice, against the misuse of congressional authority. Of course, I don't have the lofty forum that Senator Nelson enjoys nor do I have his troops.

First, I am curious about your statement saying "since that time I have had a series of polite but noncommittal letters from Senator Nelson." We searched our files, Doctor, and all we can find is one letter from you dated March 28, 1968,[1] which I will read from and then put in the record.

Dear Senator Nelson: I have followed with great interest the hearings of the Monopoly Subcommittee. The testimony of Dr. James Goddard has been very impressive. Through your efforts, the public has gained a great deal of information about drugs and drug manufacturers. I am in total agreement that such facts should be made known, both to the medical profession and the public at large. I feel certain that much more could be revealed. I also feel that the testimony of the private practicing physician, like myself, would add a useful dimension to your hearings. I would like to volunteer my services for that purpose.

and so forth.

That is the pertinent part of the letter.

In our files we have a copy of one letter which I wrote in response to your letter. It is dated April 29, 1968.[1] So 1 month after I heard from you I wrote:

DEAR DR. MCGILL. I appreciate your letter expressing an interest in testifying at our hearings on the prescription drug industry. Senator Hatfield has also contacted me in this regard.

As you know, the Committee is covering a number of facets of the competitive problems in the prescription drug industry. I would appreciate learning from you which phase you are interested in discussing.

Because of the number of witnesses who have been scheduled to appear, we have not been able to set a time in the near future for additional witnesses. However, if you will send me a copy of your statement, we will include it in the Committee records. Then, if a time can be worked out for your personal appearance, the Committee will be happy to contact you again, hopefully in not too long a period of time.

Isn't that the only letter you ever received from me?

Dr. MCGILL. I have received several letters from your committee, but some of them pertinent to this hearing today.

Senator NELSON. No, I mean, isn't that the only letter you had from me prior to your PMA speech in which you made reference to "a series of polite but noncommittal letters" you had received from me?

Dr. MCGILL. Well, there were two letters sent to me about today's appearance.

[1] See pp. 4141–42, infra.

Senator NELSON. Of course, I sent you a letter inviting you to appear today, confirming time and place and so on. But we are talking about the reference you made to a series of "polite but noncommittal letters" you said you had received from me during the course of the past year.

Dr. MCGILL. But I have also corresponded with Senator Hatfield in this area as well, and I know Senator Hatfield perhaps felt that we are still talking to the same members of the committee.

What is the point that you wish to make?

Senator NELSON. In your speech, you said that following your letter to me of March 28, 1968, in which you requested to appear, and I quote—"I have had a series of polite but noncommittal letters from Senator Nelson." Now, I can find only one and it wasn't noncommittal.

I asked for your statement. I said it would be put into the record and I offered to set up a time for you to appear, hopefully in the not too distant future. You never answered that letter. So I am wondering how you could give a public speech saying you had received a series of polite but noncommittal letters from Senator Nelson.

Dr. MCGILL. Well, Senator Nelson's committee—as a matter of fact, I did write back and wrote to Senator Hatfield that I thought the type of testimony I had would be more valuable in open hearing than it would be in a written statement.

Senator NELSON. That isn't the point I am raising. I am sure you talked to Senator Hatfield. I am referring precisely to your speech saying that, "I have had a series of polite but noncommittal letters from Senator Nelson."

I thought my letter of April 29 was quite committal. I said, "However, if you will send me a copy of your statement, we will include it in the committee record. Then if the time can be worked out for your personal appearance, the committee would be happy to have you."

How did you come to the conclusion that that is a series of noncommittal letters?

Dr. MCGILL. Well, this is a general statement in the fact that I have known of others that have made requests to this committee who have not been heard, and hopefully some of us would be heard. The difference between Senator Nelson and Senator Nelson's committee may be an error on my side, from my point.

Senator NELSON. That isn't the way I read it. It says, "I have had a series of polite but noncommittal letters from Senator Nelson."

Dr. MCGILL. Perhaps that should have been stated as Senator Nelson's committee.

Senator NELSON. Have you written a series of letters to the committee asking to appear?

Dr. MCGILL. If I count the letters of yours and also to Senator Hatfield I think it makes a series.

Senator NELSON. I would like to point out that we have searched the committee files and we find no letters from you whatsoever. Of course the committee files and my personal office files would not include any correspondence you may have had with Senator Hatfield and his office. If, however, you have any additional letters from me or the committee prior to the date of your speech, I would certainly appreciate your sending them to us. I want to make sure that our files are in order.

Dr. McGILL. I will be glad to.

Senator NELSON. I will put the full text of your speech to the Pharmaceutical Manufacturers Association convention into the record—as well as my letter to you. If you have copies of any other letters from me or the committee prior to the time of your speech, we will put that in the record also, so that the record will be clear. I want to be fair with you. If you have some other such letter or letters it will be included in the record. If you don't, I think your letter to me of March 28 and my response to you of April 29 speak quite well for themselves and your speech before the manufacturers association is rather loose with the facts.

Just one more comment and again, I quote from your speech:

> We have been exposed to a steady stream of handpicked witnesses whose testimony became as predictable as the rising sun.

I want to emphasize again that the industry itself that you are here defending, the industry itself has an open standing invitation to every single drug manufacturer in America to come before this committee any time it wishes, and any time it is criticized by any witness, to come back and reply. That firm will have precedence over anybody else because it is my feeling that if somebody in industry is criticized, he ought to have a chance to answer. The industry has had 44 witnesses, which is more than anybody else. I think that probably the fact is that many of those letters that I received from doctors or statements made by them are based upon information the Pharmaceutical Manufacturers Association has given them. It seems that doctors have been misled about what is going on at these hearings.

Dr. McGILL. Well, I think the thing we have resented the most is some of the comments that have been made before this committee describing practitioners as stethoscope carrying ignoramuses and simple boobs and other language which I resent, and I think we should have a chance to answer, and I am grateful that you have given me the chance.

Senator NELSON. OK. Thank you very much, Doctor. I apologize for having to leave but I don't have control over the proceedings in the Senate.

Dr. McGILL. I know you don't.

Senator NELSON. And I do not like to leave while a witness is still here but I must. Senator Hatfield, my very able colleague, has agreed to complete the hearings. I am going up and take care of one of his party members. [Laughter.]

Senator HATFIELD (presiding). Doctor, at the bottom of page 4 of your testimony you were talking about the materials and the sources of information that doctors receive as to a new drug or drug product, and you state that they are all valuable. We have had a number of witnesses before this committee who have testified to the effect that they received voluminous amounts of materials and many of them are duplications, repeats, and that in many instances it becomes so much an inundation of material that they don't find it as valuable.

Dr. McGILL. I agree.

Senator HATFIELD. So my question is, do you feel that all the materials which you receive from the drug manufacturers really are of value to you as a practicing physician?

Dr. McGILL. No.

Senator HATFIELD. Would you like to comment on this matter?

Dr. MCGILL. I think there is reduplication. I think many of them, in fact, put out products and information and material that is almost totally ineffective. However, this will always be a problem when a company is trying to find a specific way by saturation or special information or that will work the best. After all, they do have a product to sell. We are aware of the fact and much of it never reaches me. It ends up in the wastepaper basket by the girls in front.

Journal advertising, I think, does draw attention more because it specifically is of more help.

Senator HATFIELD. Well, in line with that, just above you mentioned, "It has also been my experience that the ethical drug houses are very careful to accurately describe their product and include all the possible side effects."

Just to make the record clear, it seems to me on page 5, second paragraph, there may be some slight contradiction.

Dr. MCGILL. Where is that, sir?

Senator HATFIELD. There is a contradiction to that statement because in the middle of the second paragraph it says, "Not long ago I ran into an unusual side effect with a drug that was not described in the package literature."

Would you like to clarify that?

Dr. MCGILL. I would be very happy to. As a matter of fact, this was only recently recognized by the company. Now, the product that was being used was one of our more common analgesics that people take for pain, modern amounts of pain. This young man had a serious back problem, should have been operated on and was trying to get by until next year when he could do it, and had taken an overdose.

I called the company and the company pointed out they had had several suicide attempts that had been recently reported. On suicide attempts there is no telling what drugs people will use or what devices. In taking an excess dose, it produced a convulsion much the same as an epileptic convulsion and in the particular copy of PDR which has the package literature, it was not listed.

He called the company and they mentioned they had just recently recognized this complication because of the suicide attempts, and it would be in the product literature. By the way, it is there now. They did it as they said they would. They didn't know this reaction either until they had a chance to see the toxic doses of the drugs used.

This will sooner or later happen with any drug. You can't very well do that on an experimental basis.

Senator HATFIELD. So there is no contradiction in this statement of yours.

Dr. MCGILL. Not really.

Senator HATFIELD. Because there has been exceptions to the fact that most generally the side effects are listed, but in this instance was there an exception?

Dr. MCGILL. Right, and many side effects are late occurring and sometimes they are hard to identify. The example of the aplastic anemia with Chloromycetin is a good one here. This was hard to identify. There are many other drugs that can produce it. Sometimes it is without apparent cause. However, once it was well recognized, the company certainly did point it out.

Senator HATFIELD. Going back to another part of your testimony relating to the larger drug operations with their research and development divisions as contrasted to the generic or the parasitic industries, as you call them. You mentioned that as to the therapeutic equivalency, the burden of proof should be on the small firms. Would you like to elaborate a little bit on that point for us?

Dr. MCGILL. Yes, and I am sure this is the value that generally will be held by the medical community. When any company brings its product on the market, I don't care whether it is a new product or whether it is a remake of an old product or whether it is somebody else's product that is now off patent, we feel the burden of proof is on them to establish the fact that it is just as good a product, and I mean therapeutically—I think this has been well heard in this committee—before they will have won our confidence to use the product on a price basis.

Their only competitive point is price. If they can establish to me that they have gone through satisfactory studies to establish their therapeutic equivalency, I will use their product.

Now, there is an element——

Senator HATFIELD. Is that not required at the present time?

Dr. MCGILL. No. That is not required at the present time. They meet USP standards which are chemical standards. There is nothing wrong with those standards and we have great confidence in USP but it doesn't go far enough to establish therapeutic equivalency and most of the drugs are becoming very sophisticated, very complex products to put out. We have learned in antibiotics that we have to have batch-by-batch certification.

Senator HATFIELD. Should the FDA perform this or some other agency and how?

Dr. MCGILL. I think the individual companies should produce their own clinical material stating "we have done a comparison study and find this product manufactured under our process is equivalent therapeutically." Then we would have no objection.

Senator HATFIELD. Would it have to be authenticated or verified by any outside agency?

Dr. MCGILL. Well, that would always be nicer if it was, but I have confidence that the companies will do this, plus there is spot checking and inspections of factories. There probably should be more of this, to be sure they are doing what they say they are doing.

Senator HATFIELD. I appreciate your approach to the committee this morning in terms of the thrust of your testimony as being positive in listing and identifying the contributions, the valuable contributions of the drug industry.

Now, as a practicing physician I am sure that you have found areas where the drug industry might improve as any industry or any organization has always something to improve them.

Dr. MCGILL. Surely.

Senator HATFIELD. Now, the committee here, even though the publicity may have been on the negative side as you point out, and I think we have had some sensational testimony that has received a great deal of headlines and the indictment always gets more play than the answer.

Dr. MCGILL. Always.

Senator HATFIELD. Surely there must be areas in which you could indicate to us where you think improvement could be made without detracting from the valuable contributions the drug industry has already made.

Dr. MCGILL. Well, possibly. You have already pointed to one of them. I think some advertising processes or procedures are excessive and anything that would encourage their research and development programs, of course, would very much have our support, although they have quite a remarkable record in this. Most of the practices that have been described in front of this committee, and this may be one of the very good effects this committee's hearings have had, have been stopped. I think more price information could be distributed. I think this would be good. And if a compendium or formulary, like the ones you have suggested in the bill you have entered, that is essentially educational and has the information for the use of the physician and is not restricted to his choice, I think that would be valuable.

We need more sources of education. One area that the drug companies are just getting into is to help sponsor postgraduate education in the use of drugs. I think this is fine that they are doing it. I think they will enlarge it at this point. Whether or not a drug journal would be valuable I am not sure. I would have to see the format, the nature of it and who put it out, but that is a possibility.

Senator HATFIELD. Do you have any comments in the area of quality control or any of that type of manufacturing?

Dr. MCGILL. Well, quality control is terribly important to us.

Senator HATFIELD. Do you feel that you are satisfied with the results of the present system used?

Dr. MCGILL. I am satisfied with the results of the present system in certain organizations. I think you will find most of us feel that no product is any better than the established reputation of the company that made it.

Now, we may be doing an injustice to a new company starting on the market, just starting to manufacture drugs. I realize that. Yet I think this way. We are not about to buy a new kind of an automobile when you know the one that you have been driving is a reliable product until the new product has established its identity and its quality. Then we will use it.

Senator HATFIELD. One of the things that has bothered me a great deal in the testimony we have heard before this committee, relating to the medical practice, has been witness after witness indicating that because of the large numbers of new drugs coming into the market each year out of the research laboratories of our pharmaceutical houses and other sources, that the average practicing physician is not in a position to actually keep abreast with all of these new drugs. It is difficult to maintain his schedule of appointments with his patients and keep abreast of the new publications or the listing of the drugs in various journals, plus the fact related to that has been the indication that in the average medical school today there is not sufficient time given in the curriculum for pharmacology and the basic better understanding of the whole use of drugs and their applications.

This really starts in with the educational program of the physician and moves right on into his practice and demands upon his time. This has been stated by professors of medicine.

Dr. McGILL. Professors of pharmacology primarily.

Senator HATFIELD. It has been made by people who are practicing physicians in hospitals and by others as well. So what I am asking is basically your view on this point.

Dr. McGILL. Well, first of all let me say keeping up with drug information and the rapidly developing advances is not easy. It is very difficult, and it is a strain on all of us to try to do this. My point is the information is available to us if an individual makes any effort at all to get it.

Now, one of the things that I have resented about the pharmacologists that have come before this committee is, well, the doctor's drug therapy or his knowledge of drugs ended at the end of the sophomore course in pharmacology. This just isn't so. I am an internist. I don't know what happens in other fields but I know what happens in my field. A very, very large part of our field deals with drug training—drugs are the tools we use, just as a surgeon uses instruments, and this occupies a large part of our time and effort. We have many professional meetings.

We have, for example, staff meetings at the hospital. Questions have come up in these hearings, that if we had better reports about Chloromycetin, we would not be using Chloromycetin. I doubt it. However, in my own hospital, and this is true in every accredited hospital in the United States, we have a death and complications conference once a month. Every death in our department—I am in the department of medicine—every death or complications is listed and is discussed and we must attend 80 percent of those meetings or lose our hospital privileges, so we have pretty effective discipline, plus the pressure of the individual's own conscience.

We would like to have our people get the best possible treatment they can.

We do have sources. I am not saying, perhaps, Senator, we should not have more. We can always use more.

Senator HATFIELD. Do you have a way to divide in your own practice the dependency that you have upon one source as, say, contrasted to another source for information of new drugs including the so-called detail men and their visits and their promotional activities and materials as contrasted, say, to a journal, as contrasted to your fellow physicians and other sources that you may have?

Dr. McGILL. I would say if we track the new drug all the way through, perhaps this can illustrate the point. The last important new drug that I think has come on the scene is Vibramycin by Pfizer Co. which is a very promising antibiotic because it is a long acting product. It has long-term effects and therefore has certain uses that are important to us.

This was reported in the New England Journal of Medicine, I recall—I may be wrong on this because I am recalling from memory—at least a year, probably 2 years before it was introduced to the market. First it was under its generic name, doxycycline. Then the American Journal of Medicine I believe had an article on it. We heard about it in other journals and then it shows up in the JAMA section on new drugs. This is sort of the process that goes on.

Now, we have a new antibiotic coming that looks very promising.

We still haven't gotten it and it is still only a curiosity until finally that detail man shows up in my office and says, Doctor, I am from the Pfizer Co. We are now producing Vibramycin. It is in your local pharmacy and you can start using it.[1]

In the meantime some of our hospital people have had it, as many do, for clinical trial and we will have heard about it in medical meetings. Then, as we start using the drugs, I can't emphasize enough the informal consultation that takes place between doctors. We will discuss among ourselves whether the current hot throats are responding to this new antibiotic or should it be used. This is informal information we trade around. We learn from each other, of course, pooling our information.

It has been said sometimes we pool our ignorance. That is possible, too, but this is the way we become familiar with a new product.

If late complications develop, and I am sure this will be the case in the future, it is the detail man who points it out very quickly because they do not wish their product to develop a reputation for bad effects.

Senator HATFIELD. Knowing you to be an exceptional man as well as an exceptional physician, are you describing to us an exceptional situation or is this an ordinary common practice that physicians engage in?

Dr. MCGILL. This always comes up. What does the average physician do? Senator Hatfield, I don't know an average physician. I hope I don't know an average lawyer either. I know that they are a dedicated, hard-working group of men. I have heard them described in here as the guy that sees 75 patients a day and hasn't read a medical journal in a year as if this is typical, and I object to this. I do not believe it is typical. It is not typical of doctors I know.

Senator HATFIELD. Another matter that has bothered me a great deal from the testimony here and in my visit to one of the major pharmaceutical houses is the lack of the knowledge today of what long-term use of certain drugs might create in a person.

Dr. MCGILL. It is always a possible hazard.

Senator HATFIELD. Now, how are we going to solve that, with greater use of primate centers or other experiments with animals, or how are we going to accomplish this? Is it the responsibility of the pharmaceutical house? Is it the responsibility of the FDA? Where does this responsibility lie?

Dr. MCGILL. Well, let me start by saying I certainly think the pharmaceutical industry shares this responsibility. They certainly are responsible for the effects of their product and if they discover by their own sources that certain long-term effects are occurring, it is their responsibility to inform us and it has been my experience that they do.

FDA—and there is a good working relationship between the FDA and the pharmaceutical manufacturers—perhaps might think more in terms of long-term testing or long-term recordkeeping on possible late complications. All of us are aware of this. Very late complications may occur many, many months, even years later.

There is no way to avoid this by trying to wait that many years for

[1] Testimony on Vibramycin will be found in Competitive Problems in the Drug Industry, Part 9, pp. 3537–3568.

clinical trial which would mean keeping a very useful drug off the market. We can't justify that either. I think we will always have to remember that when we say, well, you are getting some late complications, therefore, withdraw that drug, you may have hurt a lot of people who needed the drug.

Senator HATFIELD. But aren't there ways that they could accelerate the information-gathering activity through the generations that they could experiment with?

Dr. MCGILL. Yes.

Senator HATFIELD. Could this be done with the primate as compared to waiting for the human being to exist that long through many generations of use?

Dr. MCGILL. We can get some information on this and as you know, a good bit of this is going on in our own primate center in Portland. It does, of course, not necessarily mean they are comparable but it does give us leads that we should be watching in certain areas, and I am hoping there will be more of this.

Senator HATFIELD. We were talking to Dr. Montagna about this whole matter and the thing that disturbs me is that we have now 12 such primate centers I believe in the United States and if they are typical of ours, they are underutilized and at least this could be utilized to a greater extent. Further, it seems to me that the pharmaceutical industry has a greater responsibility than they are thus far performing in utilizing such sources and centers to do a little bit more on contractual relationship work.

Dr. MCGILL. I think that is a very worthwhile suggestion. Incidentally, Dr. Montagna has just this fall visited our medical society and described the activities of what is going on in the primate center.

Mr. GORDON. On page 5 of your statement you talk about unhappy experiences you have had with a couple of detail men. Could you give us a little more information about that, including the drug involved?

Dr. MCGILL. No. I don't have any specifics. I was thinking more in terms of the manner of the individual who attempts the hard sell type. He won't get very far with me. In fact, he won't get past the front desk the next time around.

This occasionally happens but it is rare. Most of these men are professionals and they do a good job.

Mr. GORDON. On page 4 you say it has also been your experience that "the ethical drug houses are very careful to accurately describe their products and include all the possible side-effects."

I was just wondering if you were aware of the 29 "Dear Doctor" letters that went out in the last 18 months—they were sent out by the leading drug firms, at the insistence of the FDA, to correct false and misleading statements in their advertising claims?

Dr. MCGILL. Most of which was nit picking in our opinion.

Mr. GORDON. You don't think it was really worthwhile?

Dr. MCGILL. Usually most of us already knew this. This doesn't mean it doesn't have a certain purpose and I am not against any source of information. As I mentioned, we need all the information we can get. We are glad to have it. And I don't believe any major drug company deliberately obscures complications of a drug because that would only serve to hurt them.

(The letters follow:)

Regulatory actions, remedial letters (Dear Doctor)

1. Ortho-Novum-SQ, Ortho Pharmaceutical Corp	February 1, 1967.
2. Librium, Hoffman-LaRoche Laboratories	March 10, 1967.
3. Deprol and Miltown, Wallace Pharmaceuticals	March 30, 1967.
4. Enduron and Enduronyl, Abbott Laboratories	April 13, 1967.
5. Renese, Renese-R, and Rondomycin, Pfizer Laboratories	May 22, 1967.
6. Hygroton and Regroton, Geigy Pharmaceuticals	June 2, 1967.
7. Oracon and Questran, Mead Johnson Laboratories	June 30, 1967.
8. Choloxin, Flint Laboratories	July 20, 1967.
9. Diutensin-R, Neisler Laboratories	August 11, 1967.
10. Citanest, Astra Pharmaceutical Products	August 23, 1967.
11. Mysteclin-F, Squibb & Sons	October 24, 1967.
12. Cortrophin Gel, Cortrophin Zinc, Hexadrol Phosphate Inj., and Hexadrol Tablets and Elixir, Organon, Inc.	October 27, 1967.
13. Predsem, Salcort, and Salcort-Delta, The S. E. Massengill Co	November 1, 1967.
14. Norpramin, Lakeside Laboratories, Inc	November 1967.
15. Medrol, The Upjohn Co	November 15, 1967.
16. H. P. Acthar Gel, Armour Pharmaceutical Co	November 16, 1967.
17. "PDR Products," Medical Economics	November 27, 1967.
18. Ponstel, Parke, Davis & Co	January 15, 1968.
19. Norquen and Norinyl-1, Syntex Laboratories	January 22, 1968.
20. Ovulen-21, G. D. Searle & Co	January 26, 1968.
21. Persantine, Geigy Pharmaceutical	February 15, 1968.
22. Erythrocin, Abbott Pharmaceuticals	June 3, 1968.
23. Dynapen, Bristol Laboratories	June 8, 1968.
24. Atromid-S, Ayerst Laboratories	June 12, 1968.
25. Nebair, Warner-Chilcott	June 27, 1968.
26. T A O, Roerig	September 3, 1968.
27. Enzopride, Shick Safety Razor Co	September 30, 1968.
28. Symmetrel, E. I. duPont deNemours & Co	October 14, 1968.
29. Ismelin, Ciba	January 20, 1969.

ORTHO PHARMACEUTICAL CORP.,
Raritan, N.J., February 1, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to the fact that a claim in our recent advertising of ORTHO-NOVUM SQ* may be misleading.

In our introduction of this product to the medical profession we featured the theme, "The Most Effective Sequential," based on a comparison of pregnancy rates published in manufacturers' package inserts. The Food and Drug Administration has pointed out that such a comparison is invalid because there has been neither a direct comparative study of the efficacy of the three sequential oral contraceptives in the same population nor individual studies of the three products in population groups shown to be comparable. We are therefore discontinuing the promotional theme in question.

ORTHO PHARMACEUTICAL CORP.

ROCHE LABORATORIES,
DIVISION OF HOFFMANN-LAROCHE, INC.,
Nutley, N.J., March 10, 1967.

DEAR DOCTOR: At the request of the Food and Drug Administration, we are extending the "brief summary" of prescribing information for Librium® (chlordiazepoxide HCl) which appears in medical journal advertisements by adding several phrases and items from the unchanged official package circular.

The revised "brief summary" for medical journals is attached, indicating by capitalization the requested added material. Prescribing information in all Librium (chlordiazepoxide HCl) package circulars, direct mail information and brochures is complete and requires *no* change. The safety and effectiveness of the product are *not is question.*

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*Trademark.

In addition, in future medical journal advertisements for Librium (chlordiazepoxide HCl) in geriatric patients, we are amplifying statements which have appeared concerning possible side effects and initial dosage:

The statement that "Side effects in most instances are mild in degree and readily reversible with reduction of dosage," will be extended by the observations made in our package circular which point out that drowsiness, ataxia and confusion have been reported in some patients, particularly the elderly and debilitated, occasionally at lower dosage ranges, and that in a few instances syncope has been reported.

Whereas in geriatrics, the *usual daily dosage* is 5 mg, two to four times daily, the *initial dosage* in elderly and debilitated patients should be limited to 10 mg or less per day, adjusting as needed and tolerated.

We hope the additional detail in medical journal advertising clarifies the use of the product in accordance with the enclosed package circular.

Sincerely,

ROBERT E. DIXON, M.D.,
Director, Professional Services.

Enclosure [omitted].

WALLACE PHARMACEUTICALS,
DIVISION OF CARTER-WALLACE, INC.,
Cranbury, N.J., March 30, 1967.

DEAR DOCTOR: At the request of the Food and Drug Administration, we are calling your attention to one of our recent advertisements captioned, *"The published clinical studies indicate: 3 of 4 non-psychotic depressions respond to 'Deprol'."* The FDA considers that this advertising may have been misleading.

In the advertisement, we listed 21 studies comprising the total published "Deprol" literature containing data on *non-psychotic* depressions. While the ad does not reflect the fact, data from these studies were *excluded* in whole or in part if

(*a*) the diagnosis was not entirely clear;

(*b*) the recommended maximum dose of 6 "Deprol" tablets per day was exceeded;

(*c*) other psychotropic drugs or electroshock were part of therapy.

Moderate, marked, excellent, and complete responses were counted as favorable, while mild, fair, slight, and no responses were counted as unfavorable.

Using the above criteria, the final number of patients included was 323 selected from ten of the 21 listed studies. Nine of the ten studies were uncontrolled, and most patients in the ten studies concomitantly received informal or structured psychotherapy. The reported therapeutic results (ranging from 0% in a study with two non-psychotic depressed patients, through 64% in a study with 53 such patients, to 90% in two studies with 38 and 41 such patients respectively) also include, to an undetermined degree, placebo responses and spontaneous remissions known to occur in the therapy of neurotic depression.

The factors noted above represent problems that exist in working with any literature and are present in some "Miltown" advertisements carrying the theme "one of a series". In order to avoid any misunderstanding, we have discontinued the use of these "Miltown" advertisements as well as the described "Deprol" advertisement.

Sincerely,

WALLACE PHARMACEUTICALS.

ABBOTT LABORATORIES,
North Chicago, Ill., April 13, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to a recent advertisement on Enduron® (methyclothiazide) and Enduronyl® (methylclothiazide and deserpidine). The advertisement, headlined "Thiazide-potassium problems, doctor?" is regarded by the FDA as misleading.

The ad states that the advertised drugs provide "excellent sodium output with less potassium loss than either chlorothiazide or hydrochlorothiazide."

The consensus of expert medical opinion is that there is no significant difference

in the amount of potassium loss caused by thiazide agents, including methyclothiazide (Enduron).

The ad suggests that any physician taking a patient off a thiazide-potassium combination may wish to consider Enduron as alternative therapy. It states that the product will "do an outstanding job for you, *without* routine potassium supplementation," and that it has "potassium-sparing characteristics." The FDA believes that these claims could lead to the erroneous conclusion that hypokalemia is less likely to occur, and consequently, that potassium supplementation is less often necessary with Enduron than with other thiazides.

In point of fact, the need to consider proper potassium supplementation, dietary or otherwise, is no less with Enduron or Enduronyl than with any other thiazide drug.

Because the ad's "brief summary" of warning information was considered inadequate, a new one is enclosed. The information capitalized in the attached revised "brief summary" is not present in current ads, but will be incorporated into future ads for these products.

ABBOTT LABORATORIES.

Enclosure [omitted].

PFIZER LABORATORIES,
New York, N.Y., May 22, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to recent promotional messages for our products (Rondomycin, Renese, and Renese-R) which the FDA regards as potentially misleading.

Renese and Renese-R

The monograph in the 1967 *Physicians' Desk Reference* for Renese and Renese-R is considered inadequate in presenting information necessary for their safe and effective use. To provide you with the necessary additional information, we are enclosing a revised monograph for insertion into your *PDR*. The changes include additional warnings and precautions concerned with electrolyte imbalance, hepatic coma, maintenance dosage, and, in the case of Renese-R, the possibility of Parkinsonism and confusion.

Rondomycin

The FDA has also asked us to call to your attention certain features of our current advertising for the broad spectrum antibiotic, Rondomycin. The ad does not disclose that it is a member of the bacteriostatic tetracycline family and that administration for ten days is especially important in the treatment of Beta-hemolytic streptococcal infections. In referring to the "Protective dose (PD_{50}) tests," the ad did not specify that they were performed in mice utilizing laboratory strains of organisms injected intraperitoneally. While demonstrating the activity of Rondomycin against these test strains, the PD_{50} tests cannot be extrapolated directly to the clinical situation, in which sensitivity testing is recognized to be important for selection of the most appropriate antibiotic for a specific patient's infection.

In addition, the "Brief Summary" of warning information in the above ad, and also in the current journal ad for Renese-R, is considered inadequate. We are modifying the advertisements in question and future advertising will include the requested additional warning information.

Sincerely yours,

JOHN L. WATTERS, M.D.,
Medical Director.

Enclosures [omitted].

GEIGY PHARMACEUTICALS,
Ardsley, N.Y., June 2, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to recent journal advertisements for our products (Hygroton® and Regroton®) which the FDA considers to be misleading.

Hygroton Advertisement

This ad is headlined, "Do your patients shell out too much for a diuretic?". It states that a published report on a new short-acting diuretic supports the claim that "If one considers maximum recommended doses for each product,

tablet for tablet Hygroton was clearly superior. Two tablets of Hygroton were found to produce almost 40% more natruresis and 20% more weight loss than five tablets of the other diuretic."

The FDA points out that the studies were based on small numbers of patients (6 to 13), that the actual differences reported were clinically insignificant, and that the ad's claim for superiority was not supported by the data or by the authors' conclusions. Further, the report was not a direct comparative study of the two drugs, but rather a comparison of data obtained on the new diuretic with data obtained on Hygroton in a previous study.

In addition, the tablet-for-tablet comparison in the ad is not regarded as sound because single tablets of Hygroton and the other diuretic do not contain comparable threapeutic dosages.

Regroton Advertisement

This ad displays a single Regroton tablet in relation to two sets of five tablets representing drug regiments for treating hypertension. The ad states that "in moderate hypertension" Regroton was "better than reserpine + hydralazine + hydrochlorothiazide in 41 of 43 patients and better than reserpine + methyldopa + hydrochlorothiazide in 34 of 37 patients". These numbers, taken from a paper referenced in the ad, refer specifically to a comparison of average mean blood pressures after two years on Regroton with responses to prior therapy utilizing the other drug combinations.

The FDA points out that the differences observed in the blood pressure response to the various treatments were neither statistically nor clinically significant. Further, the study was not done on patients diagnosed as "moderate hypertension", and the authors did not state that the effect of Regroton on the patients' blood pressure was "better".

The FDA also considers the summary of prescribing information in each ad to be inadequate. Each enclosed "Brief Summary" contains information in capital letters that was not included in our current ads. We are discontinuing the ads in question and future advertising will incorporate the revised "Brief Summary". The safety and effectiveness of the products are not in question when used in accordance with the official package inserts.

GEIGY PHARMACEUTICALS.

Enclosures [omitted].

MEAD-JOHNSON LABORATORIES,
Evansville, Ind., June 30, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to current medical journal advertisements for Oracon and Questran which the FDA regards as misleading.

Oracon®

The ad claims that the drug provides ". . . oral contraception with effects which closely parallel those of the natural hormonal cycle" and also contains a related slogan implying such effects are "So Close to Nature." The FDA points out that not neary all effects of oral contraceptives parallel those of the natural hormonal cycle and that some of the effects of these drugs are of profound or undetermined nature.

The ad emphasizes the low incidence of certain less serious side effects such as amenorrhea, breakthrough bleeding, weight gain, etc. However, it fails to give adequate emphasis to more serious known side effects—or adequate emphasis to the possible occurrence of thrombophlebitic, pulmonary embolism or cerebral vascular accident.

The FDA points out that the pregnancy rates claimed in the ad were incorrectly based on 1065 women instead of only 880, and that the ad improperly features a pregnancy rate of 0.2 per 100 woman-years. While available data do not provide a reliable scientific basis for a statement of true pregnancy rates, experience reported to us shows that the unadjusted rate for all women who were given Oracon was 2.0 per 100 woman-years. The rate of 0.2 used in the ad included only those patients who insisted that they had adhered to the regimen.

Questran®

The FDA considers the summary of warning information in the journal advertisement for Questran to be inadequate in that it did not contain any infor-

mation on precautions and warnings. We have attached a revised "Brief Summary," which contains the omitted precautions and warning information in capital letters.

We are discontinuing the ads in question, and future advertising will incorporate the above corrections. The safety and effectiveness of Oracon and Questran are not in question when the drugs are used in accordance with the official package inserts.

Sincerely,

P. A. WALTER, M.D.,
Director, Medical Research Department.

Attachment [omitted].

FLINT LABORATORIES,
DIVISION OF TRAVENOL LABORATORIES, INC.,
Morton Grove, Ill., July 20, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to the initial advertisements for Choloxin® (sodium dextrothyroxine), currently appearing in several journals, which are regarded by the FDA as misleading.

The headline, "A significant new advance in the management of hypercholesterolemia", does not include the qualification that Choloxin is indicated for the treatment of hypercholesterolemia in selected patients, i.e., euthyroid patients with no known evidence of organic heart disease. Also, the ads fail to stress that Choloxin is not intended to replace or to lessen the desirability of considering dietary regulation in the management of hypercholesterolemia.

The FDA points out that, while the ads emphasize that Choloxin effectively lowers blood cholesterol levels, they fail to emphasize that this effect has not been proven to alter the morbidity and mortality of atherosclerotic disease. The claim in the ads that Choloxin (sodium dextrothyroxine) is "significant in its accepted physiologic mode of action" is considered to oversimplify the extent of knowledge of its mode of action. Further, the reference to "over 6,000 patients treated in clinical studies" overstates pertinent clinical experience, since only 2,967 patients were in the diagnostic categories for which the drug is currently indicated.

The FDA also considers the summary of warning information in the ads to be incomplete. The enclosed "Brief Summary" contains information in capital letters that was not present in the current ads, but will be incorporated into future ads for Choloxin. We are discontinuing the ads in question. The safety and efficacy of Choloxin are not in question when used in accordance with the official package circular, which remains unchanged.

Sincerely,

THOMAS A. GARRETT,
Vice President, Medical Affairs.

Enclosure [omitted].

NEISLER LABORATORIES, INC.,
SUBSIDIARY OF UNION CARBIDE CORP.,
New York, N.Y., August 11, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to a recent advertisement for Diutensen-R which the FDA regards as misleading.

The Food and Drug Administration regards the warning information in the ad to be so substantially deficient that the ad represents a potential danger to health. Therefore, we have rewritten our "Brief Summary", and the nature and extent of the changes are shown in capital letters in the attached revision. We have discontinued the ad in question and all future ads will carry the new "Brief Summary".

The safety and efficacy of Diutensen-R are not in question when used in accordance with the prescribing information in the official package insert.

Sincerely,

NEISLER LABORATORIES.

Enclosure [omitted].

ASTRA PHARMACEUTICAL PRODUCTS, INC.,
Worcester, Mass., August 23, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call to your attention two of our recent mailing pieces for Citanest® which the FDA regards as so substantially misleading and lacking in adequate professional use information that in its view they represent potential hazards to health. These mailing pieces, identified as 118–67 and 119–67, should be discarded if still in your possession.

1. *Intravenous Regional Anesthesia.*—Mailing piece 118–67 recommended the use of Citanest in intravenous regional anesthesia. The FDA regards use of this drug by that technique as experimental. The package insert for Citanest contains no information for its use in intravenous regional anesthesia and the drug has not been approved for use in that procedure.

2. *Maximum Single Dosage.*—Mailing pieces 118–67 and 119–67 contained statements which implied that dosages of Citanest in excess of the maximum single dose (600 mg.) could be employed in clinical use. No such implication was intended by Astra, and Astra reaffirms that on more than 600 mg. of the drug should be used during any two-hour period.

3. *Professional Use Information.*—Both booklets omitted essential and required professionals use information. The attached page contains the warning, precautionary, and adverse reaction information which was omitted from the "full disclosure" sections of the booklets.

The safety and effectiveness of Citanest (prilocaine), when used in accordance with the conditions specified in the enclosed package insert, are not in question.

Sincerely yours,

ASTRA PHARMACEUTICAL PRODUCTS, INC.

Enclosure [omitted].

SQUIBB,
October 24, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to certain advertisements for Mysteclin®-F products which the FDA regards as misleading. The main theme of the advertising, which we have stopped, suggests that "almost every candidate for broad-spectrum antibiotic therapy, is a candidate for Mysteclin-F."

We wish to emphasize that those patients selected for tetracycline therapy who are known to be particularly susceptible to candidal superinfection are the potential candidates for Mysteclin-F therapy.

The FDA points out that recent journal advertisements for these products suggested that candidal superinfection is a serious problem with the use of ampicillin. This was not supported by the reference used in the ads. Although the reference cited included the statement that candidal overgrowth may follow ampicillin therapy, the FDA has asked that we point out that the significance of this overgrowth has not been established.

Further, the same ads omitted important warning information relating to precautions and side effects. The nature and extent of the omission are capitalized in the enclosed "Brief Summary".

Sincerely,

SQUIBB.

Enclosure [omitted].

ORGANON, INC.,
West Orange, N.J., October 27, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to the monographs for Cortrophin® Gel, Cortrophin® Zinc, Hexadrol® Phosphate Injection and Hexadrol® Tablets and Elixir in the current *Physicians' Desk Reference.* The FDA considers these monographs to be incomplete in presenting necessary information for the safe and effective use of these drugs, and, therefore, potentially misleading.

To provide you with the necessary information, we enclose revised monographs for insertion in your *PDR.* The nature and extent of the additions and other revisions in the enclosed monographs are emphasized by use of italics.

Sincerely yours,

JOSEPH D. CUONO, M.D.,
Director, Professional Services.

Enclosure [omitted].

THE S. E. MASSENGILL CO.,
Bristol, Tenn., November 1, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to the monographs for our products, Predsem, Salcort and Salcort-Delta, in the current (1967) *Physicians' Desk Reference.* The FDA considers these monographs to be incomplete in presenting the necessary information for the safe and effective use of these drugs and therefore potentially misleading.

To provide you with the necessary information, we enclose revised monographs for insertion at page 812 of your current (1967) PDR. The nature and extent of the additions and other revisions in the enclosed monographs are emphasized by use of italics.

Sincerely,

ROBERT P. EWING,
Vice President, Marketing.

Enclosure [omitted].

LAKESIDE LABORATORIES,
DIVISION OF COLGATE-PALMOLIVE CO.,
Milwaukee, Wis., November 1967.

DEAR DOCTOR: The Food and Drug Administration have requested that we call your attention to the monograph for Norpramin (desipramine hydrochloride) in the 1967 *PDR:* page 687, white section. The FDA consider this monograph incomplete (in relation to the official labeling, the package insert), and therefore potentially misleading as prescribing information to allow safe and effective use of the drug.

To provide you with the necessary adequate reference, we enclose a revised monograph for 1967 Physicians' Desk Reference in which the changes have been emphasized by italics. Please insert this revision opposite page 687.

Sincerely yours,

WILLIAM C. JANSSEN, M.D.

Enclosure [omitted].

THE UPJOHN CO.,
Kalamazoo, Mich., November 15, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to certain promotional messages for Medrol Tablets which the FDA regards as misleading.

Some journal advertisements have recommended use of Medrol 16 mg. Tablets by an alternate day dose regimen. Although reports of this usage have appeared in the literature, the FDA points out that information currently available and submitted by us to them is not adequate to justify this regimen as advertised. Consequently, we are ceasing all reference to alternate day therapy in our promotion of the product.

The monograph for Medrol Tablets in the 1967 *Physicians' Desk Reference* is considered by the FDA to be inadequate in presenting information for the safe and effective use of the product. To provide you with the necessary information, we enclose a revised monograph for insertion at page 1143 of your current (1967) *PDR.* The nature and extent of revisions in the enclosed monograph are emphasized by printing in bold type.

Sincerely yours,

FENIMORE T. JOHNSON, M.D.

Enclosure [omitted].

ARMOUR PHARMACEUTICAL CO.,
Chicago, Ill., November 16, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to the monograph for H.P.* ACTHAR ® GEL in the current (1967) *Physicians' Desk Reference.* The FDA considers this monograph to be incomplete in presenting necessary information for the safe and effective use of this drug and, therefore, potentially misleading.

*Highly purified.

To provide you with the necessary information, we enclose a revised monograph for insertion at page 527 in your 1967 *PDR*. The nature and extent of the additions of previously omitted information are indicated by the use of italics.

Sincerely yours,

J. A. HUBATA, M.D., *Medical Director.*

Enclosure [omitted].

PHYSICIANS' DESK REFERENCE,
Oradell, N.J., November 27, 1967.

DEAR SIR: The Food and Drug Administration has requested that we call your attention to the monographs for the following products in the current (1967) Physicians' Desk Reference:

	Page
HP Acthar Gel	527
Cortrophin Gel	898
Cortrophin-Zinc	898
Hexadrol	899
Hexadrol Phosphate Injection	899
Norpramin	687
Predsem	812
Salcort	812
Salcort-Delta	812

The FDA considers these monographs to be incomplete in presenting the necessary information for the safe and effective use of these drugs and therefore potentially misleading.

To provide you with the necessary information, we enclose revised monographs for insertion in your 1967 PDR at the pages indicated at the top of each sheet. The nature and extent of the additions and other revisions in the enclosed monographs are emphasized by the use of italics.

Sincerely,

ALBERT B. MILLER, *General Manager.*

Enclosures [omitted].

PARKE, DAVIS & CO.,
Detroit, Mich., January 15, 1968.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to our recent Ponstel® (mefenamic acid) journal advertisement and certain promotional mailing and detailing pieces which the Food and Drug Administration regards as misleading.

The introductory campaign featured results from non-blind clinical trials using only a single 500 mg. dose for several types of pain. The Food and Drug Administration points out that Ponstel has also been studied in several double-blind clinical trials in which the drug was compared to aspirin and other non-narcotic analgesics. These trials demonstrated that Ponstel was essentially equal to the comparison drug and better than placebo. However, in certain individual trials aspirin was found better than Ponstel and the latter could not be distinguished from placebo; in some trials pain relief with placebo was obtained in as high as 40% of the patients. In other trials the results with Ponstel were better than those with aspirin or placebo.

The Food and Drug Administration considers that the introductory campaign failed to give adequate prominence to the fact that Ponstel is indicated for short-term administration not exceeding one week of therapy. Also, in a promotional brochure, results were reported from a double-blind effectiveness comparison with codeine and placebo, which represented that Ponstel was equal in effectiveness to 25 mg. of codeine. However, the dosage of Ponstel employed in this study was at a level which is still in the investigational phase.

We are discontinuing the advertising campaign in question.

Sincerely,

J. E. GAJEWSKI, M.D.

SYNTEX LABORATORIES, INC.,
Palo Alto, Calif., January 22, 1968.

DEAR DOCTOR: The Food and Drug administration has asked us to call your attention to the fact that certain statements in recent advertising for our oral contraceptives, NORQUEN® and NORINYL®-1, may be misleading.

In the NORQUEN advertisement, the paragraph headed "Low incidence of side effects" emphasizes the low incidence of certain less serious side effects such as spotting, break-through bleeding, nausea, vomiting and other gastrointestinal disturbances, but fails to give adequate emphasis to the more serious known side effects such as cholestatic jaundice, rise in blood pressure in susceptible individuals, and mental depression which also occur in low incidence. Further, although a cause and effect relationship has neither been established nor disproved, the advertisement does not give adequate emphasis to the possible occurrence of thrombophlebitis, pulmonary embolism, and neuro-ocular lesions which have been observed in users of oral contraceptives.

The advertisements for both NORQUEN and NORINYL-1 state that "careful observation and caution are required for patients with symptoms or history of . . . cerebrovascular accident, psychic depression. . . ." The ads should have been more specific in stating:

Oral contraceptives should be used with caution in patients with a history of cerebrovascular accident and should be discontinued if there is a sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia, or migraine, or if examination reveals papilledema or retinal vascular lesions, since these may be symptoms of cerebrovascular accident.

The advertisements disclose that careful observation and caution are required for patients with symptoms or history of psychic depression but do not specifically state that oral contraceptives should be discontinued if psychic depression recurs to a serious degree. Also, the ads fail to disclose that a decrease in glucose tolerance has been observed in a small percentage of patients on oral contraceptives.

We are modifying all future advertising to reflect these changes.

Sincerely,

BEN Z. TABER, M.D.,
Medical Director.

G. D. SEARLE & CO.,
Chicago, Ill., January 26, 1968.

DEAR DOCTOR: In June 1967, the Food and Drug Administration and all manufacturers of oral contraceptives agreed on certain changes in the uniform portions of the labeling for all oral contraceptive products. These changes were to be included in all advertisements after October 1, 1967.

The FDA has asked us to call your attention to recent journal advertisements for Ovulen®-21, which departed from the new uniform labeling in several respects.

The original uniform labeling stated:

> The following occurrences have been observed in users of oral contraceptives. A cause and effect relationship has not been established:
>
> Thrombophlebitis
> Pulmonary embolism
> Neuro-ocular lesions.

Because that labeling did not accurately represent the present status of opinion concerning the possible danger of side effects, the warning statement was changed to read: "A cause and effect relationship has been *neither established nor disproved*:" (emphasis added). The FDA regards the advertisements as potentially misleading because they omitted this important change which emphasizes the possibility of these serious hazards.

Further, the advertisements failed to include the following side effects which, although causation has not been established, have been reported in users of oral contraceptives: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, backache, nervousness, dizziness, fatigue, headache, hirsuitism.

We have modified our current advertising to reflect these changes.

Sincerely,

HERBERT HELLING,
Food and Drug Administration Affairs,
G. D. Searle & Co.

GEIGY PHARMACEUTICALS,
DIVISION OF GEIGY CHEMICAL CORP.,
Ardsley, N.Y., February 15, 1968.

DEAR DOCTOR: In our promotion of Persantine® (brand of dipyridamole) for long-term therapy in anginal patients, we sent a letter to physicians stating that "Several studies document the effectiveness of Persantine in extending walking

distance and generally increasing exercise tolerance." Enclosed with the letter was a reprint of a study in the *Journal of Chronic Diseases* of March 1967 to support the claims for effectiveness.

The Food and Drug Administration has asked us to inform you that the claims for effectiveness of Persantine, and many other drugs marked prior to 1962, have been neither approved nor disapproved by the Agency. The FDA is proceeding on the basis that the Drug Amendments of 1962 require the Agency to evaluate the effectiveness of such drugs, and this is currently being done with the assistance of the drug efficacy panels of the National Academy of Sciences/National Research Council.

The FDA regards the promotional letter as potentially misleading because it presented only favorable information regarding the drug's effectiveness when there is a substantial body of opinion that does not support the claimed effectiveness of the product. For example, the AMA Council on Drugs (in New Drugs 1967) has stated that double-blind studies comparing dipyridamole with a placebo have shown equivocal results and that the drug has not been convincingly shown to be effective in the long-term treatment of angina pectoris.

Recently, in the *JAMA* issue of September 11, 1967, a paper by Sbar and Schlant disclosed results of a six-month double-blind study. The authors concluded that "The study failed to detect a statistically significant difference between the improvement in patients receiving dipyridamole and the improvement in patients receiving a placebo."

Our future promotion will express the range of expert medical opinion on the effectiveness of Persantine when any segment of that opinion is referenced.

GEIGY PHARMACEUTICALS.

ABBOTT LABORATORIES,
North Chicago, Ill., June 3, 1968.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to a promotional letter on Erythrocin® (erythromycin) directed to you in February of this year. This letter, discussing the mode of action and the *in vitro* spectrum of erythromycin, is regarded as potentially misleading.

The letter included bactericidal values for Mycoplasma pneumoniae, H. influenzae, pneumococci, Group A streptococci, and several other organisms. The FDA points out that the values cited from the referenced articles represent a limited number of strains, and that other investigators, using other strains and methods have reported that higher concentrations of drug are needed for bactericidal effect.

The letter also stated that: "In addition to cidal action, Erythrocin provides the wider *in vitro* and *in ovo* spectrum associated with the bacteriostatic 'mycins, including—

Gram positive cocci and bacilli
Gram negative cocci
Many Gram negative bacilli
(except the Enterobacteriaceae)
Spirochetes
Large viruses
Mycoplasmas
Rickettsias
Protozoa
Atypical Mycobacteria"

The FDA notes that this section can be interpreted to mean that erythromycin is bactericidal against all organisms in the listed caegories. In point of fact, the statement refers to the results of *in vitro* testing designed only to demonstrate inhibition of organisms by the drug; distinctions between bacteriostatic and bactericidal effects were rarely made. The letter failed to make clear that erythromycin is active against only certain organisms within these broad categories. Also, clinical experience with erythromycin in certain of these categories, particularly Rickettsias and Atypical Mycobacteria, is limited and does not presently warrant the use of erythromycin. They particularly note that the term "Enterobacteriaceae" inadequately identified the fact that it includes such important pathogens as Salmonella, Shigella, Proteus, Pseudomonas, Escherichia, Aerobacter, and Klebsiella, against which erythromycin is not generally active.

In reference to the letter as a whole, we wish to emphasize that bactericidal activity is an *in vitro* effect, subject to variation accoding to the organism and strains involved, and the conditions of the study. Further, *in viro* activity does not necessarily imply clinical effectiveness, and direct extrapolation to the clinical situation, therefore, is not justifiable. In clincal use, as opposed to laboratory tests, no methodology exists which can accurately determine whether a drug's action is bactericidal or bacteriostatic in the patient. Some authorities, however,

have expressed the opinion that erythromycin is primarily bacteriostatic under some clinical conditions.

The promotional letter did not mention the advisability of choosing or continuing Erythrocin therapy on the basis of appropriate sensitivity tests. Furthermore, while the letter did state tha Eryhrocin has ". . . no known toxic effects on body organs or systems," it did not point out that serious allergic reactions, through extremely infrequent, do occur.

We sincerely regret that the construction of the letter may have allowed interpretations extending beyond the limits of the approved package labeling and the full content of the cited references. We are discontinuing the current advertising campaign in question. Future advertising will be appropriately modified.

ABBOTT LABORATORIES.

BRISTOL LABORATORIES,
DIVISION OF BRISTOL-MYERS CO.,
Syracuse, N.Y., June 8, 1968.

DEAR DOCTOR: The Food and Drug Administration has asked that we call your attention to our letter of May 17, 1968 which announced the coming availability of Dynapen (sodium dicloxacillin monohydrate). The Food and Drug Administration has expressed concern that our discussion of this drug in terms of treating skin and soft tissue infections created misleading impressions concerning the proper use of Dynapen in its limited appropriate indications.

Therefore, we wish to specify the indications and limitations for use of this drug in detail as follows:

1. The principal indication for Dynapen is in the treatment of infections known to be due to penicillinase-producing staphylococci which have been shown to be sensitive to it.
2. If antibotic therapy is considered necessary in potentially serious infections while awaiting reports of cultures and sensitivity studies, Dynapen may be used to initiate therapy in such patients in whom a penicillinase-producing staphylococcus is suspected. (See Important Note below.)

Important Note

Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When it is judged important that treatment be initiated before definitive culture and sensitivity results are known, the choice of Dynapen should take into consideration the knowledge that it has also been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci and penicillin G-sensitive staphylococci. In serious, life threatening infections oral preparations of the penicillinase-resistant penicillins should not be relied on for initial therapy.

Methicillin, a compound working through a similar mechanism against penicillin G-resistant staphylococci, has been available for nine years. It is a fact that strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. It has been demonstrated that such strains are almost always resistant to other penicillinase-resistant penicillins, such as the isoxazole group of which Dynapen is a member. When such a strain is isolated, use of routine antibotic discs cannot be relied on to differentiate relative sensitivity. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, the Food and Drug Administration is concerned the widespread use of the penicillinase-resistant penicillins in infections other than those due to penicillin G-resistant staphylococci may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Therefore, if the bacteriology report indicates the infection is not due to a penicillin G-resistant staphylococcus, the physician is advised to continue therapy with a drug other than Dynapen nor any other penicillinase-resistant semi-synthetic penicillin.

Indicated surgical procedures should be performed.

Contraindications

A history of allergic reactions to penicillin should be considered a contraindication.

Information in our announcement letter, or that you may have received from one of our sales representatives, should be carefully considered in light of the preceding clarification.

We have discontinued the advertising in question. Future advertising will be appropriately modified. The drug is not available for prescription at this time. We will notify you when it becomes available.

Sincerely,

H. C. PELTIER, M.D.,
Vice President, Medical Director.

AYERST LABORATORIES,
DIVISION OF AMERICAN HOME PRODUCTS CORP.,
New York, N.Y., June 12, 1968.

DEAR DOCTOR: A recent advertisement for ATROMID-S® (clofibrate), "Answers to some questions physicians are asking about ATROMID-S," is regarded by the Food and Drug Administration as misleading. Accordingly, we have been asked to clarify certain points in the ad relating to effectiveness and safety of this drug.

Among other things, the ad contains statements which imply there is an association between the lipid-lowering effect of ATROMID-S and a beneficial effect on atherosclerosis or atherosclerotic heart disease. We emphasize that the drug is indicated solely for the reduction of serum lipids. In the absence of substantial evidence that reduced serum lipids results in amerlioration of the atherosclerotic process, no claim may be made for ATROMID-S in this regard.

Further, we wish to state that any implication in the ad that ATROMID-S reduces the risk of recurrence of heart attacks is not a valid one. Any relationship between the lowering of serum lipids by drug therapy and a reduction in initial or recurrent coronary thrombosis will not be known until present long term clinical studies have been completed.

The FDA also pointed out that the ad failed to stress the important role of diet in the management of elevated serum lipids. Because of the possibility of long term administration of clofibrate, adequately repeated baseline studies should be performed to determine that the patient has significantly elevated serum lipid levels. If so, attempts should be made to control serum lipids with appropriate dietary regimens before considering the addition of therapy with clofibrate.

In addition, while the ad copy did emphasize some side effects of more frequent occurrence but mild severity, it did not likewise call attention to a number of the more serious side effects which have been reported to occur (e.g., weakness, urticaria, stomatitis, and polyphagia; as well as leukopenia and alopecia although relationship to clofibrate administration has not been established).

We have discontinued the advertisement in question. Future advertising will be appropriately modified.

Sincerely yours,

JOHN B. JEWELL, M.D.

WARNER-CHILCOTT LABORATORIES,
DIVISION OF WARNER-LAMBERT PHARMACEUTICAL CO.,
Morris Plains, N.J., June 27, 1968.

DEAR DOCTOR: We have been asked by the Food and Drug Administration to call to your attention recent advertisements for Nebair, an inhalation aerosol containing isoproterenol and thonzonium bromide. It regards these ads as potentially misleading because the insufficient distinction between severe bronchospasm and severe bronchospastic disease can be constructed to extend recommendations for use of Nebair beyond approved indications. In addition, FDA maintains that these ads fail to balance important warning ideas in the same section of the ads containing claims of safety, and cite some abstracts of research reports in such a fashion as to exaggerate the performance and efficacy of Nebair.

Recent advertising reads "For the patient with severe bronchospasm it [Nebair] may be more effective than isoproterenol alone." This statement does not sufficiently reflect the fact that Nebair is not indicated for all forms of "bronchospasm," but is indicated for patients with moderately and markedly severe chronic obstructive pulmonary disease with reversible bronchospasm. Specifically, Nebair is indicated for the relief of acute bronchospasm only in those patients with the following disease states:

1. Moderately and markedly severe bronchial asthma.
2. Moderately and markedly severe chronic bronchitis with reversible bronchospastic components, and
3. Emphysema.

It is only in the above mentioned subgroup of patients that there is some evidence to indicate Nebair may be more effective than isoproterenol alone.

The FDA has expressed concern that the ads did not list those side effects which may occur in association with any isoproterenol aerosol therapy. These side effects include: vomiting, headaches, flushing of skin, tremor, weakness, sweating, and anginal type pain. In addition, it feels adequate prominence was not given to the fact that frequent or continuous use of Nebair on a long-term basis is not recommended, and that use in children under twelve years of age is not indicated.

The above mentioned advertisements have been discontinued. All future promotion, including advertising, will be appropriately modified.

Very truly yours,

WARNER-CHILCOTT LABORATORIES.

J. B. ROERIG & CO.,
DIVISION, CHAS. PFIZER & CO., INC.,
New York, N.Y., September 3, 1968.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to our advertising and promotion of TAO (triacetyloleandomycin) which the FDA regards as misleading.

At our display booth at the recent American Medical Association Convention in San Francisco, two TAO promotional pieces were distributed to physicians. One of these, a folder titled, "Travel on Us," emphasized that TAO does not cause tooth staining (a side effect of tetracyclines). The FDA regards this as an implied comparison suggesting that triacetyloleandomycin and tetracycline have a similar antibacterial spectrum of effectiveness, and that triacetyloleandomycin has less toxic potential. Any such implication is not intended and of course would be invalid.

The other promotional piece—a booklet—emphasized that TAO is indicated "for the frequently seen respiratory infection in the office or the problem pathogen . . ." (the latter identified as *Staphylococcus aureus*). In the opinion of FDA, the booklet suggested that the antibiotic is useful in the treatment of diseases caused by microorganisms including viruses beyond the spectrum of its effectiveness, and did not provide adequate prominence to the fact that it should be used only as a possible alternative to other less toxic agents.

We emphasize that:

(1) Triacetyloleandomycin is recommended only for acute, severe bacterial infections where adequate sensitivity testing has demonstrated susceptibility to this antibiotic and resistance to other less toxic agents.

(2) In view of the possible, but reversible, jaundice and hepatotoxicity of this drug, other less toxic agents should be used unless the organism is resistant to those agents, or in those cases where hypersensitivity precludes their use.

(3) TAO (triacetyloleandomycin) is contraindicated in pre-existing liver disease or dysfunction, and in individuals who have shown hypersensitivity to the drug.

We are discontinuing the promotional pieces in question and correcting the journal advertisements in which the same themes were featured.

Sincerely yours,

J. RALPH FOWLER, M.D., *Medical Director.*

SCHICK SAFETY RAZOR CO.,
DIVISION OF EVERSHARP, INC.,
Culver City, Calif., September 30, 1968.

DEAR DOCTOR: Recently you received a booklet entitled "Alcohol—Who is Allergic?" In it reference was made to a drug product, Enzopride®, [DPN (Diphosphopyridine Nucleotide)], which is currently being tested by our subsidiary, Enzomedic Laboratories, Inc.

The Food and Drug Administration has asked us to inform you, in relation to statements made in the booklet, that Enzopride® is still in the investigational phase and that available data are inadequate to substantiate its safety or efficacy in the treatment of chronic alcoholism. In addition, the theory that alcohol may produce a condition leading to chronic alcoholism as a result of an enzymatic deficiency is not proven.

Sincerely,

P. J. FRAWLEY, Jr.,
Chairman of the Board.

E. I. DU PONT DE NEMOURS & CO., INC.,
Wilmington, Del., October 14, 1968.

DEAR DOCTOR: This letter is sent to you at the request of the Food and Drug Administration to correct implications about "Symmetrel" (amantadine hydrochloride) in our recent statement to the medical press. It implied there may be outbreaks of influenza this winter due to the recently identified new strain of A_2/Hong Kong/68, as reported by the National Communicable Disease Center (NCDC) in Atlanta. According to our press release, laboratory tests suggested that "Symmetrel" can be used for the prevention of illness from this new strain of influenza virus, and such a suggestion is regarded by the FDA as misleading.

We are writing to inform you that there have been no clinical tests in man with respect to infections due to the new A_2/Hong Kong/68 variant. We are attempting to arrange for appropriate controlled clinical tests of this new A_2 strain under conditions of natural exposure. However, it will be many months before definitive results can be obtained. Until such time as these tests are completed, we are not in a position to claim that "Symmetrel" is efficacious in man for the prevention of influenza due to A_2/Hong Kong/68 strain.

The FDA has asked us to point out that the NCDC, in a recent release, has stated that "amantadine hydrochloride is not presently recommended as a public health measure for community control of influenza nor as a substitute for influenza vaccine immunoprophylaxis." Furthermore, according to FDA, "current information from the NCDC suggests that influenza due to the Hong Kong variant may be mild, of short duration (one to three days), and generally without serious sequelae. Even so, the sequelae may be significant, especially in the known high-influenza risk patient groups, such as those of all ages who suffer from chronic debilitating diseases and persons in older age groups."

However, our press release did not point to the fact that it is in these special groups where precautionary considerations in the use of "Symmetrel" are most important. For example, when "Symmetrel" is administered to patients with central nervous system disease, particularly geriatric patients with cerebral arteriosclerosis and patients with a history of epilepsy or other "seizures", possible untoward central nervous system effects may occur.

Very truly yours,

ROBERT E. ROWAND, M.D.,
Medical Manager.

CIBA PHARMACEUTICAL CO.,
Summit, N.J., January 20, 1969.

DEAR DOCTOR: At the request of the Food and Drug Administration, we are calling your attention to a recent advertisement for our antihypertensive drug, Ismelin® (guanethidine sulfate), which the FDA regards as misleading.

This advertisement suggested that Ismelin will prevent stroke if the drug is added ". . . before organ damage complicates hypertension." The FDA believes that in the absence of substantial and convincing clinical evidence, we are not in a position to validate any claim that Ismelin has such prophylactic benefit.

In addition, the FDA regards the "Brief Summary" section of the advertisement as misleading because it failed to provide all of the necessary side effect and warning information. For example, the ad failed to appropriately emphasize that exertional hypotension is a potential hazard in the use of guanethidine, that patients should be cautioned to avoid exercise while taking the drug, and that guanethidine causes blockade of the sympathetic nervous system. Also,

the advertisement omitted listing side effects such as bradycardia and angina, and omitted warnings that guanethidine may cause congestive heart failure, weight gain or edema, and may cause excessive postural hypotension, excessive bradycardia and depression when used concurrently with rauwolfia derivatives.

We are discontinuing the Ismelin advertisement in question and other promotional material of a similar nature.

Sincerely yours,

CIBA PHARMACEUTICAL CO.

Mr. GORDON. Well, suppose that I read to you part of an affidavit, where a particular drug company, Richardson-Merrell, asked its employees to fake data. Let me read it to you.

Dr. MCGILL. Well, you are submitting in evidence a study that I have never had any opportunity to see and I am quite sure where this sort of thing might have happened, disciplinary devices would be used very quickly.

Mr. GORDON. Yes. As a matter of fact, they were convicted in a criminal case, but here is an affidavit [1] signed by Beulah Jordan, an employee of Richardson-Merrell. She swore that the officials in the company, doctors, by the way, asked her to substitute data to the Food and Drug Administration. I just want to point out that this sort of activity goes on.

Dr. MCGILL. Mr. Gordon, I am not denying that such things can happen and where they happen, they should be disciplined just as they have there. Certainly FDA has this authority——

Mr. GORDON. Yes.

Dr. MCGILL (continuing). And should have it. I don't think even the pharmaceutical industry disagrees with this.

I might point out the AMA, my own organization, was one of the instrumental groups to get the FDA originally formed and has supported it. No argument there.

Mr. GORDON. Just one more question regarding the parasitic companies you referred to.

Now, I think that you defined a parasitic company as one that didn't do research.

Dr. MCGILL. No research and development.

Mr. GORDON. No research at all or no research on a particular item?

Let me give you an illustration. Carter Products did the research and has a patent on meprobamate. Carter Products licensed American Home Products and American Home Products exclusively. The latter company did not do the research on it. That wouldn't make American Home Products Co. necessarily a parasitic company, would it?

Dr. MCGILL. Does the American Home Products have a research and development laboratory where they are searching for new drugs?

Mr. GORDON. I presume they do.

Dr. MCGILL. If they do, then they are not a parasite. This is my definition. I am thinking about getting more products, new tools we can use.

Mr. GORDON. How about the new process, a new process producing maybe the same drug more efficiently at a lower cost?

Dr. MCGILL. That is research.

[1] Information begins at p. 4142, infra. See also app. V, "The MER–29 Case," beginning at p. 4202, infra.

Mr. GORDON. Isn't that a type of research?

Dr. MCGILL. It certainly is.

Mr. GORDON. Many of these small companies do research in that line. They try to produce drugs at a lower price.

Dr. MCGILL. If you want me to give you a good example of that, the original adrenal steroids, since they were taken from the adrenal glands of cattle, they would always be limited. We would never have a supply that was adequate. It wasn't until our research scientists synthesized it and made it that they became useful tools. Certainly I don't object to that and I don't object to price competition. I think I have made that point clear, as long as reliability goes with it.

Mr. GORDON. So you would include new processes or better methods of production as a type of research, is that right?

Dr. MCGILL. Well, again we get into semantics here and I will define my terms if you wish to define yours.

Developing a new product, process, that makes it a more effective agent, that makes it do what it is supposed to do better or to bring it within the reach of the patients where it has been expensive, yes, I would consider that within research and development.

Not quite in the same sense of developing new products but that is still worthwhile.

Mr. GORDON. What about a company not necessarily a drug company but any company, that can bring to the consumer a product at a much lower price, whether he eliminates certain things or adds certain things? Would you call that company an innovative company?

Dr. MCGILL. No, not really.

Mr. GORDON. Not according to your definition.

Dr. MCGILL. Not by my definition.

Mr. GORDON. I have nothing further.

Senator HATFIELD. Dr. McGill, once again we express our appreciation. I have heard many witnesses and I must say that I think you have been one of the most articulate. You have handled the dialog and the questions in a most admirable fashion. You make us all very proud of the medical profession and of the kind and quality of people who make up their vast numbers.

I wish to express, and I am sure I speak on behalf of my colleague, Senator Nelson as well, our appreciation, our deepest appreciation for your presence here today.

Dr. MCGILL. Could I just finish by adding one personal observation? I think the mere fact that a practicing physician like myself from nearly 3,000 miles away who happens to have strong feelings on a given subject, as you know I do in this area, the fact that I can get before a U.S. Senate subcommittee and be heard I think in itself is a remarkable thing. And I think this is the third time I have testified before Congress and I always go away feeling better about my Government. However ponderous and distant it might seem to the individual citizen, the system works and I am delighted. Thank you for inviting me.

Senator HATFIELD. Thank you very much.

The committee will recess until 1:30 and Dr. Ayd will be given his opportunity to testify.

(The information previously referred to follows:)

NATIONAL ACADEMY OF SCIENCES—NATIONAL RESEARCH COUNCIL
Division of Medical Sciences

DRUG EFFICACY STUDY

Form A
(To be submitted in duplicate by applicant)

NDA 6655

1. NDA Number 6D302 2. Date Originally Approved December 8, 1950 3. Rx ☒ OTC ☐

4. Brand Name Chloromycetin, 50 mg. & 100 mg. Capsules, 250 mg. Kapseals

5. Applicant's Name Parke, Davis & Company

and Address Joseph Campau at the River; Detroit, Michigan

6. Quantitative Formula

Established (Non-Proprietary) Name of Active Ingredients (in order shown on label)	Amount (per tablet, per ml., etc.)
1. Chloromycetin, 50 mg. Capsule	
Chloramphenicol	50 mg./capsule
2. Chloromycetin, 100 mg. Capsule	
Chloramphenicol	100 mg./capsule
3. Chloromycetin, 250 mg. Kapseal	
Chloramphenicol	250 mg./kapseal

7. Dosage Form (tablets, etc.) capsules and kapseal

8. 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).

Chloramphenicol 50 MG, 100 MG capsules, 250 MG kapseals, NDA 6655, LOG 2396.

PANEL ON ANTI-INFECTIVE DRUGS (III)

INDICATIONS

I. Staphylococcal infections, by implication of the discussion on the first page of the insert, may be an indication: "in a survey of experimental and clinical experiences of susceptibility of staphylococci to chloramphenicol, it was found that the incidence of chloramphenicol-resistant staphylococci appears unrelated to frequency or to intensity of use of this antibiotic. Development of resistance to chloramphenicol can be regarded as minimal for staphylococci and many other species of bacteria."

Evaluation

Possibly effective.

Comments

Although chloramphenicol was useful for the treatment of some staphylococcal diseases during the mid-1950's, it now seeems to be rarely indicated. Its major trial was in the staphylococcal pneumonias accompanying the influenza epidemic of 1957. Its effectiveness was somewhat less than expected, even for sensitive strains. The statement concerning resistance is not true in the opinion of the Panel (see below). In the description of *in vitro* work just before the sentence quoted above, there is no reference to the transfer of episomal particles carrying chloramphenicol resistance. The advent of better agents for staphylococcal disease relegates this drug to a very rarely needed alternate choice.

Documenation

1. Bloomer, W. E., S. Giammona, G. E. Lindskog, and R. E. Cooke. Staphylococcal pneumonia and empyema in infancy. J. Thorac. Surg. 30:265–274, 1955.
2. Carmichael, D. B., Jr. Fatal bacterial endocarditis due to staphylococcus aureus. U.S. Armed Forces Med. J. 4:287–294, 1953.
3. Hausmann, W., and A. J. Karlish. Staphylococcal pneumonia in adults. Brit. Med. J. 2:845–847, 1956.
4. Kanof, A., B. Epstein, B. Kramer, and I. Mauss. Staphylococcal pneumonia and empyema. Pediatrics 11:385–392, 1953.
5. Lepper, M. H., P. Tillman, and R. Devetsky. Patterns of transmission of staphylococci. Ann. N.Y. Acad. Sci. 128:404–427, 1965.
6. Martin, C. M., C. M. Kunin, L. S. Gottlieb, and M. Finland. Asian influenza A in Boston, 1957–58. II. Severe staphylococcal pneumonia complicating influenza. A.M.A. Arch. Intern. Med. 103:532–542, 1959.
7. Wallman, I. S., R. C. Godfrey, and J. R. H. Watson. Staphylococcal pneumonia in infancy. Brit. Med. J. 2:1423–1427, 1955.

II. Rickettsial diseases: epidemic and murine typhus, Brill's disease, scrub-typhus, Rocky Mountain spotted fever, and rickettsial pox.

Evaluation

Effective, but * * *

Comments

That chloramphenicol is effective in the diseases listed is well established, except in rickettsial pox, a conditon so infrequently seen that few data are available. However, if the warning is to be taken seriously—"chloramphenicol should not be used when other less potentially dangerous agents will be effective"—the tetracyclines, which have been shown to be as effective as chloramphenicol, should be considered the choice and chloramphenicol used only if toxicity to these or failure to respond has occurred. The duration of therapy recommended appears adequate.

Documentation

1. Knight, V. W., McDermott, and F. Ruiz-Sanchez. Aureomycin and chloramphenicol: use in typhus, typhoid and brucellosis. J. Clin. Invest. 28:1052–1053, 1949. (abstr.)
2. Knight, V., F. Ruiz-Sanchez, and W. McDermott. Chloramphenicol in the treatment of the acute manifestations of brucellosis. Amer. J. Med. Sci. 219:627–638, 1950.
3. Ley, H. L., Jr., T. E. Woodward, and J. E. Smadel. Chloramphenicol (chloromycetin) in the treatment of murine typhus. J.A.M.A. 143:217–219, 1950.
4. Murray, E. S., G. Baehr, G. Schwartzman, T. A. Manderbaum, N. Rosenthal, J. C. Doane, L. B. Weiss, S. Cohen, and J. C. Snyder. Brill's Disease; clinical and laboratory diagnosis. J.A.M.A. 142:1059–1066, 1950.
5. Pincoffs, M. C., E. G. Guy, L. M. Lister, T. E. Woodward, and J. E. Smadel. The treatment of Rocky Mountain spotted fever with chrloromycetin. Ann. Intern. Med. 29:656–663, 1948.
6. Smadel, J. E., T. E. Woodward, H. L. Ley, Jr., and R. Leuthwaite. Chloramphenical (chloromycetin) in the treatment of tsutsugamushi disease (scrub typhus). J. Clin. Invest. 28:1196–1215, 1949.

III. Typhoid fever.

Evualation

Effective, but * * *

Comments

Chloramphenicol has often been listed as the drug of choice in typhoid fever. It is not clear that ampilicillin has changed this claim, but if they were of equal activity, the claim of "drug of choice" would have to be revised because of the toxicity warning. There is no mention of the carrier problem and relapses of positive stool cultures.

Documentation

1. Knight, V., W. McDermott, and F. Ruiz-Sanchez. Aureomycin and chloramphenicol: use in typhus, typhoid and brucellosis. J. Clin. Invest. 28:1052–1053, 1949. (abstr.)
2. Smadel, J. E., H. L. Ley, Jr., and F. H. Diercks. Treatment of typhoid fever. I. Combined therapy with cortisone and chloramphenicol. Am. Intern. Med. 34:1–9, 1951.

IV. Other salmonelloses.

Evaluation

Possibly effective.

Comments

Because of variability of clinical course with each species and the large variety of species, there is litle reason to presume that a generalization is possible. In a condition of short symptomatic duration like gastroenteritis, the use of the drug is most difficult to evaluate. The variable courses of the systemic forms do not allow the assurance of effectiveness that has been derived for typhoid fever, which is more uniform. These differences between typhoid and the other salmonelloses illustrate the difficulty or generalization from one species to the next. It is likely that localized salmonella infections, such as osteomylitis, empyema or other diseases should have a therapeutic trial with chloramphenicol. The treatment of carriers with positive stool cultures should not be recommended and the insert should so state. Although the stools may be negative while the drug is continued, there is no evidence that the carrier state is terminated more frequently than would occur otherwise with a similar passage of time. Obviously, the inability to define drug effectiveness in salmonelloses also applied to other drugs, such as ampicillin; hence a reliable comparison between drugs is not possible.

Documentation

1. Woodward, T. E., and C. L. Wisseman, Jr. Chloromycetin, pp. 56–58. Antibiotics Monographs No. 8. New York: Medical Encyclopedia, Inc., 1958.

V. Urinary tract infections.

Evaluation

Effective, but * * *

Comments

As specified in the insert, outcome of treatment of urinary tract infections is influenced by anatomic factors, but these have little importance in the choice of drug except that, in situations in which cure is unlikely, the use of toxic agents is probably not justified. The susceptibilities of the organisms involved are of prime importance (chloramphenicol does not work any better against chloramphenicol-susceptible organisms than other agents work against organisms susceptible to them.) Hence, when organisms are susceptible to less toxic agents, chloramphenicol should not be used even if it is effective *in vitro* unless the others have failed. It is unusual for chloramphenicol to succeed when other agents with satisfactory *in vitro* activity have failed. Of the three species singled out, *Escherichia coli* is often treatable with other chemotherapy, but chloramphenicol may be a secondary choice. *Streptococcus fecalis* infections are probably better treated with other agents, such as penicillin and streptomycin or erythromycin. Various Proteus species are different in their susceptibility to different drugs; hence, the generalization "*Proteus species*" should be avoided. *Proteus morgani, vulgaris,* and *rettgeri* are often susceptible only to chloramphenicol.

Documentation

1. Woodward, T. E., and C. L. Wisseman, Jr. Chloromycetin, pp. 105–108. Antibiotics Monographs No. 8. New York: Medical Encyclopedia, Inc., 1958.

VI. Surgical infections: postoperative wound infections.

Evaluation

Possibly effective.

Comments

Postoperative wound infections have a variety of etiologic agents, but *Staphylococcus aureus* is the single most common. Chloramphenicol is effective against many of these agents, but is not the most effective against the Staphylococcus. For this reason, plus the toxicity warning, it is not the first choice in most infections unless an organism is isolated against which chloramphenicol is most active *in vitro*, or other preferred drugs cannot be given or have been ineffective.

Documentation

Most favorable report is reference 1 (Altemeier).

1. Altemeir, W. A., and W. R. Culbertson, Chloramphenicol (chloromycetin) and auremycin in surgical infections. J.A.M.A. 145:449–457, 1951.
2. Bloomer, W. E., S. Giammona, G. E. Lindskog, and R. E. Cooke. Staphylococcal pneumonia and empyema in infancy. J. Thorac. Surg. 30: 265–274, 1955.
3. Carmichael, C. B., Jr. Fatal bacterial endocarditis due to staphylococcus aureus. U.S. Armed Forces Med. J. 4:287–294, 1953.
4. Hausmann, W., and A. J. Karlish. Staphylococcal pneumonia in adults. Brit. Med. J. 2:845–847, 1956.
4. Kanof, A., B. Epstein, B. Kramer, and I. Mauss. Staphyloccal pneumonia and empyema. Pediatrics 11:385–392, 1953.
6. Lepper, M. H., P. Tillman, and R. Devetsky. Patterns of transmission of staphylococci. Ann N.Y. Acad. Sci. 128:404–427, 1965.
7. Martin C. M., C. M. Kunin, L. S. Gottlieb, and M. Finland, Asian influenza A in Boston, 1957–58. II. Severe staphylococcal pneumonia complicating influenza. A.M.A. Arch. Intern. Med. 103:532–542, 1959.
8. Wallman, I. S., R. C. Godfrey, and J. R. H. Watson, Staphylococcal pneumonia in infancy. Brit. Med. J. 2:1423–1427, 1955.

VII. Surgical infections: cellulitis.

Evaluation

Possibly effective.

Comments

Cellulitis (other than postoperative) is most often caused by streptococci or staphylococci for which chloramphenicol is not the most effective drug. For this reason, plus the toxicity warning, it is not the first choice unless an organism against which chloramphenicol is the most active has been isolated, or the preferred drug cannot be given or has failed.

Documentation

Same as for Indication VI.

VIII. Surgical infections: infected sinus tract.

Evaluation

Possibly effective.

Comments

Chloramphenicol may be useful in some instances in which the organisms have been shown to be sensitive only to it. Many sinus tract infections are caused by tuberculosis and actinomycosis. Chloramphenicol is not indicated in tuberculosis, and other agents are preferred in actinomycosis. Some sinus tracts associated with fistulas from viscera, including intestines, may be predominantly infected with fecal flora. In these, chloramphenicol may be the single most effective agent. When other agents appear equally effective in laboratory testing, they should be tried first. There is rarely great urgency in treating sinus tract infections with antibiotics.

The specific organisms for which chloramphenicol has been proved effective therapy (in this condition) should be listed.

Documentation

1. Altemeier, W. A., and W. R. Culbertson. Chloramphenicol (chloromycetin) and aureomycin in surgical infections. J.A.M.A. 145:449–457, 1951.

2. Bloomer, W. E., S. Giammona, G. E. Lindskog, and R. E. Cooke. Staphyloccal pneumonia and empyema in infancy. J. Thorac. Surg. 30: 265–274, 1955.
3. Carmichael, D. B., Jr. Fatal bacterial endocarditis due to staphylococcus aureus. U.S. Armed Forces Med. J. 4:287–294, 1953.
4. Hausmann, W., and A. J. Karlish. Staphyloccal pneumonia in adults. Brit. Med. J. 2:845–847, 1956.
5. Kanof, A., B. Epstein, B. Kramer, and I Mauss. Staphylococcal pneumonia and empymea. Pediatrics 11:385–392, 1953.
6. Lepper, M. H. P. Tillman, and R. Devetsky. Patterns of transmission of staphylococci. Ann. N.Y. Acad. Sci. 128:404–427, 1965.
7. Martin, C. M., C. M. Kunin, L. S. Gottlieb, and M. Finland. Asian influenza A in Boston, 1957–58. II. Severe staphylococcal pneumonia complicating influenza. A.M.A. Arch Intern. Med. 103:532:542, 1959.
8. Wallman, I. S., R. C. Godfrey, and J. R. H. Watson. Staphylococcal pneumonia in infancy. Brit. Med. J. 2:1423–1427, 1955.
9. Woodward, T. E., and C. L. Wisseman, Jr. Chloromycetin, pp. 122–124. Antibiotics Monographs No. 8. New York: Medical Encyclopedia, Inc., 1958.

IX. Surgical infections: peritonitis or intra-abdominal abscesses from ruptured intestines, diverticula, or appendix.

Evaluation

Possibly effective.

Comments

These infections are often caused by mixed flora from the intestinal content. In the acute stage of peritonitis, a drug often must be selected empirically for surgical preparation or immediately postoperatively. Judged by statistical probability chloramphenicol is a good choice in such a situation. It should be given parenterally, however, because oral therapy in these infections is probably inappropriate. In other less acute complications listed in the insert, chloramphenicol should be shown to be the most effective agent against the organisms isolated before it is used, or other less toxic agents should have failed or be contraindicated.

The specific causative organisms for which chloramphenicol has been proved effective therapy (in these conditions) should be listed.

Documentation

Same as for indication VIII.

X. Respiratory tract infections.

Evaluation

Possibly effective.

Comments

This heading is ambiguous. The package insert should list specific organisms (and the site of respiratory infection) for which chloramphenicol has been proved effective therapy.

In general, the etiology of these conditions is varied and chloramphenicol is the best agent for only a few. In streptococcal, pneumococcal, and staphylococcal diseases of the respiratory tract, other drugs are preferable. Chloramphenicol should be used only in Klebsiella infections and perhaps other necrotizing pneumonias caused by *E. coli* or related organisms when they are shown *in vitro* to be resistant to ampicillin, cephalothin, and kanamycin. Hemophilus influenzae infections of the respiratory tract respond well to ampicillin; hence chloramphenicol is best used only when ampicillin is not tolerated or fails.

Documentation

1. Woodward, T. E., and C. L. Wisseman, Jr. Chloromycetin, pp. 63–72. Antibiotics Monographs No. 8. New York: Medical Encyclopedia, Inc., 1958.

XI. Meningeal infections.

Evaluation

Probably effective.

Comments

The three most common causes of meningitis are the meningococci, pneumococci, and *Hemophilus influenzae*. All are susceptible to chloramphenicol, as are many staphylococci and the gram-negative aerobic rods that often infect newborns. Moreover, it is true that the drug does get into the spinal fluid well. As a drug of choice for empiric use, however, it is probably not first, because it is likely to be less effective in pneumococcal disease than is penicillin. Although many believe it is first choice in Hemophilus infections, tetracycline is probably as good and ampicillin is, too. It is likely that this claim (drug of choice in *H. influenzae* meningitis) is no longer justified. In menigitis of the newborn kanamycin is preferred as the drug of choice for empiric treatment. In older patients, when a diagnosis has been made and the organisms shown to be more susceptible to chloramphenicol than to other agents, it may be the drug of choice. As indicated, in the insert, initial treatment should be parenterally administered.

The package insert should list the specific organisms for which chloramphenicol has been proved effective therapy in meningitis.

Documentation

1. Parker R. T., M. J. Snyder, R. S. J. Liu, J. W. Looper, Jr. and T. E Woodward. Therapeutic range of chloramphenicol in purulent meningitis. Antibiot. Med. Clin. Ther. 1:192–200, 1955.

XII. Brucellosis.

Evaluation

Effective, but * * *.

Comments

Chloramphenicol, like other drugs, is capable of controlling symptoms of acute brucellosis, but the relapse rate is high. It does not appear to be superior to the less toxic tetracyclines.

Documentation

1. Knight, V., F. Ruizz-Sanchez, and W. McDermott. Chloramphenicol in the treatment of the acute manifestations of brucellosis. Amer. J. Med. Sci. 219:627–638, 1950.
2. Spink, W. W. The Nature of Brucellosis. Minneapolis: The University of Minnesota Press, 1956. 464 pp.
3. Woodward, T. E., J. E. Smadel, W. A. Holbrook, and W. T. Raby. The beneficial effect of chloromycetin in brucellosis. J. Clin. Invest. 28:968–976, 1949.

XIII. Bartonellosis.

Evaluation

Probably effective.

Comments

Chloramphenicol is reported to be an effective antibiotic in these infections. Of the references suggested by the manufacturer (see Documentation below): two are reports of studies involving a total of 25 patients whose bartonellosis was treated with chloramphenicol with good success, and two are textbook discussions of bartonellosis and its treatment. Of the latter discussions, one feels that the effectiveness of chloramphenicol is best documented, the other feels that other agents are probably as good.

Documentation

1. Bartonellosis, pp. 603–606. In G.W. Hunter, III, W. W. Frye, and J. C. Swartzwelder, Eds. A Manual of Tropical Medicine. (3rd ed.) Philadelphia: W. B. Saunders Co., 1960.
2. Payne, E. H., and O. Urteaga. Carrion's disease treated with chloromycetin. Antiobiot. & Chemother. 1:92–99, 1951. Pinkerton, H. Bartonellosis (Carrion's disease, Oroya fever, Verruga peruviana), pp. 327–329. In P.B. Beeson and W. McDermott, Eds. Cecil-Loeb Textbook of Medicine. (11th ed.) Philadelphia: W. B. Saunders Co., 1963.
3. Urteaga, B. O., and E. H. Payne. Treatment of the acute febrile phase of Carrion's disease with chloramphenicol. Amer. J. Trop. Med. 4:507–511, 1955.

XIV. Relapsing fever.

Evaluation

Possibly effective.

Comments

Treponema (Borrelia) recurrentis infections in experimental animals are susceptible to chloramphenicol. On a weight basis, however, penicillin G is more active. In human infections, no direct comparison has been made, and, although chloramphenicol has been used successfully, penicillin should be tried first if it is tolerated.

Documentation

1. Hirschboeck, M. M. Use of chloramphenicol in relapsing fever. Amer. J. Trop. Med. 3:712–713, 1954.

XV. Granuloma inguinale.

Evaluation

Effective, but * * *.

Comments

It has been reported that chloramphenicol caused the disappearance of Donavan bodies more rapidly than either tetracycline or streptomycin. Relapses after chloramphenicol have seemed to be less than 10%. Although chloramphenicol may be slightly better than tetrocycline, the latter may be preferred for toxicologic reasons.

Documentation:

1. Greenblatt, R. B., W. E. Barfield, R. B. Dienst, R. M. West, and M. Zieses. Five-year study of antibiotics in treatment of granuloma inguinale. Amer. J. Syph. 36:186–191, 1952.
2. Robinson, R. C. V., and T. L. Wells. Intramuscular chloramphenicol in the treatment of gonorrhea and granuloma inginale. Amer. J. Syph. 36:264–268, 1952.

XVI. Plague.

Evaluation

Effective, but * * *.

Comments

All forms of plague have been shown to respond to chloramphenicol when it is given in large doses early in the disease. There is no clear evidence that it is superior to tetracycline or streptomycin.

Documentation

1. McCrumb, F. R., Jr., S. Mercier, J. Robic, M. Bouillat, J. E. Smadel, T. E. Woodward, and K. Goodner. Chloramphenicol and terramycin in the treatment of pneumonic plague. Amer. J. Med. 14:284–293, 1953.

XVII. Ornithosis.

Evaluation

Possibly effective.

Comments

In embryonated eggs and experimental animal infections, chloramphenicol is less effective than the tetracyclines. Results of therapy of human infections have been variable and relapses have been frequent. The role of the drug in this disease is not well established.

Documentation

1. Woodward, T. E., and C. L. Wisseman, Jr. Chloromycetin, pp. 70–71. Antibiotics Monographs No. 8. New York: Medical Encyclopedia, Inc., 1958.

General comments

The "Warning" section appears justified in view of the seriousness of aplastic anemia.

Absorption after oral administration is good, in that 70–90% of a dose can be accounted for by metabolic products found in the urine. Tissue distribution appears to be favorable. The distribution into the cerebrospinal fluid is good, as pointed out in the insert, and is reasonably good into brain tissue, which is

important when cerebritis accompanies meningitis. The distribution into bile is not as high as that of the tetracycline and some of the penicillins. The very small amount in the feces is of interest as is the fact that the fecal content is higher when the palmitate has been given.

The penetration into the eye is a plus factor for this drug. Transplacental transfer was shown by chemical methods which may not measure the active drug.

Emphasis should be put on the recommended dose, because a smaller dose is often given, particularly postoperatively. The fate of the drug when the metabolic mechanisms are disturbed should remain as stated. As to blood dyscrasias, it should be mentioned that frequent blood counts do not necessarily assure that aplastic anemia can be prevented.

In fact, it may occur after the drug has been stopped.

The roles of organisms other than canida and staphylococci in resistance and superinfection have been demonstrated, particularly Pseudomonas and some other gram-negative aerobic rods that are resistant. This should be pointed out in the section discussing resistance.

Intravenous administration of chloramphenicol produces a rapid peak in blood levels and is preferred over oral or intramuscular administration in critically ill patients. However, because the oral form is so highly absorbed, as soon as the patient can take it, there is little reason to continue the I.V. use.

This package insert is identical in every way with that for Chloromycetin Palmitate Oral Suspension, Log 2263. This preparation is the straight drug without palmitate.

The dose recommendations are accurate.

Approved by:

WM. KIRBY, *Chairman.*

The Drug Efficacy Study of the National Academy of Sciences-National Research Council has requested that the following qualifying addendum be conveyed with their reports to the ultimate recipients of these reports:

> "Drugs of identical chemical composition (so-called generic drugs) formulated and marketed by numerous individual firms under generic or trademarked names have been evaluated for efficacy as a group without consideration of 'therapeutic equivalence.' In the event that no evidence for pharmacological availability or therapeutic efficacy in man can be presented for any of the indications claimed for the use of any of the drugs in the attached listing, their classifications of effectiveness may need to be modified if regulations of the Food and Drug Administration require such proof."

A PRACTICING PHYSICIAN LOOKS AT THE NELSON HEARINGS

(Remarks by Clinton S. McGill, M.D., Portland, Oreg., before Pharmaceutical Manufacturers Association, New York Hilton, Dec. 3, 1968)

Mr. Chairman, ladies and gentlemen, I consider it a privilege to be here today and to address your mid-year meeting. For the record, let me make my position clear. I'm here today representing no vested interest except the health of the American Public. I earn my living in the full-time practice of internal medicine in Portland, Oreg. I have never been employed by a drug firm nor have I ever owned stock in any pharmaceutical house. My interest in your present dilemma stems solely from my concern for the welfare of my own patients and for our health care system.

For the past 18 months I have watched with increasing alarm the proceedings of Senator Gaylord Nelson's subcommittee. It was evident from the very beginning that the hearings here slanted and the facts were being distorted. We have been exposed to a steady stream of hand-picked witnesses whose testimony became as predictable as the rising sun. Over and over again we heard the same tired charges of excess profits, price gouging, unreasonable patent protection, and the like . . . without even the pretense of fairness or objectivity.

Not that I was surprised by the tenor of the hearings. . . . I'm aware that Senator Nelson is not one of our admirers. Then too, none of us in the health industry has been treated gently in the halls of Congress these past several years.

But, I kept expecting to hear testimony from the "other side." I thought surely they would call witnesses from the various specialty groups, the Academy of General Practice, the AMA, and individual practitioners like myself. When none was forthcoming, I decided to have a try at it.

As is happens, one member of the subcommittee is Senator Mark Hatfield from my own State. Last spring I had occasion to visit the Senator in Washington and we discussed the Nelson hearings at some length. He was sympathetic to my point of view that the hearings were being used to malign the drug industry and the medical profession for political purposes. He agreed to help me get called as a witness.

Since that time I have had a series of polite but non-committal letters from Senator Nelson. I discussed the situation again with Senator Hatfield just ten days ago and he also expressed his frustration in the selection of witnesses before the committee. It seems *very clear* that Senator Nelson does not want anyone to tell the story from the private practitioner's point of view * * * or even to allow us to defend ourselves against the scurrilous attacks that are now a part of the public record.

Fortunately, Joe Stetler learned of my dilemma and invited me here today to express my views. I'm indebted to Joe for finally giving me a platform. I think it's about time somebody speaks out against this travesty of justice * * * against the misuse of congressional authority. Of course, I don't have the *lofty forum* that Senator Nelson enjoys, nor do I have his "troops".

But, I think I do have one thing going for me * * * and that is the *truth* * * * and perhaps * * * just perhaps * * *. I can stir the members of the press to take a second look at what's really going on in the Nelson hearings.

From the start, the fundamental theme has been that all of you drug manufacturers are liars and thieves * * * gouging excess profits out of the sick and the poor. And, we doctors are simple boobs, so snowed under by drug advertising that we can't select the right therapeutic agents for our patients. Well * * * I deeply resent this slur on the clinical integrity of the American physician and I equally resent the slashing attack on our great pharmaceutical industry.

But let me be more specific. I'd like to submit to you the views of one practicing physician on some of the charges made by the Nelson subcommittee.

First, the nonsense of "*Therapeutic Equivalency*". This morning we have heard convincing evidence to the contrary by Dr. Cavallito and I don't think it would serve any purpose for me to belabor the point. Yet Senator Nelson has allowed such unfounded statements to become part of the public record. We've heard high-placed government officials, such as Wilbur Cohen, Dr. James Goddard, Dr. Milton Silverman and Dr. Philip Lee, state that therapeutic equivalency *exists* * * * on mere *assumption* * * * without a shred of scientific evidence to back it up!

I'd like to make just one point on the issue of "therapeutic equivalency" and that is how it can effect me in my everyday practice. I'd like to choose Chloromycetin as an example. Probably no drug in history has received as much adverse publicity as this drug has because of the very occasional blood dyscrasia it produces. The uses and abuses of Chloromycetin became a personal vendetta between Dr. James Goddard and the Parke-Davis Company * * * and all the while Dr. Goddard was indicting the medical profession for using it. Why is it that so little was ever said about the thousands of lives that were *saved* by this marvelous antibiotic?

The truth is—Chloromycetin is a life-saving drug. It's use involves a small but *significant* risk of serious abreactions. But, calculated risks are nothing new in medicine. There are many such small but significant risks * * * every anesthetic, every surgical operation, in fact, almost all medical procedures contain them. This does not mean that such risks are taken lightly * * * they are not, and every effort is made to eliminate them. But it is my contention that risk must be weighed against the value of a given drug or a given procedure and the decision made accordingly. Making this type of decision is a part of our everyday experience.

However, this is only part of the story. The patent rights ran out on Chloromycetin and last year competitive brands of chloramyphenicol appeared on the market. Bear in mind, if you will, that we were being told, over and over again, that we doctors should be prescribing by *generic* name *only*, since after all the products were *therapeutically equivalent*. Well * * * such was not the case. The competing brands of chloramphenicol were *not* equally effective and the FDA,

somewhat reluctanly, ordered them withdrawn from the market * * * and I should add, on evidence developed by Parke-Davis instead of their own laboratory.

This isolated incident may seem like an academic exercise in pharmacology * * * but I would submit that to a practicing physician it is much *more* than that.

There is *just one way* we would have learned about the ineffectiveness of those products * * * when the patient *died!* I refuse to subject my patients to such a risk. I will continue to insist on *product indentification.* I wonder how may people died as a direct result of the bureaucratic jungle? I dare say *more* than ever died from sensitivity to Chloromycetin.

It seems to me that if the Nelson subcommittee were seriously considering the best interests of the public they would be the first to demand product identification. Then * * * any kind of an abnormal reaction, any question of therapeutic value, any problem involving the quality of the product * * * could be traced right back to the source.

Why then, this bull-headed insistence on generic prescribing, regardless of the source of the product? You know the answer and so do I. For the Nelson committee to do otherwise would be an admission that there *is* a difference between products bearing the same generic lable that there *is* such a thing as quality control * * * and that the well-earned reputation of the ethical drug companies *is* something of value!

I commented earlier on the false impression Senator Nelson* * * and others * * * have tried to create on the competence of the average physician in his drug prescribing habits. I have here in my hand a letter dated November 7, 1968, from Dr. Philip Lee, Assistant Secretary for Health and Scientific Affairs of HEW. I would like to read just one paragraph from that letter, which was sent to all doctors in this country:

"As you know, *most of the drug information used by physicians comes from the advertising and promotional activities of drug manufacturers.* The task force has seriously questioned whether these sources provide or should be expected to provide the objective and comparative information needed by prescribers. We believe that an independent group of well qualified clinicians and pharmacologists could provide objective evaluations of new drugs and reassessments of older ones through a regularly published journal of prescribing. The task force has recommended that such a publication be made available on a regular basis to all physicians, and it has recommended Federal support for this activity."

I find it *incredible* that Dr. Lee would write such a letter. If he did, in fact, write the letter, it tells me that Philip Lee has *forgotten* he's a doctor and is now thinking like a bureaucrat. Anyone with even a casual acquaintance with medical literature knows that long before an important new product is ever marketed there will be a number of articles on it in our professional journals. Next, it will be described in some detail in the JAMA section on new drugs. We may likely hear of it when reported in a scientific paper in one of our many professional meetings. In all probability we will read about it, or have it pointed out to us in the Ladies' Home Journal, Reader's Digest, or the Sunday supplement!—all of this, mind you, *before* the product is distributed.

I can see little value in his recommendation that a federally supported drug journal be published. Dr. Lee conveniently ignores the important work being done by the AMA's Council on Pharmacy and Drugs. The obvious bias of HEW would discredit the journal before it was ever published.

I am sure the physicians of this country have a great deal more confidence in our own council on drugs than we would *ever* have in a publication of the Department of HEW at least, as long as the present atmosphere exists.

I do not mean to down-grade the importance of information provided us through journal advertising. It's been my experience that the reputable drug companies are *very* careful to correctly describe their new products, and take great pains to point out the possible side effects and contraindications.

And, right here, I'd like to say a few words in defense of the "detail man." I'm sick of hearing him described as a fast-talking con-artist, something akin to the snake oil peddler of the nineteenth century. The vast majority of detail men are trained professionals who provide us with valuable information. We learn from them such important details as package size, how a given drug is supplied—liquid, tablet, injectable, suppository, and price information. They provide many services for us, and we are grateful. Can anyone really believe that

a fast-talking hard-sell type would ever get past the front desk let alone take up the doctor's time?

It's a curious paradox that our system of medical care is being subjected to its severest criticism at a time when that very system is producing its greatest progress. We have managed to create a "health miracle" that is beyond the wildest dreams of the last generation. There can be little doubt that a great share of the credit is due the pharmaceutical industry.

I consider myself fortunate to have been born at a time when I could share in this exciting process. In my twenty years of practicing medicine I have seen the development of more important therapeutic agents than were produced in the entire history of medicine. You have made it possible for me and others like me to be better doctors than we ever dreamed we would be. I'm very grateful for the wonderful products you have given me.

I can't help but feel alarmed when I see the drug industry under attack. Some very unfair charges have been made by Senator Nelson and others about excessive profits and unreasonable patent protection. I'd like to give you *my* point of view on this issue. I sincerely hope you *continue* to make a profit—a very *good* profit. I hope you can afford to hire the very best research talent you can find so that you can continue to provide us with the great new products that you have in the past, and in this effort, I wish you God's speed!

CLINTON S. MCGILL, M.D.,
Portland, Oreg., March 28, 1968.

SENATOR GAYLORD D. NELSON,
U. S. Senate, D.C.

Dear Senator Nelson: I have followed with great interest the hearings of the Monopoly Subcommittee. The testimony of Dr. James Goddard has been very impressive. Through your efforts, the public has gained a great deal of information about drugs and drug manufacturers. I'm in total agreement that such facts should be made known, both to the medical profession and the public at large. I feel certain that much more can be revealed.

I also feel that the testimony of a private practicing physician, like myself, would add a useful dimension to your hearings. I would like to volunteer my services for that purpose. After all, we are the ones involved in direct patient care and the cost of that care. We are the ones who prescribe the drugs and must evaluate their worth on a day-by-day basis. We are also the ones towards whom the pressures and promotions of the drug companies are directed.

I feel I have certain qualifications that may be of interest to your committee. I am a specialist in Internal Medicine and have been in private practice for the past twenty years. Earlier in my career I taught in the Physiology and Pharmacology departments of the University of Oregon Medical School where I participated in drug research.

Perhaps of greater interest to your committee is the fact that I served ten years as the Medical Director of the Oregon State Public Welfare Commission, part of that time under Governor Mark Hatfield. It was during this period (1949-1959) that the great boom in drug usage first began. The cost of drug therapy increased so rapidly that we could not realistically budget it. My chief problem was to relate the cost of a given drug product to its therapeutic efficiency. In an attempt to control these costs, I compiled and published a Drug Formulary for Welfare recipients, which I believe was the first of its kind. I have first hand knowledge of the pressure and the problems encountered in this kind of undertaking. I would be happy to make this information available to your committee.

If in your judgment you feel that the information I have would serve a useful purpose to your committee, I will be happy to make myself available at your convenience.

Sincerely,

CLINTON S. MCGILL, M.D.

cc: Senator Mark O. Hatfield.

U.S. SENATE,
Washington, D.C., April 29, 1968.

CLINTON MCGILL, M.D.
Portland, Oreg.

DEAR DR. MCGILL: I appreciate your letter expressing an interest in testifying at our hearings on the prescription drug industry. Senator Hatfield has also contacted me in this regard.

As you know, the committee is covering a number of facets of the competitive problems in the prescription drug industry. I would appreciate learning from you which phase you are interest in discussing.

Because of the number of witnesses who have been scheduled to appear, we have not been able to set a time in the near future for additional witnesses. However, if you will send me a copy of your statement, we will include it in the committee records. Then, if a time can be worked out for your personal appearance, the committee will be happy to contact you again—hopefully in not too long a period of time.

Sincerely yours,

GAYLORD NELSON,
U.S. Senator.

cc: Senator Mark Hatfield, Senate Monopoly Subcommittee.

AFFIDAVIT

STATE OF OHIO,
County of Hamilton:

Before me, Thomas M. Rice, an employee of the Department of Health, Education, and Welfare, Food and Drug Administration, designated by the Secretary, under authority of the Act of January 31, 1925, 43 Statutes at Large 803 (5 U.S.C. 521); Reorganization Plan No. IV, Secs. 12–15, effective June 30, 1940; and Reorganization Plan No. 1 of 1953; Secs. 1–9, effective April 11, 1953, to administer or take oaths affirmations, and affidavits, personally appeared Mrs. Beulah I. Jordan in the county and State aforesaid, who, being first duly sworn, deposes nd says:

My name is Mrs. Beulah L. Jordan. I reside at 3825 Trebor Drive, Cincinnati 36, Ohio.

I worked as a technician in the Toxicological Laboratory of the William S. Merrell Co., Cincinnati, Ohio, for approximately 2½ years from the fall of 1956 to the early summer of 1959.

During this time I assisted in a toxicological study on Mer 29 using monkeys. This experiment ran approximately 16–18 months. It involved 6 to 8 monkeys of which 3 or 4 were in a control group, and 3 or 4 were in the drug group. Three control and three drug monkeys were carried through the entire experiment, while one of each group was autopsied after approximately 6 or 7 months.

My duties included bleeding the monkeys, runing blood counts, assisting with the autopsies making up capsules of Mer 29 and placebos for the drug groups and control groups, assisting with dosing both control groups and drug groups by pushing the respective capsules down the throats of the monkeys, make notes about the food the monkeys ate or refused to eat, weighing the monkeys weekly, checking the monkeys reactions, preparing weight graphs each week and after autopsy, and weighing each organ at autopsy.

Notes of observations made were recorded in ink in a loose leaf 3 ring black note book, together with the recordings of the drug and placebo dosages and weights of the monkeys. This note book was always retained in the laboratory, and was never turned in to the firm's record office. The estimates of food eaten by the monkeys and the observations of eating habits were entered on a separate sheet and maintained in a separate loose leaf note book which was also retained in the laboratory.

During the first part of the experiment, I was under the direction of Mr. James Knox Smith, but toward the close of the experiment he was replaced by Dr. William King.

Toward the end of the experiment one male drug monkey was sick and doing very poorly, and weighed approximately 8 or 9 pounds. He had lost approximately 5 pounds or more during the course of the experiment.

This sick male drug monkey had become somewhat mean and acted angry. He had been a healthy, active monkey at the start of the experiment. After being on the drug he first became more active than usual, but later became very inactive and lay on the bottom of the cage. The expression in his eyes and his disposition indicated he was very ill. He could not jump into the box from his cage for weighing, and back into his cage as the other monkeys could. During the first part of the experiment, this monkey could also do this very easily. Later on one occassion when he tried to do this he missed the box.

At the close of the experiment I worked up the weight graphs, and showed them to Dr. King. He in turn discussed them with his superior, Dr. E. F. Van Maanen.

Dr. Van Maanen, with the concurrance of Dr. King, decided to throw out the sick male drug monkey mentioned above, and substitute another control monkey in his place which had never been on Mer 29. The male monkey substituted weighed about 18 or 20 pounds, or about 10 pounds more than the sick monkey for which he was substituted. Dr. Van Maanen then called me into his office and instructed me to make this substitution in working up the weight chart. Because of this decision, I had to make up the charts 3 times. The sick male monkey was never autopsied in my presence, but the substitute control monkey was autopsied in his place. The weight charts would have been very much different, had the data from the sick male drug monkey been retained in the final reports because of his loss of weight from approximately 13 pounds at the start of the experiment to approximately 8 pounds at the close of the experiment.

Dr. King ordered me to never mention the substitution. I was told this was the way the company wanted it and to forget it. I was told that the order had come from higher up.

Also during this experiment, I know that on a number of occasions the capsules of Mer 29 were not given to the monkeys as they should have been. This would happen over a weekend, when people in other groups would work relief shifts in the place of regular employees of our group. I knew this because I was the one who weighed up the capsules for each individual drug monkey for a week at a time, and prepared just enough to last 1 week until the monkeys were weighed again and the calculations were made in terms of the monkey's new weight. My routine was to have 1 capsule left for Monday morning, but sometimes there would be 2 or 3 capsules remaining. During the experiment the monkeys on the drug became difficult to catch for doseing, which would explain why the weekend relief employees may not have always dosed the monkeys. The charts however, were always marked as if the capsules were given.

I also participated in similar studies on dogs and white rats involving Mer 29. I had similar duties in respect to these studies. I noticed nothing unusual about the conduct of these dog and rat studies. I participated in the autopsies of the dogs and rats on these studies, and also worked up the weight charts at the close of these experiments.

In the case of the rat studies, duplicate records were kept by means of recording the data into a bound book with carbon paper, but this was not the case with the monkey studies, and dog studies.

Other employees who helped with the monkey studies were:

Bruce Umberger. He was still with the firm a few months after I left, but is no longer with the firm. He now lives in Columbus, Ohio. His duties included conditioning and handling the monkeys prior to the start of the experiment. He helped autopsy the monkeys at the close of the experiment. During the studies he helped weigh, dose, observe, and care for the monkeys. He helped catch, weigh, and dose monkeys.

He had nothing to do with working up the final data at the close of the experiment on the monkeys. He also did similar work with respect to the studies on dogs and white rats.

Dorthy Miner. This individual also no longer associated with this firm, and left 1 to 1½ months after I did. She is presently in Florida, but I do not know her exact address. She was employed during the Mer 29 studies on monkeys. Her job was primarily the preparation and staining slides. These were simply from the organs supplied her.

Mary Ann Stephens. This individual is now married and her present name and address is not known. Her duties primarily involved making blood counts on rats. She did not work directly with the monkeys. She has also left the firm.

Mike. I do not know this individual's last name. He worked for the firm during the last part of the Mer 29 studies on monkeys. He assisted Bruce Umberger, and his primary duties were to take care of the monkeys. He also helped weigh the rats on Mer 29 studies.

I resigned my position with the firm at the conclusion of the Mer 29 studies on the monkeys, because of my dissatisfaction with the way the work was being run by Dr. King.

BEULAH L. JORDAN.

Subscribed and sworn to before me at Cincinnati, Ohio, this 13th day of March 1962.

THOMAS M. RICE,
Employee of the Department of Health, Education, and Welfare designated under Act of January 31, 1925, Reorganization Plan IV effective June 30, 1940; and Reorganization Plan No. 1 of 1953, effective April 11, 1953.

(Whereupon, the subcommittee recessed at 12 o'clock to reconvene at 1:30 p.m., the same day.)

AFTERNOON SESSION

Senator NELSON. Doctor, I apologize for holding you up this way.

Dr. AYD. No apologies necessary.

Senator NELSON. Thank you, Doctor. The committee appreciates your taking the time to come here today to testify. You may proceed to present your testimony in any way you see fit.

STATEMENT OF DR. FRANK J. AYD, JR., FAPA, EDITOR, INTERNATIONAL DRUG THERAPY NEWSLETTER, BALTIMORE, MD.

Dr. AYD. With your permission, Senator, I will dispense with my qualifications since they are on the last page of my prepared statement.[1]

I appreciate the opportunity to be here today to outline some of the advances made in the last 15 years in the care and treatment of the psychiatrically ill. I requested this opportunity to testify because, in my opinion, too much of the testimony presented to the committee to date has been critical of the medical practitioner and the pharmaceutical industry. In my opinion, the outstanding accomplishments of both should be acknowledged and spelled out in detail in the interest of a more balanced record.

Senator NELSON. May I say at this stage, Doctor, that the statements are always made in the interest of a balanced record. I just want to emphasize that we have heard more testimony from the drug industry than from any other source. We have given them an open invitation to come in at any time they feel the record needs further balance. They have had the greatest chance of anybody to offset any criticism that is made here. We have had only a half dozen general practitioners, although we have had a number of distinguished doctors who practice in the finest hospitals in America who are recognized by their colleagues throughout the profession as distinguished physicians, and they are not just theoreticians. They are practicing in the major teaching hospitals and general hospitals.

So, I just keep emphasizing, I think the record is being kept in balance.

Furthermore, I just want to make clear to you that I recognize that the industry has made great contributions. You know, it is somewhat like when I introduced the tire safety legislation and the auto safety legislation, I was attacked all across the country as being anti-auto industry and I was told how many good things the auto industry does. Of course, they do a lot of good things, but the fact is they have some classical weaknesses and one is the neglect of safety. So, we took this up as a matter of public interest.

[1] See p. 4171, infra.

So, I personally object to continuous argument of Mr. Stetler, the president of the PMA, and others, about the balanced record. We are keeping it as balanced as we can. They are free to come back at any time. Certainly, they have a thousand times more resources than I have. I have myself, Mr. Gordon, and his research assistant, Mrs. Dye. The industry is not put upon. They have at their disposal, many technicians, scientists, and doctors and they are always welcome here.

If they cannot balance the record, it will be because the merits are not on their side.

Dr. AYD. Senator, I would like to retort in this respect.

No. 1. I am not here as a representative of the pharmaceutical industry.

No. 2. What I have to say represents exclusively my own personal opinion, the opinion of no one else. It has not been influenced by anyone else.

No. 3. I am acquainted, because of professional activities, with many of the witnesses who have appeared before your committee. I do not question their sincerity, their integrity, their professional standing. However, I must say that in a large number of instances these are academic individuals who are not involved in the everyday practice of medicine and who, therefore, are not in full appreciation of the complexities of the everyday practice of medicine, or I might point out since I am here not only as a private practitioner, but as an individual who has devoted the greater portion of my professional career to the clinical evaluation of drugs, many of these individuals have not been in this area and, therefore, although they are competent to speak in one direction, they are not as qualified to speak in another area.

And I think that I am correct in saying that if we are going to have a balanced record, then testimony from individuals who have taken upon themselves the grave responsibility, and it is a grave responsibility, to clinically evaluate drugs in a patient and who have also, in addition, taken upon themselves the grave responsibility in day-to-day practice of medicine treating patients with drugs, and I would insist that the record clearly show that what I have to say represents not the opinion of Mr. Stetler or the PMA or the pharmaceutical industry, but the opinion of Dr. Ayd and no one else.

Senator NELSON. I did not suggest that but it coincides with Mr. Stetler's in many respects. I did not say your statement was written by them or that you were here in behalf of them. Mr. Stetler travels throughout the country saying, "We have got to have a balanced record. Senator Nelson is not producing a balanced record." Then I get letters from doctors who believe what Mr. Stetler says and they say I have not produced a balanced record. I ask them if they have read the record, and in the vast majority of cases they have not. They tell me they simply read or heard somewhere that the record of these hearings is not balanced.

All I am pointing out is I do not know how you can get a better balance.

If you have hearings extending over a long period of time—almost 2 years now—and they will go on for another 2 or 3 years, then, of course, you are going to have 2, 3, or 400 witnesses. I suppose the one who is called last can always say, "Well, your record is not balanced."

He can say that to the day he is called. There is no way to avoid that. But, you see, if you are undertaking to conduct hearings to evaluate the problems as we see them, it does not make much sense to call in a general practitioner or an internist and say, now, there has been no criticism of the way medicine is practiced in this country but will you give us your answer to the criticisms that you anticipate we might get here.

That is rather ridiculous. Mr. Stetler wanted to testify before we had any witnesses that were critical of the industry. In fact, he gave a speech 2 months before our first hearing indicting the hearings as unfair, and that they were going to be unfair and dishonest.

We are scheduling witnesses as fast as we can. I do not see how you can ask people to testify until they have something to respond to.

We are glad to have the profession come in and tell us how good they are. I come from a medical background. My father is a doctor, my wife a nurse, my uncle a male nurse. I have lived with doctors. I am not antidoctor. But if you are going to examine a given situation you have to have the opinions of people who are critical of it, you must know why they are critical and then you must give the parties of whom they are critical a chance to respond. And that is just what we have been trying to do.

Dr. AYD. I appreciate that.

Well, to proceed, Senator, in commenting on the health of the Nation, former President John F. Kennedy in a talk said:

> * * * Mental illness and mental retardation are among our most critical health problems. They occur more frequently, affect more people, require more prolonged treatment, cause more suffering by the families of the afflicted, waste more of our human resources, and constitute more financial drain upon both the public treasury and the personal finances of the individual families than any other single condition.

The history of 20th century psychiatry is an exciting narrative of the evolution of psychodynamic and physical methods of treatment, of therapeutic nihilism yielding to the spirit of expectant optimism, of a struggle against prejudice, inertia, and indifference, of the blossoming of multidisciplinary scientific interest in mental illness, of an unprecedented availability of money and manpower for psychiatric research, and of remarkable strides forward in the conquest of diseases of the mind.

These accomplishments constitute a tribute to the genius and the boldness of dedicated men and women who persisted in the pursuit of their goal despite many obstacles. They made slow but steady progress until the early 1950's. Then came the chemical revolution in psychiatry. This began when the pharmaceutical industry made available chlorpromazine and resperine, the first of the major tranquilizers for the treatment of emotional and mental aberrations.

Senator NELSON. Who produced chlorpromazine?

Dr. AYD. Chlorpromazine was synthesized in France by the Rhone-Poulenc Laboratories. If you want, sir, I am thoroughly familiar with the history of chlorpromazine.

Senator NELSON. I got the information from the Library of Congress. I just raise the point because there is a tendency, I might say, on the part of the industry itself, to claim credit for everything that happens. They do not think that NIH does very much nor do they think anyone else does.

The Library of Congress research indicates that most of the drugs you are talking about, major ones, were discovered elsewhere—not by the industry. I think that is an important point to make.

Dr. AYD. Well, sir, here I would like to state very categorically since I was one of the first in the United States to administer chlorpromazine to a human being, that although it was synthesized by the Rhone-Poulenc Laboratories, its efforts were to find a substance which would be a potentiator of other pharmaceuticals. And in the course of evaluating or looking at in the animal a variety of derivatives, chlorpromazine was discovered.

This was early 1952 and 1953 when this initial work was done. It was then used—historically these are the correct facts—initially not in psychiatry but to test it as a potentiator of anesthetic agents.

In the course of this work, two observations of clinical significance were made. First, that in addition to potentiating anesthetic agents this particular compound possessed the property known as an antiemetic property in that it reduced the tendency to cause emesis or vomiting.

An observation was also made that it produced not only potentiation of anesthetic agents and antiemetic effects but that it had sedative properties as well.

It was this third observation that led to the possibility of its use in the management of certain psychiatric conditions.

Now, by this time we are talking of late 1953, at which time Smith, Kline & French in this country also were looking at chlorpromazine as a potentiator of anesthetic agents, as an antiemetic, and almost simultaneously as a possible tranquilizing agent.

Now, I know this because in February of 1954 I received my first supplies of chlorpromazine to administer to patients for psychiatric evaluation, and if you look——

Senator NELSON. When was that?

Dr. AYD. February 1954.

Senator NELSON. The Library of Congress does mention Smith, Kline & French finding it highly effective in the prevention of vomiting. This factor was to be the major sales promotion idea. However, Lehman and Hanrahan had begun in the Protestant Hospital in Montreal to report the successful use of chlorpromazine in the treatment of psychotic cases. Apparently, they think they were first to use the drug in this way.

Dr. AYD. Well, to be absolutely correct it is true that the first publication on the use of chlorpromazine was by my good friends Heinz Lehman and Hanrahan and this was published in September of 1954. I would point out to you that just a few weeks after that, I reported on the use of chlorpromazine in the treatment of psychiatric patients at the Southern Medical Association meeting in the United States and even preceding that, Dr. John Kinross Wright of Texas now—he was not in Texas at that time—gave a paper in May of 1954 at the American Psychiatric Association's meeting in St. Louis and also Dr. Nathan Winkleman from Philadelphia had published a report in the Journal of the American Medical Association on the use of chlorpromazine in the treatment of psychiatric patients.

Now, if you go through the bibliography of chlorpromazine in psychiatry, you will find, sir, that the bulk of the work that was done

demonstrating its efficacy in this area was done principally by psychiatrists in the United States.

Now, I am not saying that others did not do work. It is certainly true that my friends Delay and Deniker in Paris did work in this area and friends that I have since made in England also did work. But I must say to you in all honesty since I have lived with chlorpromazine from its birth in psychiatry that the chemical revolution not only began with the introduction of this drug and reserpine but as I say in my statement, psychiatrists, primarily in the United States, quickly demonstrated that these drugs were invaluable agents which radically altered the treatment, the course, and the prognosis of various psychiatric ailments.

Senator NELSON. I just want to make the point that this was originated by Rhone and Poulenc in France.

Dr. AYD. Rhone and Poulenc synthesized the drug. They were not the first to demonstrate its efficacy as a neuroleptic.

Senator NELSON. Who was the first to do that? What year?

Dr. AYD. The first real definitive demonstrations on a large scale in a short period of time of the neuroleptic efficacy of chlorpromazine was done in the United States by American psychiatrists who were supplied this drug in 1954. Beginning—actually some got it in late 1953. As I say, I got it in February of 1954.

This was way before the drug ever became commercially available. And we did the work and I think if you speak to the French or to the British or anyone else who is familiar with the history of chlorpromazine in psychiatry they would say that the lion's share of credit for demonstrating the value of this drug in psychiatry goes to the American psychiatrist.

Senator NELSON. The Library of Congress has a date 2 years in advance of your date, 1954. It says the first use of chlorpromazine alone in the treatment of mental illness was undertaken by Delay and his associate in 1952. That was in France.

The only point I am making is that the thrust of your argument is to say the pharmaceutical industry has done great things, which I concede. I just want to point out that it appears from the Library of Congress research, which may not be exhaustive but consists of several pages, that a large proportion of the drugs used in your specialty originated in foreign countries, and I just want the record to show that.

Dr. AYD. Well, that record is incorrect.

Senator NELSON. Since it does not support any particular argument about the pharmaceutical industry as to this particular field?

Dr. AYD. No, no. I agree. But I think the record should show that although it is true that the initial psychiatric evaluation of chlorpromazine was done by Delay and Deniker and that this work was initiated in late 1952—there is no question about this—this was a very small study involving a very small number of patients. It would hardly be accepted by scientists as demonstrative of the neuroleptic efficacy of this drug.

What I am saying is this, that it is one thing to say that the French did the first study but it is another thing to say who did the important studies, who demonstrated whether or not this particular drug is not only a neuroleptic but an effective neuroleptic and in what kind of conditions.

If you compare the fact that just in the American literature alone, before the drug came on the market, thousands of patients had been treated with this drug, compared to a few hundred patients, say, in France, with this drug. One reason for that was they did not have the facilities that we had to do clinical evaluations, and I think that the record should show justifiable pride in the fact that there is no doubt that if it had not been for the aggressive pursuit of clinical leads by American psychiatrists, that the neuroleptic efficacy of chlorpromazine might not have been demonstrated at all or at least not for many years.

In fact, I feel a personal pride in the role that I played in demonstrating this at a very early stage. As I say, I started working with this drug in February 1954.

The only information available to me at that time was a very brief report on the results obtained by Delay and Deniker, and a very brief report on the results obtained by Heinz Lehman which was not even published yet. This information was supplied by Smith, Kline & French to me. If you look in the medical literature, my article, which was one of the first published in an American journal where you have to give a bibliography referring to what previous work had been done, cites only one publication and that is Lehman's publication because that was the only one in the English language prior to the publication of mine.

Senator NELSON. Doctor, I would not——

Dr. AYD. I am sorry. I beg your pardon. And Winkleman's.

Senator NELSON. All right. I defer to your superior knowledge about the quality and importance of the work done by American psychiatrists including yourself. But the thrust of your statement has to do with expounding how much the pharmaceutical industry in this country has done, and no one denies that they have done a good deal. The report from the Library of Congress indicates that a substantial or major porportion of the drugs being used in the area of mental illness were developed or originated elsewhere. I want the record to show that.

You know, the fellow who invents the wheel is the fellow I have the highest regard for—not the fellow who makes the most rounds with it—although, of course, both functions are important. I just think the invention is the major step. Since you were making comparisons, I just thought——

Dr. AYD. I am afraid, Senator, in due respect, that it is not yet clear that this vital distinction must be made between synthesizing chlorpromazine, recognizing that it possesses certain pharmacological problems, and then demonstrating it has a certain clinical efficacy. This is a different situation. What I am trying to say is the clinical efficacy of chlorpromazine as a neuroleptic was demonstrated by American psychiatrists who were supplied this compound by Smith, Kline & French.

The Americans were the first to demonstrate also not only its efficacy, I must say, but also some of its complications. I have the dubious distinction of being the first one to have had a patient develop jaundice on chlorpromazine in the world. At least that is my understanding because when it occurred, since this was so new, Smith, Kline & French

had not had it reported to them nor had Rhone-Poulenc who had been contacted immediately. So we did the real pioneer work in demonstrating its application in the field of psychiatry.

Now, what we did with it as a potentiator, as an antiemetic, that I am not familiar with, but I am familiar with chlorpromazine frankly, from the day of its clinical birth.

Senator NELSON. As I understand it, Smith, Kline & French was licensed by Rhone-Poulenc and that is why they got the compound. They get credit for experimenting with it but without the compound they could not have done the job.

Dr. AYD. Being licensed to have a compound is one thing, but having the ingenuity to exploit and find out what this compound is really good for, that is another kettle of fish. I agree with you, it is perfectly true, no one can deny that the original synthesis of this compound was done by Rhone-Poulenc, nor can anyone dispute the historical fact that it was licensed to Smith, Kline & French. What I am trying to stress, so that this was what I mean by a balanced record, is the fact that demonstrating the efficacy of this compound as a neuroleptic agent and, therefore, really contributing to the revolution that took place in psychiatry, the credit for this must go to the American psychiatrists, the clinical investigators, who did this initial work with the supplies made available to them by Smith, Kline & French, and the financial support to do the necessary work.

Senator NELSON. I do not quarrel with that. This is what I mean by a balanced record, too. Your statement gives no credit to the development of the compound by Delay, so I thought I had better put——

Dr. AYD. I acknowledged in the beginning, Senator, that it was synthesized by Rhone-Poulenc. But I am sure that if you really investigate the facts as demonstrated in the medical literature or, for example, the American College of Neuropsychopharmacology last year had a 10th anniversary type thing in which we reviewed the history of the psychopharmaceuticals. There was no question in anyone attending this particular conference, which is a conference of the best men in the field today, that chlorpromazine's efficacy as a neuroleptic was primarily, not totally, but primarily, demonstrated by American psychiatrists beginning in late 1953 and early 1954.

Senator NELSON. I have no reason to doubt that at all. I am sure you have—I just wanted the record balanced to show where it came from.

(The material follows:)

THE LIBRARY OF CONGRESS,
LEGISLATIVE REFERENCE SERVICE,
Washington, D.C., January 16, 1969.

To: Senate Committee on Small Business, Subcommittee on Monopoly
From: Education and Public Welfare Division
Subject: Origins of certain drugs used in the treatment of mental illness

This is in reply to a request from the Chairman of the Subcommittee for a brief review of the origins of certain drugs used in the treatment of mental illness. Because of the deadline attached to the request, we have had to rely upon published references to the origins of these drugs and have included relevant quotations in each case from a number of sources. In the event you require a more complete review of the development of these drugs, please let us know.

There is a wide-range of pharmaceutical agents now used in the treatment and management of mental diseases. Each of these agents is usually classified

according to the anticipated changes in behavior likely to result from using each drug. Among these classifications are the major tranquilizers, the minor tranquilizers, certain narcotics, the antidepressants, psychomotor stimulants, and the psychotomimetics.[1] In connection with this request, we have limited the discussion of origins to the major and minor tranquilizers. In the case of the major tranquilizers, the references are to the phenothiazines and also to the rauwolfia alkaloids, the latter being included because of the role they have played in the development of psychopharmacology. As far as the minor tranquilizers, the drugs for which references are provided are meprobamate and the benzodiazepine derivatives.

Among the drugs included in the phenothiazine category are chlorpromazine hydrochloride (Thorazine, Largactil, Megaphen), promazine hydrochloride (Sparine), trifulpromazine hydrochloride (Vesprin), fluphenazine hydrochloride (Permitil, Prolixin), perphenazine (Trilafon), prochlorperazine maleate (Compazine), triflurperazine hydrochloride (Stelazine), and thioridazine hydrochloride (Mellaril).[2]

Among the rauwolfia alkaloids are rauwolfia serpentina (Raudixin, Rauserpa, Rauval), alseroxylon (Rauwiloid), reserpine (Serpasil, Serpate, Sandril, reserpoid, Rau-sed Serfin, Vio-Serpine), deserpidine (Harmonyl), rescinnamine (Moderil, and syrosingopine (Singoserp).[3]

Among the minor tranquilizers, the references are to meprobamate (Miltown, Equanil) and to the benzodiazepines, such as chlordiazepoxide hydrochloride (Librium, Libritabs) and diazepam (Valium).[4]

The Phenothiazines.—According to the *Pharmacological Basis of Therapeutics*, phenothiazine itself was synthesized in 1883, but it was not until 1934 that it was first used as an anthelmintic, urinary antiseptic, and insecticide.[5] In the late 1930's a derivative of phenothiazine, promethazine, was found to have antihistamic properties, and like many antihistamines, a strong sedative effect. The French had made some unsuccessful attempts at treating psychoses with antihistamines in 1943, and others attempted to use promethazine in the treatment of agitation in mental disease in 1950.[6]

The developments leading to the findings associated with chlorpromazine are recounted as follows:[7]

> Meanwhile, the ability of promethazine to cause a marked prolongation of barbiturate sleeping time in mice was discovered, and in 1950 the French surgeon Laborit introduced the drug into clinical anesthesia as a potentiating agent. This prompted a search for other phenothiazine derivatives with potentiating actions as well as greater central activities, and in the same year Charpentier synthesized drug number 4560 RP, or chlorpromazine. Two years later, Laborit and co-workers (1952) described the ability of this compound to potentiate anesthestics and produce "artificial hibernation." They noted that chlorpromazine by itself did not cause a loss of consciousness but produced only a tendency to sleep and a marked lack of interest in what was going on.
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> In 1952, Courvoisier and her associates described an amazingly large number of actions manifested by chlorpromazine (hence *largactil*, the French trade name). These included gangliolytic, adrenolytic, antifibrillatory, antiedema, antipyretic, antishock, anticonvulsant, and antiemetic properties. In addition, chlorpromazine was found to enhance the activity of a number of other analgesic and central depressant drugs.

The first use of chlorpromazine alone in the treatment of mental illness was undertaken by Delay and his associates in 1952.[8] Not until 1954 did there appear

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[1] See, for example, "A Rational Framework for the Development, Evaluation, and Use of Psychoactive Drugs," in *Drug Therapy—Supplement to the American Journal of Psychiatry;* vol. 124, No. 8, February 1968.

[2] List is not exhaustive. See the *Pharmacological Basis of Therapeutics*, the MacMillan Company, New York, or *New Drugs*, American Medical Association, Chicago. Words in upper-case designate trade-names of drugs within class. (See Appendix A.)

[3] See Footnote No. 2 above.

[4] There are a large number of other agents used as anti-anxiety drugs, many of which resemble meprobamate in their actions. See Footnote No. 2.

[5] "The Phenothiazine Derivatives," *The Pharmacological Basis of Therapeutics*, The MacMillan Company, 1965; page 163.

[6] "Essai de therapeutique abortive d'access maniacodepressifs par le 2339 RP (antergan)," Annls med.-psychol, 1943, 101, 432–435, Daumezon, G. and L. Cassan. "Traitement de l'agitation motice par un antihistaminique (3277 RP ou phenergan)," XLVIII Congres des Al. et Neurol; Paris 1950, Guiraud, P., and C. David.

[7] See Footnote No. 5.

[8] See footnote No. 5.

a report in the Western Hemisphere (Lehmann and Hanrahan) of the use of chlorpromazine in the treatment of psychomotor excitement and manic states.[9] The Pharmacological Basis of Therapeutics notes:[10]

> Subsequently, the drug was released for marketing in the United States. It was first employed as an antiemetic, but it was also noted that it produced sedation, relaxation, and hypothermia . . .
>
> In the mid-1950's, many psychiatrists expressed skepticism that chlorpromazine was any more effective than a placebo and felt that it would not long endure in the treatment of mental disease . . .
>
> With the rapid success of this drug, it was natural that congeners should soon be introduced. Variations of the phenathiazine molecule have resulted in compounds that differ in potency and toxicity from chlorpromazine, but the relative therapeutic superiority of one over the other has yet to be demonstrated clearly.

The 1968 *Merck Index* attributes chlorpromazine to Charpentier in 1952 with a U.S. patent, 2,645,640 in 1953 to Rhone-Poulenc.[11] In the case of promazine, the *Merck-Index* lists "Charpentier U.S. pat. 2,519,886 in 1950 to Rhone-Poulenc."[12]

The preparation of triflupromazine is attributed to Yale and others in 1957, with a British patent 813,861 in 1959 assigned to Smith, Kline, and French.[13] In the case of fluphenazine, the preparation is attributed to Yale and Sowinski in 1960 with a British patent 829,246 in 1960 to Smith, Kline, and French and 833,473 in 1960 to Sherico Ltd.[14] In the case of perphenzzine, the preparation is given to Cusic together with a patent in the United States 2,766,235 in 1956 and to Sherlock and Sperber under U.S. patent 2,860,138 in 1958 to the Schering Corporation.[15] Prochlorperazine is attributed to Horclois, British patent 780,193 in 1957 to Rhone-Poulenc, a French patent in 1958, 1,167,627, to Rhone-Poulenc, and U.S. patent 2,902,484 in 1959 to Rhone-Poulenc.[16] In the case of trifluoperazine, the *Index* attributes the preparation to Craig and others in 1957, with British patents 813,861 and 829,246 assigned to Smith, Kline, and French in 1959 and 1960 respectively.[17]

In the case of thioridazine, the preparation is attributed to Borquin and others (Sandoz), and no patent indication is reported.[18]

Most of the literature we have reviewed indicates that the phenothiazines produce substantially the same effects, although each is purported to have differing specific side-effects and intensity for use in different circumstances. Most of the literature which discusses the origins of the phenothiazines gives the credit to the French. For example, the British psychiatrist, Donald Blair, in *Modern Drugs for the Treatment of Mental Illness* observes:[19]

> Chlorpromazine (Largactil) was the first of the ataractic phenothiazine drugs to be synthesized (in 1950). This synthesis was the outcome of the thorough systematic study of the many phenothiazine derivatives by the Rhone-Poulenc Specia Laboratories of France in an endeavor to discover a drug with a more pronounced and extensive central depressant action than Promethazine (Phenergan) . . .

In *Price and Profits in the Pharmaceutical Industry*, Michael H. Cooper comments:[21]

> . . . the start of psychotropical medicine only dates back to the invention, ironically enough by the French of chloropromazine in 1956.

In 1961, the Canadian Director of Investigation and Research of the Department of Justice submitted a report to the Restrictive Trade Practices Commission in which the history of chlorpromazine was described:[22]

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[9] See footnote No. 5.
[10] See footnote No. 5.
[11] The Merck Index of Chemicals and Drugs, Merck and Co., Rahway, New Jersey, 1968; in the 1968 revision of the *Index* there is a reference to Cailliot and Gaudechon, as well; page 250.
[12] See footnote No. 11; page 869.
[13] 1968 *Merck Index*; page 1074.
[14] 1968 *Merck Index*; page 466.
[15] 1968 *Merck Index*; page 800.
[16] 1968 *Merck Index*; page 867.
[17] 1968 *Merck Index*; page 1073.
[18] 1968 *Merck Index*; page 1045.
[19] "The Ataractic Drugs," *Modern Drugs for the Treatment of Mental Illness*, Staples Press, London, 1963; by Donald Blair; page 37.
[21] "Price, Patents, and the International Scene," *Price and Profits in the Pharmaceutical Industry*, Pergamon Press, London 1966; by Michael H. Cooper; page 149.
[22] "Development of New Drugs Within Recent Years," *Report of the Restrictive Trade Practices Commission concerning the Manufacture, Distribution, and Sale of Drugs;* Ottawa, Canada, 1963: See *Appendix Q—Material Collected.*

> Chlorpromazine was discovered by the Rhone-Poulenc company of France while searching (by synthesizing new compounds of basic antihistamine structures) for a compound that would potentiate the action of sedatives. In the course of use, the French psychiatrists noted that chlorpromazine seemed to cut through the psychotic state. This report was somewhat casually received by the American psychiatrists who at the time did not evidence too great an interest. Smith, Kline, and French had found that Thorazine (chlorpromazine) was highly effective in the prevention of vomiting. This factor was to be the major sales promotion idea. However, Lehmann and Hanrahan (Verdun Protestant Hospital, Montreal) reported the successful use of chlorpromazine in the treatment of psychotic patients.

The Rauwolfia Alkaloids. The origins of the rauwolfia alkaloids can be found considerably far back in history. According to the *Pharmacological Basis of Therapeutics*, the use of the rauwolfia plant can be found among the writings of primitive Hindu medicine.[23] The climbing shrub of the Apocynaceae family was named in 1703 by a French botanist named Plumier in honor of Dr. Leonard Rauwolf of Augsberg, a 16th Century botanist, who apparently never even knew of the plant's existence.[24]

The modern therapeutic uses of rauwolfia serpentina, according to the *Pharmacological Basis of Therapeutics* are as follows:[25]

> Therapeutic applications of the whole root for the treatment of psychoses and hypertension were described in an Indian medical journal in 1931 by Sen and Bose. Little attention was paid to this finding until 1955 when Vakil wrote the first report in a Western medical journal of its antihypertensive effects. In the meantime, Schlittler and colleagues (1954) isolated a number of alkaloids, one of which was then named reserpine. In 1953. Wilkins was the first American investigator to report on the results of a trial of rauwolfia in the treatment of hypertension. About the same time, Bein (1953) found that remarkably low doses of the purified alkaloid, reserpine, were enough to keep rabbits quiet for several hours . . . In 1954, Kline reported that rauwolfia or reserpine was helpful in the treatment of psychotic patients, particularly those manifesting marked anxiety reactions, restlessness, and hypermotility . . .

According to the *Fond Du Lac* study, published in the Kefauver hearings, efforts to isolate the active ingredients in rauwolfia serpentina were undertaken by the Swiss firm of CIBA in 1947.[26] In 1952, the company isolated reserpine. In May 1953, CIBA marketed the powdered whole root under the name of Raudixin, while in November 1953, it placed on the market the isolated reserpine under the name of Serpasil. The products were originally marketed as new hypertensive agents, until, according to the Canadian report:[27]

> Nathan S. Kline, Rockland State Hospital, treated approximately 400 patients (mostly schizophrenics), some with reserpine, some with placebos. The results were astounding. Twenty-two percent of the patients (chronically psychotic females) who had not responded previously to other treatment were sufficiently improved so that they could be discharged.

According to one source, Kline's attention to reserpine was drawn on the basis of a report by the American heart physician, Robert W. Wilkins:[28]

> Reserpine was first administered in the United States to a group of heart patients whose physician, Dr. Robert W. Wilkins (now president of the American Heart Association), had read about its beneficial effects on high blood pressure in a British medical journal article by an Indian doctor. When Wilkins and his associates reported in 1952 on the drug's effectiveness in reducing hypertension, they observed also that patients using the drug seemed more relaxed, less anxious, happier.

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[23] See footnote No. 5.
[24] See footnote No. 5.
[25] See footnote No. 5. This account of events appears to be inconsistent in one respect. Other sources indicate that Wilkins became interested in the drug after reading Vakil's report in a British medical journal. According to the account in the *Pharmacological Basis of Therapeutics*, Wilkins was already working with the drug (1953) before Vakil's article appeared in a Western journal (1955). *Editorial Research Reports* indicates that Vakil's article appeared in a British journal in 1949 which at least provides a logical sequence of events. We have not had the time to verify this sequence, but would be happy to do so.
[26] "The Story of CIBA's Serpasil," *Hearings before the Senate Subcommittee on Antitrust and Monopoly on S. 1552*: part 2, page 744.
[27] See Footnote No. 22; Appendix Q.
[28] "Drugs and Mental Health", *Editorial Research Reports*, No. 20, 1957, page 868.

Each of the other sources we have reviewed establishes a similar sequence of events for the origins of reserpine and other rauwolfia alkaloids. For example, in *Medicine At Risk*, the author observes: [29]

> . . . the root of the shrub Rauwolfia Serpentina (snake root) was taken up for investigation by CIBA after the war. It was found that out of 24 alkaloids present, only three had sedating and antihypertensive properties of the preparations from the whole root. Separation by chemical means proved virtually impossible so CIBA worked out the structures of the isolated alkaloids and devised synthetic methods for making them. The result was reserpine, CIBA's Serpasil.

The *Merck Index* credits the isolation of reserpine from the root of rauwolfia serpentina to Dorfman and others with U.S. patent 2,833,771 awarded (Schwyzer, Mueller) to CIBA in 1958.[30]

The *Merck Index* provides the following data for the alkaloids (other than reserpine) of rauwolfia serpentina: rescinnamine (MODERIL) attributed to Haack and others with the U.S. pat. 2,876,228 (Ordway, Guerico) in 1959 to Chas. Pfizer and Company and to Riker Laboratories (Klohs and others) in 1961 under U.S. pat. 2,974,144; [31] deserpidine (HARMONYL) isolated by several researchers including Stoll, Hoffman, Schlittler, Klohs, and others with British patents (in 1958) to Penick and Company, Inc. (791,241) and to CIBA (1959) under 809,912 and a Canadian pat. 678,216 to Roussel-UCLAF; [32] syrosingopine (SINGOSERP) attributed to R. A. Lucas and others with a U.S. pat. 2,813,871 in 1957 to CIBA; [33] and alseroxylon (RAUWILOID) which the *Index* simply notes is the generic name for fractionally purified extract of rauwolfia serpentina.[34]

Meprobamate. According to a number of sources, the origins of meprobamate can be traced to work with mephenesin. The *Pharmacological Basis of Therapeutics* notes: [35]

> Developed by Berger (1954) as a longer-acting successor to mephenesin, meprobamate was originally synthesized as a potential muscle relaxant (Ludwig and Piech, 1951). Mephenesin had been introduced in 1946 and tried in a variety of conditions involving not only muscle spasm but also different types of neuroses and psychoses. Its usefulness was felt to be seriously limited because of its short duration of action and unreliable absorption following oral administration. Over 1,200 compounds were investigated before meprobamate was selected and its pharmacological properties were described. The first papers reporting its use in clinical psychiatry appeared in 1955 (Borrus, 1955; Selling, 1955).

The origins of the drug were discussed during the Kefauver hearings: [36]

> Early in the 1940's, Dr. Frank M. Berger as working on muscle relaxants for British Drug Houses in England and there discovered mephenesin. Because of the statutory absence of patent protection on drug products in England at that time, he could not secure a product patent. In 1947 Dr. Berger emigrated to the United States; in 1949 he became director of research for Carter Products; and in the following year a patent application was filed on meprobamate, assigned to Carter Products. In 1953 an arrangement was made for Berger to receive a share in the profits derived from the sale of drugs developed by him. The patent was issued on November 22, 1955, and will run until 1972.

The Canadian report notes: [37]

> Meprobamate was developed as a result of initial work in synthesizing preservatives for use in penicillin preparations. Frank M. Berger had noticed that one of the compounds tested on mice had a muscular relaxant effect. In the search for a more efficient muscle relaxant, Berger and Bradley developed mephenesin. Further work on mephenesin-like compounds resulted in the synthesis of meprobamate.

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[29] See footnote No. 20; page 58.
[30] *1968 Merck Index*; page 912.
[31] *1968 Merck Index*; page 912.
[32] *1968 Merck Index*; page 331.
[33] *1968 Merck Index*; page 1010.
[34] *1968 Merck Index*; page 41.
[35] See footnote No. 5.
[36] "A Study of Administered Prices in the Drug Industry," *Senate Report No. 448; 87th Congress, 1st Session;* July 27, 1961; page 143.
[37] See footnote No. 22; appendix Q.

The *Merck Index* attributes preparations to Ludwig, Piech and to, Berger, with U.S. patents 2,724,720 in 1955 to Carter Products Inc.; for synthesis to Fries, Monkemeyer under a Swiss patent 373,026 in 1963 to Chemische Werkehüls.[38]

Chlordiazepoxide Hydrochloride, and Diazepam. The *Pharmacological Basis of Therapeutics* observes that two benzodiazepine derivatives are presently available, chlordiazepoxide and diazepam. Both are used for the same purpose as meprobamate, mainly for the treatment of anxiety but also for skeletal muscle relaxation and combating alcoholism. According to this source:[39]

> Compounds of this type were initially synthesized by Sternbach in Poland in 1933, and congeneric substances were studied in the United States (see Sternbach and Reeder, 1961). Animal tests indicated that chlordiazepoxide had interesting muscle relaxant, antistrychnine, and spinal reflex-blocking properties. Randall and coworkers (1960) reported that it produced "taming" of a number of species of animals in doses much lower than those producing ataxia or measurable hypnosis. The difficult problem of defining "taming" in animals and of relating this effect to human therapeutic needs has been discussed by Cook and Kelleher (1963); but it was this "taming" effect in monkeys that led to the clinical trial of the drug in human subjects for the determination of antianxiety effects (Randall et al., 1961).

Cooper comments:[40]

> In the 1960's the Swiss have added Librium and Valium to the field . . .

Speaking of Roche, he observes:[41]

> Their discovery, Valium, was actually being marketed in Italy by Ravizza under the name "Noan" one and a half years before Roche had even registered the drug there. In fact clinical trials of the drug were still in progress in the U.S.A. Librium, its slightly older discovery, is being sold by eighteen other companies under eighteen different brand names . . .

The reference in the *Merck Index* to chlordiazepoxide (LIBRIUM) shows the preparation to Strenbach under U.S. patent 2,893,992 in 1959 to Hoffmann-La-Roche:[42] the reference to diazepam (VALIUM) attributes the preparation to Sternbach and Reeder. U.S. patents 3,109,843 in 1963 to Hoffmann-LaRoche and 3,136,815 in 1964 to Hoffmann-LaRoche.[43]

If additional information is needed in connection with any of the above, or a more detailed analysis is required, please let us know.

GLENN MARKUS.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
HEALTH SERVICES AND MENTAL HEALTH ADMINISTRATION,
Chevy Chase, Md. January 22, 1969.

MR. BENJAMIN GORDON,
Staff Economist, Senate Committee on Small Business, Room 424, Old Senate Office Building, Washington, D.C.

DEAR MR. GORDON: Although many of the psychotropic and autidepressant agents were synthesized or "discovered" by private pharmaceutical companies, there were some notable exceptions. Dr. H. Laborit, of the French Army, first noted the tranquilizing properties of chlorpromazine when he used this substance as an anesthetic. The first clinical trials of chlorpromazine with psychiatric patients were performed by Drs. Delay and Deniker of St. Anne's Hospital in Paris. These latter investigators have received some financial support from NIMH but I do not believe their early work with chlorpromazine was under NIMH support. The pioneer work with demethylated analogs of imipramine, an antidepressant drug, were performed by Dr. B. B. Brodie of the National Heart Institute. Dr. Brodie synthesized desmethylimipramine which is reported to be a faster acting antidepressant than the parent compound, imipramine. Finally, the early work with lithium salts for the treatment of psychotic excitement was performed by an Australian, Dr. J. F. J. Cade.

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[38] *1968 Merck Index*; page 687.
[39] See footnote No. 5.
[40] See footnote No. 21; page 6.
[41] See footnote No. 21; page 163.
[42] *1968 Merck Index*; page 235.
[43] *1968 Merck Index*; page 341.

For many years, both the VA and NIMH have been supporting research on the clinical efficacy of the major tranquilizers and antidepressants. The first multi-hospital collaborative study of drug treatment with schizophrenics was conducted by the VA in 1957. This study compared the clinical efficacy of compazine, chlorpromazine and a placebo on 640 schizophrenic patients and definitively established the superiority of chlorpromazine over a placebo in the treatment of schizophrenia. Both the VA and NIMH have also conducted multi-hospital trials of drug efficacy in chronic schizophrenia and in depression. A recent report on the NIMH chronic schizophrenia study indicated that high doses of chlorpromazine were especially efficacious for younger patients, i.e., those under 40, with at least five years of continuous hospitalization. These large collaborative studies have been of particular value in delineating the subgroups of schizophrenic and depressed patients who are likely to be helped most by certain of the tranquilizers and antidepressants. For example, Dr. Colomon Goldberg of the Psychopharmacology Research Branch of NIMH has developed equations, based on pretreatment symptom profiles, that predict the response of schizophrenics to a variety of tranquilizers including chlorpromazine and thioridazine. Drs. Hollister and Overall of the VA have also reported that thioridazine, a tranquilizer, was particularly efficacious in a subgroup of anxious depressions whereas imipramine, an antidepressant, was especially efficacious for an additional subgroup of withdrawn-retarded depressions. Similarly, a recent NIMH supported collaborative study of drug treatment in depression revealed that imipramine was efficacious for psychotic depressions, but of little value for neurotic depressions.

The collaborative VA and NIMH studies have also made major contributions with regard to the methodology of evaluative drug trials. Symptom rating scales for evaluating patient change were developed which are now widely used and accepted by investigators at individual hospitals. Statistical techniques for discerning drug effects were also developed.

The VA and NIMH have also been very active in establishing centers for early clinical trials with new agents for the treatment of mental disorders. Dr. Hollister of the VA has established a drug screening center at the Palo Alto VA Hospital. The Psychopharmacology Research Branch has an Early Clinical Drug Evaluation Unit which includes investigators from approximately 15 psychiatric hospitals. Standard rating forms are used by these investigators to facilitate comparisons of drug effects across hospitals.

Finally, as you know, the VA and NIMH have recently undertaken a joint effort to evaluate the effects of lithium carbonate in both manic and depressed patients. As you are also aware, Dr. Cole, who was formerly Chief of the Psychopharmacology Research Branch, was instrumental a number of years ago in making this compound available to investigators in this country for early clinical trials.

If I can be of further assistance, please let me know.

Sincerely yours,

STANLEY F. YOLLES, M.D.,
Director.

Senator NELSON. Please go ahead.

Dr. AYD. All right. It came from France, but its value was demonstrated in the United States. We both agree. All right, sir.

Within 3 years after chlorpromazine and reserpine were made available, American psychiatric hospitals were reporting a decrease in the use of physical restraints, seclusion rooms, hydrotherapy, shock therapies, and other somatic methods of treatment; a reduction in destructiveness, combativeness, and assaultiveness; a greater number of ground privileges; and, above all, an increase in the discharge rate, especially of chronic patients who previously had been considered hopeless cases, and by some as "the living dead." Private practicing psychiatrists claimed that, properly used, these drugs increased the number of patients who could be treated in the office, facilitated psychotherapy, and made hospitalization unnecessary in many cases, thereby decreasing the number of admissions to overcrowded public mental hospitals and reducing the cost of psychiatric care.

IMPORTANT ADVANCE

The therapeutic successes with chlorpromazine and reserpine stimulated an intensive search for additional psychopharmaceuticals. Within 5 years pharmaceutical firms produced not only more major tranquilizers, such as prochloperazine, perphenazine, and fluphenazine, but minor tranquilizers, such as meprobamate and, equally important, for the millions who suffer from melancholia, antidepressants, such as imipramine and amitriptyline. And because medical progress will not be checked, additional tranquilizers and antidepressants have been and are being developed by the pharmaceutical industry. The tranquilizers and antidepressants now available have made it possible for all American physicians—not just psychiatrists—to treat their emotionally and mentally disturbed patients—something previously not possible.

Concurrent with these significant developments were other trends which augured well for the psychiatric patient. A steadily increasing number of general hospitals became general in fact as well as in name by admitting psychiatric patients who now could be treated with psychoactive drugs. Prior to this, despite the prevalence of psychiatrically ill patients, more than half of the general hospitals in the United States would not admit a known psychiatric patient, one-third admitted such patients solely for diagnosis or emergency treatment, and only 1 percent had a psychiatric ward. Yet in the first 4 years after these drugs became available the National Association for Mental Health and the American Psychiatric Association reported that studies of psychiatric admissions in 1958 showed 257,300 patients in community general hospitals as against 210,117 in the public mental hospitals. Furthermore, among community general hospitals, the number of beds set aside for psychiatric patients increased in 1954–58 from 10,608 to 14,383. This trend has continued so that today most general hospitals admit and provide treatment (primarily with psychoactive drugs) for more psychiatric patients than at any time in history. Simultaneously, there was a sharp increase in the number of outpatient clinics and aftercare programs, and the opening of day and night hospitals.

Within psychiatric hospitals an attitude of pessimism and despair toward mental illness was replaced by one of hopefulness and confident optimism. Mental hospitals were transformed into active treatment centers and no longer were primarily places of detention. Many discarded the "lock and key" system of imprisoning patients in favor of an "open door" policy which provided liberties more consonant with the individual needs and the human rights of the psychiatric patient. It can be stated forthrightly that these significant changes were due largely to the advent of the tranquilizers and antidepressants.

HOSPITAL PATIENTS DISCHARGED

In 1955—I must point out to you this would be 1 year before the tranquilizers became commercially available in the United States—Dr. Francis J. Braceland, past president of the American Psychiatric Association, cognizant of the annual national increment to the mental hospital population, wrote:

However we try to minimize or rationalize the figures, the fact remains that if any other disease reached such stratospheric proportions, a national emergency would be declared.

One year later, due to the advent of chemopsychiatry and the improvement made in other forms of treatment, psychiatric hospitals became able to discharge patients at an unprecedented rate. In 1956, for the first time in 175 years, the number of patients in U.S. psychiatric hospitals began to decline. By 1963, a U.S. Senate committee noted "with pleasure" continued progress in the field of mental health. For the seventh straight calendar year the population of mental institutions dropped, this time by the largest number in any year to date, leaving 516,000 patients in the institutions in December 1962.

Senator NELSON. What is the best estimate of the total, the maximum total number we ever reached and in what year, do you recall?

Dr. AYD. If I may, sir, I can show this with a chart.

Senator NELSON. Fine.

Dr. AYD. This is getting a little ahead of schedule but to answer your question I will be glad to do that.

As I mentioned, for 175 years the patient population had been going up. Now, this chart,[1] sir, demonstrates the patients, number of patients in thousands, so that you can see in 1950 we had 511,000 patients confined.

Senator NELSON. 511?

Dr. AYD. 511,000.

Senator NELSON. Is that the top, the highest figure?

Dr. AYD. The top figure was 559,000 in 1955. You see, it was going up from 511,000 in 1950, 1951, 518,000; 1952, 530,000; 1953, 543,000; 1954, 552,000; 1955, 559,000 patients.

Now, in 1955 the tranquilizers were first being used on a large scale in psychiatric hospitals in the United States, and immediately look what happened. In one year we dropped from 559,000 patients down to 551,000 patients, and as this chart shows, it has continued to decline right on down.

I apologize for not having for you, because the figures are not yet released by the National Institute of Mental Health, the 1968 figures and unfortunately, I got the 1967 ones too late to put on this particular chart.

But let me say that the 1967 figures show that the resident population had dropped again, this time by 26,000, to an all time low of 426,000 patients.

Mr. GORDON. Doctor, may I ask a question?

Dr. AYD. Yes, sir.

Mr. GORDON. Do the drugs relieve the symptoms or do they actually cure mental diseases?

Dr. AYD. I would have to say in all honesty that the drugs do for the psychiatric patient what practically speaking all therapies do for all other patients. They do not cure. They relieve symptoms, minimize disability, they rehabilitate.

We do not cure diabetes. We do not cure cancer at this moment. We do not cure tuberculosis, nephritis, and things of this sort. We do our best to rehabilitate.

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[1] See p. 4172, infra.

Now, whether the drug is curative or not at this particular moment is immaterial. The question is, does it sufficiently control the symptoms of the patient so that it is possible for him to return to the community and to live with his family, and I must point out to you, as I did, incidentally, when I first testified before Senator Lister Hill's committee in 1955, I pointed out then that already we were showing that many patients who were a tax liability are now becoming an asset because they are earning money and paying taxes.

Senator NELSON. How good are the statistics? That is, how accurate a survey are we able to make of the number of mental patients in hospitals?

Dr. AYD. These particular figures, sir, are compiled by the U.S. Government, National Institute of Health. They are released annually by the National Institute of Mental Health and I assume because they are very able people working there that these are the most accurate figures one could possibly obtain.

They are obtained because it is my understanding that in each State the hospitals report to the local State authorities, the local State authorities in turn send their figures into Washington, and then all the compilations are done. I believe this comes under the HEW. They do it in their statistical division.

Now, I would point out, sir, that I was quoting from that 1963 Senate committee report. We had gotten to the point of the reduction in the number of patients.

"The reduction in the population of these institutions," this committee reported, and I am quoting again, "over the last 7 years is estimated to have saved $700 million." I am still quoting and I would stress this. "This is more than the total accumulated appropriations of the National Institute of Mental Health since its founding in 1948. This $700 million is only part of the savings, however. Some 559,000 patients were overcrowded in hospitals in 1955. Replacement of obsolete beds and addition of new ones would have required about 89,000 additional beds to maintain the 1955 level of hospital occupancy. The cost of adding each bed would be $15,000; thus, there has been an additional saving in capital investment of $1,300 million by virtue of the declined in patient population, or a noteworthy total in patient maintenance and construction of about $2 billion since 1956." (Senate Committee Report No. 383, Aug. 1, 1963, on DHEW appropriations for 1964.)

At the end of 1965, 10 years after the psychoactive drugs appeared, the total reduction in patients in State and county public mental hospitals was roughly equivalent to the combined mental hospital populations of 19 States: Alabama, Arizona, Arkansas, Colorado, Connecticut, Delaware, District of Columbia, Florida, Idaho, Kansas, Kentucky, Maine, Mississippi, Missouri, North and South Dakota, Minnesota, Vermont, and Washington. Statistics reported by the National Institute of Mental Health showed that the resident population in public mental institutions dropped from 475,202 in 1965 to 452,000 in 1966—a decline of 4.8 percent and the largest annual reduction.

There is a little discrepancy between the figures here and on that chart. These figures that I have on this chart came from preliminary

reports and then the final report I got later. But it does not change the basic downward trend.

This NIMH report pointed out that although more money was being spent for each patient in 1966 than a decade earlier, overall hospital costs of mental illness had fallen because of the drop in the resident patient population. Patient care cost $1,301 million in 1966, the report said, whereas, if the hospital population had grown at the pre-1955 rate, some 720,000 patients would have cost State and local governments $4,400 million. Commenting on these facts Dr. Stanley F. Yolles, Director of NIMH, stated that "the break in the upward trend occurred in 1955 because of a number of factors, *the principal one, perhaps, the introduction of the tranquilizing drugs.*" (Emphasis mine). In 1967 the resident population in State and county mental hospitals dropped again, this time by 26,000, to an all time low of 426,000 patients. This prompted Dr. Yolles to remark: "If the old pattern had continued uninterrupted, there would be over 717,000 patients in our mental hospitals—291,000 more than is actually the case."

In July 1965 the Psychopharmacology Service Center bulletin of the NIMH contained this significant report:

> When the first of the modern tranquilizing drugs was introduced in 1952, hope was expressed by a number of clinical investigators that these drugs would lead to a drastic reduction in the number of patients in our public mental hospitals. For a variety of reasons, including the effective use of drugs and other improvements in psychiatric treatment, the number of resident patients in our public mental hospitals has been declining at the rate of approximately 1 percent per year since 1955. However—

And this is important, Senator—

> if one examines the population changes within the mental hospitals in a good deal more detail, it is apparent that a more substantial decrease in the number of resident schizophrenic patients between the ages of 25 and 44 is underway. The number of hospitalized patients in the 25- to 44-year-old age group carrying a diagnosis of schizophrenia has been decreasing at a rate of 3.3 per year. If the present rate of decrease continues, the number of resident schizophrenic patients in this age group by 1970 will be one-third fewer than the corresponding number resident in 1960. There is a concomitant decrease in the number of patients being admitted to public mental hospitals carrying either the diagnosis of manic depressive psychosis or involutional melancholia. From this it can be seen that two major psychiatric conditions, severe depression and schizophrenia, insofar as they cause prolonged hospitalization of individuals in their adult years, are being relatively well controlled.

Sir, if I may digress for a moment from my prepared statement, I had the good fortune of getting my psychiatric training in the Navy. In part of my duties I was assigned at the U.S. veterans' hospital at Perry Point. While at this hospital for 2 years I worked in what was called the continuous treatment service which was a euphemism, frankly, for the chronic patients.

There were approximately 800 patients under the care of myself and my colleagues, who were few in number. Very few of these patients were over 60 years of age and the majority of them had been in that hospital no less than 20 years. Some of them had been there 30 years. Most of them had only one hope, and this is in the predrug era, and that was that death would give them a merciful release from their schizophrenia. And yet since the advent of the drugs, we not only can

get schizophrenics better so that they do not have to stay in the hospital but we can do it in a very short period of time, and for these people and their families and for the American public, this is a phenomenal accomplishment.

Now, if I may also have the next chart,[1] I would like to show you—this shows you what has happened on a national level. With the permission of my good friend Dr. Milton Greenblatt, who is the commissioner of mental hygiene for the Commonwealth of Massachusetts, I would like to show what happened in the Boston State Hospital where he was superintendent prior to becoming commissioner of mental hygiene for the Commonwealth of Massachusetts.

This just shows what happened, the same thing that has happened nationally, in a large State hospital each year, a continuous decline in the resident patient population of the hospital. This never happened in the history of Boston State Hospital as it never happened in the history of any psychiatric hospital in the United States until we got the psychoactive drugs.

Because of continued development of psychoactive drugs and their effective use, there are good reasons to believe that the decline in mental hospital patient populations will persist. It is a worldwide phenomenon which deserves to be called one of the most dramatic events of this century in medicine.

Ever since the famous French psychiatrist, Phillippe Pinel, in 1795 unshackled the institutionalized insane in Paris and promoted a humane regimen of treatment of the mentally ill, psychiatrists have yearned to care for most psychiatric patients in the community. This dream is now becoming a reality. When it was realized what had been and could be accomplished by the judicious use of psychopharmaceuticals, the late President Kennedy called for the Congress to pass legislation for the establishment and staffing of community mental health centers. In 1966 Federal grants totaling $57 million were made for the construction and/or staffing of 128 new community mental health centers in 42 States, Puerto Rico, and the District of Columbia to make mental health services available to some 22 million Americans in their home communities in a way not possible before. In 1967 President Johnson requested and Congress approved a 3-year, $238 million extension of the program of Federal aid for building and staffing community mental health centers. This is laudatory, indeed, but what must be stressed is the undeniable fact that without effective drugs to treat patients community mental health centers could not achieve their objective.

If I may have the next chart,[1] I would like to show you again material from Massachusetts which Dr. Greenblatt put together. This shows what happened.

I have to give you a little bit of background, Senator. When the drugs first came out, we were not as expertise in their use as we are today and many people had the idea that when patients improved, they did not have to have the drugs any longer, and they could be discontinued.

Patients left the hospitals, did not continue to take their medicine, they relapsed and they came back in. This led to what we psychiatrists

[1] See pp. 4172–73, infra.

call the revolving door syndrome where the patient came in, got better, went out, relapsed, and came back in.

To stop this revolving door, State hospitals began to set up outpatient departments, making drugs available to patients after release from hospitals, to keep them out of hospitals and in some instances to keep them from ever coming in in the first place, thus avoiding the stigma of having been in a mental institution.

Dr. Greenblatt compiled these figures showing the number of prescriptions written year by year as psychiatrists in the hospitals began not only to discharge greater numbers of patients but to recognize the value of these drugs not only in controlling the symptoms so that mad men were no longer acting like mad men but their value in keeping patients in a state of remission so that they could continue to reside in the community.

Now, if I may have the next chart,[1] there is just one other point I would like to make because in reading through the testimony which has been presented before this committee, reference from time to time has been made to drug advertising and things of this sort.

Now, I would like to stress for you that at least from the standpoint of psychiatrists, drug advertising is important in that it acquaints us with the existence of a compound and gives us some information about its indications, its contra-indications, dosage, et cetera. However, it is not the most influential thing in deciding whether a particular drug should be used. What is important is the demonstrated effectiveness of the drug.

Consequently, if you look at this chart, you will see that some drugs which were introduced early have been replaced by other drugs which have proven to be more effective, and some drugs which initially were widely used like chlorpromazine or thorazine which was the first one we had, as other ones came along and their effectiveness for individual patients was demonstrated to be superior to that of thorazine, psychiatrists began to use those.

What I am simply saying is that what dictates the use of a drug is effectiveness and safety. Safety, of course, is relative and I will have a word to say about that later. But I must stress for you that statements which have been made which would imply that physicians are very much influenced in their prescribing habits by what the advertising and promotion says, by what the detail men say, and so forth and so on, are not consonant with the facts.

I know of some psychopharmaceuticals which have been very widely advertised and promoted but they are not used very often at all. Why? Because they have been made obsolete by more effective drugs.

The primary obligation of the prescribing physician is to choose for his individual patient that drug which offers the greatest hope of relief with the least risk and at the least expense.

Now, I would like, because I have portrayed for you, sir, what happened since the advent of the drugs, to tell you what it was like before we had the drugs because fortunately, or I should say unfortunately, I worked in psychiatry before we had the drugs.

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[1] See p. 4173, infra.

HORRORS OF PREDRUG ERA

So to return to the predrug era in psychiatry, it would be well to recall what conditions were like then. This makes it possible to appreciate what has been accomplished.

Within the bare walls of isolated, prisonlike asylums were housed many screaming, combative individuals whose animalistic behavior required restraint and seclusion. Catatonic patients stood day after day, rigid as statues, their legs swollen and bursting with dependent edema. Their comrades idled week after week, lying on hard benches or the floor, deteriorating, aware only of their delusions and hallucinations. Others were incessantly restive, pacing back and forth like caged animals in a zoo.

Periodically the air was pierced by the shouts of a raving patient. Suddenly, without notice like an erupting volcano, an anergic schizophrenic would burst into frenetic behavior lashing out at others or striking himself with his fists, or running wildly and aimlessly about.

Nurses and attendants, ever in danger, spent their time protecting patients from harming themselves or others. They watched men and women who either refused to eat or gorged themselves. They tube fed to sustain life. Trained to be therapists, they functioned as guards and custodians in a hellish environment where despair prevailed and surcease by death offered the only lasting respite for their suffering charges.

Compounding this ghastly situation was the restricted therapeutic armamentarium of the psychiatrists. How frustrated and impotent they felt and I know this because I felt this way, as they watched the number of chronically ill swell the burgeoning population of long-term resident patients. They knew from bitter experience that psychotherapy for psychotics was fruitless, that insulin-coma and electroshock therapy offered little or no improvement to schizophrenics continuously ill for more than 2 years, and that psychosurgery benefited only a very small percentage of the chronically ill. For lack of more effective remedies, they secluded dangerously frenetic individuals behind thick doors in barred rooms stripped of all furniture and lacking toilet facilities. They restrained many others in cuffs and jackets or chained them to floors and walls. Daily they sent patients for hydrotherapy, where they were immersed for long hours in tubs, or packed in wet sheets until their disturbed behavior subsided. These measures, barbaric and inhumane as they appear in retrospect, euphemistically called therapy, at best offered protection to patient and personnel and a temporary respite from the most distressing symptoms of psychoses.

This lack of effective antipsychotic therapies accounted for the bleak outlook for the chronically ill. Unless they were released within 2 to 3 years of admission, they were destined to remain indefinitely, prisoners of psychoses—unresponsive to the existing therapies.

Chlorpromazine and reserpine were the first therapies to change the dire prognosis for the chronic schizophrenic. Shortly after these became available psychiatrists realized that, unlike previous psychological and physical methods of treatment—the effectiveness of which

declined to near zero for patients ill for more than 2 years—these drugs benefited many chronically ill psychotics to a degree heretofore unattainable. Soon other psychotropic drugs were added to the list of effective antipsychotic agents. The result: unprecedented hope for chronic psychotics, an incredible change in mental hospitals, in the organization of mental health services, and the virtual abolition of involuntary admissions.

The transformation that has occurred in mental hospitals in the past two decades defies description. Visit one today. You will be impressed by the serenity you observe and feel. You will sense the attitude of realistic optimism which predominates. Flowers, curtains, paintings, music, fresh air, comfortable tidy lounges make a pleasant environment for clean, tranquil patients being offered a myriad of therapies designed to make their hospitalization profitable and not a living hell. Some modern psychiatric hospitals have almost a country club atmosphere. All are becoming what we have always wanted—attractive, active centers of treatment, offering hope of rehabilitation and return to the community, to family and friends, after a relatively short period of effective treatment.

This brief review of the current revolution in psychiatry is essential, if we are to maintain a proper perspective. There are people who seem unaware of what has been accomplished and of what has made these salutary achievements possible. A lion's share of the credit in justice goes to the major pharmaceutical companies. As a pioneer in the clinical evaluation of most of the available psychopharmaceuticals, I can testify that these firms—not university or Government research—developed the drugs which have transformed the care and treatment of the mentally ill. These drug companies were responsible for the basic research—the biochemical, the pharmacologic, the toxocologic evaluations of these invaluable medicines. These drug companies sought the services of able, highly competent physicians to clinically test their psychoactive drugs and financed clinical trials which otherwise would not have been possible. In short, the innovative manufacturers provided the medical profession, especially psychiatrists, with the essential tools—available from no other source—which have enabled us to do what has not been done before in the history of medicine.

No psychiatrist, I assure you, absolutely no psychiatrist, would want to return to the predrug era. We are justifiably proud of what we have accomplished with the products developed by their manufacturers. We sincerely hope that what we have achieved with psychopharmaceuticals and other therapies will cause mankind to finally realize that mental illness does not make its victims inferior members of society. We are painfully aware, Senator, of the 426,000 patients still in U.S. public mental hospitals and the large number of patients in the community making only a marginal adjustment. These are "silent witnesses" who have not benefited optimally from the drugs we have, and it is for these silent witnesses I am here today. They bear witness to the need for more psychopharmaceuticals. These we rightfully expect will be developed by the unrelenting research of the creative scientists employed by the progressive drug firms, large and small.

Other conditions for which present-day pharmacotherapy is not very effective are mental deficiency, criminal psychopathy, and drug addic-

tion. Psychiatrists are concerned about the increasing admissions, compulsory detentions, and the trend toward longer stay in the hospital because of these disorders. The drugs required to help these unfortunate people we also expect will be developed by the research-oriented manufacturers.

There are those who think there are too many psychoactive drugs and those who contend that the number of such drugs in a hospital formulary should be restricted. These individuals fail to recognize that none—and I stress this—none of the available compounds is universally effective and safe. They overlook the indisputable fact that, despite all the psychoactive drugs on hand, there are in and outside of mental hospitals many thousands of patients either partially or totally refractory to these drugs or intolerant of them. For these unfortunate, suffering individuals there is an urgent need for more psychoactive drugs. Those who would limit the number of psychoactive drugs also ignore what every psychiatrist experienced in testing and using these drugs knows; namely, that some patients benefit only from one compound and are unresponsive to, or are intolerant of, all other drugs. Thus, for those patients who respond to a particular tranquilizer or antidepressant—old or new—that one drug is invaluable; it means for them the difference between sickness and health even if, in comparison to all other drugs, it would seem to be the least effective. This is most important for these patients because humans and not a statistic suffer.

Furthermore, physicians dedicated to easing emotional and psychic suffering, to eradicating or minimizing disability and to restoring mental health should be able to prescribe whatever drugs in his professional judgment offer the greatest prospect of benefiting his individual patient. Physicians cannot achieve their objectives and patients will suffer, if the physician's right to independent medical judgment is infringed by a hospital formulary which does not include all available psychoactive drugs or insists on the use of products other than those specifically prescribed.

The challenge, Senator, to the medical profession comes not from the number of drugs available, but from the need to learn the art of using these drugs correctly. The simple clinical fact is that the more drugs we have at our disposal, the greater is the number of patients who will be helped.

For 15 years it has been my privilege to evaluate clinically drugs for the mind. During this time I have never once been asked by the manufacturer of strictly "me too" products to test a compound for them. Nor, to the best of my knowledge, have any of the reputable and dedicated physicians who evaluate psychopharmaceuticals in the United States ever been requested to study a new compound developed by the research of such a manufacturer. I polled by mail 130 members, which is practically I must say the entire membership, of the American College of Neuropsychopharmacology, which is composed of the most experienced and well-trained specialists in the testing and evaluating of tranquilizers and antidepressants in the United States and Canada, asking if any producer of what are commonly called "generic drugs" ever requested them to test a new psychopharmaceutical or provided them with any financial support for any of their research in psychopharmacology.

I received replies from 119 or 91.5 percent, which is a very good record, I am sure you will agree. Not one had been asked by such a manufacturer to test a new psychopharmaceutical or had received support from such a manufacturer for their research in psychopharmacology. The reason for this is simply that these manufacturers have not developed any effective major or minor tranquilizers or antidepressants. By contrast, every effective psychopharmaceutical which a physician can prescribed for our citizens has been developed and made available by the well known and research based drug houses. It is this truth which compels me to forthrightly acknowledge the debt of every American to these manufacturers for they are helping immeasurably in the conquest of mental illness. This indisputable fact merits your recognition and serious consideration.

Senator NELSON. I do not understand that last sentence.

Dr. AYD. This indisputable fact?

Senator NELSON. Yes.

Dr. AYD. Well, the sentence makes sense, sir, if you read what precedes it. What I am trying to say, in essence, is that the only drugs that we have ever had made available to us to treat the psychiatrically ill have come from the research oriented pharmaceutical firms, and no other source. They have not come from the Government, they have not come from the university centers, they have come only from the research oriented manufacturers.

We have a debt to these people. They provided the psychiatrists with the tools, not only psychiatrists, every physician in America, with the tools to take care of the emotionally and mentally ill in a way heretofore impossible. They have done this. Nobody else. And I think this fact is not only indisputable but I think it merits recognition and consideration in evaluating their contribution.

Senator NELSON. Well, I might say that no one on this committee, nor anyone who has testified, has been at all reluctant to pay appropriate tribute to the drug industry for its contribution. I do not think we have had a single witness who addressed himself to the question who was not prepared to pay the appropriate tribute. The implication is that somehow or other we have not given recognition.

It is not the purpose of these hearings to fill volumes with the laudatory things that the drug industry has done. The purpose is to explore some very serious problems which exist in the industry. And incidentally, many companies privately concede that problems do exist and some of them even acknowledge this publicly. That is our purpose here. Any time they want to come in and tell us about the great things they have done, they may do so. If there were no problems in the industry, if it were a perfect industry, if it were making no mistakes and the public had no interest in evaulating some of the things the industry was doing, we would not be having any hearings.

We are exploring the problems of the industry. We are glad to have you be laudatory of them. I am glad to be laudatory myself. But at the same time, there are serious problems which have got to be called to the public's attention and we are doing that. The pharmaceutical industry is doing things that it should not be doing and that is the purpose of the hearings.

So, I just point that out to you. There is hardly any criticism of the industry in this country. Everybody thinks of miracle drugs, and so forth and so on. We are pointing out some of the problems in it.

Dr. AYD. May I make two observations, Senator?

Senator NELSON. Surely.

Dr. AYD. One, I am well aware of the fact that you are not out, shall I say, to damn the pharmaceutical industry. I am appreciative of that fact. What I think, though, needs to be stressed is, No. 1, much of what your hearing has brought out is an indictment, not of the pharmaceutical industry, but of physicians.

Senator NELSON. And some of it is very justifiable, I must say.

Dr. AYD. Yes. I have become known worldwide as an expert on the side effects of the psychopharmaceuticals. I write a great deal on this, lecture a good deal on this, and I am well known for repeatedly making the statement that frequently when I review the world's literature each year on the side effects and complications of the psychopharmaceuticals, I am compelled to draw the conclusion that it is not the drug that should be condemned but the prescribing physician who should be indicted.

Senator NELSON. That has been suggested before the committee.

Dr. AYD. Yes. Now, that is point No. 1.

Point No. 2. It is all well and good, sir, for any of us, senatorial committee, a body of physicians, to get together and to recite the litany of side effects that a compound can cause. But this can do a grave injustice, a grave injustice not only to the compound and to its manufacturer, but it can do a grave injustice to patients because there is no doubt in my mind that concern about side effects can be responsible, in fact, it has been responsible for denial of treatment. I wrote an editorial on this last year.

I think, for example, to say that a compound causes agranulocytosis is all well and good, but what needs to be said is how often it causes agranulocytosis. If it does it one in 25 million cases, that is not a very grave risk as, say, one in 25 cases.

The prescribing physician's moral obligation as well as his professional duty is to always balance risk against benefit. To do this, he must know several things. He must first know the patient for whom he is prescribing, not just an illness but the patient with the illness. He must know the physical condition independent of the illness. He must also know that we live and work today in an era of what I call polypharmacy. Patients are receiving multiple drugs for multiple conditions. You keep people alive and they develop high blood pressure and they develop diabetes and this, that, and the other thing each of which requires treatment. So that many patients receive multiple drugs.

The physician who does not take this into consideration can get into difficulties by producing drug interactions. This is a matter of medical information, how to evaluate a drug, when to prescribe a drug, under what circumstances.

But I must point out to you, sir, that there has been and there is a trend in the United States for individuals who would like to take over the control of the prescribing of medicine. I mean, I wrote an editorial also entitled "Drug Use by FDA Fiat," in which I take issue with the fact that a physician is supposedly limited by dosage recommendations in the package insert.

If the physician chooses to prescribe doses in excess of those in the package insert, he does so, to quote Dr. Goddard whom I respect very highly, "He does so at his own peril."

No. 2, I would point out to you that, for example, there are indications for drugs which have been well validated in the scientific literature worldwide which are not in the package insert, however, and, therefore, the physician who would prescribe a drug for that particular indication again "does so at his own peril."

A physician's right to independent medical judgment, to assume responsibility for the care and treatment of the patient, to decide what is the best drug for this particular patient in what dosage, and so forth, is an obligation that he can never escape. He just cannot escape this obligation. And yet if we have people who say that we have too many drugs already, we should not have any more, or that this drug is the least effective of the series, therefore, we will not have this drug available, and so forth, he is by that statement infringing upon the right of the physician to treat the patient. He is also denying the patient the right to treatment. And I would stress for you, sir, that much of the emphasis which the press has given to the complications of drugs which have been mentioned in these hearings has increased concern about side effects and this is one of the reasons why I wrote the editorial last year in Medical Science called "Concern about Side Effects and Denial of Treatment," because I see patients who have been denied effective treatment because of concern about side effects.

Instead of their being not only ineffectively treated, the cost of their illness in dollars and cents was increased, but their personal human suffering was prolonged and magnified because an alarmist attitude has been created by side effects. This is what I mean by let us have a balance. If we are going to say such and such a drug is responsible for this, this and this, fine. Let us also say what the incidence of these complications is. Let us also say how can we find out who are the risk patients. Did the physician balance risk against benefit in this particular case? Did he take a legitimate risk? And should we not take legitimate risk? If we do not take legitimate risk there will be no medical therapy at all.

Senator NELSON. We have not had anybody before the committee who suggested we should not take any form of risk. The most classic case is still chloramphenicol, which we will have further extensive hearings on.

That is a dramatic case of a widely abused drug in which a number of people have died because of the carelessness of the doctor in not knowing what he was doing. I have now two friends, two acquaintances, who because of what they read in the paper, when their child just got chloramphenicol prescribed as a broad spectrum antibiotic for a not very sick child, they refused to take it. The child got perfectly well. There was no clinical test given the child, no testing to find out what was causing the fever to find out if it should be treated by chloramphenicol. If that child had gotten it and died, it would have been a catastrophy.

This has happened hundreds of times in this country and the best experts we have, and we are going to get more, say that this has been a widely abused drug. We have had nobody in here say to the contrary.

Now, if the publicity of this committee has had the consequence of warning the doctors who are abusing this drug, as the experts say, and I will be glad to have any doctor in the country come in and present the evidence that they are not, if that publicity has done that and he

had indicated the profession, all the time spent by this committee is well worthwhile.

Now, I said several times the tragedy was that the American Medical Association did not throw up the alarms, call a special conference, warn the doctors, do everything it could. It took a congressional committee with no expertise at all to bring it out and we cut the usage in one 6-month period from 20 million grams to four compared to the previous year.

I have seen no one come in and say we quit using it for indicated cases. They quit using it for nonindicated cases. We have had testimony here—and we are going to get into this much more deeply later—from doctors who specialize in drugs and the use of drugs, saying that six to seven, perhaps $8 out of $10 spent on drugs are spent needlessly. I think this ought to be made a matter of public knowledge. I think the profession ought to discipline itself and in many ways they have not, and if these hearings contribute to that, which I think they are, they will be worthwhile.

Now, when you get to the question of limiting a doctor's prescribing, referring to a formulary, I do not know of any better way to get the collective judgment of the best people in the profession and in a hospital formulary, as you are well aware, if the doctors on the staff are competent and if the formulary committee and the specialists there know what they are talking about, I would guess that the collective judgment of the internist and the surgeon, the pharmacologist, and the pharmacist and all the rest of the specialists sitting down and deciding on a formulary, that their collective judgment based on their special knowledge is better than a single judgment of any single doctor.

I would guess that that is true in any operation and that is why formularies are used in hospitals.

Now, if the formulary committee is so ignorant or careless that they will bar the use of a drug that will do a job that no other drug in the formulary will do, well, that is another indication to this committee of the incompetence of the profession or at least of this formulary committee. But to have doctors saying, as individual practitioners, without special expertise, just reading the literature, that they are better prepared to decide what drug ought to be given than a group of people who practice and have experience in it, I think is a lot of nonsense and so does every professional man I know of.

Dr. AYD. Senator, there are several comments I would make. One, I did not have in mind chloramphenicol when I was talking about side effects.

No. 2——

Senator NELSON. I think that is the one that has gotten big publicity here.

Dr. AYD. I agree with you wholeheartedly that there has been injudicious prescribing of medications, not only in the United States but in every country in the world.

Now, this I must stress, is due in part to the fact that there are physicians who are casual individuals, just as there are lawyers who are casual individuals, or businessmen who are casual individuals, and so forth. Even in the 12 Apostles there was a Judas. We cannot hope to eliminate human frailty by legislation.

I applaud your committee for calling attention to some things. I sincerely believe that there are areas in which the practice of medicine can be improved upon. That, however, I say is the responsibility of the medical profession, not the pharmaceutical industry.

For example, I agree and have written editorials urging doctors to label prescriptions so that when a patient walks into my office and puts down a brown paper bag full of bottles of medicine I can easily identify what they are. I think this should be done. I think it should not only have the name of the drug, it also should have the strength of the medication.

Senator NELSON. I have introduced a bill to that effect. I hope you will come and testify for it.

Dr. AYD. Well, I would be very happy to, sir, because I feel very strongly about this.

Let me illustrate one of the reasons why. Today's drugs are very potent. They can smite and they can heal. Let us face that fact. We are dealing with potent remedies. Their judicious use is imperative.

Now, if a doctor is unaware of what the patient is taking, he may add another drug which can really be tragic for the patient.

This would lead me to point out something to you which I think this committee needs to seriously consider. If we are going to have an array of generic drugs when patents go off of a particular substance, this is fine. I have no objections to this at all. I have this one thing, though, that I consider imperative and this is based on actual everyday practice of medicine experience, that that generic drug be in some way identifiable.

Now, let me illustrate. In the city of Baltimore where I practice, if the patient gets a generic drug at a hospital pharmacy and I am called on a Saturday or a Sunday to see this patient because some complication has arisen, and you get this unidentifiable thing and the hospital pharmacy is closed, you cannot find out what the patient is taking. Now, at least we have this advantage today, I can recognize every commercially available brand name psycho-pharmaceutical. I cannot recognize the generic ones.

If we are going to have them when the patent comes off of a particular one, fine. There is nothing wrong with that. But let us make sure not only that it is identifiable but I do think that in the interests of protecting the health, not just the pocketbook, the health of the American public, that you should have some way of making sure through congressional action that these generic equivalent drugs are indeed not only labeled but that they have been tested and proven to be therapeutically effective, therapeutically equivalent. This is not always the case, as you know. If we have this, fine, I am for you 100 percent.

I think the last part of my statement does not need to be read except that I would stress that at the rate we are going, in 50 years we may not have mental hospitals as we know them today.

We need more drugs, not less. That is why I said the task of the physician is not the number of drugs we have available but learning the art of how to use them judiciously.

Now, in this area, I must say in defense of the pharmaceutical industry, I think that they have made fantastic efforts to educate physicians. I know how difficult it is to educate doctors. I have been trying

to do this, teaching interns, teaching residents, lecturing at State medical society meetings, and so forth and so on. It is tough, a very tough job. And I do not know if there is ever going to be a simple solution to the question of educating physicians.

I must also point out something else, that we speak of having so many drugs in this country but we are in a small ball park when it comes to the number of drugs compared to the other Western nations.

One thing is going to happen if we look into the future a little bit. Doctors are going to have less and less time to spend with patients. It is going to be a production line thing as it has become in England where the average general practitioner has 3 minutes to see a patient, write a precription and hand it to him.

This may happen in this country. All the more reason why your committee and everybody else ought to be stressing for the profession how important it is for physicians to recognize that today's drugs are like the hand of God. They can heal and they can smite and from this standpoint I have no quarrel with you or your committee and I hope I did not give you the impression that I came here as an attacker. That was not my objective.

My objective, sir, was to come and plead for those patients to whom I have dedicated my life, that we will not, in our desire to rectify some errors in any way infringe upon the continued development of the drugs that these people need if they are going to be restored to health, and for that reason I am here and I think you for the opportunity to be here.

Senator NELSON. We would not want to infringe in any way and the committee appreciates very much your testimony and your taking the time from your busy practice to come over here and testify before the committee. We appreciate it very much. It was very useful. Thank you.

I am sorry again that I had to delay you.

Dr. AYD. No apologies necessary.

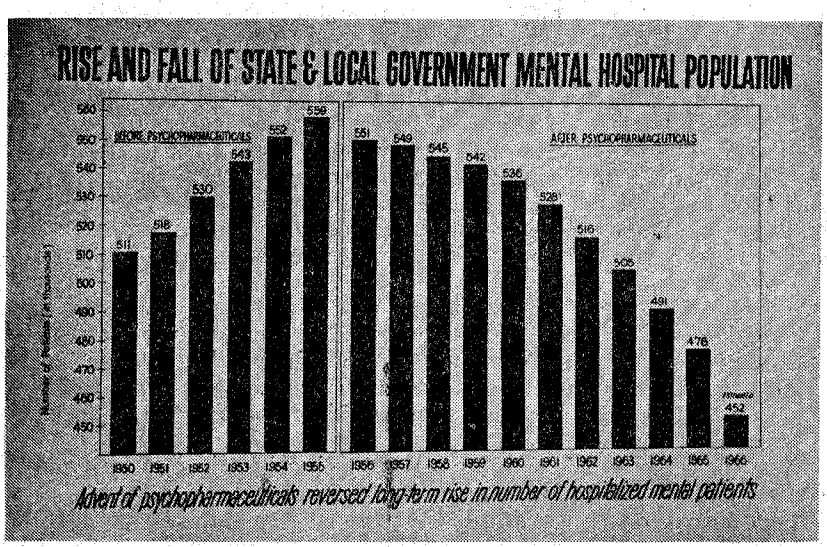
Thank you, sir.

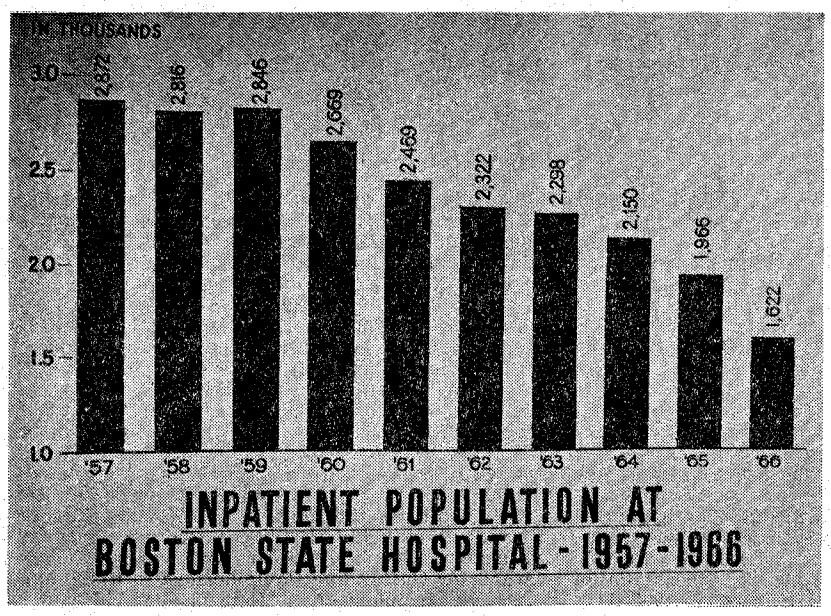
(The supplemental information submitted by Dr. Ayd follows:)

BRIEF BIOGRAPHICAL SKETCH

Frank J. Ayd, Jr. received his medical degree from the University of Maryland, School of Medicine, in 1945. The American Board of Psychiatry and Neurology, Inc. certified him as a Diplomate in Psychiatry in 1951. Dr. Ayd is an internationally known lecturer, writer, and psychiatrist. He has lectured in Europe, Asia, Africa, The Orient, Australia, New Zealand, and North America. He is a member of numerous national and international medical societies. He is a Fellow of the American Psychiatric Association, The American Academy of Psychosomatic Medicine, The American Geriatrics Society, a Fellow and a founder of the American College of Neuropsychopharmacology. In 1955, Dr. Ayd was the recipient of the Distinguished Service Award and designated Most Outstanding Young Man of the Year by the United States Junior Chamber of Commerce for Baltimore and the State of Maryland. In 1960, Ayd was the recipient of the Holy Name Society Award for outstanding service to Church and Community. In 1962, Dr. Ayd began broadcasting over the Vatican Radio on a program called Religion and Science. In 1963, Dr. Ayd was honored by being the first American Layman to be appointed to the Faculty of the Pontifical Gregorian University in Rome. In 1964, Xavier University (Cincinnati, Ohio) conferred on Dr. Ayd an honorary Doctor of Laws degree. Also in 1964, Dr. Ayd was the recipient of the St. Vincent Pallotti Award for Oustanding Contributions to Religion and Psychiatry. In 1965, Dr. Ayd was the recipient of the Rev. Joseph M. Kelly, S.J.

Medal awarded to an Outstanding Alumnus of Loyola High School. Dr. Ayd has published over two hundred scientific articles. He is a contributor to over thirty books. He is editor and publisher of The Medical-Moral Newsletter and the International Drug Therapy Newsletter. Dr. Ayd is Associate Editor of Medical Counterpoint and is on the editorial staff of several other medical journals. Dr. Ayd is listed in Leaders in American Science, American Men of Medicine, and the American Catholic Who's Who. He is a member of The National Association of Science Writers, Inc. Dr. Ayd is married and the father of twelve children.





BOSTON STATE HOSPITAL
PRESCRIPTIONS FOR OUTPATIENTS

Year	Prescriptions
1958	658
1959	2,100
1960	2,731
1961	4,601
1962	8,506
1963	11,261
1964	16,702
1965	20,353
1966	over 24,000 (estimated)

BOSTON STATE HOSPITAL PSYCHOPHARMACEUTICALS

	Generic Name	Mfr.	Year Introduced	Total Tablets Dispensed 1965
Major Psychopharmaceuticals				
THORAZINE	Chlorpromazine HCl	S.K.F.	1954	455,413
STELAZINE	Trifluoperazine HCl	S.K.F.	1958	312,497
MELLARIL	Thioridazine HCl	Sandoz	1959	190,273
TRILAFON	Perphenazine	Schering	1957	90,305
PROKETAZINE MALEATE	Carphenazine Maleate	Wyeth	1962	32,770
TARACTAN	Chlorprothixene	Roche	1962	31,800
COMPAZINE	Prochlorperazine	S.K.F.	1956	23,988
PROLIXIN	Fluphenazine HCl	Squibb	1959	17,388
SPARINE HCl	Promazine HCl	Wyeth	1956	10,906
Minor Psychopharmaceuticals				
LIBRIUM	Chlordiazepoxide HCl	Roche	1960	90,828
MILTOWN	Meprobamate HCl	Wallace	1955	24,261
EQUANIL	Meprobamate	Wyeth	1955	
VALIUM	Diazepam	Roche	1963	11,496
	Reserpine	Ciba	1953	348
Antidepressants				
TOFRANIL	Imipramine HCl	Geigy	1959	248,562
ELAVIL HCl	Amitriptyline HCl	Merck S&D	1961	122,888
NARDIL	Phenelzine Sulfate	Warner Chilcott	1959	1,355
DEPROL	Meprobamate	Wallace	1958	962
	Benactyzine HCl			

(Subsequent information follows:)

MEMORANDUM

APRIL 15, 1969.

To: Senator Gaylord Nelson, Chairman, Monopoly Subcommittee.
From: Benjamin Gordon, Staff Economist.
Re: Dr. Frank Ayd's connection with the pharmaceutical industry.

Dr. Frank Ayd has been employed over a long period of time by the pharmaceutical industry in the evaluation of its products. A list of the specific firms and the drugs involved follows:

1. IND 248, Wy #3263, Wyeth Laboratories.
2. IND 535, MCN–JR #1625, McNeil Laboratories.
3. IND 564, MK #240, Merck, Sharpe & Dohme.
4. IND 749, Etrafon, Schering Corporation.
5. IND 1155, MRL #44, Wm. Merrell & Company.
6. IND 1389, NDR #5061A, National Drug Company (subsidiary of Richardson-Merrell).
7. IND 1667, P #3693 A, Charles Pfizer & Company.
8. IND 1669, Mebutamate, Wallace Laboratories.
9. IND 2246, RP #7162, Ives Laboratories.
10. IND 2317, SK&F #14336, Smith, Kline & French.
11. IND 2980, Abbott #30400, Abbott Laboratories.
12. IND 3213, Pipradral Hydrochloride, Wm. Merrell & Company.
13. IND 3289, EN #1733 A, Endo Laboratories, Inc.
14. IND 3593, WY #8601, Wyeth Laboratories, Inc.
15. IND 3999, BC #105, Sandoz Pharmaceuticals.
16. NDA 11–006, Atarax, J. B. Roerig & Company.
17. NDA 12–611, Kavadon (Thalidomide), Wm. Merrell Company.
18. NDA 12–703, Elavil, Merck, Sharpe & Dohme.
19. NDA 12–704, Elanil, Merck, Sharpe & Dohme.
20. NDA 13–270, Teejel Gel, Purdue Frederick & Company.
21. NDA 13–448, Eutonyl, Abbott.
22. NDA 13–615, Quide, Pitman-Moore.
23. NDA 13–617, Quide, Pitman-Moore.
24. NDA 13–620, Pertofrane, Geigy.
25. NDA 14–684, Aventyl, Eli Lilly & Company.
26. NDA 14–685, Liquid #38 Aventyl, Eli Lilly & Company.
27. NDA 14–715, Triavil, Merck, Sharpe & Dohme.
28. NDA 16–012, Vivactil, Merck, Sharpe & Dohme.
29. NDA 16–792, Surmontil, Ives Laboratories, Inc. (subsidiary of American Home Products).
30. NDA 16–816, Teejel Gel, Purdue Frederick Company.

(Whereupon, at 3:15 p.m., the subcommittee was adjourned, subject to the call of the Chair.)

APPENDIXES

(4174A)

APPENDIX I

[From The New England Journal of Medicine, vol. 279, No. 23, Dec. 5, 1968]

BRIEF RECORDING

ACUTE RENAL FAILURE AFTER DRIP-INFUSION PYELOGRAPHY [1]

Lawrence A. Bergman, M.B., B.Sc., M.R.C.P. (Lond.),
Maceo R. Ellison, M.D., and George Dunea, M.B., M.R.C.P. (Lond. & Ed.)

Drip-infusion pyelography, first described by Schencker [2] in 1964, has become widely used to evaluate renal size and exclude urinary obstruction in patients with renal insufficiency. The procedure is usually done without prior dehydration, and serious side effects have not been reported.

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[1] From the Hemodialysis Unit and the Department of Medicine, Mount Sinai Hospital Medical Center and Chicago Medical School (address reprint requests to Dr. Dunea at 2750 W. 15 Pl., Chicago, Ill. 60608).

[2] Schencker, B. Drip infusion pyelography: indications and applications in urologic roentgen diagnosis. *Radiology* 83:12–21, 1964.

We have recently observed a patient in whom fluids were restricted inadvertently before pyelography, and in whom acute oliguric renal failure of three days' duration developed.

"A 52-year-old normotensive diabetic man was known to have had proteinuria and diabetic retinopathy for several years. Elevation of blood urea nitrogen was first recorded some 12 months earlier, and further deterioration in renal function occasioned admission to the hospital (with a blood urea nitrogen of 63 mg and serum creatinine of 4.5 mg per 100 ml). His general condition was good. The urine volume was about 2000 ml, and protein excretion 1.3 gm per 24 hours.

"Shortly after admission drip-infusion pyelography was done with the use of 150 ml of meglumine diatrizoate[3] in 150 ml of 3 per cent sodium chloride, the infusion being completed in 10 minutes. There were no immediate adverse reactions, but severe oliguria (excretion of less than 400 ml per day) developed within several hours after the procedure was completed. An attempt to induce diuresis with annitol failed. Oligura persisted for three days, after which a spontaneous diuresis ensued. Subsequent progress has been uneventful."

DISCUSSION

Acute oliguric renal failure after infusion-drip pyelography has not previously been reported. Since fluids were inadvertently withheld in our patient, the situation seemed akin to the renal failure in multiple myeloma that may follow standard intravenous pyelography. This has been attributed to dehydration causing precipitation of proteinaceous material in the renal tubules.[4,5] A similar mechanism may have been responsible in our patient. However, since thousands of diabetic patients must have been subjected to standard intravenous pyelography, with its necessary preliminary dehydration, one would have expected many cases of acute renal failure to have been rported. It is tempting to conjecture that the increased dosage of contrast material employed in conjunction with dehydration helped precipitate renal shutdown.

APPENDIX II

[From the New England Journal of Medicine, vol. 279, No. 23, Dec. 5, 1968]

CHRONIC NITROFURANTOIN PULMONARY REACTION*—Report of Five Cases

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Abstract in five cases diffuse interstitial pneumonitis or fibrosis, or both (as proved by lung biopsy), was seen after long-term therapy with nitrofurantoin. The acute form of nitrofurantoin pneumonitis is characterized by the sudden onset of cough, dyspnea and fever, and the rapid disappearance of the symptoms and findings when the use of the drug is discontinued. The chronic form is insidious in onset, is not associated with a febrile reaction, produces a nonspecific histologic and radiologic picture of diffuse interstitial pneumonitis or fibrosis, or both, and may be at least partially reversible when the drug therapy is discontinued and steroids are employed.

Pulmonary reaction caused by systemically administered drugs has been well described in the literature, and the association has been seen with antituberculosis chemotherapy, (1) with hexamethonium therapy, (2, 3) after mecamylamine therapy (4) and with busulfan, (5) hydrochlorothiazide, (6) methysergide (7) and sulfonamides. (8) Since 1962 pulmonary infiltrations considered due to nitrofurantoin have been reported with increasing frequency, and most of the reported cases have dealt with acute nitrofurantoin pneumonia. (9, 19) The term "nitrofurantoin pulmonary reaction" was proposed by Nicklaus and Snyder (19) for

[3] In the form of Renografin 60, E. R. Squibb & Son, New York, N.Y.

[4] Brown, M., and Battle, J. D. Jr., Effect of urography on renal function in patients with multiple myeloma. *Canad. M.A.J.* 91 : 786–790, 1964.

[5] Morgan, C., Jr., and Hammack, W. J. Intravenous urography in multiple myeloma. *New Eng. J. Med.* 275 :77–79, 1966.

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the clinical syndrome of acute, febrile, noncardiac pulmonary edema caused by the drug.

We have seen five patients at our institution who received nitrofurantoin for periods from six months to six years before pulmonary symptoms developed. The purpose of this report is to present the observations on these five patients and to record what we believe represents chronic nitrofurantoin pulmonary reaction. Lung-biopsy specimens taken from the five patients showed a nonspecific pattern of diffuse interstitial pneumonitis and fibrosis.

We have no proof that nitrofurantoin caused the pulmonary changes presented in the five cases reported herein. Nevertheless, since nitrofurantoin has been strongly implicated in the genesis of interstitial pneumonitis on an acute basis, the five cases indicate the possibility of a spectrum of nitrofurantoin-induced pulmonary disease on a chronic basis. Because nitrofurantoin is used extensively today and because of the dire consequences of interstitial pneumonitis, it seems justifiable to call attention to another possible untoward effect of the drug.

CASE REPORTS

CASE 1. A 68-year-old woman came to the Mayo Clinic in January, 1968, for a general examination. In 1960, she had received nitrofurantoin (Furadantin) for chronic recurring urinary-tract infections, and for 6 or 7 years before examination she had been taking 50 mg a day. In 1962, 2 years after the nitrofurantoin therapy was begun, cough and dyspnea on exertion developed. The onset of symptoms was gradual, and there were no febrile episodes associated with the early manifestations of the pulmonary disease. Several months after the onset of pulmonary symptoms, examination at another institution resulted in the diagnosis of Hamman-Rich syndrome on the basis of the histologic appearance of an open lung-biopsy specimen. (Our pathologist reviewed the tissue and reported "marked chronic interstitial pneumonitis and fibrosis compatible with Hamman-Rich syndrome.") After the biopsy, the patient was given dexamethasone, 0.75 mg twice each day. During the interval from the time of biopsy until she came to the Mayo Clinic, she was seen by her family physician for the urinary-tract complaints but had no follow-up examination for the pulmonary problem.

On examination at the Mayo Clinic, she complained of minimal cough but definite dyspnea with any exertion. Physical examination revealed inspiratory rales at the bases and anteriorly. The hemoglobin was 11.3 gm per 100 ml, and the white-cell count 7000, with a normal differential. Rheumatoid-factor and L.E.-cell clot tests were negative. An electrocardiogram showed an abnormal ventricular depolarization, with a questionable old anteroseptal infarction. The urine was normal, and 2 urine cultures were negative. A roentgenogram of the chest gave evidence of a bilateral diffuse process, most severe at the bases.

Complete pulmonary-function studies demonstrated a significant amount of restrictive disease.

The use of nitrofurantoin was stopped, but the dexamethasone therapy was continued. A follow-up letter 6 weeks later revealed that the patient's condition was improved and that she had less dyspnea with exertion. She has not returned for a follow-up roentgenogram or evaluation of pulmonary function.

CASE 2. A 62-year-old man was admitted to the hospital on June 28, 1967, with a history of febrile episodes 3 or 4 times each year during the past 4 years. The episodes became more frequent and were attributed to recurring urinary-tract infections, for which he was treated intermittently with nitrofurantoin. During the last year, the treatment with nitrofurantoin was on a continuous basis (averaging 100 to 200 mg per day) to prevent attacks. The patient had noticed increased shortness of breath during the past 6 months. One year before, a roentgenogram of the chest taken at another institution had shown no abnormality.

Results of physical examination were normal, except for decreased chest expansion and leathery crackling rales at both bases posteriorly.

Abnormal results of laboratory tests included an elevated sedimentation rate of 60 mm in 1 hour (Westergren method), pyuria of Grade 3 and a urine culture growing *Escherichia coli* and *Aerobacter aerogenes*. The gamma-globulin fraction

of the protein electrophoresis was elevated to 2.53 gm per 100 ml of serum. The lactic dehydrogenase enzyme level was elevated to 364 units per liter (normal, to 127 units per liter); the L.E.-cell clot test and the test for rheumatoid factor were negative.

A roentgenogram of the chest showed a diffuse interstitial process throughout both lungs. A smear of induced sputum revealed no acid-fast bacilli or fungi. Results of the tuberculin skin test, with the use of 5 and 250 tuberculin units, were negative.

Pulmonary-function tests showed a restrictive ventilatory disorder with an abnormal carbon monoxide diffusing capacity. An electrocardiogram disclosed a repolarization abnormality.

Transbronchoscopic lung biopsy revealed a mild interstitial pneumonitis, and a diagnosis of diffuse interstitial pneumonitis secondary to nitrofurantoin was made. Nitrofurantoin use was terminated, and the patient was treated with prednisone, 10 mg 3 times each day.

His condition had improved when he returned to our clinic 4 months later, and the dose of prednisone was reduced gradually to 5 mg twice a day. A roentgenogram of the chest on January 29, 1968, showed definite clearing, and pulmonary-function tests on the following day indicated improvement. The level of lactic dehydrogenase had decreased to 148 units per liter.

The patient returned on May 8, 1968, not having received steroid therapy for 6 weeks, X-ray study and tests of pulmonary function showed that the improvement had been maintained, and he was asymptomatic.

CASE 3. A 75-year-old housewife was admitted to the hospital on March 26, 1968, because of shortness of breath and dry cough of 7 weeks' duration. She had been admitted to another institution on February 19 because of shortness of breath and had received digitalis, without benefit.

She had taken nitrofurantoin intermittently for recurring urinary-tract infections since 1961. She had an average of 5 urinary-tract infections each year and took nitrofurantoin, 50 mg 4 times a day, for 2 or 3 weeks during each episode, until symptoms subsided.

Physical examination revealed an elderly woman who was cyanotic and moderately dyspneic. She had decreased chest expansion and leathery crackling rales at both bases of the lungs.

A roentgenogram of the chest showed diffuse interstitial fibrosis in both lungs. The urine was normal, but a urine culture grew more than 100,000 *Esch. coli* organisms per milliliter. An electrocardiogram revealed T-wave changes, with poor progression of the R wave in the precordial leads. The lactic dehydrogenase level was elevated to 251 units per liter. Results of routine laboratory tests were normal, and the L.E.-cell clot preparation and rheumatoid flocculation were negative. Electrophoresis demonstrated hypoalbuminemia. A smear of induced sputum was negative for acid-fast bacilli and fungi. Pulmonary-function tests showed a restrictive ventilatory abnormality and a severe decrease in the carbon monoxide diffusing capacity.

Transbronchoscopic lung biopsy revealed chronic inflammatory infiltration with focal interstitial fibrosis. Chronic interstitial pneumonitis secondary to nitrofurantoin was diagnosed.

On discharge, the patient was receiving digoxin, 0.25 mg daily, and prednisone, 5 mg 4 times a day. She was seen again 5 weeks later, when she had improved symptomatically. A roentgenogram of the chest indicated almost complete clearing, but the carbon monoxide diffusing capacity had shown little improvement.

CASE 4. A 70-year-old farmer had been seen at the Mayo Clinic on numerous occasions. In 1962, when a long history of genitourinary symptoms was evaluated, cystoscopic examination revealed an obstructive prostatic gland with a trabeculated bladder and a transitional-cell carcinoma of the bladder. Transurethral resection and excision and fulguration of the vesical neoplasm were carried out. Before operation, therapy with nitrofurantoin, 100 mg 4 times daily, was started.

Between October, 1962, and April, 1965, he was seen on 3 other occasions for re-examination of the urinary bladder and because of chronic dysuria and pyuria, for which he was accustomed to taking nitrofurantoin on an intermittent basis (averaging 100 mg per day). During this interval, mild dyspnea on exertion and a slight cough had developed. In February, 1965, an acute influenza-like illness

characterized by general malaise developed, but there was no fever and no worsening of the cough or dyspnea. Pneumonia was diagnosed by his physician on the basis of findings on a roentgenogram of the chest. The patient did not respond to routine antibiotic therapy. He was given a short course of corticosteroids, and his symptoms decreased in severity. He was seen again at our clinic in April, 1965, when a diffuse interstitial pulmonary process was noted. A previous roentgenogram of the chest taken at this clinic in April, 1964, had revealed no abnormality. During this time, he had continued to take nitrofurantoin.

Sputum cultures were negative for acid-fast bacilli and fungi. Tuberculin skin tests (5 and 250 tuberculin units) were negative. Results of routine laboratory tests were within normal limits.

The patient refused to undergo an open lung biopsy recommended for definitive diagnosis.

He returned on March 1, 1966, complaining of increased dyspnea and cough; in the interim he had continued to take nitrofurantoin because of intractable urinary symptoms. A roentgenogram (Fig. 1*A*) at this time revealed an increase in the diffuse pulmonary process, and pulmonary-function studies demonstrated a restrictive pattern, with impaired carbon monoxide diffusion. Subsequent transbronchoscopic lung biopsy showed moderate, chronic interstitial pneumonitis with slight fibrosis. Therapy with prednisone, 10 mg 4 times a day, was started, and the use of nitrofurantoin was discontinued.

A maintenance dose of 20 mg of prednisone a day was prescribed, and follow-up examination 6 weeks later revealed a dramatic improvement in the dyspnea. A roentgenogram of the chest (Fig. 1*B*) and pulmonary-function tests gave evidence of the improvement.

The patient died unexpectedly 4 weeks later; autopsy performed at another institution revealed findings of pulmonary fibrosis, mild bronchiectasis, bronchopneumonia of both lower lobes, cor pulmonale and atherosclerosis of the coronary arteries. A known sequel to pulmonary fibrosis is bronchiectasis, and we assume that this is the order of the cause-and-effect relation in this case; no abnormality had been noted on a roentgenogram taken 2 years before the onset of the present illness, and we assume that he did not have chronic bronchiectasis.

CASE 5. A 66-year-old housewife was seen at the Mayo Clinic on January 26, 1967, for evaluation of a 5-month history of progressive nonproductive cough, dyspnea on exertion and pain in the anterior part of the chest of gradual onset. There was no history of fever or chills. She had been receiving daily doses of nitrofurantoin for 15 months because of chronic recurrent urinary-tract infections. Examination revealed crackling rales at both lung bases and dyspnea on exertion. On x-ray examination there was evidence of a diffuse bilateral interstitial process (Fig. 2*A*) that had not been present on the last examination at our clinic in June, 1965.

Results of routine laboratory studies were normal. The lactic dehydrogenase level was 452 units per liter, and the L.E.-cell clot preparation revealed clumps of rosettes but no classic L.E. cells. The urine culture was positive for *Esch. coli*. Sputum studies did not disclose any acid-fast bacilli or fungi. Pulmonary-function studies showed abnormalities consistent with a restrictive pattern as well as an impairment of the carbon monoxide diffusion capacity. Transbronchoscopic lung biopsy indicated moderate chronic interstitial pneumonitis with fibrosis.

Therapy was started with prednisone, 10 mg 4 times a day, and the use of nitrofurantoin was discontinued. Follow-up evaluation 4 weeks later revealed definite improvement, with notable clearing of the diffuse process seen on the roentgenogram. The patient had been taking prednisone for 11 days at that time. Therapy was continued with smaller doses of prednisone for the next 7 months. When she returned to the Mayo Clinic 8 months after the initial examination, the roentgenogram of the chest showed no abnormality (Fig. 2*B*). The lactic dehydrogenase level had decreased from 452 initially to 163 units per liter, and the carbon monoxide diffusing capacity had increased from 9 to 14 ml per minute per millimeter of mercury.

DISCUSSION

Since Israel and Diamond (9) reported the first case of pulmonary nitrofurantoin reaction in 1962, all but two of the subsequent reports have dealt with the *acute* onset of pulmonary symptoms. Typically, in the acute onset, symptoms

FIGURE 1. Roentgenograms of the chest in Case 4, when Chronic Nitrofurantoin Pneumonitis was suspected, and a diffuse bilateral interstitial process was present (A), and 6 weeks later (B), showing a moderate decrease in the diffuse pulmonary process.

FIGURE 2. Roentgenograms of the chest in Case 5 on admission (A), showing a diffuse bilateral pulmonary process that is most severe at the bases (a Roentgenogram 18 months earlier did not show any abnormality) and 8 months later (B), showing almost complete clearing of the diffuse pulmonary process.

begin two hours to 10 days after the initial dose of the drug and consist of fever of acute onset, chills, cought and dyspnea. Sollaccio and his associates (20) were the first to point out that the pulmonary reaction can be delayed, occurring after the drug has been taken during a prolonged period (one year), and that the symptoms may persist for a "subacute" period (four weeks) without causing the patient to be acutely ill, as in the usual case. David et al., (21) from our clinic, have described a seven-year-old child with chronic pulmonary symptoms of one year's duration who had taken the drug for three years before the reaction developed.

Strauss and Griffin (11) summarized the eight cases reported up to 1967 and added two of their own. In all 10 cases, the onset of pulmonary symptoms was acute, beginning two hours to nine days after the initial dose of nitrofurantoin. Of the 10 patients, six were women, with an age range of 31 to 61 years. The pulmonary infiltrates were in the lower lobes and usually in both lower lobes. Three of the 10 patients had associated pleural effusion. Symptoms consisted of fever, cought and dyspnea, and all patients had symptoms that disappeared 24 to 48 hours after the use of the drug was discontinued. Four of the 10 patients had eosinophilia. In all cases the diagnosis was substantiated by the disappearance of symptoms and the rapid clearing of the roentgenographic findings after the use of the drug was discontinued. None of their patients underwent lung biopsy, but in most, a provocatory test was confirmatory. Steroids were not used.

The onset of pulmonary symptoms was gradual in the five patients discussed in this report. The duration of pulmonary symptoms varied from seven weeks to six years before the nitrofurantoin therapy was stopped. Only one patient (Case 2) had a history of febrile reaction associated with the onset or occurring during the course of the pulmonary symptoms, as has been characteristically present in patients with the acute-onset variety. The interval between the initial dose of nitrofurantoin and the onset of pulmonary symptoms ranged from six months to six years.

The five cases presented above suggest that nitrofurantoin can be taken for a prolonged time (six months to six years) before pulmonary side effects occur, and that pulmonary symptoms may be chronic (seven weeks to six years) rather than acute, which has been the most commonly recognized manifestation of nitrofurantoin pulmonary reaction.

In all cases the roentgenogram of the chest gave evidence of a nonspecific, diffuse, bilateral interstitial pulmonary infiltrate that frequently was most severe at the bases. Roentgenographically, the lung bases have also been most frequently involved in the cases of acute onset. Pleural effusion was not seen in any of our patients.

Pulmonary function was abnormal in all five patients and was typical of restrictive disease with an impairment of the carbon monoxide diffusing capacity. Two of the three patients who were retested showed great improvement. No patient had cosinophilia. The level of lactic dehydrogenase enzyme was elevated in the three patients tested. De-Remee (22) has reported that this test is a reliable indicator of active interstitial pulmonary disease and frequently correlates with the clinical course. The level of this enzyme, rechecked in the follow-up study of two of the three patients, correlated with improvement in the clinical course.

A transbronchoscopic lung biopsy (23) was done on four patients, and an open lung biopsy on the fifth. In all five patients, both types of biopsy revealed chronic interstitial pneumonitis or fibrosis or both. The histologic appearance was not diagnostic, and was not unlike that seen in idiopathic, chronic, diffuse interstitial pneumonitis.

All patients were traced, and four of the five had moderate to definite improvement after the use of nitrofurantoin was discontinued and after administration of steroids. Only one patient (Case 1) did not improve significantly after withdrawal of the nitrofurantoin. She had had pulmonary symptoms for six years, in contrast to the other four patients, who had pumonary symptoms for seven weeks to one and one-fourth years. A few months after the onset of the symptoms, She was seen at another institution, where chronic Hamman-Rich syndrome was diagnosed on the basis of an open lung biopsy. Therapy was started with steroids, but the nitrofurantoin dosage of 50 mg twice a day was continued (for a total of eight years). In a study of patients with chronic interstitial pneumonitis and fibrosis, Sheridan et al. (24) have shown that the degree of fibrosis present determines whether the condition can be reversed by steroids. The patient who does not improve with withdrawal of nitrofurantoin and with

treatment by corticosteroids probably has a considerable fibrosis and thus, predictably, is not likely to improve greatly. In the patients who improve, there appears to be a correlation between the duration of pulmonary symptoms and the amount of improvement. There does not appear to be any correlation between the length of time on nitrofurantoin therapy and the severity of the illness, or its reversibility.

Although pulmonary symptoms were present for only seven weeks in Case 3, the pulmonary infiltrate probably was present for a considerably longer time; the finding of fibrosis on biopsy of the lung usually implies that a process has been present for several months, but this is only conjecture. Also, because some of the measures of pulmonary function did not improve, this indicated that the process may have been going on for a long time.

The role of steroids in the improvement of the clinical condition in four of the patients is difficult to assess. These patients may have improved, although more slowly, without steroids and only by the withdrawal of the nitrofurantoin use, as is true in the acute onset variety. However, nitrofurantoin pulmonary reaction is a hypersensitivity reaction involving the interstitial tissue of the lung, for which prednisone therapy is probably indicated and may contribute to the prevention of irreversible pulmonary fibrosis. The exact nature of the apparent hypersensitivity phenomenon has not been established. Treatment should consist of terminating the use of the offending drug and of preventing irreversible fibrosis.

The diagnosis can be suspected from the history and physical examination when the roentgenogram of the chest gives evidence of diffuse interstitial infiltration. The only absolute way of establishing a diagnosis is by lung biopsy, as was carried out in our five patients.

Another method of diagnosing this condition is the provocative or rechallenge test (the first being to note improvement after withdrawal of the drug), but this was not done in any of the cases discussed here. It would be of interest to do this in the so-called chronic form of nitrofurantoin pulmonary reaction. However, the return of symptoms and abnormal pulmonary finding may be insidious and may produce further irreversible changes before they can be detected.

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APPENDIX III

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RENAL FAILURE AND INTERSTITIAL NEPHRITIS DUE TO PENICILLIN AND METHICILLIN*

(David S. Baldwin, M.D., Bernard B. Levine, M.D., Robert T. McCluskey, M.D., and Gloria R. Gallo, M.D.)

Abstract Nephropathy due to penicillin or methicillin was observed in seven patients. Maximum dosage ranged from 20 to 24 gm per day for methicillin and from 20,000,000 to 60,000,000 units for penicillin. Fever appeared in a minimum of eight days, associated with marked eosinophilia and rash (in four patients). Urinary abnormalities and azotemia (blood urea nitrogen of 50 to 130 mg per 100 ml) occurred in all. All but one recovered. Renal tissue, examined in four patients, showed tubular damage and interstitial accumulation of mononuclear cells and eosinophils without glomerular abnormalities or arteritis. In the only patient investigated immunologically an unusually intense immune response to penicillin was found. Immunofluorescent studies showed penicilloyl hapten firmly bound to his kidney tissue and the presence there of gamma globulin. The clinical features of an allergic reaction together with the immunologic findings support, but do not prove, a hypersensitivity mechanism for this nephropathy.

Since the introduction of penicillin G (benzylpenicillin) as an antibiotic, 15 cases of nephropathy have been ascribed to this drug. (1, 11) In general these reactions have been attributed to hypersensitivity, and in the few cases in which pathological material has been available, the kidney has shown the lesions of periarteritis with proliferative or necrotizing glomerulonephritis. In none of the reports, however, was there convincing evidence that the nephropathy was in fact due to penicillin therapy.

In contrast, the evidence for nephropathy due to methicillin (dimethoxyphenylpenicillin) appears to be well documented. Thirteen cases have been cited in the literature since 1961, (11, 17) and they were characterized by a rather typical clinical picture consisting of fever, rash and eosinophilia with hematuria, proteinuria and occasionally some degree of renal insufficiency; clinical recovery occurred in all. The pathological findings in the kidney have been reported in only 2

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NOTE.—Numbered references at end of article.

cases, (16, 17) and were described as showing severe interstitial nephritis; the glomeruli and blood vessels were described as normal.

During the past five years, we have observed seven patients in whom the clinical featurs of an allergic reaction associated with renal failure developed while they were receiving prolonged large doses of penicillin or methicillin. The renal disease subsided in in each when the antibiotic was discontinued, except for one, who died while administration of penicillin was continued. Pathological material, which was obtained for study in two of the patients who received penicillin and in two who were given methicillin, showed a characteristic type of interstitial nephritis without glomerulitis or arteritis. Immunologic studies were carried out in one patient, and the findings support the hypothesis that the renal lesion is due to hypersensitivity. The clinical features and pathological findings in these seven patients, and the immunologic observations in the one patient who was so investigated form the basis of this report.

MATERIALS AND METHODS

Immunofluorescent studies were carried out on renal tissue from one patient (L.C.). The biopsy specimen was submitted fresh in iced saline solution, and a portion was imbedded in gelatin, frozen and sectioned at 6 μ on a cryostat microtome; the tissue was fixed in Zenker's solution.

PREPARATION AND CONJUGATION OF ANTISERUMS

Rabbit antihuman gamma globulin was obtained by immunization of rabbits with purified gamma globulin. The antiserum was repeatedly absorbed and characterized as previously described. (18) Rabbit antiserum to human fibrinogen was prepared as previously described. Goat antiserum against human beta$_1$A-beta$_1$C components of complement was obtained from Hyland Laboratories. On immunoelectrophoresis it gave a single strong line against normal human serum.

Goat antiserums to IgG, IgM and IgA were obtained from Hyland Laboratories. On immunoelectrophoresis the anti IgC serum showed a single line to cord serum and a single line to normal human serum; the anti IgM showed a weak line to cord serum and a strong line to normal human serum, and the anti IgA showed no line to cord serum and a single line to normal human serum. The IgM antiserum was absorbed with cord serum until no line was seen by the Ouchterlony method against cord blood. The specific antiserum for the benzylpenicilloyl (BPO) haptenic group was prepared by primary immunization of rabbits with 5 mg of BPO-bovine gamma globulin conjugate (BPO_{35}-BGG) in complete Freund's adjuvant injected subcutaneously and three weeks later boosted by the intravenous injection of 5 mg of BPO_{35}-BGG. Bleedings were taken on the seventh, eighth and ninth days after the second injection. The serums from eight animals were pooled. Antidimethoxyphenylpenicillolyl antiserum was prepared by primary immunization of rabbits with 0.5 mg of DPO-bovine fibrinogen (DPO_{65}-BF) in Freund's adjuvant injected into the foot pads. One month later, the animals received boosters of 5 mg of DPO_{65}-BF injected intravenously, and were bled on the seventh, eighth and ninth days after the second injection. Serums from five animals were pooled. Antihapten antibody concentrations were determined by quantitative percipitin assays against multivalent penicilloylpolylysine conjugates. Anti-BPO antibody concentraton was 1.2, and anti-DPO antibody was 1.5 mg per milliliter of protein. The antiserums were fluoresceinated and purified by chromatography as described previously. (18)

PREPARATION OF UNIVALENT HAPTEN

Dimethoxyphenylpenicilloyl amylamine (DPO-amyl) was prepared by reaction of methicillin with 5 molar equivalents of n-amylamine in water at pH 11.5, at 25°C for 60 minutes. DPO-amylamine was precipitated from the reaction mixture at pH 3.7, gathered, washed and dried under vacuum. Reaction with parachloromercuribenzoate (PCMB) caused the expected development of a penamaldate absorption peak at λ max 285 m$\mu\epsilon$=23,500. Further preparative details are reported elsewhere. (19, 21)

RESULTS

CLINICAL AND PATHOLOGICAL OBSERVATIONS

The clinical features in seven patients in whom signs of nephropathy developed during methicillin or penicillin therapy are summarized in Table 1.

TABLE 1.—CLINICAL FEATURES IN 7 PATIENTS IN WHOM NEPHROPATHY DUE TO METHICILLIN OR PENICILLIN DEVELOPED

Patient	Sex	Age	Diagnosis	Drug	Dosage per day	Duration of drug treatment (days)	Fever	Rash (days) [2]	Eosinophilia [1]
S.F	Male	47	Staphylococcal sepsis	Methicillin	6 to 20 gm	40	37–42	None	33–59 (38)
L.C	do	37	Osteomyelitis	do	24 gm	32	13–23	None	22–40 (25)
W.K	do	79	Staphylococcal sepsis	do	6 to 24 gm	44	31–37	44–51	26–50 (14)
A.J	Female	57	Bacterial endocarditis	do	4 to 6 gm	19	13–24	None	13–24 (13)
				Penicillin	20,000,000 units	17			
O.O	Male	54	do	do	12,000,000 to 20,000,000 units	16	8–20	16–20	22–31 (5)
M.L	Female	57	do	do	30,000,000 units	42	21–27	30–35	23 (26)
F.H	do	70	do	do	40,000,000 to 60,000,000 units	41	22–29	11–20	13–64 (44)

Patient	Proteinuria	Hematuria (days) [2]	Pyuria (days) [2]	Azotemia [3]	Outcome	Pathological findings	Other findings
S. F	18–29	18–33	26–33	14–48 (74 mg/100 ml)	Recovery	Interstitial nephritis (on 53d day)	Gross hematuria; defective concerntration acidosis.
L. C	18–32	18–32	18–32	29–40 (80 mg/100 ml)	do	Interstitial nephritis (on 35th day)	Defective concentration; acidosis; anemia.
W. K	34–73	35–42	None	36–71 (101 mg/100 ml)	do	(4)	Gross hematuria; defective concentration; acidosis.
A. J	16–20	16–20	16–20	24–48 (50 mg/100 ml)	do	(4)	Defective concentration; acidosis.
O. O	8–24	7–24	None	9–34 (130 mg/100 ml)	do	Interstitial nephritis (on 29th day)	Gross hematuria; defective concentration.
M. L	32	32	34	32 (120 mg/100 ml)	Death (on 42th day)	Interstitial nephritis (on 42d day)	Acidosis; oliguria.
F. H	30–46	34–46	32–46	38–77 (75 mg/100 ml)	Recovery	(4)	Gross hematuria; defective concentration; acidosis; anemia.

[1] Peak eosinophil counts in parentheses.
[2] Elapsed time from start of antibiotic treatment.
[3] Peak blood urea nitrogen values in parentheses.
[4] No biopsy.

The first three patients listed in Table 1 (S.F., L.C. and W.K.) were receiving methicillin in doses of 6 to 24 gm per day; the fourth (A.J.) was given penicillin, 20,000,000 units per day, in addition to methicillin, 4 to 6 gm per day, and the last three (O.O., M.L. and F.H.) received penicillin 12,000,000 to 60,000,000 units per day. The underlying infection for which the antibiotic was being given was staphylococcal sepsis in two patients receiving methicillin, and osteomyelitis in the third. A.J., who was given both penicillin and methicillin, was being treated for presumed bacterial endocarditis without the isolation of an organism. The three patients who received penicillin were being treated for bacterial endocarditis, caused by *Streptococcus viridans* in O.O. and F.H. and by neisseria in M.L.

In each patient the fever associated with the underlying infection had subsided within a few days of the start of treatment, only to recur after a variable period, which ranged from eight to 44 days. In four cases the fever was preceded or followed shortly by a morbilliform rash, and in all seven eosinophilia occurred being marked in six. Urinary abnormalities and azotemia appeared eight to 36 days after the institution of antibiotic therapy, following the recurrence of fever by a few days in six of the seven patients, and preceding the fever by almost three weeks in the seventh (S.F.). Hematuria occurred in all patients, minimal to moderate proteinuria in all, and pyuria in five of the seven. Blood urea nitrogen increased in all patients, the maximum level in individual patients ranging from 50 to 130 mg per 100 ml. The duration of urinary abnormalties was as short as four days and as long as 39 days, whereas the period of renal insufficiency was usually somewhat longer. Impairment of urinary concentrating ability and metabolic acidosis occurred in six patients. In four patients, acidosis persisted beyond the time that the blood urea nitrogen and urinary abnormalities had returned to normal.

Recovery, as judged by clearing of urinary abnormalities and return of blood urea nitrogen to normal levels, ensued in six of the seven patients. The interval between the appearance of urinary abnormalities and the discontinuation of penicillin or methicillin varied between three and 32 days, and recovery then followed within five weeks. However, in S.F. (Fig. 1) the urinary abnormalities subsided while methicillin was still being given, although the blood urea nitrogen did not return to normal until eight days after the drug was discontinued. In the single patient who died (M.L.) fever developed on the twenty-first, eosinophilia on the twenty-third, and rash on the thirtieth day of penicillin therapy, followed by seizures, coma, urinary, abnormalities and progressive renal insufficiency, with death occurring on the forty-second day. Penicillin was continued throughout this period. Urinary output was less than 300 ml on the last three days of life; this was the only case in which significant oliguria was observed.

Renal biopsies were obtained in S.F. and L.C., who manifested nephropathy to methicillin, and in O.O., who received penicillin. In addition, post-mortem material was available for study in M.L., who had been given penicillin. The lesions were characterized by irregular interstitial accumulation of leukocytes and by tubular damage (Fig. 2 and 3).

The infiltrate contained large numbers of mononuclear cells and eosinophils. Most of the mononuclear cells appeared to be large or small lymphocytes, although a few typical macrophages were present. In most areas mononuclear cells predominated, and in a few places eosinophils were absent. Few neutrophils were seen, and they were generally in direct association with necrotic tubules. No plasma cells were found. Tubular damage and intertitial edema were observed in association with the leukocyte accumulation; the damage was manifested by changes ranging from slight distortion of cells to destruction of a portion or the entire cross-section of the tubule. Many of the damaged tubules contained amorphous or fibrillar eosinophilic casts as well as desquamated epithelial cells and neutrophils. In most cases the affected segment of tubule could not be identified, but all levels appeared to be involved. Necrosis was conspicuous in two of the four cases. Regenerating tubular epithelium was also found in areas. The lesions were irregularly distributed; in the case studied at autopsy, they were seen to be predominantly in the cortex, although a few were present in the medulla. Most of the glomeruli appeared normal, but in one patient (L.C.), a few showed equivocal increase in neutrophils. The blood vessels appeared normal. In M.L., who was studied at autopsy, arteritis was found in the kidneys or in other organs.

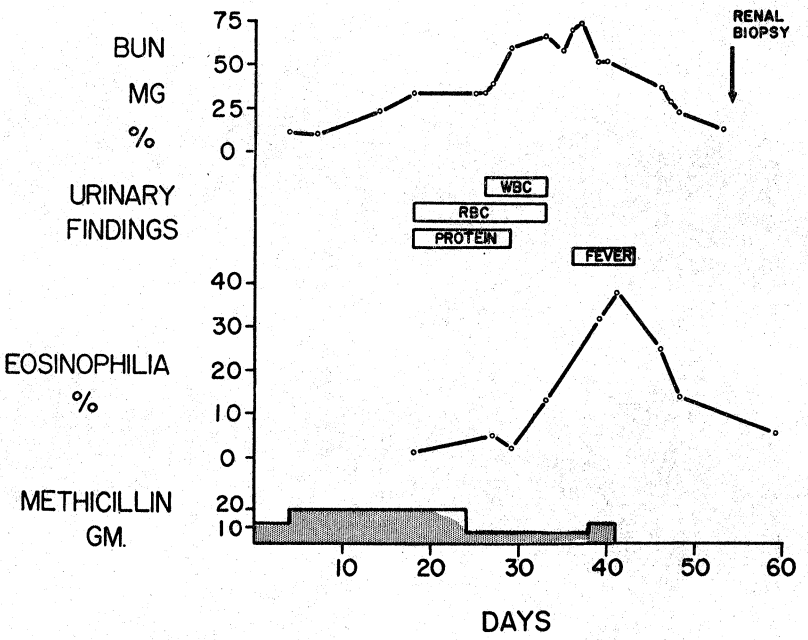


FIGURE 1. *Clinical Course in S.F., a 47-Year-Old Man in Whom Nephropathy Followed Methicillin Therapy for a Scrotal Abscess and* Staphylococcus aureus *Septicemia.*

IMMUNOLOGIC OBSERVATIONS

Immunologic studies were carried out in one patient (L.C.). His serum assays for benzylpenicilloyl-specific antibodies were done by passive hemagglutination. (22, 23) Serums obtained seven and fourteen days after methicillin therapy was discontinued both showed a titer of 1:1600. After treatment with mercaptoethanol the titers were 1:640, indicating the presence of both IgM antibodies (mercaptoethanol sensitive) and IgG antibodies, mercaptoethanol resistant), (22, 23) Direct skin tests (21) for skin-sensitizing antibody with 10^{-6}M penicilloyl-polylysine were positive when tested 40 days after methicillin had been discontinued. Tests with dimethoxyphenyl-penicilloyl-polylysine (the methicillin homologue) were negative. Delayed skin tests (24) 14 days after methicillin was discontinued were positive with 0.1 M methicillin and negative with 0.1 M penicillin.

IMMUNOFLUORESCENT OBSERVATIONS

In the first experiments an attempt was made to determine whether dimethoxyphenylpenicilloyl (DPO) haptenic groups, the major haptenic antigenic determinant of methicillin, were present in the kidney sections. It is known that methicillin can react with protein to yield hapten protein conjugates in which DPO is bound covalently to lysine epsilon amino residues. (25) Sections of kidney were treated with fluorescein-conjugated rabbit anti-DPO antiserum. Figure 4 shows that intense staining was seen in a well defined, continuous linear pattern outlining glomerular basement membranes and to a lesser extent tubular basement membranes, as well as in tubular epithelium and the interstitium. That this staining was specific for the DPO hapten group was indicated by two kinds of controls; renal biopsies from patients with acute glomerulonephritis,

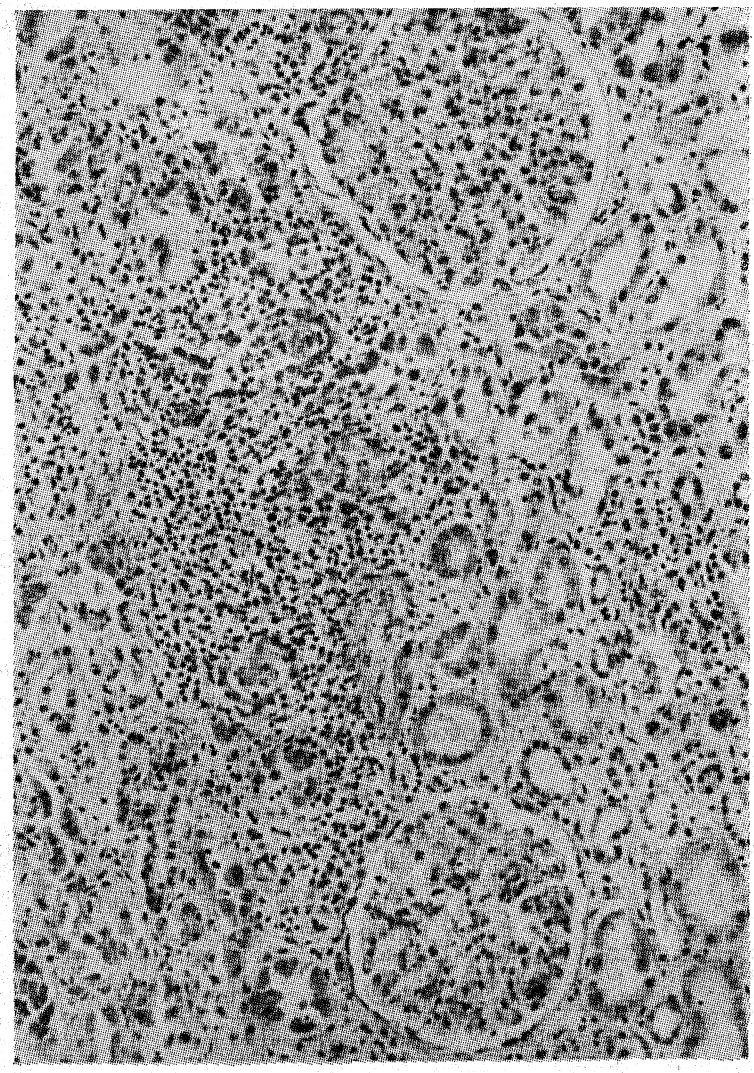


FIGURE 2. *Section of Renal Cortical Tissue from M.L. (Hematoxylin and Eosin Stain).*

Irregular interstitial leukocytic infiltration and edema are seen with necrosis of some of the tubules. The glomeruli appear normal.

lipoid nephrosis, lupus nephritis and sections from normal kidneys obtained at autopsy did not stain with this serum; and addition of the univalent hapten, DPO-amylamine, at a final concentration of 10^{-2}M to the fluorescein-conjugated anti-DPO antiserum completely inhibited the staining. Inhibition was specific since the same concentration of DPO-amylamine did not inhibit fluorescent staining by the antiglobulin serum. The kidney section stained very faintly

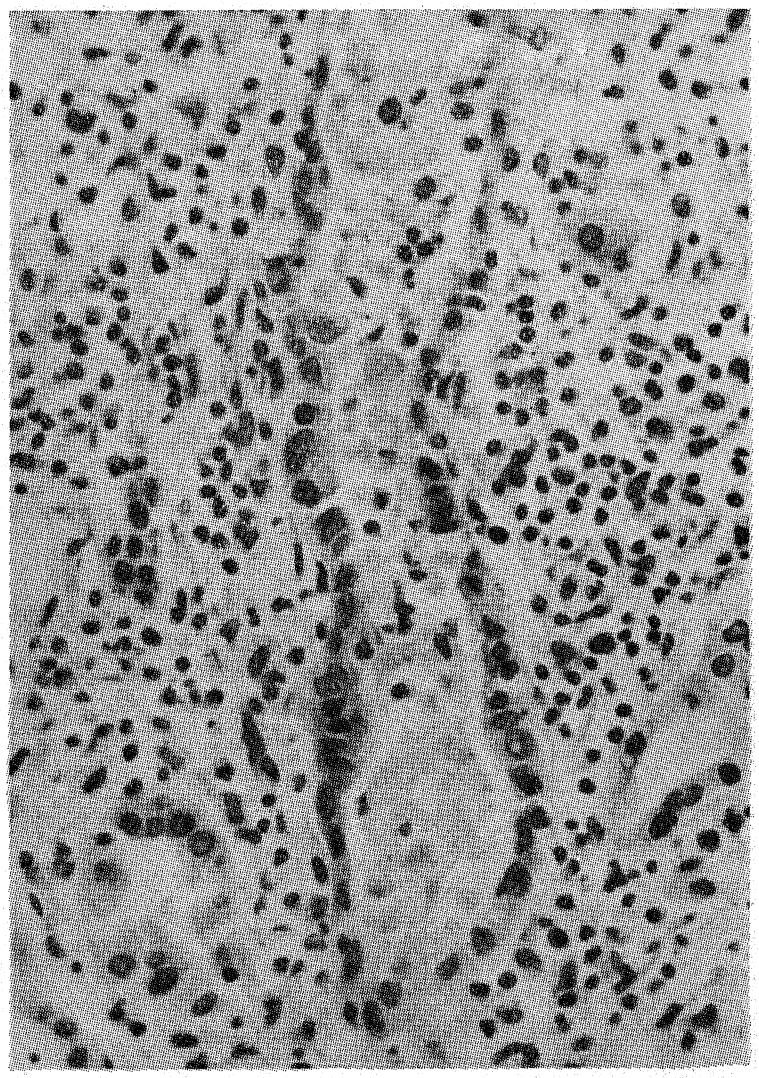


FIGURE 3. *Interstitial Accumulation of Leukocytes in Biopsy of M.L.*

Most of the leukocytes are mononuclear cells although numerous eosinophils are also seen. The tubule shows various degenerative changes and several areas of necrosis.

with antibenzylpenicilloyl serum. Thus, the presence of DPO haptenic groups was demonstrated in the kidney.

Whether the DPO groups were coupled directly to the kidney structural protein or whether they were present as part of soluble antigen-antibody complexes

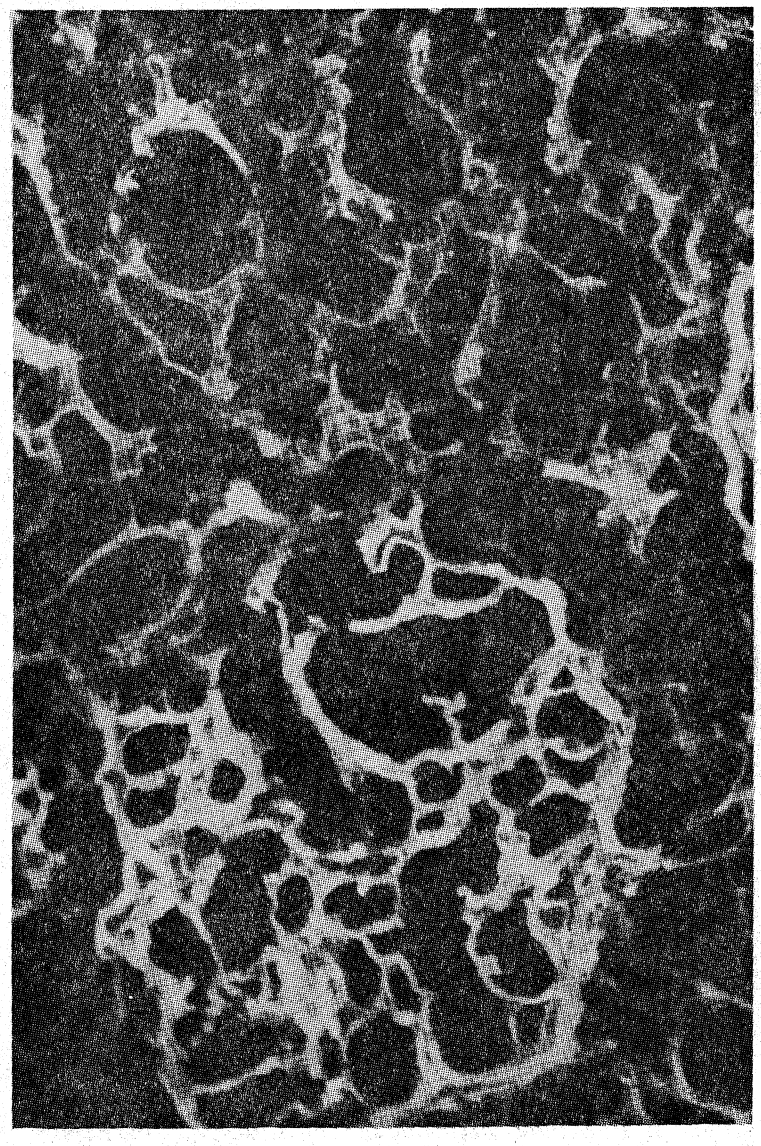


FIGURE 4. *Frozen Section of Renal Biopsy of L.C. Stained with Fluorescein-Conjugated DPO Antiserum.*

Bright, smooth staining is seen outlining glomerular (on the right) and tubular basement membranes.

deposited in the kidney was investigated in the next experiments. If the DPO hapten were part of deposited complexes, extensive washing of the sections with univalent penicilloyl hapten would be expected to dissolve these complexes, thus

reducing or preventing subsequent staining of the sections with fluorescein-conjugated anti-DPO serum. Accordingly, the sections were washed six times with BPO-propylamine or with DPO-amylamine 2×10^{-2}M, washed thoroughly with saline solution and then stained with the fluorescein-conjugated anti-DPO antiserum. No reduction in staining with the anti-DPO serum was seen. On the contrary, staining of glomerular and tubular basement membranes appeared to be enhanced. The staining in areas of tubular necrosis was markedly enhanced; in these areas, clusters of brightly stained droplets appeared that were not evident in sections that were not first washed with hapten. These findings indicate that the DPO hapten detected was bound to kidney structural proteins rather than being part of a deposited antigen-antibody complex. The enhancement of staining produced by washing with hapten may have been due to specific elution of antibody, which would make more DPO haptenic sites available to bind the fluorescein-conjugated anti-DPO antiserum. This enhancement did not appear to be due to binding of DPO-amylamine by the tissue, since treatment of sections from other kidney diseases in the same fashion did not cause staining with the anti-DPO serum.

Sections were also stained for IgM, IgG, IgA, fibrinogen and complement ($beta_1A$-$beta_1C$). IgC was seen in a pattern similar to that observed for DPO hapten, whereas no staining was seen for IgA, IgM, complement or fibrinogen. Gamma-globulin staining appeared to be specific, since the antiserum did not stain normal kidney, and specific staining was obliterated by absorption of the antiserum with purified gamma globulin. Whether or not the gamma globulin was antipenicilloyl antibody could not be determined.

Discussion

The sequence of events in the seven cases included in the present report leaves little doubt that in each the nephropathy could be attributed either to methicillin or to penicillin therapy. The clinical picture was remarkably similar in the seven patients, and in all, high doses of the drug were used for relatively long periods. The histologic findings were principally interstitial nephritis and tubular damage. Arteritis or glomerular lesions were not seen by light microscopy. Similar pathological findings have been described as manifestations of methicillin reactions in two reports (16, 17) and of a penicillin reaction in one patient who had also received, sulfonamide and died with sepsis. (2) In addition, several cases of interstitial nephritis due to drugs have been reported in association with phenindione (26, 27) and sulfonamide therapy. (28, 29) Although we and others have referred to the lesion as interstitial nephritis, tubular damage was present as well, and it is not clear whether the initial event occurs in the tubules, the tubular basement membrane or the renal interstitium.

The pathogenesis of the nephropathy that occurs with methicillin or penicillin is unknown, but several considerations indicate that the lesions result from hypersensitivity. In the first place, in our patients a syndrome characterized by fever, rash and eosinophilia, which is generally accepted as evidence of an allergic reaction, developed. Secondly, only a small number of patients receiving methicillin or penicillin, even in very large amounts, have such a reaction, suggesting that it is not due to direct toxicity of the drug. Thirdly, DPO hapten (derived from methicillin) and gamma globulin were found in the kidney of the one patient studied by immunofluorescence (L.C.). Fourthly, the same patient, whose antibody response to penicillin was investigated, was found to have an unusually intense immune response, characterized by a high IgM titer, the presence of IgG and skin-sensitizing antibodies against penicilloyl determinants, as well as by delayed hypersensitivity. This kind of immune response is rarely observed in patients treated with penicillin without an allergic reaction. (24, 30) The IgG, IgM and skin-sensitizing antibody were shown to be specific for the benzylpenicilloyl group rather than the dimethoxyphenylpenicilloyl group. (31) The observation that serum antibodies specific for the benzylpenicilloyl group rather than for the dimethoxyphenylpenicilloyl group were stimulated by methicillin may be due to an anamnestic immune response, because he had been treated with benzylpenicillin three years previously. (31) The delayed hypersensitivity, however, appeared to be specific for methicillin rather than for penicillin, as indicated by the results of delayed skin tests to these drugs. Delayed hypersensitivity may thus represent a primary immune response.

These considerations favor a hypersensitivity basis for the renal lesions. How-

ever, conclusive evidence is lacking, and probably could not be obtained without a suitable experimental model, which is not available at present.

If one provisionally accepts the interpretation that the renal lesions result from hypersensitivity, it remains to be determined what the underlying pathogenic mechanisms are, and why this reaction occurs in only a small percentage of the many patients receiving these drugs. Two general possibilities can be considered: in patients receiving large amounts of methicillin or penicillin, derivatives such as penicilloyl hapten may normally couple with structural renal proteins, and the damaging immune reaction may depend primarily upon an unusual immune response; or, alternatively, it may be considered that the patients in whom nephropathy develops, in contrast to the vast majority of persons, are uniquely capable of forming these hapten-kidney conjugates from the penicillins. The first explanation seems more likely, since penicillins are known to be chemically reactive with a wide variety of proteins. However, the data do not permit a definite decision. We have no immunofluorescent observations of renal tissue from patients given large amounts of methicillin or penicillin in whom interstitial nephritis has not developed. Such observations would provide information concerning this problem.

The question of the type of immunologic mechanism responsible for the damage remains. Despite the presence of gamma globulin (presumably specific antibody) and hapten in the lesions of the patient studied by immunofluorescence, several considerations indicate that the renal damage may not be initiated by antigen-antibody interaction. First of all, complement ($beta_1A$-$beta_1C$) was not detectable in association with the gamma globulin and hapten. Secondly, although gamma globulin and hapten were present in glomeruli, glomerular abnormalities were not apparent; since it is well established that glomerular damage is readily brought about by antigen-antibody complexes, (32) it seems likely that the type of complexes present in this patient were not tissue damaging (possibly because complement was not fixed). Finally, the histologic character of the lesion, with a predominantly mononuclear cell infiltrate, suggests the possibility that the damage was due to delayed hypersensitivity.* This possibility is further supported by the observation that the patient exhibited delayed sensitivity to methicillin.

Dosage of drug appears to have a role in the nephropathic reaction since the patients receiving methicillin were given a maximum dosage of 20 to 24 gm per day except for one patient (A.J.), who received only 6 gm per day. However, this patient was also receiving penicillin in a daily dosage of 20,000,000 units, and the other three in whom nephrotoxicity developed during penicillin therapy were receiving up to 20,000,000, 30,000,000 and 60,000,000 units per day. Furthermore, the shortest interval between the initiation of therapy and the appearance of urinary abnormalities was eight days, with a range between 16 and 34 days in the other six patients. Thus, it appears that high doses of drug for prolonged periods are more likely to produce nephropathy. At lower dosages of penicillin or methicillin the extraction by the kidney is almost complete, leaving little or none of these materials in the peritubular capillaries or interstitial fluid beyond the proximal tubules. At higher blood concentrations, the rate of transport by the proximal tubules increases, but extraction is incomplete, resulting in greater concentrations of drug in the blood leaving the proximal peritubular capillaries and in the interstitium. It sems likely that the increased rate of tubular transport and the increased concentrations of drug in peritubular capillaries and interstitial fluid that exist during administration of large doses have some effect on the occurrence of nephropathy. Since equivalent doses are frequently administered without any clinical evidence of renal damage, it is obvious that dosage is not the only factor responsible for nephropathy, and it is likely that the kind of immune response made to the drug is the critical feature.

The mechanism responsible for the marked azotemia that occurred in each of our patients is not clear. The absence of glomerular abnormalities and the consistent finding of interstitial inflammation and tubular damage might lead one to postulate that the reduction in glomerular filtration was due, at least in part, to increased interstitial pressure opposing filtration. Additional hemodynamic alterations other than those attributable to increased interstitial pressure, or perhaps tubular back diffusion, might also be involved. The impairment of urinary concentrating ability and the presence of striking metabolic acidosis even

*The question could be raised why a delayed sensitivity reaction did not occur in the glomeruli. Although the reason is not known, it can be stated that there is no experimental evidence that it is possible to produce a delayed reaction in glomeruli.

beyond the period of azotemia suggest the occurence of distal tubular dysfunction as well as glomerular insufficiency.

Hematuria, which was gross in four of the seven patients, pyuria and proteinuria occurred consistently. Although it is possible for these to be glomerular in origin without demonstrable structural glomerular abnormalities, it seems more likely that these urinary findings arose from damaged tubules.

Thirteen other cases of nephropathy to methicillin have been reported in the literature. (11, 17) The clinical picture of fever, often with skin rash and eosinophilia, as observed in the present series, was also typical of the previously reported cases. Hematuria was observed in all, and in nine of the 13 patients was gross. In six of the 10 cases in which such data are given there was an increase in blood urea nitrogen or serum creatinine. All patients appear to have recovered, although in two serum creatinine was still elevated at the time of last observation. The pathological findings are described in two patients, both of whom showed interstitial nephritis without glomerular abnormalities. (16, 17).

The clinical and pathological features of alleged nephropathy to penicillin as previously reported in the literature (1, 11) differ greatly from what has been reported to follow methicillin, and from what we have observed after either methicillin or penicillin. The dosage of penicillin has been relatively low, in no case more than 1,200,000 units per day, and the evidence of nephropathy has appeared promptly, usually on the second day and occasionally a few days later. Although skin rash is cited in most cases as evidence for a hypersensitivity reaction, eosinophilia and fever have been noted only rarely. The clinical and pathological features of the renal disease have varied widely among the 15 cases reported. Two groups seem to predominate. In one group of five patients the findings were characterized by periarteritis and glomerulonephritis, either diffuse or focal necrotizing in type. In another group of five patients acute renal failure and anuria developed in association with infection. All the five patients in this second group underwent diuresis and survived; no pathological data are available. Two other patients had antecedent renal disease, and two showed the clinical picture of Henoch-Schönlein's syndrome and have had persistent evidence of renal disease.

The evidence supporting a causal role of penicillin in these cases of nephropathy cited in the literature is not conclusive. The patients, mostly children, in whom acute renal insufficiency with oliguria followed a single injection of penicillin may have been suffering from renal failure due to circulatory failure and sepsis, or perhaps from acute diffuse glomerulonephritis. The pathological findings in the kidneys have not been reported in any of them. The patients with periarteritis and glomerulonephritis or with Henoch-Schönlein's syndrome (presumably with a form of glomerulonephritis) who have received penicillin may be suffering from a reaction to the drug, but the apparent relation could be coincidental, since either of these conditions can occur in the absence of any penicillin administration. In fact, it seems likely that in some cases the clinical features for which penicillin was given were those of already existing periateritis or glomerulonephritis. In any event, if periarteritis or glomerulonephritis can, in fact, represent manifestations of hypersensitivity to penicillin, the mechanism appears to differ from that responsible for the occurrence of interstitial nephritis as reported here. It must be concluded that the lesions commonly accepted as evidence of a hypersensitivity reaction—that is, arteritis and glomerulitis—are much less firmly established than interstitial nephritis as manifestations of penicillin hypersensitivity.

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APPENDIX IV

STATEMENT OF DR. DONOVAN F. WARD, PRACTICING PHYSICIAN, DUBUQUE, IOWA

Mr. Chairman, I am Donovan F. Ward, a practicing physician, of Dubuque, Iowa, and I appreciate this opportunity to offer my views on questions regarding the prescribing of drugs, which have been raised before your Committee since May 15, 1967.

A considerable store of technical and scientific testimony has been adduced in the course of this inquiry. This is as it should be, of course. You must have scientific explanations for vastly complicated scientific questions if you are to begin to resolve differences in statements and claims which stud the record—not only of this hearing—but also that of the public controversy over drug prices and the relative efficacy of drug products.

But there are other considerations, too, and that is why I asked for an opportunity to testify. I would like to discuss for a few minutes the subject of drugs from the standpoint of the physician who prescribes them, and who, alone, is responsible to his patient for their effects. It is, after all, the delivery of the care most likely to meet a particular illness situation that is the urgent and immediate concern of the physician at his patient's bedside.

At that moment—and I cannot overstate this point—the physician *must know* what he is prescribing, what it does and where it came from. He must have every freedom to select those medicines which he knows are of the highest quality and which his experience tells him will produce the best results.

Frankly, my apprehensions have been aroused by statements and proposals, which are becoming increasingly familiar—and a good many of which have been heard here—that seem to discount the importance of that freedom, or appear designed to take it away altogether.

Let me, at this point, provide some brief biographical information. I am a graduate of the University of Iowa College of Medicine, Class of 1930. I have practiced medicine and surgery in Dubuque since 1931, interrupted only by years spent in additional professional training and war service, 1942–1946, in the U.S. Navy Medical Corps.

In 1964 and 1965, I was president-elect and president of the American Medical Association. Over the years, I have also served on a number of AMA councils and committees, including the Joint Council to Improve Health Care of the Aged, of which I was director from 1963 to 1965, the Committee on Medical Practices, the Committee on Medical Education and Hospitals and the special AMA Advisory Committee to the Department of Health, Education and Welfare; at present, a member of the AMA Council on Legislative Activities and medical advisor on the Advisory Board to the Bureau of Veterinary Medicine under the F.D.A.

I am a Fellow of the American College of Surgeons and of the International College of Surgeons and a past president of the Iowa Clinical Surgical Society. I am presently serving as senior surgeon at The Finley and Mercy Hospitals in Dubuque and consulting surgeon at Xavier Hospital. Since 1956, I have been the U.S. Public Health Service Designated Physician in Dubuque and since 1962, the F.E.C.A. Designated Physician. From 1950 to 1965, I was the Dubuque County Designated Health Officer.

I am a member of the Iowa Division of the American Cancer Society, was co-editor of its early manuals, and have served on its Professional Education Committee since 1952. More than a dozen papers and articles, which I have written on medical and surgical problems, have been published in professional journals.

As I have indicated, Mr. Chairman, I do not represent any organization or group. Rather, I am submitting this statement as an individual who has had the good fortune to participate in an era of unparalleled medical and scientific advances and who sincerely believes that this progress may be retarded or halted by the emotionally-charged actions which are being urged.

There is far more involved in your hearings than criticism of the drug industry's merchandising and pricing policies, although I will say that if the industry is made the victim of some kind of restrictive legislation, its ability to contribute to medical progress cannot fail to suffer—and the patient will be the ultimate loser. Also at stake here is the threat of scientific truths being submerged and lost in a raging national debate over socio-economic questions

with strong political overtones. In jeopardy, too, is the historic right of the physician to prescribe the precise treatment for his patient which he believes to be the most suitable in each instance, based on his professional knowledge. *This is the point of deepest concern to me.*

Under the American system of medical care, the physician *alone* arrives at a diagnosis and he *alone* should decide what medicine is to be administered to his patient. This is a vital part of the physician's professional responsibility and it cannot be delegated without endangering the quality of the care each individual receives.

Much has been said before this Subcommittee about the so-called "therapeutic equivalence" of drugs—regardless of who produces them—if they contain the same active ingredient and meet U.S.P. or N.F. standards. The argument is made that products sold under their generic names are generally cheaper than those bearing the brand name of a particular manufacturer; hence, patients would save money if their physicians would only prescribe by generic names.

The popular appeal of this approach is undeniable. If a less expensive drug will accomplish as much, why pay for the higher-priced one? I would like to answer that by stating categorically, on the basis of some 36 years in the practice of medicine, that the argument is fallacious on its face. There are no such things as identical or equivalent drug products, which can be depended upon to have the same effects on all patients under all conditions—any more than there are identical or equivalent patients, who can be counted on to react the same to the same product under the particular condition of their illnesses.

I am sure I do not have to take your time to discuss the many variables existing among drug products, from different manufacturers, even though they bear the same generic name. In previous testimony, you have heard of the differences in manufacturing processes. You are aware, from the hearing record, that substances such as binders, excipients or lubricants added to the active ingredient by one producer may be omitted or unlike those used by another producer. The active ingredient itself may vary in important respects—degree of fineness, crystalline state, etc., even assuming compliance with standards set forth in the specifications for the drug product in the official compendia.

Each of these differences can have significant effects in the treatment of illness. As a physician, I know—I have learned—that individual patients react differently to same treatment. The physician's task is to find the most effective medicine to meet the situation with which he is confronted. And I believe it must be accepted that the judgment of the therapeutic results of a medicine can only be made by the physician in cooperation with his patient. Thus, it follows, the patient's interests will best be served under a system which continues to permit the physician to specify those pharmaceutical products which the physician knows are of the highest quality and which his experience tells him will most effectively meet the patient's individual needs.

Most of us prescribe by specifying the brand name of the desired drug or by selecting the product of a particular manufacturer. From time immemorial, this has been our means for making sure our patients get their medicines from sources we can trust.

Under legislation, which would require—by direct or indirect means—the prescribing of drugs by their generic names, the physician would lose the control over the medicines he designates for his patient, and the patient would lose this safeguard over the quality of medicines he receives.

We know that substandard drugs are being marketed every day. These are often sold under their generic names. We cannot be certain who produced them or under what conditions. They may or may not give consistent therapeutic results. Yet, one of these questionable products, of indeterminate origin, could be used to fill a generic prescription. I cannot imagine a member of my profession, who would willingly gamble with his patient's health in this fashion.

I do not, for a moment, assert or imply that all generic-named products are inferior to brand-name products. To the contrary, there are excellent generic-named products on the market. Many quality drugs have no brand names. Many of these are produced and sold under generic names by ethical drug houses that also manufacture brand-name drugs. The fact remains that unless the product (whether marketed under generic or brand name) is made by a reputable and qualified manufacturer, there is absolutely no way to tell which is good and which is poor before it is used, without access to analytical and biological laboratory facilities more elaborate than most physicians, pharmacists and hospitals are likely to possess.

There is another point I would make here. When the treatment is long-term, several refills of the same prescription probably will be required. Under a prescription, specifying the drug by name or by the name of its manufacturer, each new supply would have the same variables as the one before—coating, base, solubility, disintegration time, etc.—and could reasonably be expected to produce the same response from the patient. But, with a generic prescription, the refills could come from products of different manufacturers with different production methods and different quality standards, depending on whose products the pharmacist might have on hand when the refill was ordered. There could be, in this situation, changes in therapeutic response, which might mislead the physician in his diagnosis or alter the patient's progress. The effect simply would be to deprive the physician of a margin of control over this patient's treatment.

It may be that in certain instances and with certain drugs, there is no significant therapeutic difference among competing products. Indeed, they may have all been checked and found reliable. Moreover, I am aware of no limitation existing at the present time which prevents a physician from prescribing generically, if he so desires. I do myself, on occasion when I feel it is compatible with the best interests of my patient. But, if there is the slightest question in my mind, I prescribe only those pharmaceutical products with which I am familiar. If a pharmacist wishes to use another preparation, he would have to assure me that the product he was recommending measured up to very rigorous criteria. And, unless I had confidence in the pharmacist, and unless he in turn could assure me of his faith in the integrity of the manufacturer, I doubt that I'd permit my choice to be altered.

Chances should not be taken with any drug; they absolutely cannot be taken in the area of critical drugs. When, for example, I prescribe digitalis or nitroglycerin for my heart patients, I must know—beyond any doubt—the precise medicine that is being administered. Therefore, in every case, I will specify a product of demonstrated reliability, manufactured by a firm whose reputation I know and whose products I trust. There can be *no* other way. The range between a therapeutic dose and a toxic dose is too narrow for me to be able to sleep nights if I thought my prescription were being filled from a bottle bearing simply the generic label of an unknown or unfamiliar manufacturer or repackaging firm.

I would have nothing on which to base an evaluation of the medicine; of the care with which the raw materials were selected; of the quality controls exercised during production; of how products from the same manufacturer have performed in the past under given conditions; of what the manufacturer's reputation is for marketing drugs of proven potency, purity and safety. Indeed, if the drug has passed through the hands of a repackager and jobber, I have no way of knowing who the manufacturer is, and neither does the pharmacist in this situation.

The dispenser is obliged to use reasonable care in selecting a drug and no one doubts that 999 out of 1,000 do. But, under the conditions I have outlined, this is meaningless. An experienced salesman can separate quality from trash in such commodities as clothing on the basis of the feel of the material, the skill of the cutter, the fineness of the stitch. What can the pharmacist do? Look at the pills or capsules? There is hardly a clue here, since even the most vilely impure drug may look completely normal and pure. The pharmacist has neither the time nor the equipment to establish the potency and purity of medicine cloaked behind the anomymity of the generic name of its active ingredient.

An altogether different situation exists when the medicine bears the trademark identification of a reliable manufacturer, or, if packaged under its generic name, is identified as the product of a reliable manufacturer. For all of us—the physician, the pharmacist, the nurse—this has to be our most practical measure of trust. We know that the makers of quality drugs stake their reputations on, and are answerable for, the integrity of medicines carrying their names.

For very simple and direct economic reasons they cannot afford to be linked with shoddy merchandise. They have invested great amounts of effort and money in gaining their position in the drug field. With greater folly could there be than for them to risk it all through the distribution of even one or two inferior products? How long could they hope to remain pre-eminent in the eyes of the medical profession?

In our competitive system, this is the patient's strongest safeguard, far more effective than any government policing efforts could provide for an industry as fragmented and scattered as is the pharmaceutical industry. It is also my greatest assurance, as a physician, that my prescription is being filled with a medicine of high quality, which is exactly the same as a medicine I have used in the past under similar circumstances and found to be effective.

As far as I am concerned, I will state quite candidly that when a manufacturer fails me the first time—and I don't care how renown he may be—it is the last time. The drug industry is fundamentally a supplier of a service to the medical profession. Such has been its historic and highly-useful role. I am as critically concerned with the merit of this supplier and the quality of his service as I am with the services of the nurses, the hospital technicians and other staff members, my medical assistant and all others associated with my efforts to serve my patients. In no case is second best good enough.

The prescribing system that places a premium on product and manufacturer identification exerts a strong and unrelenting pressure on the supplier to excel and thereby earn the specification of his products in the market place. It encourages him, not only to adopt practices most likely to result in superior products, but also to increase his commitment to research that may lead to still newer and better products.

Yes, the phrase "newer and better products" has real meaning for a physician of my generation. Perhaps that is why I feel so strongly on this subject.

I remember a bustling and eager young doctor in Dubuque almost four decades ago, who came out of medical school with every confidence and faith that he would conquer the ills of mankind. Then when I think of how pitifully limited his resources were, I marvel at the boldness of youth. It is a wonderful attribute, not always realistic.

In those early years of my career—for I was that new doctor—I was destined to watch patients die by degrees from tuberculosis without the means to do anything about it. I learned what it was to sit the night through at the bedsides of typhoid fever victims and sufferers from pneumonia, doing what I could but watching them slip away because I could not stop the infection. Today it is all different. Drug development, medical progress—these are not abstract terms to me.

Since I began practicing medicine, the world has seen the emergence of new drugs, new vaccines, new therapies and new techniques at a pace remarkable beyond belief. Tremendous inroads have been made in our battle against infectious diseases. The fear of contageous disease, which once swept entire communities, has become largely a thing of the past. Drugs have been developed that are so extraordinary in their curative and preventative powers that the American people—not the physicians or the pharmaceutical industry—have named them "wonder drugs."

With the advent of penicillin in the late 1940's, many bacterial infections were conquered for the first time. Then came the broad spectrum antibiotics, which worked against infections penicillin couldn't reach. Tranquilizers, steroids, radioactive materials—the list is long—all have come into wide use in the past quarter of a century. An amazing 80% of the drugs commonly prescribed today were unknown just a decade ago.

These valuable pharmaceuticals didn't just pop out of the ether. They are the fruits of years of research by a comparative handful of drug manufacturers. We know their efforts are constantly frustrated by failure. But we are also aware that they go on maintaining expensive facilities and highly specialized teams of scientists, whose sole mission is to attack and, as we have seen, to solve disease problems. These firms are known to physicians as stout allies in a never-ending struggle against man's deadliest adversaries. We respect their intense rivalry as they strive to outstrip their peers in the manufacture of the best products and the discovery of new ones. We trust their products and we prescribe them.

Now, it seems to me, a fundamental question which cries for an unequivocal answer is being raised by this issue and by certain easy generalizations, which have been made regarding it. Do the American people want the best medicines that science and the industry know how to make, or, will they settle for the lowest-priced generic drug? Will they support continued pharmaceutical research for new and more effective drugs, or, will they say, "Let the next generation worry about its own disease problems and medicines to cure them?"

The peril in the debate now raging is that the generic case will be overstated in the consuming zeal of its advocates, and the public will be convinced that *price* is the primary consideration in the choice of drugs. *This is wrong and it is dangerous!* Quality must remain the paramount consideration if people are to continue to receive the maximum benefits from a system that produces the best, the safest and the most effective drugs in the world. And quality must continue to be recognized in the market place if the system is to remain strong and creative.

If the aim is to grind all drug manufacturing firms down to the lowest common denominator, which I cannot believe, there will be no incentive to excel, no motivation (indeed, no resources) for discovery, and we will begin an unprecedented process of medical retrogression in this country. There can be no other result.

On the question of the price of drugs, about which so much has been said in hearings, let me first point out that this is by far the smallest part of the cost of sickness. Moreover, I believe figures from government sources have been placed before you, showing that this is the one element of health care expenses which has declined in recent years—both as to the prices of drugs themselves and the proportion of the total bill for a sickness which they represent. It is a remarkable record in this inflationary period when the prices of virtually all other commodities have been rising steadily.

It should also be remembered that the efficacy of modern drugs has reduced the average length of stay in hospitals, as has been demonstrated in testimony before you, and thus has helped to *reduce* hospital costs to the patient.

However, I do not want to be misunderstood on this point. Let me state categorically, no physician should overlook the opportunity to prescribe a drug costing less if there is no risk to the patient's health or if it makes no difference in the therapy of the patient.

The AMA, on at least three occasions including the period when I was president of the Association, adopted resolutions urging physicians to supplement their medical judgment with cost considerations when prescribing for their patients. I am heartily in accord with that position and, I might add, it is a rule of professional conduct I have followed throughout my career. I am no stranger to practice among people of limited means.

The memory of some of my earliest experiences as a doctor has been awakened by this controversy, involving, as it does, the attempt to institute government control over the prescribing of drugs for the elderly and financially unfortunate.

I came out of medical school and completed my internship in the depths of the Depression. As a member of the Dubuque County Medical Society, I agreed to do my part in the community to help care for the needy. Accordingly, I received a list of the drugs that could be prescribed for the so-called county patients and for which the county would pay from its slender resources of the time.

That was more than 30 years ago; yet the system was strangely similar to the legislation which was proposed last year on a national scale for millions of beneficiaries of federally-financed health programs, proving. I suppose, that there is really nothing new under the sun!

I had, as I have noted, just finished my internship and supposedly was in command of the pharmacology of the day. But, when I looked at the list of drugs for welfare patients, I found to my dismay that I was not familiar with half of them. My inquiries disclosed that many dated from before I had started medical school and by then were largely obsolete. I was, I realized, unable to use the knowledge I had gained as a medical student if I were to prescribe from this list which was the only way my welfare patients could have free drugs.

There was no choice for me. I had to confide my dilemma to the patients and explain that I could not write a suitable prescription in a great number of cases. How well I remember their answer, which I heard—not once or twice, but time after time, "Okay, Doctor, give us the prescription which you think is the best and we will get the money to pay for it."

The attitude of those people made a lasting impression on me. More than any other experience which I have had, it led to the formulation of beliefs which I hold very strongly to this day: *No man* in his illness and misfortune should be treated as *second class.*

No one insulated in a government bureau from contact with human need and suffering should have the authority in this day and age to tell those who are devoting their lives to the treatment of disease what they can or cannot prescribe for any patient; particularly for the most pathetic group of patients

of all—those whose lack of financial resources has deprived them of control over their own destinies and made them dependent on the government for care. They are the helpless ones and should be the subjects of our most compassionate concern.

Mr. Chairman, I abhor the thought of a national formulary for federal welfare patients, selected "by committee," listing the only drugs available at government expense to this group of Americans, and favoring generic terminology as an economy measure unrelated to medical considerations.

Generic drugs will *not* assure quality, as I have tried to show; often they will not meet individual illness requirements. Thus, the proposed formulary would discriminate against the beneficiaries of government programs. The number and kinds of drugs which their physicians would be able to prescribe for them—for which they would be reimbursed—would be limited. Other more fortunate citizens would continue, as a matter of course, to enjoy the advantages of the full range of the nation's drug armamentarium.

I foresee the time when, under this arrangement, countless physicians across the country would face the same impossible quandry I faced years ago with the county welfare's list of acceptable drugs—whether to prescribe a drug from the formulary so the patient could be reimbursed, even though the drug might not be the most desirable under the circumstances, or whether to prescribe a drug not listed in the formulary, and thereby penalize the patient financially.

There is the further problem of combination products, those medicines containing two or more active ingredients. There are no generic names for these. Yet the supporters of the national Formulary proposal are placing all their emphasis on generic names for their listings. Would combinations be excluded? Certainly they would be disadvantaged in competition for a place on the list by limitations which have been placed on the acceptance of non-generic drugs by the Formulary Committee. There are many outstanding combinations. I have used them for years. About 100 medicines which would fall under this particular stricture were among the 200 most frequently prescribed by physicians in 1966.

While the legislation to which I have referred is not before this Committee, I am sure it is in your minds. It is significant, for purposes of discussion, because it illustrates so clearly the manner in which enforced generic prescribing by any approach can interfere with sound medical practice; can discriminate against any segment of the population at which it is aimed, and can jeopardize the ability of top-quality pharmaceutical companies to perform effectively by sapping their resources and robbing them of the incentive to compete for recognition.

Getting back to my original premise, when all the emotional polemics which have been evoked by this issue are stripped away one fundamental point remains:

Some companies consistently make medicines of high quality and some do not. The names of the drugs, in themselves, really have very little to do with the problem except as they indicate the source.

What is important to me as a physician is the demonstrated reliability of a product and my being able to act with confidence on the reputation and resources of a particular company. Even a new product with which I have no direct experience carries a greater presumption of safety and effectiveness if the past performance of the manufacturer bespeaks excellence.

It is not simply a commodity that the pharmaceutical manufacturers are delivering; it is relief from aches and pains and conditions that bedevil people. Just as a man who goes to a hardware store to buy a brace and bit isn't only buying a brace and bit, he is buying holes; so drug firms are delivering therapy which just happens to come in the form of pills, capsules, elixirs, etc. But it is that therapy that counts and there is more to it than merely stirring together certain proportions of chemicals and other substances. Quality and performance must be built in and the hard fact is, as all physicians know, some manufacturers do not do this. My guide in selecting a medicine (whether by generic or brand name) which I am sure will provide the desired therapy, has to be the maker of whom I have some knowledge and in whom I have confidence.

Before I conclude, I would like to take a moment more to refer to services to the medical profession which leading drug manufacturers perform and which

also contribute to the best standards of medical care. To the extent that they impose an extra financial burden on the companies, they enter into questions regarding drug prices. Are these services helpful and worthwhile? Do they achieve results commensurate with their costs? I would certainly say a loud "Yes" to both questions.

The information which we are provided about new drugs—and the periodic updating of information about established products—is an invaluable aid to physicians. Without the journals, the mailings and the personal visits from manufacturers' representatives, I would be hard-pressed to keep abreast of today's rapid medical advances and still work 12 to 18 hours a day at my practice. Invention of a drug is pointless if the medical profession doesn't have knowledge of it—its indications, contraindications, dosage forms, etc.

I have noted a tendency in some of the earlier testimony to deride doctors because they deal with detailmen. I don't understand this. While I cannot speak for other physicians, I know for myself I have found detailmen helpful and informative. They bring me information on new developments. They can answer preliminary questions. They often serve for the exchange of information with other doctors. If I have a problem relating to one of their products, they can, and frequently do, contact their home offices to get me an answer.

I realize they are trying to sell me. That's their job. I don't have to be sold if I don't want to be. My feeling about them is the same as about the products of their firms. I trust them on the basis of my past experience with them and my belief in their integrity.

It is pure hogwash, of course, to suggest that any physician worthy of the name would depend on detailmen and advertising pages of professional journals for his continuing medical education. It is true the ads and the company representatives often provide the first information on a new product. If I am interested, I would turn to the package insert and the literature. Then I would check it out with my colleagues in my county and state societies and, perhaps, consult the hospital pharmacist. Finally, if the product seems to have possibilities for my practice and I am satisfied after these inquiries, I might give it a try under close observation.

This is the point where the services of the reputable companies really shine. I know that whatever the dosage form in which I want to use the drug, the company will make it available in my community in its full line. I don't have to prescribe a tablet when I want to prescribe a tablet when I want to prescribe an injection because the manufacturer hasn't found it profitable to produce or widely distribute less popular forms.

Further, if questions arise about the action of the drug, I can report promptly to the manufacturer because I know who the manufacturer is. If it is necessary, I know I will obtain the assistance of the company's medical staff in identifying and evaluating the problem, and applying the proper corrective measures. This is not only true for new drugs but holds equally well for older, established products. When I have identified the manufacturer in my prescription, I know precisely where to go if difficulty arises. This would not be true in cases of generic prescriptions filled by the pharmacist from whatever stocks he has on hand.

He might or might not be able to determine where the medicine came from. If he could identify the source, the company might or might not have a medical staff capable of advising me. If it were a small company engaged in copying successful drugs, the chances are it would have a limited staff and would not be able to support the scientific personnel to provide service.

Beyond this, it must be assumed that the originating company, whose laboratories discovered the drug, is going to be far better acquainted with its good and bad points than the secondary manufacturer who produces the imitation after the originator has already demonstrated its worth and successfully made the medical profession aware of its existence. The manufacturer who has developed a drug must keep an accurate and up-to-date record of adverse reactions and other data pertaining to its effectiveness. I know I can get the swiftest and most accurate information from him about his product when I need it. This is not true of the imitator in many cases. Moreover, the originator has every incentive to make sure his product serves the public in the best possible way to preserve his reputation among physicians and protect his name in the market place.

In closing, I should like to point out that throughout my professional life I have been concerned with the economic factors affecting the quality of medical

care. I believe, and I have often stated, that he who controls the economics will control the quality of care. The quality of drugs is inescapably a vital part of the quality of care.

Now, there is growing clamor to make the price of drugs the primary consideration in their selection to relegate quality to secondary consideration. Any such approach could not fail to adversely affect the quality of care. It would not, as I have tried to show, appreciably lower the nation's health care bill. It could do irreparable harm to the nation's health care system. I present this statement to you because I am anxious to do my small part in alerting you to this peril.

Our present balanced and flexible health care system is the wonder of the rest of the world. As you proceed with your inquiry, I sincerely hope you will conclude that it is in the best interests of all concerned to keep it that way, and that you will summarily reject demands for such chancy experiments as the imposition of controls over the prescribing of drugs for economic, not health reasons.

APPENDIX V

THE MER–29 CASE

STATEMENT BY THOMAS M. RICE, ACTING CHIEF INSPECTOR, BUFFALO DISTRICT, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Mr. Chairman, it is a pleasure to appear before you today to discuss my part in the investigation of MER/29.

During the time of the field investigation of MER/29, from 1961 to 1963, I was employed as a Supervisory Inspector at FDA's Cincinnati District Office. I was the principle field investigator in the MER/29 case.

In early 1962, there was considerable publicity in the Cincinnati area, as a result of the drug warning letter mailed by the William S. Merrill Company to all physicians, the previous December. This warning letter informed physicians of the incidence of cataracts, hair changes, ichthyosis, and other skin changes, depression of adrencortical function and other side effects associated with MER/29 therapy.

This publicity was the topic of a conversation in my Cincinnati car pool in February 1962. One of the car pool members, Mr. Carson Jordan, who knew that I was employed by the Food and Drug Administration said that his wife had been involved in animal studies on MER/29 during the time she worked at Merrell, when this drug was being developed. His wife, he said, suspected the records on the animal studies had been falsified to make the reports look good. He told me that Mrs. Jordan later resigned her job in the animal testing laboratory, where she was employed under the supervision of Dr. William M. King, because she was dissatisfied with the way Dr. King was directing the work. He said she felt very strongly that Dr. King would have no qualms about "doctoring" the results of the studies.

Recognizing the importance of what Mr. Jordan had said, if true, I reported this incident to our Bureau of Field Administration. At the request of our Bureau of Field Administration, I interviewed Mrs. Jordan on the evening of February 26, 1962. She told me that she had the responsibility of dosing and weighing both the test monkeys and the control monkeys during a toxicological study of MER/29. Mrs. Jordan said that at the end of the study, which took a number of weeks, she worked up charts depicting the observations and weights. Three or four monkeys were on MER/29 and a similar number were in the control group in the study, she said.

Dr. King and his superior, Dr. Evert F. Van Maanen, were not satisfied with the charts, Mrs. Jordan said. She said one test monkey on the drug, MER/29, had been sick and doing very poorly; its eyes "did not look right." This monkey subsequently was not autopsied with the rest. In addition, her superiors decided to substitute a control monkey in its place. Because of this decision, Mrs. Jordan said it was necessary for her to rework the charts three different times. She believed that the results on the charts would have been very unfavorable if the sick monkey had been left in the test group. She stated that she was told never to mention this substitution of data on the charts because this was the way the

company wanted it. She named other former Merrell employees who were familiar with this experiment, particularly Bruce I. Umberger.

I interviewed Mr. Umberger that night of March 12–13, 1962. Since his recollections substantiated Mrs. Jordan's to a considerable extent, they were prepared in affidavit form. I again interviewed Mrs. Jordan on March 13, and her recollections were also prepared in affidavit form.

Following this, I attended a conference in Washington, D.C., to plan further investigation. It was decided to send a three-man inspection team, consisting of a medical officer, a pharmacologist, and me, to inspect the firm and review the raw data from the chronic studies on rats, dogs, and monkeys, and to get up-to-date information on adverse effects to humans.

I made the inspection on April 9 and 10, 1962, with Dr. John O. Nestor and Dr. Edwin I. Goldenthal, from FDA Headquarters.

During this inspection, discrepancies were found between the raw data notebooks and charts kept by the firm with respect to the monkey chronic oral toxicity studies and the data and charts on these studies which had been submitted to FDA by the firm in support of the MER/29 NDA. For example, as submitted in the NDA, monkey M51 was reported as having received 40 mg/kg body weight MER/29 for six months and 20 mg/kg for ten months. The NDA data showed no weight loss at the end of the experiment. The raw data showed that monkey M51 was started on MER/29 about half way through the experiment and was placed on 20 mg/kg body weight of MER/29 for only about eight months. There was a significant weight loss toward the end of the experiment.

Monkey F49, according to the NDA submission, showed a wieght gain in the last month of the experiment, but the raw data showed a significant weight loss from 9.9 kg to 7.5 kg—a loss of 2.4 kg (5.3 lbs) in this last month.

Furthermore, discrepancies were found between the NDA submission and raw data in the dates of autopsies of the monkeys. In particular, no record of any autopsy on drug monkey M34 was found in the raw data.

The charts showing discrepancies with the NDA submission were copied, but the firm refused to permit us to take the raw data notebooks the evening of April 9, although promising to make copies of the pages we wanted. No one at the firm was able to explain the discrepancies noted. We returned to the firm on April 10, 1962, and still no one could explain the discrepanies. They did not have the copies of the pages of the raw data notebooks as promised. However, they assured us that copies would be made available as soon as possible.

On April 12, 1962, I called Mr. E. R. Beckwith. Executive Vice President of Merrell, because we still had not received the promised copies. He said they were trying to get a complete picture of the situation, but because of changes in personnel during the time the data was compiled, information was scattered. He told me it was taking time to get the pieces of information together. He again assured me he would get me the copies as soon as possible.

On April 17, 1962, I paid another visit to the firm because we had still not been supplied with the copies of the pages from the raw data notebooks. At the same time, we discussed the details and status of the firm's recall of MER/29, which was by then, underway. At this time, I was told by Mr. Fred Lamb, attorney for the firm, that he could not give me copies of the requested pages because the notebooks had been sent to an attorney for the firm in New York City for examination. He said it was up to this attorney, dealing at the Washington level, to decide whether the pages would be made available.

I understand that copies of the requested pages were finally turned over to a Food and Drug Inspector in New York on April 19, 1962.

On April 24, 1962, I interviewed Dr. King at his home, accompanied by Mr. T. C. Maraviglia, Director of FDA's Cincinnati District.

At this time, Dr. King told us that a control monkey, M35, had actually been on an analogue of MER/29, known as compound 5066, for a time prior to being used as a control animal. He also stated that his findings from the autopsy of monkey F49, which had received MER/29, indicated morphological changes in the ovaries. He said that it was Dr. Van Mannen's decision to omit this information from the second edition of the MER/29 brochure so that the investigators supervising clinical studies on MER/29 wouldn't know about it.

I again visited Mr. Umberger the night of May 3 and 4, 1962. He reviewed copies of pages from the bound raw data notebooks which had been supplied to me by this time. From these, he was able to recall that the sick test monkey was number M34. He recalled that at autopsy he was told that the monkey,

M34 had had a "reverse heart attack," when he asked why this sick monkey behaved abnormally—for example, missing a box it attempted to jump into after being weighed. He could not explain why there were no autopsy results recorded in the raw data notebooks for M34. The autopsy report submitted with the NDA on this monkey indicated nothing abnormal about the heart. After reviewing the raw data, Mr. Umberger signed another affidavit reaffirming the affidavit of March 13.

On May 30, 1962, I interviewed Mrs. Jordan again. This time, she was shown copies of the pages from the raw data notebooks and charts which she had helped prepare, including Figure 7 submitted with the NDA. She now was able to recall that the sick monkey she referred to in her earlier affidavit was M34, which agreed with Mr. Umberger's recollection, and that this monkey did not lose a dramatic amount of weight, but did poorly.

She confirmed the fact that M34 was the monkey that was mean, withdrawn, and couldn't see properly, missing the box when he tried to jump into it. She also recalled that monkey, M34 was not autopsied in her presence, which was the reason no record was in the raw data book. She advised us that Dr. Van Mannen was the one that told her to falsify the chart (Fig. 7) turned in with the NDA. He supplied the weights to be used for the curve on monkey M34, which did not agree with those in the raw data notebooks, and insisted on the other changes which: (1) showed M51 as being on MER/29 during the entire experiment rather than the last eight months only; (2) showed monkey M35 as being a control monkey for the entire time, though she knew it was on 5066, another test drug, during the first part of the experiment; and (3) eliminated weight figures for the closing weeks of the study—figures which would have shown the dramatic weight loss of F49 and the weight loss of M51.

She also knew there were some suspicious looking rats on MER/29 studies and that about one-third of the MER/29 rats died.

On June 19, 1962, I interviewed Dr. K. S. Grady. He had been a consultant veterinarian for Merrell since about June 1961. He said he had made specialized examinations on dogs' eyes once a week for three or four months for Merrell and noted abnormalities which developed slowly until some were diagnosed as cataracts. Some of the dogs' eyes showed fingernail-like opacities. He also noted dermatological problems in the dogs. These findings were reported to the firm, primarily to Dr. King. Dr. Grady later found that these dogs were being dosed with MER/29.

On June 20, 1962, I interviewed Frank A. Nantz, M.D. He is an ophthalmologist and had done some examinations of dogs' eyes for Merrell on November 9, 1961. These dogs had developed cataracts while on a high-level MER/29 study. He later made about six trips to the firm over a four-month period to examine these dogs. In addition to cataracts, he noted that these dogs developed skin rashes.

On June 22, 1962, I interviewed Dr. Irvine H. Page, M.D., Director of Research, Cleveland Clinic, at the request of our Bureau of Enforcement. A dog study on MER/29 which had been performed by his group and which had been completed about two years previously, had shown results which were unfavorable to Merrell. This was submitted for publication in the Archives of Pathology, but Dr. Page decided to withdraw publication after he had sent his manuscript to Merrell and they urged him to delay publication. I understand that the paper eventually was published in June 1962.

This was the final field investigation I made of any significance in respect to this case.

If you have any questions, I will try to answer them for you.

STATEMENT BY EDWIN I. GOLDENTHAL, PH. D., ACTING DEPUTY DIRECTOR, OFFICE OF NEW DRUGS, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Mr. Chairman, I appreciate the opportunity of appearing before you today to discuss my involvement with the drug triparanol, or MER/29, with regard to (1) the initial review of the pharmacological and toxicological data submitted in support of safety of the drug, and (2) the investigation at the William S. Merrell Company and the subsequent review of some of the raw data upon which the reports submitted to FDA were based. MER/29 is a drug formerly marketed by the William S. Merrell Company for lowering cholesterol levels.

With your permission, I will submit for the record a statement of my educational and professional background.

At the time of the review of data submitted in support of MER/29, I was a pharmacologist in the Division of Pharmacology. At that time, pharmacologists reviewing data on New Drug Applications (NDAs) were located organizationally in the Division of Pharmacology of the Bureau of Biological and Physical Sciences, and not part of the Bureau of Medicine. Comments or recommendations by the pharmacologists on NDAs were of an advisory nature. In this same advisory capacity, individual pharmacologists frequently participated in meetings at the Bureau of Medicine with representatives of the pharmaceutical industry.

The New Drug Application for MER/29 was submitted by the William S. Merrell Company on July 21, 1959. I did not make the initial review of the application but was involved, in a supervisory capacity, with pharmacological reviews of all New Drug Applications. Based on the pharmacology review of the application, FDA notified the drug's sponsor, in a letter dated September 14, 1959, that the application was incomplete because of a questionable margin of safety. We suggested a one-year oral study in rats and a three-month oral study in dogs, with one dosage level in each of these experiments selected with production of specific evidence of toxicity as a goal. Dr. F. Joseph Murray, Executive Assistant to the Director of Research of the William S. Merrell Company, by letter of September 24, 1959, to Dr. Jerome Epstein, the medical officer assigned this application, indicated his firm's disagreement with our conclusions. Dr. Murray maintained that the submitted animal data, particularly the results of the monkey study, showed MER/29 to have an "exceptionally good" margin of safety.

On October 6, 1959, Dr. Murray and another Merrell representative, Dr. William King, met with several members of the Division of Pharmacology to discuss the New Drug Application. I was present at that meeting. They advised us that they had some additional animal studies underway; specifically, a six-month dog study and a six-month rat study. They indicated that these tests were not mentioned in the initial NDA submission because no results had been obtained. We recommended that they administer the drug to one group of dogs for a minimum of three months, at the highest dose the dogs could tolerate, in an attempt to produce some evidence of toxicity.

We also recommended that they start an additional two groups of rats at dosage levels higher than those used in previous studies, and that treatment be continued for a period of one year.

In a letter to Dr. Epstein of October 13, 1959, Dr. Murray again asserted that the animal studies had demonstrated safety of MER/29, and stated: "We feel that the significance of the studies carried out in monkeys has been entirely overlooked."

On October 16, 1959, representatives of the William S. Merrell Company met with members of the Administration to discuss further the toxicological studies which we felt were necessary to support the safety of MER/29. They indicated they were planning to initiate a six-month dog study at dosage levels expected to produce toxicity and a rat study of twelve months' duration. In a letter dated November 6, 1959, the Administration acknowledged the firm's correspondence of September 24 and October 13, and said the results of the additional toxicity studies agreed upon would be reviewed when submitted.

On February 12, 1960, the firm submitted additional toxicity data on MER/29 consisting of results of three-month and nine-month studies in rats and a three- to six-month study in dogs. These data were reviewed in my memorandum, dated February 23, 1960, to Dr. Frank Talbot, the medical officer who was handling the MER/29 application at that time. The conclusion was that, on the basis of the animal toxicity data, there was little margin of safety with the drug. I indicated my serious concern about the safety of the use of such a drug for reducing blood cholesterol. I was concerned about the inherent toxic potential of the drug and the possible long term effects of elevated blood desmosterol. MER/29 was believed to reduce cholesterol levels by blocking the metabolic conversion of desmosterol to cholesterol. My recommendation was that the application should not be approved in the absence of satisfactory results from extensive, well-controlled clinical studies in which individuals received the drug for a period of several years. This was based on the high potential toxicity of the drug shown in the animal studies. By letter of February 29, 1960, Dr. Murray referred me to our telephone conversation in which adverse effects of MER/29 on the eyes of rats were discussed. He alleged that "the corneal changes have now been found in the

control animals" and stated that the firm's consulting pathologist "feels that the changes are inflammatory," and not caused by the drug.

By letter of March 28, 1960, FDA acknowledged six communications from the firm and commented that the application was incomplete in that it failed to report clinical studies in full detail. Our letter further stated:

"As brought out in our meeting of March 7, 1960, with representatives of the William S. Merrell Company, we are unable to resolve the apparent discrepancy in interpretation of the pharmacologic studies in dogs between your people and ours. Because of this dispute, because of the potential hazards of liver toxicity with this dog, and further because of the highly theoretical value of taking such a drug as MER/29 (to our minds), we are making the application incomplete until longer term clinical studies have been made utilizing periodic liver function studies to show that this blocker of intermediate cholesterol metabolism is not producing liver damage."

On March 31, 1960, FDA received personally from Dr. Murray, a tabulation of liver function tests. The firm continued to emphasize that an earlier toxicity study in monkeys, had likewise shown a total absence of toxicity from MER/29, and that monkeys being primates, were phylogenetically closer to man than either rats or dogs. Thus, he argued, the drug was safe under the conditions of use set forth in the New Drug Application. On April 19, 1960, FDA notified the William S. Merrell Company that the application was made conditionally effective and that the action allowing the application to become effective was based solely on the evidence of the safety of the drug. On May 12, 1960, FDA acknowledged receipt of the final printed labels and labeling and made NDA 12-066 fully effective, subject only to the terms set forth in the FDA letter of April 19, 1960.

My next involvement with this application was on November 7, 1961. I sent a memorandum to Dr. John Nestor, the medical officer then handling the application, in which additional data were reviewed. In light of reports of adverse reactions in humans, particularly the eye changes, the question had been raised as to whether or not the application should be suspended. While I agreed that the application should be suspended, I was not convinced that the new data submitted by the firm would be sufficient to support a revocation of the application. On November 13, 1961, various personnel within the Administration met to evaluate the situation and to decide on a course of action. The decision reached was that the drug should be removed from the market and the application suspended. In the absence of new clinical evidence that the drug was unsafe, however, this could not be done under the provisions of the Federal Food, Drug, and Cosmetic Act at that time. This question was reviewed with FDA scientists and the conclusion was reached that the available evidence would not support suspension action. On November 27, 1961, a drug warning letter was agreed upon by the William S. Merrell Company and FDA. This letter informed physicians of the incidence of cataracts and the necessity of early detection by slit lamp examination. It also advised that they be on the look out for hair changes, ichthyosis and other skin changes, depression of adrenocortical function, and other side effects associated with MER/29 therapy.

In March 1962, FDA was informed by a former employee of the firm that some parts of the chronic monkey data on MER/29 submitted to the Food and Drug Administration had been falsified. We were advised that one of the drug-treated monkeys had become ill and lost considerable weight during the latter part of the study and that a normal, untreated, healthy animal had been substituted. She stated that the report submitted to the FDA by the William S. Merrell Company, as part of the New Drug Application, had been modified to include data on this untreated monkey instead of the monkey receiving MER/29. There was also some question as to whether or not this sick monkey had been subject to autopsy.

It was decided that members of the Administration should visit the William S. Merrell Company to investigate this alleged falsification. On April 9, 1962, Dr. John Nestor of the Bureau of Medicine, Supervisory Inspector Thomas M. Rice, and I visited the firm's Cincinnati facilities and met with representatives of the firm. During the morning, a discussion was held regarding clinical experience with MER/29, particularly reports of the adverse effects. In the course of our discussion, we asked to see the raw data from the monkey studies. Pertinent laboratory records were made available to us. Our search for specific data was difficult because of the confusing manner in which these records had been kept. Upon reviewing some of their laboratory notebooks and weight charts, however, it became evident that the data were somewhat different from those submitted in the New Drug Application.

Discrepancies such as the following were uncovered: Notebooks and weight charts indicated that a marked loss of weight occurred in one monkey during the last five weeks of the reported study; the data submitted in the New Drug Application indicated that there was a weight increase of this monkey during that period. We could not find the record of autopsy for another monkey in this study. According to the NDA, a third monkey had received MER/29 for 16 months, whereas the firm's notebook and charts indicated that this monkey had received MER/29 for only 8 months. The laboratory records on three of the monkeys showed three different dates for the autopsy of these animals. Moreover, the autopsy dates given in the New Drug Application did not correspond to those found on the charts and notebooks. Delving further into the records, I discovered reports on another monkey which had been treated with MER/29, apparently as part of a second toxicity study in this species. Only one monkey study had been mentioned in the New Drug Application. The officials of the firm responsible for these studies were asked if they could explain the discrepancies. They had no immediate explanation.

Before leaving the firm that day, we were asked if we were satisfied with the results of our visit. We replied that while we had received the utmost cooperation, we had discovered some discrepancies in the monkey studies which had not been explained to our satisfaction. The senior officials of the firm indicated that they would discuss our findings with their personnel in an attempt to clarify the matter. We indicated that we would return on the following day.

On the morning of April 10, 1962, we again visited the firm. A conference was held with company representatives. An official told us that, although they had worked late into the evening, they were still unable to find any explanation for the discrepancies which we had noticed on the previous day. We met further with the officials of the firm who were directly involved with these studies and they, too, indicated they had been unable to explain the discrepancies.

On April 11, 1962, a memorandum summarizing our findings was sent to our Division of Regulatory Management. I indicated that we had found certain discrepancies between the chronic monkey studies submitted in Merrell's New Drug Application and those found in their laboratory records. We felt that these discrepancies did not represent an oversight on the part of the William S. Merrell Company, but constituted evidence of the submission of fradulent and misleading data to the FDA. I indicated that the net effect of these misleading data was to make the drug appear less toxic to monkeys than was actually the case. These data were of particular significance at the time of our consideration of the NDA, when representatives of the William S. Merrell Company had vigorously maintained that evidence of safety obtained in these monkey studies outweighed any questionable findings in lower species, i.e., rats and dogs. It was apparent that the discrepancies uncovered in our visit supported the allegation by the former Merrell employee that fradulent monkey data had been submitted to the Food and Drug Administration.

On the basis of these findings, I recommended that the NDA be suspended. Moreover, I felt that sufficient evidence had been obtained to support prosecution of the William S. Merrell Company and the individuals involved and recommended such action.

On April 12, 1962, representatives of the firm met with FDA and advised us that they were immediately withdrawn MER/29 from the market. They requested that we suspend the New Drug Application. On May 22, 1962, a formal order suspending the New Drug Application for MER/29 was signed by the Commissioner of Food and Drugs.

Subsequently, as our investigation continued, we found that two of the reports of rat toxicity studies submitted in the New Drug Application contained falsified data. Regarding a six-week, two-dosage level study, the William S. Merrell Company reported in the NDA that four of the eight females at the high dosage (75 mg/kg) had died during the course of the experiment. Examination of Merrell's notebooks revealed that *no* females at that dosage level were alive at the end of six weeks. Seven of the female rats had died, and the eighth had been sacrificed. The firm's failure to report truthfully the results of this experiment resulted in further complications. Final organ weights and hematological values were reported in the NDA for these animals at the six-week period. In checking the firm's laboratory records, no organ weights or hematological values were found for these animals. This is not surprising since the animals did not survive for these determinations. The values which were reported were

identical to those reported for rats in another study on MER/29—at a different dosage level and for a different duration.

In a second rat study, according to the New Drug Application, 20 rats per dosage group received MER/29 for three months. The NDA states that "In the rats receiving 40/mg/kg/day of MER/29, 8 out of 20 had grossly visible opacity of the cornea . . . there was also an associated conjunctivitis." The firm held that this was not a drug induced phenomenon since it was also observed in control rats. When we checked their laboratory records, however, we found that actually 60 rats per dosage level had been administered MER/29. At the time of our review of the New Drug Application, we had no knowledge of these further studies.

These additional data, which were withheld by the William S. Merrell Company, established conclusively that MER/29 was capable of inducing cataract formation. After the three month sacrifice, there were approximately 40 rats per dosage level still receiving MER/29. On March 28, 1960, approximately four months after the start of the experiment, and *before the New Drug Application was approved*, the eyes of the remaining rats were examined. The firm's notebooks state that the eyes of many of the rats receiving MER/29 "did not react to light or motion, therefore giving the appearance of being blind." At the highest dose level, 25 out of the 36 rats showed this blinding effect. Only 1 of the 38 control rats showed this effect. None of this data was submitted for inclusion in the New Drug Application. This omission is extremely serious since knowledge that MER/29 was causing cataracts in rats certainly would have caused the FDA to delay, and probably to withhold, permission to market the drug. As it developed, cataracts were one of the most disturbing features of toxicity which occurred in patients after the drug was released.

As early as November 1960, the William S. Merrell Company had been notified by another pharmaceutical firm, Merck, Sharp and Dohme, that MER/29 had shown extremely serious adverse effects in their experiments with rats and dogs; the drug had produced cataracts and other eye changes. Moreover, Merrell representatives had actually visited Merck, Sharp and Dohme during January 1961, to examine the affected animals. No mention of these findings to the Food and Drug Administration was made by the William S. Merrell Company until January 2, 1962, when FDA and the William S. Merrell Company had received reports that this drug caused cataracts in human beings.

The original brochure contained a caution that MER/29 should not be administered during pregnancy. On September 23, 1960, approximately five months after the New Drug Application became effective. Dr. Talbot sent a letter to the William S. Merrell Company. In this letter, Dr. Talbot made mention of adverse effects of MER/29 in pregnant rats. He stated his concern over the administration of MER/29 to premenopausal women who would know whether they were in the first trimester of a pregnancy. On October 23, 1961, Dr. Nestor requested the William S. Merrell Company to submit all data concerning adverse and toxic reactions resulting from MER/29 therapy in both animals and humans. On October 26, 1961, the William S. Merrell Company submitted results of fertility and sterility studies on MER/29 in rats to Dr. Nestor. Part of this study was conducted by the William S. Merrell Company and another part was conducted by Endocrine Labs., Madison, Wisconsin. These studies showed that at certain dosage levels MER/29 caused a marked reduction in the rate of conception. In addition, the percentage of the litters surviving was also affected. These effects were observed when the female received MER/29 prior to and during cohabitation with male rats. These experiments were all completed in March of 1960 and a final report was prepared in October of 1960. However, these results were not submitted to FDA until one year later, and only at the urgent request of Dr. Nestor. The William S. Merrell Company did not submit these data even though Dr. Talbot questioned them about this matter in his letter of September 23, 1960. These data should have been submitted much earlier. If we had had this information in the file, we would certainly have inserted at least a caution in the brochure against the use of MER/29 in women of childbearing age. Dr. Talbot was even considering this caution without having these adverse data at his disposal.

In this statement I have described my part in the MER/29 investigation and outlined the major aspects of those investigations insofar as my involvement was concerned. I feel that it can be concluded, from the evidence available, that the William S. Merrell Company withheld some important information and mis-

represented other important information with the result that an unsafe drug was allowed to go on the market.

Thank you for your attention. If you have any questions concerning MER/29, I will be happy to answer them for you.

CURRICULUM VITAE

Personal data:

Name: Edwin I. Goldenthal.

Place and Date of Birth: Plainfield, New Jersey, February 2, 1930.

Marital Status: Married in 1950; 3 children.

Education:

B.S., 1952—The George Washington University, Major: Chemistry.

M.S., 1953—The George Washington University, Major: Biochemistry.

Ph. D., 1956—The George Washington University, Major: Pharmacology.

Present Position: Acting Deputy Director, Office of New Drugs, Bureau of Medicine, Food and Drug Administration, Department of Health, Education and Welfare (July 1966 to Present).

Previous Positions:

Chief, Drug Review Branch, Division of Toxicological Evaluation, Bureau of Science, Food and Drug Administration, Department of Health, Education and Welfare (May 1963 to July 1966).

Research Pharmacologist, Division of Pharmacology, Bureau of Biological and Physical Sciences, Food and Drug Administration, Department of Health, Education and Welfare (February 1962 to May 1963).

Pharmacologist, Division of Pharmacology, Bureau of Biological and Physical Sciences, Food and Drug Administration, Department of Health, Education and Welfare (April 1956 to February 1962).

Research Fellow, Pharmacology Department, The George Washington University Medical School (February 1952 to April 1956).

Society Memberships:

Society of Sigma XI.

Society for Experimental Biology and Medicine.

European Society for the Study of Drug Toxicity.

American Society for Pharmacology and Experimental Therapeutics.

Publications:

Lamar, J. K., Jackson, C. E., and Goldenthal, E. I., Effects of Penicillin-G on the Reproductive Processes in the Mouse, Rat, and Rabbit, Fed. Proc., 1968.

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Nadkarni, M. V., Goldenthal, E. I. and Smith, P. K.; The Distribution of Radioactivity Following Administration of Triethylenimino-s-Triazine-C^{14} in Tumor Bearing and Control Mice, Cancer Research, 1954.

STATEMENT BY ROBERT C. BRANDENBURG, DIRECTOR, OFFICE OF CERTIFICATION SERVICES OFFICE OF ASSOCIATE COMMISSIONER FOR COMPLIANCE, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Mr. Chairman, it is a great privilege and pleasure to appear before this Subcommittee this morning to discuss my part in the investigation of MER/29.

During 1962, my duties included the direction of investigations, the evaluation of their results, and the preparation of recommendations for legal actions appropriate to the offenses demonstrated, if any.

During early May 1962, I was assigned the direction of an investigation involving the new drug, MER/29 or triparinol. This investigation had already begun in April 1962, with the inspection of the drug firm, the William S. Merrel Company, Cincinnati, Ohio, by Supervisory Inspector Thomas Rice, Dr. E. I. Goldenthal, and Dr. John O. Néstor, of the Food and Drug Administration.

During May and June 1962, I had the FDA inspection force visit all William S. Merrel employees who had participated in these studies, and a number of other individuals who had been concerned with animal studies of the drug. As we compared the results of these investigations and the raw data on animal studies (which we obtained from the firm), with the data on these studies submitted to FDA in the new drug application, it became obvious that the submissions to FDA had been changed to conceal or withhold adverse effects of the drug on the test animals.

Our investigation developed leads concerning animal studies performed by other firms and individuals on MER/29, of which the William S. Merrell Company was aware, and I had the FDA inspectional force conduct the indicated visits.

In addition to the significant descrepancies and withholdings in animal studies which Dr. Goldentahl and Mr. Rice has dicussed, our investigations disclosed that the firm was aware of additional animal studies on the drug which showed it to be extremely toxic, and not only failed to report the results of these studies to FDA, but had actively attempted to keep some of this information from both FDA and the medical community.

In one instance, by letter dated November 3, 1961, Dr. Murray of William S. Merrell, sent FDA a manuscript entitled "Lethal Effect in Dogs of Prolonged Oral Administration of Triparinol" written by Doctors Scanu, Hawk, and Page of the Cleveland Clinic Foundation. Dr. Nestor of FDA, had heard of this paper and has requested the firm to submit it. This paper reported extremely toxic effects produced by the drug in the test animals.

At my request, Mr. Rice visited the Cleveland Clinic and interviewed Dr. Page on June 26, 1962. He found that the William S. Merrell Company had been apprised of the results of the Cleveland Clinic study in January 1960, almost two years previously. Drs. Blohm and King of the William S. Merrell Company had actually visited the clinic sometime in March 1960, to discuss the study with those who had performed it.

This investigation revealed that the William S. Merrell Company had prevailed upon those who had prepared a paper concerning the results of this study to permit representatives of the firm to edit it, since they claimed that the adverse effects of the drug found by the researchers could possibly have been caused by some other factor. Due to this intervention, the paper was not published until June 1962. We also learned that although no brochures, proposed labeling, or other documents submitted to FDA had referred to any blood dyscrasias produced by MER/29 in rats, the firm had actually prepared a brochure, never submitted to FDA, which did refer to this condition.

Our investigations revealed that a number of these so-called "preliminary" brochures had been distributed, including one to the American Medical Association. From this brochure and from information obtained during an interchange of correspondence with the firm, the American Medical Association prepared a proposed monograph on MER/29 which was to appear in the 1962 edition of the book "New and Non-Official Drugs," now known as "New Drugs," which the Association publishes yearly. The interchange of correspondence shows clearly that the firm made determined efforts to have any reference to a blood dyscrasia in rats associated with MER/29 deleted from this monograph.

We also learned that the Upjohn Company, like Merck, Sharpe & Dohme and the Cleveland Clinic group, had conducted a MER/29 dog toxicity study in March 1961, which showed the drug to be quite toxic; had notified the William S. Merrell Company of this fact by July 14, 1961; and had shown their data on this study to Dr. King of the William S. Merrell Company on July 31, 1961.

No report of this study was ever submitted to FDA by the William S. Merrell Company.

The results of our investigations were subsequently submitted to a Federal Grand Jury, and a twelve count true bill was returned on December 20, 1963, against the William S. Merrell Company and three employees, Dr. Harold W. Werner, Dr. Evert F. Van Maanew, and Dr. William M. King. All the defendants entered pleas of nolo contendere on June 4, 1964. The firm was sentenced to pay a total fine of $80,000, and the individuals were each placed on probation for a period of six months.

Thank you for the opportunity in allowing me to discuss my part in the MER/29 investigation. I will be glad to respond to any questions which the Committee may have.

AUGUST 19, 1959.

To: New Drug Branch. Attn: Dr. Epstein.
From: Division of Pharmacology.
Subject: NDA 12-066, M.E.R. 29, The Wm. S. Merrell Co.

This application lacks information on the safety of the drug in animals with respect to the selection of: (1) animals in chronic toxicity studies and (2) doses.

Since the drug may be used for long periods of time, one year oral studies in rats and three month studies in dogs would be desirable. In both groups a dose causing toxic effects should be included. The evidence presented in the NDA suggests that the margin of safety of the drug is low.

The chronic toxicity study in monkeys included in the application is helpful but lacks (1) a "toxic dose" and (2) enough animals to be significant, particularly for long term studies.

R. MEGIRIAN.

U.S. DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE,
Washington, D.C., September 14, 1959.

The WM. S. MERRELL CO.,
Lockland Station,
Cincinnati, Ohio.
(Attention of Dr. Joseph Murray.)

GENTLEMEN: Reference is made to your new drug application dated July 31, 1959, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation M. E. R.-29 (Triparanol Capsules).

This also acknowledges your letter of August 14, 1959.

The application is incomplete under section 505(b) (1) of the Act as follows:

The drug is by nature one which will receive chronic use. The data you have submitted suggests a low margin of safety. We feel that the following studies are in order to demonstrate safety.

A one year oral study in rats and a three month oral study in dogs should be performed. In both animal groups one dosage level should be selected to produce toxicity.

We shall reserve our comment on the labeling until the foregoing has been resolved.

Since the application is incomplete under section 505(b) (1) of the Act, it may not be filed as an application provided for in section 505(b).

Sincerely yours,

JEROME H. EPSTEIN, M.D.,
Medical Officer, New Drug Branch,
Bureau of Medicine.

THE WM. S. MERRELL CO.,
SCIENTIFIC DIVISION,
Cincinnati, Ohio, September 24, 1959.

JEROME H. EPSTEIN, M.D.,
New Drug Branch, Food and Drug Administration,
Washington, D.C.

DEAR DOCTOR EPSTEIN: I have your letter of September 14 advising us our New Drug Application for M. E. R.-29 (NDA 12-066) is incomplete. We are somewhat surprised by the statement that our data "suggest a low margin of safety."

We felt we had demonstrated a reasonably high margin of safety, and after careful reevaluation of the data we still feel we have demonstrated a low level of toxicity with a wide margin of safety.

The dosage we are recommending for M. E. R.–29 is 250 mg. once daily. On a weight basis, this would constitute a dose range of 3.6 to 4.16 mg./Kg. The acute toxicity studies we reported showed the LD_{50} dose to be 1600 mg./Kg. intraperitoneally and 2000 mg./Kg. orally. We consider this to be extremely low acute toxicity.

Data submitted showed no untoward hematopoietic response at dose levels used in rats or monkeys. The dose range used in rats went as high as twenty times our proposed clinical dose, and monkey dosage was ten times the proposed clinical dose. Body weight gains were not affected in rats or monkeys at doses far in excess of the proposed clinical dosage. Relative organ weight changes in rats were due to total body weight changes, and in each case histopathologic examination failed to suggest other causes for such change.

Three male and three female dogs with appropriate controls have been on M. E. R.–29 for better than 3 months at 25 mg./Kg. We have evaluated hematopoietic response, body weight and food consumption, and liver studies (serum bilirubin, alkaline phosphatase, serum transaminase, and BSP retention determinations). At 3 months all were within normal limits. We plan to autopsy these animals after 6 months to complete our records. We are agreeable to making the autopsy data available to you at that time. However, we strongly feel that the 16-month study in monkeys has more than adequately demonstrated the safety of M. E. R.–29. We would, of course, be willing to withdraw the product from the market if real toxicity problems were uncovered in our autopsy work.

As I indicated, we have very carefully and objectively re-evaluated our safety data and we feel that the margin of safety demonstrated is exceptionally good for a metabolic drug. I hope this will enable you to complete your consideration of our New Drug Application for M. E. R.–29. I should greatly appreciate a telephone call if there are any further problems needing discussion.

Sincerely yours,

F. JOS. MURRAY.

OCTOBER 6, 1959.

MEMORANDUM OF INTERVIEW

Present:

Dr. Wm. King and Dr. F. Jos. Murray, The Wm. F. Merrell Company, Cincinnati, Ohio.

Dr. E. L. Goldenthal, Dr. R. Megirian, and Dr. B. J. Vos, Division of Pharmacology, Food and Drug Administration.

The visitors called to discuss their NDA 12-066, M.E.R.–29, Triparanol capsules, intended for lowering blood cholesterol. They have a 6-month dog study which has been in progress 5 months at dose levels of 10 and 25 mg./kg. No adverse effects have been noted. A rat study at 3 and 10 mg. per kg. has also been completed in 5 months. These tests were not included in the original NDA because no results had been obtained. We said the top dose in both the dog and the rat tests should be higher. We advised starting a minimum of one group of dogs for a minimum of three months at the highest dose they could tolerate in the hope of producing some evidence of toxicity. Also, we advised starting 3 additional dosage groups of rats as the dosage employed was far too low. The rat study will go for one year. We stated the earliest that we could pass on safety was after these rats had completed 6 months.

B. J. Vos, M.D.

THE WM. S. MERRELL CO.,
SCIENTIFIC DIVISION,
Cincinnati, Ohio, October 13, 1959.

DR. JEROME H. EPSTEIN,
New Drug Branch, Food and Drug Administration,
Washington, D.C.

DEAR DOCTOR EPSTEIN: This will confirm our plans for meeting in your office at 10:00 a.m. on Friday, October 16, to discuss our M. E. R.–29 New Drug Application.

We have once again reviewed our animal studies in the light of your Pharmacology Division's opinion that we have not satisfactorily demonstrated safety

of the product. We, of course, continue to have confidence in the safety of M. E. R.–29, as evidenced by our intention to market in Canada where we have an effective New Drug Submission. As you well realize, we can ill afford to be wrong in our judgment on the introduction of any new product, and we do not feel that M. E. R.–29 is going to spoil our record.

We feel that the significance of the studies carried out in monkeys has been entirely overlooked. We submitted data on three monkeys dosed continuously for sixteen months. If a new drug fails to show untoward effects in three animals, such effects would probably show up only in unreasonably large groups of twenty-five or more. Such groups are impractical and not used generally.

As discussed with representatives of your Pharmacology Division, we have drug diet experiments in progress in rats at 3 mg./Kg. and 10 mg./Kg. This was set up to be a lifetime study for our own information, and because of this objective we used a dose which we were sure would not interfere with eating.

A second rat experiment was carried out with oral tubing for six weeks at 75 mg./Kg. and 37.5 mg./Kg. Some adrenal and liver (fatty infiltration) changes were recorded at the higher dose. If we had continued at this dose, we assume this would have led to more serious damage. However, it is obvious that this damage could have been nutritional instead of drug-induced, since food consumption decreased.

A third rat study was carried out with tubing for three months at 25 mg./Kg. and 50 mg./Kg. At the higher dose level there was a 36 per cent reduction in body weight gain in males starting in six weeks. Again, it is our feeling that when the animals stop eating and lose weight there is no point in going on with the experiment, since nutrition enters into the picture and findings on the tissues would be meaningless.

Your Pharmacology Division has insisted that it is essential to show toxicity (even though we feel it is more important to show lack of toxicity at therapeutic dosage and at reasonable excesses of therapeutic dosage), and we would like to point out that lack of eating has been a consistent sign of toxicity in the rats. On this basis, one might assume that the first clinical evidence of toxicity would be loss of appetite. This is borne out by our clinical experience. You will note that the Hollander and Chobanian paper reports four cases of nausea, epigastric distress or heartburn on a daily dosage of 750 mg. The symptoms disappeared on a dosage of 250 mg. The paper by Oaks and Lisan reports 13 per cent (5) subjects with nausea and vomiting at 1000 mg. per day. It was not necessary to discontinue the drug in these patients. No side effects were encountered at 250 mg. We again stress that the decrease in food consumption in animals on moderately high doses suggests we will not be able to obtain tissue damage in animals (other than fatty infiltration of the liver) without complicating the picture with inadequate nutrition.

I appreciate your taking the time to meet with me, and I hope we may be able to reach some satisfactory solution on this problem.

Sincerely yours,

F. Jos. Murray.

MEMORANDUM OF A CONFERENCE

OCTOBER 16, 1959.

Present: Dr. F. Jos. Murray, Dr. R. McMaster, The Wm. S. Merrell Company, Cincinnati, Ohio; Dr. Robert Megirian, Dr. Edwin Goldenthal, Division of Pharmacology, Food and Drug Administration; and Dr. Irwin Siegel (part time), Dr. J. H. Epstein, New Drug Branch, Bureau of Medicine.

Subject: Toxicity data for M.E.R.–29, FDA 12–066.

The representatives of the Wm. S. Merrell Company came in to discuss the existing differences concerning the toxicity data submitted in support of their new drug application for "M.E.R.–29."

Since there is a wide difference of opinion concerning what they feel is sufficient data and what we feel is sufficient, it was agreed that the company would submit additional animal work in support of their application.

The following types of studies shall continue or be instituted:

(1) Present animal work will be continued to completion.

(2) A six-month study in dogs will be run at these level(s) calculated to produce toxicity.

(3) Rats will be run for 12 months at several dose levels, one group being a pan-fed control group to determine the actual toxicity of the drug.

Results of the above studies will either be submitted at the end of three or six months for our review.

JEROME H. EPSTEIN, M.D.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., November 6, 1959.

THE WILLIAM S. MERRELL CO.,
Lockland Station, Cincinnati, Ohio.
(Attention of Dr. F. Jos. Murray.)

GENTLEMEN: Reference is made to your new drug application dated July 21, 1959, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation "M. E. R.–29."

We also acknowledged receipt of your additional communications dated September 24, 1959 and October 13, 1959.

As agreed upon by you and your colleague, Dr. R. McMaster, you will perform additional toxicity studies to further demonstrate the safety of this drug in chronic administration. We shall be happy to review this data when you feel that the evidence in the animal work is conclusive.

We shall withhold any comment on the revised labeling until the aforementioned toxicity studies are complete.

The application remains incomplete as stated in our letter of September 14, 1959.

Sincerely yours,

JEROME H. EPSTEIN, M.D.,
Medical Officer, New Drug Branch, Bureau of Medicine.

Office Memorandum, U.S. Government.

FEBRUARY 23, 1960.

To: New Drug Branch: Attn: Dr. Talbot.
From: Division of Pharmacology.
Subject: Triparanol Capsules, MER–29 (Wm. S. Merrell Co.) NDA 12–066.

The additional toxicity data submitted by Merrell have been reviewed. The original toxicity data submitted for rats included a 3 week study at 40 mg/kg/day, a 3 month study at 25 and 50 mg/kg/day and a 6 week study at 75 mg/kg/day. The consistent finding in these studies was a marked decrease in weight gain.

The new data include a 9 month study in rats administered 3 and 10 mg/kg/day in the diet. No significant effects attributable to drug administration were observed with respect to weight gain, food consumption, hematology and pathology. In addition, rats were administered 20 and 40 mg/kg in the diet for 3 months. Reductions in weight gain of 15–20% in the 20 mg/kg dosage group and 32–40% in the 40 mg/kg dosage group were observed. The food consumption paralleled the body weight response (15% less at 20 mg/kg and 36% less at 40 mg/kg). If the concentration of the drug in the diet was not increased to compensate for the reduced food intake, the actual dosage given to the animals would have been considerably less than stated. The relative weights of the liver, heart and adrenals were significantly increased over control values at both 20 and 40 mg/kg in both the male and female rats. In the rats receiving 40 mg/kg, 8 out of 20 animals had grossly visible opacity of the cornea at the end of the 3 month study. There was also an associated conjunctivitis. Several drugs (e.g. more potent narcotics, certain insecticides) have caused this effect in either mice or rats acutely and has been reversible. However, we would consider this observation in a chronic study of a more serious nature and something to be concerned about. Histologic examination of the cornea revealed inflammatory changes.

The company states that an evaluation of the dog studies is difficult because of concomitant, spontaneously occurring diseases in their dog colony with four cases of distemper being diagnosed. Whether the effects described below were due to poor animals, distemper or drug administration would be hard to evaluate. However it is our opinion that the drug is producing some of the observed effects. Three dogs were administered 10 mg/kg of MER–29 for 4 months. No effect on the peripheral blood counts were observed and in general the weights of the animals remained constant. However, both of the male dogs in the study showed some inhibition of spermatogenesis upon histological examination.

Six dogs were administered 25 mg/kg for 6 months. Three of the male dogs died early in the study. They indicated that one died of congestive heart failure secondary to heart worm infestation, and the cause of death of the other 2 was undetermined due to post mortem changes. Two of the three dogs surviving the study had distended gall bladders but the organs were normal upon histologic examination. In the one male dog surviving the study there was no indication of an effect on spermatogenesis.

Five dogs were administered MER–29 for 3 months at a dosage of 40 mg/kg/day. Three of these animals died within 6 weeks after the start of the experiment. With respect to the cause of death, they indicated that in the first dog the changes in the liver and massive interstitial hemorrhage are changes consistent with canine viral hepatitis. They indicated that the cause of death of the second animal could have been due to either the bronchial pneumonia, the acute hemorrhagic pneumonia, or hepatic failure secondary to the necrosis and inflammatory response of the liver. Gross examination of the third animal revealed the liver dark and mottled and the entire intestinal tract edematous and hemorrhagic. Histological examination of the liver showed a general ballooning of the parenchymal cells, some disruption of the hepatic cord, areas of coagulative necrosis, and extensive inflammatory response. They indicated that the most likely cause of death in this animal was hepatic failure secondary to chronic inflammatory response and cirrhotic changes in the liver.

In the two dogs surviving the study, no effect was seen in the hematological studies. Gross examination revealed the gall bladders distended and in one of the animals the liver was mottled and there was extensive mesenteric lymphadenopathy. The urinary bladder was very thick and purulent material was present in the urethra. Histological examination revealed some changes in the liver and a reduction in the number of mature spermatocytes in the seminiferous tubules, and a paucity of spermatozoa in the vas. The lymph nodes showed simple hyperplasia.

As you know the clinical dose of this drug is 250 mg daily or about 4–5 mg/kg. We would conclude on the basis of the animal toxicity studies conducted that there is little margin for safety with this drug. Certain changes seen in these animals appear to be due directly to the toxic action of the compound. The inhibition of the spermatogenesis in the dog, the effect on the cornea in the rat, the marked reduction in weight gain in the rats at relatively low dosages, all the liver changes, and the deaths of the animals lead us to conclude that this compound is producing toxic effects in the animals at relatively low dosages. We are not convinced that the changes observed in the dogs were due to distemper or hepatitis, particularly since the inclusion bodies characteristic of these diseases, particularly viral hepatitis, were not mentioned.

We are seriously concerned about the safety of the use of such a drug for reducing blood cholesterol. In the first place, we don't know if a reduction in blood cholesterol really helps the patient. To use a compound that is potentially toxic to produce such an effect is highly questionable. Besides the specific toxic potential of the drug itself, we are worried about the effects of a build-up of desmosterol in the blood. What are the long term effects of this material in the blood stream? It is certainly an abnormal condition. We do not know that perhaps desmosterol is itself atherogenic?

On the basis of the results of the studies conducted so far, we cannot see the necessity for any further animal studies. On the basis of the studies seen so far we would be opposed to this type of compound being marketed for reduction of serum cholesterol. Of course, the final evaluation of safety must be in the clinical studies. Before we release this drug for general distribution, it is our view that the company should submit results of well controlled extensive clinical studies in which the individuals have received the drug for periods of several years.

E. I. GOLDENTHAL.

THE WM. S. MERRELL CO.,
Cincinnati, Ohio, February 29, 1960.

Dr. EDWIN GOLDENTHAL,
New Drug Branch, Food and Drug Administration,
Washington, D.C.

DEAR DOCTOR GOLDENTHAL: This will confirm our recent telephone discussion on the corneal opacity reported in rats in our MER/29 NDA. As I indicated, these corneal changes have now been found in the control animals.

These findings have been discussed with our consultant, Dr. Joel G. Brunson of the University of Mississippi Medical School, who advises that such corneal changes are common in the laboratory rat. Dr. Brunson has studied sections of the eyes of rats autopsied at Merrell and he feels that the changes are inflammatory and he reports the presence of acute inflammatory cells in the sections.

I regret that this information was not available to us at the time we submitted data on corneal changes.

Sincerely yours,

F. JOS. MURRAY.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., March 28, 1960.

The WM. S. MERRELL Co.,
Lockland Station,
Cincinnati, Ohio.
(Attention of Dr. F. Joseph Murray).

GENTLEMEN: Reference is made to your new drug application dated July 21, 1959, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation "M.E.R.–29 (Triparanol Capsules)."

We also acknowledge receipt of your additional communications dated January 26, 1960, February 4, 12, 22, and 29, 1960, and March 7, 1960.

We also acknowledge receipt of a communication dated February 5, 1960, from Maumee Chemical Co., 2 Oak Street, Toledo 5, Ohio, outlining the methods, facilities, and controls they will employ in manufacturing the new drug substance, 1-p-(beta-diethyl (aminoethyl) phenyl-1-(p-tolyl)-2-(p-chlorophenyl) ethanol, they will supply you.

We have not received any statement from Strong-Cobb-Arner concerning their methods, facilities, and controls they will employ in encapsulating the material for you.

The supplemental application is incomplete under section 505(b) (1) of the Act as follows:

It fails to report the clinical studies in full detail.

The reports should include detailed information pertaining to each individual treated, including age, sex, conditions treated, dosage, frequency of administration, duration of administration of the drug, results of clinical and laboratory examinations made, and a full statement of any adverse effects and therapeutic results observed.

As brought out in our meeting of March 7, 1960 with representatives of the Wm. S. Merrell Co., we are unable to resolve the apparent discrepancy in interpretation of the pharmacologic studies in dogs between your people and ours. Because of this dispute, because of the potential hazard of liver toxicity with this drug, and further because of the highly theoretical value of taking such a drug as MER-29 (to our minds) we are making the application incomplete until longer term clinical studies have been made utilizing periodic liver function studies to show that this blocker of intermediate cholesterol metabolism is not producing liver damage.

Since the application is incomplete under section 505(b)(1) of the Act, it may not be filed as an application provided for in section 505(b).

Sincerely yours,

FRANK J. TALBOT, M.D.,
Medical Officer, New Drug Branch,
Bureau of Medicine.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., April 19, 1960.

The WM. S. MERRELL Co.
Lockland Station, Cincinnati, Ohio.
(Attention of Dr. F. Joseph Murray.)

GENTLEMEN: Reference is made to your new drug application dated July 21, 1959, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation "M.E.R.–29 (Triparanol)."

We also acknowledge receipt of your additional communication dated March 31, 1960.

Our action in allowing this application to become effective is based solely on the evidence of the safety of the drug. All claims are on your own responsibility.

It is our understanding that liver function studies will continue to be periodically carried out in all of the patients who are on long term study with this drug as discussed with your representatives Dr. F. Joseph Murray and Dr. McMaster personally on March 31, 1960. It is also our understanding that immediate report will be made to the administration of all abnormalities developing in liver function tests in patients on long term study as they relate to this drug. We further understand that precautionary remarks regarding the advisability of periodic liver function tests will be made in the proposed brochure.

In accord with the provisions of section 130.10 of the regulations and with the understanding that all of the conditions agreed to and listed above will be met, the application is now conditionally effective. It will be effective when you submit specimens of final printed labeling, incorporating the changes agreed to above, and when all of the other agreed to conditions are fully met. If the new drug is marketed prior to the submission to the New Drug Branch of specimens of such labeling, or without meeting all of the above stated conditions, the application will be considered not effective.

We recommend that you give consideration to the provisions of section 502(c) of the Act by designing the printed labeling to bear information required by the Act prominently and conspicuously as compared to other words, statements, designs, and devices; and to those of section 301(1) which prohibits the use in the labeling or in any advertising of any representation or suggestion that an application with respect to the drug is effective under section 505, or that the drug complies with the provisions of this section.

Paragraph (9) of the new drug application form is regarded as a commitment on your part that all representations in this application regarding the components, composition, manufacturing methods, facilities, controls, and labeling apply to the drug produced until an effective supplement provides for a change or the article is no longer a new drug.

Section 505(e) of the Act provides for the suspension of the effectiveness of the application if further experience and tests with the article show it to be unsafe for use or if it is found that the application contains any untrue statement of a material fact. The application may contain an untrue statement of a material fact by reason of any labeling or advertising in which you prescribe, recommend or suggest conditions of use of the drug differing from the conditions of use provided for in the application (see regulation 130.30 and paragraphs (6) and (9) of the new drug application form).

The effectiveness of this application does not extend to the drug labeled with another distributor's name, or repacked or relabeled by another person, unless covered by an effective original or supplemental application.

The effectiveness of this application under section 505 in no way relieves you of the responsibility for complying with all other provisions of the Act.

Please submit five copies of the final printed labels and other labeling and three finished market packages of the drug when available.

Sincerely yours,

FRANK J. TALBOT, M.D.,
Medical Officer, New Drug Branch,
Bureau of Medicine.

U.S. DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE,
Washington, D.C., May 12, 1960.

The WM. S. MERRELL CO.,
Lockland Station, Cincinnati, Ohio.
(Attention of Dr. F. Jos. Murray.)

GENTLEMEN: We acknowledge the receipt on April 25, 1960, of your communication dated April 22, 1960, enclosing printed labeling pursuant to your new drug application for "M.E.R.-29 (Triparanol Capsules)."

We have completed our study of this application which became conditionally effective on April 19, 1960, and in accord with the provisions of regulation 130.10 under the Federal Food, Drug, and Cosmetic Act it is effective. Our letter of April 19, 1960, detailed the conditions relating to the effectiveness of this application.

Sincerely yours,

FRANK J. TALBOT, M.D.,
Medical Officer, New Drug Branch,
Bureau of Medicine.

U.S. DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE,
Washington, D.C., October 23, 1961.

The WM. S. MERRELL CO.
Division of Richardson-Merrell Inc., Lockland Station,
Cincinnati, Ohio.
(Attention of Dr. Robert McMaster.)

DEAR DOCTOR MCMASTER: This is in reference to our forthcoming meeting at 10:00 A.M. on Thursday October 26, 1961 to discuss the problem adverse reactions attendant on the use of MER/29.

As discussed at our recent conversations while we were both attending the American Heart Association Annual Meeting, it is our considered opinion that the meeting on Thursday must include a detailed discussion of all that is known from both experimental and clinical studies concerning the toxicity of MER/29.

Since your labeling and promotional literature has repeatedly stressed the freedom from major side-effects and lack of danger connected with the use of this drug, we feel it is now necessary for you to give us the complete background information to date.

Of necessity, this would include all the information concerning eye changes in humans and animals with reference to both the corneal and lenticular (cataracts) changes. It would include information concerning the role of MER/29 in the interference with steroid hormone metabolism and endocrine balance with resulting effects on ovulation, potency, reproduction, and response to stress. Of particular importance would be information that this drug has been shown to produce a reticulocytosis in animals which implies that it produces a compensated hemolytic anemia. Of lesser importance, but still necessary, are the skin and hair changes (icthyosis, thinning, color changes, and baldness).

We feel that it is particularly important that you correct the information previously provided concerning the degree of cholesterol lowering activity exerted by MER/29. Detailed analysis of your data indicates: (1) that the degree of cholesterol lowering effect is markedly less than you have previously indicated, (2) that the distribution of cholesterol levels on patients with heart disease in the MER/29 studies is significantly higher than that expected in the typical coronary population.

These factors are important since your data indicate to us that there exists a relationship between pre-treatment cholesterol levels and the cholesterol lowering effect of MER/29. The implications are that a significant proportion of patients with coronary artery disease do not experience the degree of hypocholesteremic effect stated.

In conclusion we re-emphasize the point made in the phone conversation with Dr. F. Joseph Murray on October 19th to the effect that the William S. Merrell Co. must furnish us all data concerning adverse and toxic reactions resulting from MER/29 therapy in both animals and humans.

Sincerely yours,

JOHN O. NESTOR, M.D.,
Medical Officer, Division of New Drugs,
Bureau of Medicine.

U.S. Government memorandum.

NOVEMBER 7, 1961.

To: Division of New Drugs; attention: Dr. Nestor.
From: Division of Pharmacology.
Subject: MER–29, TRIPARANOL; The Wm. S. Merrell Co., NDA 12–066 (AF 1–542).

We have reviewed the new data submitted. We are in agreement that this application should be suspended, but are not sure of how much help we can be on the basis of this recently submitted data. We were of the opinion that this application should never have been made effective because we were not sure of its safety (See our original comments 2/23/60). On the contrary, the compound appeared to be unsafe on the basis of the chronic animal toxicity studies. However, the data submitted by the firm might not be sufficient to support a revocation of the application.

We are particularly concerned with the ability of the adrenal of patients treated with the drug to respond to stress. In animals large doses of the drug

caused adrenal enlargement with depletion of the steroids in the zona fasciculata. A recent study (Hollozy and Eisenstein, Proc. Soc. Exper. Biol. & Med. *107*, 347, 1961) shows that triparanol feeding to rats results in a reduction in the amount of corticosterone (the main glucocorticoid produced by the rat) secreted by the rat adrenal in response to the stress of surgery and bleeding.

The list of publications cited by the firm to show that a dose of 250 mg. per day has no effect on the adrenals of humans is not convincing. The paper by Melby, et al., New England J. of Med. *264*, 583 (1961) refers to this dose only in a footnote and submits no data although the paper does show that the adrenal function is severely impaired on 1000 mg. per day. The paper by Ford in Progr. Cardiov. Dis. 2, 548 (1960) shows a trend towards adrenal depression but the author says it is not significant. However, the original data was not given for calculation of the significance. In the unpublished paper by Ford, data are presented, and although the author states that the response to ACTH is not significantly changed due to the treatment with 250 mg. of triparanol daily, we have recalculated this data and find it is significant at the 5% level and approaches significance at the 1% level. The paper by Hollander, et al., J.A.M.A. *174*, 5 (1960) states that following treatment of 13 patients with 250 mg. of triparanol daily, there was a non-significant increase in the 17-ketosteroid excretion and a significant decrease in the 17-hydroxycorticosteroid excretion. The patients were not challenged with ACTH or stress in this study. This raises the question as to whether or not the pattern of steroid production by the adrenal may not be altered under triparanol therapy, so that less glucocorticoids are secreted by the adrenals or those that are secreted are less active. So far as we have been able to ascertain whether or not this question has not been studied. The paper by Goodman, Avigon and Wilson presented at the First International Congress of Pharmacology, Stockholm, 1961, may have a bearing on it but the details are lacking. In addition, this paper does not mention the dose of triparanol to the humans nor the period of treatment.

If the NDA is not suspended, we strongly recommend that a caution on impairment of adrenal function be included in the brochure.

E. I. GOLDENTHAL.
ERNEST J. UMBERGER.

MEMORANDUM OF CONFERENCE

WILLIAM S. MERRELL CO.,
Cincinnati, Ohio, November 13, 1961.

William M. Kessenich, M.D.
John. O. Nestor, M.D.
Memo of meeting.

(1) *Eyes.*—Cataracts, Corneal opacities.
(2) *Hair.*—Loss of hair, thinning and changes in color and texture.
(3) *Skin.*—Icthyosis, Urticaria, Drying, scaling, and Itching.
(4) *Reproduction.*—Impotence, Loss of Libido, Reduced Spermatogenesis, Prevention of Ovulation and conception. Abnormal offspring. Vaginal smear alterations, temporary menstrual bleeding.
(5) *Adrenals.*—Reduced production of adrenocorticoids with associated diminished ability to respond to stress.
(6) *Blood.*—Hemolytic Anemia. Leukopenia.
(7) *Liver.*—Fatty Metamorphosis. Transient increase in BSP retention.
(8) *G. I.*—Nausea and vomiting.

JOHN O. NESTOR, M. D.

DRUG WARNING—MER/29 (TRIPARANOL)

DEAR DOCTOR: In cooperation with the United States Food and Drug Administration, we are writing to inform and caution you concerning adverse effects, including some unpublished reports, associated with the use of MER/29 (Triparanol). Although comparatively few serious clinical injuries have been reported to date, their possible significance is emphasized by findings from animal studies.

Cataracts.—Four cases of cataracts in humans are reported in patients who have received MER/29. One of these cases occurred in a patient receiving the recommended dosage of 250 mg. of MER/29 daily. Cataracts and corneal opacities have also been produced with MER/29 in animals. Slit lamp examinations are necessary for early detection of developing cataracts. For this reason such examinations are indicated prior to and periodically during therapy. Before this problem came to our attention, approximately one thousand persons being treated with MER/29 were patients of ophthalmologists. Most of them have had careful eye examinations, including use of the slit lamp, before and during drug therapy. Results on these patients will be reported to you as soon as they are available.

Hair Changes.—There have been many cases of hair loss, either baldness or thinning of hair, changes in hair color and texture, and loss of body hair. Such hair changes may be related to the skin changes discussed below as well as to the eye changes described above. It is recommended that MER/29 therapy be discontinued promptly at the first evidence of hair or skin changes to minimize progressive effects possibly including eye injury.

Ichthyosis and other skin changes.—There are reports of skin reactions ranging from dryness, itching, and scaling to severe exfoliation, and ichthyosis. Some of these changes were also associated with hair loss and cataracts. It is recommended that MER/29 therapy be stopped immediately if such skin changes occur.

Depression of Adrenocortical Function.—Adrenocortical function depression as shown by reduced output of adrenal steroids has been produced by MER/29 in animals, and in man at high dosage levels. This effect has not been ruled out in humans at recommended dosage levels. Appropriate precautions should be observed if MER/29 is employed in patients with suspected borderline adrenocortical function or in patients who are subjected to stress.

Other Adverse Effects.—Other adverse clinical effects reported include 4 possible cases of leukopenia and scattered cases of abnormal liver function tests, impotence, diminished libido, vaginal smear alterations, nausea, vomiting and urine test changes simulating proteinuria. At a level of 25 mg/kg per day of MER/29 deaths have occurred in some dogs within 35 days, with liver damage in some animals. It has caused abortion and prevented conception in rodents, diminished spermatogenesis in dogs, stopped egg laying in chickens, and was assumed to cause acute intravascular hemolytic episodes in some dogs in one study.

The side effects of all types reported to us to date total substantially less than one percent of the patients treated. This includes a number of patients who have been treated with MER/29 in clinical research studies for continuous periods of more than a year, including a few in excess of three years.

In view of all reports concerning adverse effects, it is recommended that MER/29 be used only in patients who can be maintained under very close supervision and frequent observation. Dosage should never exceed 250 mg. per day.

Further studies are under way to assess more fully the incidence and seriousness of adverse effects, with a view to a re-evaluation of the conditions and indications for use of MER/29. We will appreciate any information you may contribute from your clinical experience with MER/29.

Sincerely,

CARL A. BUNDE, Ph. D., M.D.
Director of Medical Research.

U.S. Government Memorandum.

WILLIAM S. MERRELL CO.,
Cincinnati, Ohio, April 9, 1962.

To : Administration : Attention : Division of Regulatory Management.
From : Cincinnati District.
Subject : MER 29 investigation.

As arranged in the telephone conversation between Mr. Goldhammer and Mr. Maraviglia of 4/3/62, Dr. John O. Nestor, Dr. Edwin Goldenthal, and Supervisory Inspector Thomas M. Rice proceeded to the referenced firm on April 9, 1962. Mr. Fred Lamb, Attorney for the firm was first interviewed and given the Notice of Inspection, copy attached.

This notice was given at 10:55 A.M., and shortly thereafter, Mr. Lamb arranged for a conference with officials of the firm and the callers.

Those present during the morning are as follows: Fred Lamb; Dr. George O. Sharp; Dr. F. Joseph Murray; Dr. Harold W. Werner; Dr. Carl Bunde; Dr.

Robert H. McMaster; Frank Getman; E. R. Beckwith; and Dr. E. F. Van Maanen.

During the morning, only three of the above individuals participated actively in the discussion and were present during the bulk of the morning visit. These were Dr. F. Joseph Murray, Dr. Robert H. McMaster and Dr. Carl Bunde.

The morning discussion was spent primarily in discussing clinical problems relating to the work on humans, primarily between Dr. Nestor and these three gentlemen.

Dr. Nestor pointed out that he was primarily interested in getting details of reports concerning adverse effects of MER 29 since February 23, 1962. During this phsae of the investigation, it was agreed that the firm had already furnished a list up to March 9, but without individual case histories. The representatives of the firm assured Dr. Nestor that these case histories would be forwarded to him.

During the morning, we had a general discussion concerning the incidence and prevalence of cataracts in both the general population and in people who are treated with MER 29.

At this time, Dr. McMaster informed us of two additional cases of cataracts which had been reported to the company since March 9th. One of these was a six year old boy at the Mayo Clinic.

We agreed to meet with Dr. Van Maanen after lunch to discuss some animal toxicity studies on MER 29.

After lunch, we met with Dr. Van Maanen, Dr. F. Joseph Murray and Dr. William King in Dr. King's office. Dr. King asked us what information we desired to see, and Dr. Goldenthal advised him that we desired to see some of the raw worksheet data on the chronic studies on rats, dogs and monkeys administered MER 29. First, a general discussion was had in regard to the general occurrence of cataracts in these three species who had received MER 29 chronically.

Dr. King stated that in their recent dog studies, all of the dogs receiving 40 milligrams per kilogram body weight of MER 29 developed cataracts after six and a half months of treatment. They had conducted similar studies in dogs in which the dogs had received supplemental vitamin administration, and after approximately 7 months of MER 29 administration, the compound was stopped, and the animals were given 2 gm of cholesterol per animal daily. Two of the five dogs in the study died earlier in the study. They showed all the signs typical of adrenal insufficiency. The three surviving dogs were not sacrificed and were kept on a normal control diet plus cholesterol supplement. Dr. King reported that the cataracts in these dogs appeared to be regressing.

At this point, Dr. King was asked if they saved all tissues and slides from the autopsies on all of the animals receiving MER 29. Dr. King replied in the affirmative.

At this point, Dr Nestor asked if they had any way of detecting MER 29 in the tissues. Dr. Van Maanen replied that they had no method for detecting MER 29 in the tissues.

Dr. Nestor then asked if the eyes of the monkeys had been examined, and if they had been preserved. Dr. King checked and then replied that the eyes had not been studied and had not been preserved.

As a result of this line of questioning, we then asked to see the raw data on the monkey studies. Dr. King then got a bound notebook and showed us a monkey study on MER 29. However, the notebook produced contained a monkey study which was not included in their New Drug Application. None of the monkey identification numbers matched the numbers in the New Drug Application. During this time, Dr. Murray had sent from his office a copy of their animal data on MER 29 which was part of the NDA. On the autopsy sheet of the monkeys in the New Drug Application, it was stated that the data on the monkeys was contained in Notebook 848 R. We then asked Dr. King if we could see this notebook. Dr. King ordered this notebook produced. A reference to these monkeys labeled M25, M34, and M51 were found on page 16 of this notebook. On this page, it was stated that the monkeys were started on the drug, MER 29 on 4/7/58 at a dose of 10 milligrams per kilo body weight twice a day. From the autopsy sheets in the NDA, these three animals were autopsied in February, 1959. Dr. King was asked how this represented sixteen months of administration as represented in the NDA. At first, he was unable to explain this and later Dr. Van Maanen stated that this was a second phase of this study and that the animals had received a higher dose of MER 29 for six months prior to this.

At this point, it should be noted that the raw data was not recorded on separate sheet in sequence, but was reported in four separate notebooks together with many other studies. These notebooks were labeled numbers 770 R, 799 R, 848 R, and 904 R. These were bound notebooks which contained carbon copies of the original data. These originals reportedly have been filed in the firm's library.

Upon review of the raw data, it was observed that animal M51, a male monkey first appeared on 6/19/58. This animal was started on MER 29 on 6/23/58. On page 19 of Notebook 904 R, it was stated that this animal was autopsied on 3/4/59. As submitted in the NDA, this animal had received sixteen months of medication with MER 29. Dr. King was asked to explain this discrepancy of approximately 8 months. He had no immediate explanation, in fact he could not explain this discrepancy. He searched through the earlier part of this study and could find no mention of animal M51. At this point, he asked one of his assistants to obtain the original weight charts on this study. Dr. King then presented a weight chart titled Fig. 8 on three monkeys receiving MER 29 and three control monkeys. A copy of this is attached. Dr. King looked over this weight chart, and admitted that monkey M51 had not been started on MER 29 at the beginning of the experiment (9/9/57). At this point, Dr. Goldenthal pointed out that the weight charts submitted with the NDA indicated that this animal had received MER 29 for sixteen months. In fact, monthly weights were given for this animal from zero to seventeen months.

Dr. King was asked to explain this discrepancy. Dr. King then asked his assistants to see if they could get more information on this point. During this time, Dr. Goldenthal pointed out that on this chart (Fig 8) that monkey #49 had a severe weight loss between 45 and 50 weeks of the experiment. At this point, Dr. King's assistant brought in four additional weight charts which were titled, "Monkeys Chronic Oral Toxicity WSM 5052 (MER 29) Body Weights". (Copies attached). Dr. King studied these charts for several minutes and then said these were the original weight charts of this monkey study. This study covered from 0 to 352 days. It is apparent that this is only the last year of the study rather than the full study. On the first sheet, it is indicated that monkey #51 was started on the drug (MER 29) on day 96. Dr. Goldenthal again asked Dr. King about the severe weight loss on monkey M49 on the last sheet of these charts between days 2/5/59 and 3/5/59. Dr. King could not explain this weight loss. Dr. King and Dr. Goldenthal then looked over the notebooks to find the source of these body weights. On page 100 of Notebook 848 R, the weights for monkey 49 on 2/5/59, 2/12/59 and 2/19/59 were given. On the continuation of this study on page 18 in Notebook 094 R, the weight of monkey 34 was given at 7.5 kilograms on the day of autopsy 3/5/59. These body weights in the notebook corresponded to the weights in the fourth page of the charts. Dr. Goldenthal asked Dr. King to explain the discrepancy between this data and the data reported in the NDA. In the NDA, animal 49 showed a weight gain in the last month of the study rather than a weight loss. Dr. King was unable to explain this discrepancy. It should be noted that this weight loss was from 9.9 kilograms to 7.5 kilograms or a loss of 2.4 kilograms equivalent to 5.3 lbs. Dr. Goldenthal asked Dr. King who prepared the four weight charts. Dr. King was also asked if he prepared them personally. Dr. King replied that he did not prepare the charts personally, but that he assumed that they were prepared by the two employees named Jo Jordan and B. Umberger whose names were signed at the bottom of the raw data sheets.

Dr. Goldenthal pointed out to Dr. King that monkey # M25 from data in the NDA was autopsied on July, 1958, monkey # M34 was autopsied on 2/19/59, monkey # M51 on 2/19/59, and monkey F49 on 2/26/59. Dr. Goldenthal asked Dr. King the meaning of the autopsy numbers. Dr. King replied that the first number 59 indicated the year of autopsy, and the second number indicated the number of the animal autopsied that year. Dr. Goldenthal asked Dr. King if the autopsy numbers were assigned in sequence as the monkeys were autopsied. Dr. King replied in the affirmative. Dr. Goldenthal then asked Dr. King why monkey F49, which the NDA states was autopsied on 2/26/59, actually had an autopsy number of 59–101, while animals M34 and M51 which the NDA states were autopsied on 2/19/59 actually had autopsy numbers of 59–102 and 59–103. Dr. King was unable to explain this break in normal sequence. Dr. King speculated that perhaps animal F49 had been planned to be autopsied earlier than animals M34 and M51. However, no satisfactory answer was given.

We then turned our attention to pages 18 and 19 of Notebook 904 R. On these pages, it was stated that monkeys number F49 and M51 were autopsied on 3/4 and 3/5/59. The NDA states these days as 2/26/59 and 2/19/59 respectively. Dr. King was asked to explain these discrepancies between autopsy dates and those given in the NDA. Dr. King asked who initiated the date in the NDA and soon saw that he had initialed it. He had no explanation for this discrepancy. Dr. King then asked his assistant to see if he could get some explanation for this from the Pathology laboratory. Dr. Goldenthal pointed out that weights for these animals were given through 3/5/59 on the company's own charts. (Copies attached.)

Dr. King's assistant returned and said that hematology studies were performed on monkey M49 on 3/3/59, so this animal had to be alive on this date. Dr. King then assured us that this animal was sacrificed on 3/5/59 as given in their worksheet (Bound notebook 904 R) rather than on 2/26/59 as reported in the NDA. Dr. Goldenthal asked Dr. King the location of the autopsy notes in their bound notebook on monkey M34. Dr. King was unable to answer or find this autopsy information in the bound notebooks. At this point, Dr. Van Maanen questioned Dr. King as to the location of this data and stated that this data should be in the notebook. Dr. King assured Dr. Van Maanen that this data was somewhere in the notebooks, and that he would search all of the notebooks and locate it. Dr. King's assistant then came in with some information from the firm's Pathology laboratory which gave new dates for autopsy of these animals. These were on 5 x 8 cards, and gave autopsy dates of other monkeys in addition to those monkeys receiving MER 29. Dr. King then explained that the Pathology lab received the tissues on the same date that the autopsies were conducted. A third date for the autopsy for animal M34 was obtained from these 5 x 8 cards, namely 2/26/59. From these cards also was obtained an autopsy date of 2/19/59 for monkey M51. This date agreed with that given in the NDA for monkey M51, but differed from the date of autopsy found in the raw data notebook, which was 3/4/59. From these 5 x 8 cards, an autopsy date of 3/5/59 was given for monkey number M49. This agreed with the data in the bound notebook, but differed from that given in the NDA which was 2/26/59. Dr. Goldenthal pointed out that on their own weight charts (copies attached) weights were given for these 3 monkeys through 3/5/59. Dr. Goldenthal asked Dr. King to explain these discrepancies. Dr. King had no explanation for these discrepancies in the autopsy dates.

Dr. Goldenthal then asked Dr. King if the charts could be borrowed reproduction purposes. Dr. King turned to Dr. Van Maanen and Dr. Murray and obtained their permission to lend us these charts. Dr. King was then asked for permission to borrow the raw data notebooks for purposes of reproducing the data sheets. Dr. King stated that he would have to have higher authority for this. Dr. Murray consulted with Mr. Lamb, the firm's attorney, and then reported that it was against company policy to permit removal of the notebooks from the premises, but that the firm would duplicate any pages we desire. We indicated we would like copies of the following pages:

Notebook 770–R—page 40.
Notebook 770–R—page 78.
Notebook 799–R—page 16.
Notebook 799–R—page 45.
Notebook 799–R—page 59.
Notebook 799–R—page 75.
Notebook 848–R—page 16.
Notebook 848–R—page 56.
Notebook 848–R—page 75.
Notebook 848–R—page 100.
Notebook 904–R—page 18.
Notebook 904–R—page 19.

These pages were to be reproduced from the originals in the firm's library, and also the firm was going to attempt to copy the carbon copies in the bound notebooks.

We then left Dr. King's office, and while proceeding from Dr. King's laboratory to the firm's conference room in the Administration Building, Dr. Van Maanen stated that Dr. King had already called the firm's librarian to locate the desired pages and start the desired reproductions.

Before leaving the firm, Dr. Murray stated that Dr. Werner wanted to confer with us.

We then met in the conference room in the Administration Building and the following people were present during the final discussion on April 9, 1962: Mr. E. R. Beckwith; Mr. R. H. Woodward; Dr. H. W. Werner; Mr. Fred Lamb; and Dr. F. Joseph Murray.

Dr. Van Maanen was excused at this time to return to work and to collect the data which we had requested. During this final conference, Mr. Beckwith asked if we were satisfied with the results of our visit and Dr. Nestor replied that we had received the utmost cooperation and that nothing was denied us except the bound notebooks which the firm agreed to duplicate for us. We stated that we had discovered some discrepancies in the monkey studies which had not been explained to our satisfaction.

Mr. Beckwith thereupon stated he intended to discuss this matter with Dr. King and get some explanations of his own. Dr. Murray asked if we would be returning to their firm on the following day. We replied that we would like to have some answers to the questions we had raised and we would either phone or return the following day. Inspector Rice promised to return the borrowed weight charts as soon as copies had been made.

We left the plant at approximately 5:15 P.M.

Dr. NESTOR.
Dr. GOLDENTHAL.
THOMAS M. RICE, *Inspector.*

Enclosures [omitted].

U.S. Government Memorandum.

WILLIAM S. MERRELL CO.,
Cincinnati, Ohio, April 10, 1962.

To: Administration; Attn: Division of Regulatory Management.
From: Cincinnati District.
Subject: MER 29.

Refer to our memorandum of April 9, 1962 concerning this investigation. This is a continuation of this same investigation. On the morning of April 10, 1962, Dr. Nestor, Dr. Goldenthal, and Supervisory Inspector Rice returned to the firm. Mr. Fred Lamb was first interviewed and he was asked if he desired another Notice of Inspection. He replied that insofar as he was concerned, he would consider this a continuation of the inspection of April 9, 1962.

At this time, a conference was held between the callers, Mr. Fred Lamb, Mr. E. R. Beckwith, Mr. R. H. Woodward, and Dr. F. Joseph Murray, and the weight charts we had borrowed to reproduce were returned to Dr. Murray.

These gentlemen were first asked whether or not they had uncovered any explanations for the discrepancies in the monkeys receiving MER 29 which we noticed on April 9, 1962. Mr. Beckwith replied that although they had worked late the evening of April 9th, and the morning of April 10th prior to the time we had arrived, they had still not been able to find any explanation for the discrepancies we had noticed.

Mr. Beckwith asked that we set forth in detail a summary of the discrepancies we had noticed. Dr. Nestor enumerated the following points:

1. Marked loss of weight in monkey F49 during the last five weeks of the study which was not reported in the NDA, but which was in the raw data in their notebooks, and on the charts.

2. No record of any autopsy was found on monkey #M34 in the raw data recorded in the notebooks.

3. The conflict in dates of autopsy for monkeys #M34, M51, and F49. We had found there were up to three dates given for the autopsy of some of these animals. The dates for the autopsies in the NDA were at variance with the dates found on the charts, the notebooks, and the 5 x 8 cards kept by the Pathology laboratory.

4. The fact that monkey #M51 according to the NDA had been on MER 29 for sixteen months, while in the notebooks and the charts supplied by the firm, this monkey was placed on MER 29 about the midpoint in the experiment and received MER 29 for only eight months.

5. A discrepancy was noticed in the autopsy numbers as to proper sequence in respect to the date of the autopsy, especially with respect to monkey #F49.

Dr. Nestor brought out the fact again that there were no studies on the eyes of the monkeys on MER 29 and these tissues had not been examined nor had the eyes been preserved. In connection with this, Dr. Nestor pointed out the great significance we had attached to these monkey studies in connection with approving the NDA for MER 29. Dr. Nestor pointed out that our Division of Pharmacology had made an issue of the Pathology in rats and dogs, and the William S. Merrell Co. representatives had countered by pointing out that monkeys were of a higher order and, therefore, closer to man, and that their monkey studies had not demonstrated any pathology and that this was, therefore, a very strong argument for making their NDA effective. Dr. Nestor further pointed out that had the Food and Drug Administration known of these discrepancies in the monkey studies, it was conceivable that the NDA would never had been made effective.

Dr. Nestor stated that we desired to make some further checks on raw data of the monkeys, and in particular we desired to review any data they had in regards to the feeding of the monkeys. Dr. Nestor stated that in particular, we were interested in any notes which could be located which would bear upon any abnormalities observed in connection with monkey #F49 which had lost so much weight during the final month of the studies. Dr. Nestor stated that we were interested particularly in any notes regarding the monkeys appetite, activities, and any evidence of illness.

At this point, Mr. Beckwith arranged for us to interview Dr. King again in his office, and asked that we return and see him prior to leaving the firm.

We then proceeded to Dr. King's office with Dr. Murray, and Dr. Van Maanen. Dr. King was then interviewed and he was asked whether or not he had been able to account for the discrepancies which we had observed the previous day. Dr. King stated that up to this point, he has not been able to explain any of these discrepancies.

At this point, we again checked the data on monkey #F49 to be sure that there was no misunderstanding on our part concerning the duration of the experiment, the weight loss, and the dates. We found our previous understanding to be completely correct, and although Dr. King attempted to convince us that there had been an error on projecting the data onto the charts and that the loss of weight was small, he finally had to admit that our figures were correct, in that monkey F49 had lost 2.4 kg. during the last 5 weeks of the study.

Dr. King then recalled that monkey F49 had lost considerable weight toward the end of the experiment and that he would attempt to find some notes to explain what happened.

Dr. King was asked for any records or notes he might have of observations concerning the feeding of the monkeys on this MER 29 experiment. Dr. King said that he could not recollect whether or not they had any such records, but he had a hazy memory that there was something. He said that up to this point, he had not been able to locate any such records, but that he would continue searching for such. Dr. King said that it was very difficult to keep an actual record of food consumed because the monkey threw the food around a great deal, making calculation of food consumed very difficult. Dr. Nestor asked Dr. King the name of the employee who had secured the charts for us yesterday. Dr. King said that this was one of his assistants and his name was Fred Holthaus. Mr. Holthaus came in briefly during this interview. Mr. Holthaus said that he had been employed by the firm during the time the MER 29 studies were being conducted, but he was in a different department, and knew nothing of the studies himself. He said he had been working with Dr. King since June of 1959.

Dr. Nestor then asked Dr. King as to the whereabouts of Jo Jordan and B. Umberger whose names appeared at the bottom of the raw data charts in the bound notebooks. Dr. King said that he had heard nothing from Jo Jordan for sometime and did not know her whereabouts, but B. Umberger had left the firm to attend Ohio State University at Columbus, Ohio. He said neither of these employees were with the firm at this time.

Also, we inquired as to Mr. J. K. Smith whose name appeared at the top of the raw data charts in the bound notebooks. Dr. King stated that Mr. Smith was his predecessor. He said that Mr. Smith left the firm in June, 1959. He said Mr. Smith is now with Riker Laboratories in North Ridge, California. Dr. King stated that he joined the firm in September of 1958 and was definitely in charge of the MER 29 studies at the close of the experiment. He admitted that he personally had conducted all of the autopsies.

Prior to leaving the firm, we returned to the conference room in the Administration Building and conferred with Mr. E. R. Beckwith, Dr. Harold W. Werner, R. H. Woodward, Fred Lamb, and Dr. F. Joseph Murray.

We told these gentlemen that we had not been able to find any notes regarding the food consumption and observations made on the monkeys, and that Dr. King still had not been able to offer any explanation for the discrepancies noted.

Mr. Beckwith reconfirmed his earlier statements of their intention to explore this very thoroughly to try to find answers for their own satisfaction. Mr. Beckwith also stated that he would try to get all of the copies of the records we desired as soon as possible.

DR. JOHN O. NESTOR.
DR. EDWIN GOLDENTHAL.
THOMAS M. RICE,
Supervisory Inspector.

Enclosure [omitted].

U.S. Government Memorandum.

WILLIAM S. MERRELL CO.,
Cincinnati, Ohio, April 11, 1962.

Division of Regulatory Management, Attn: Mr. Goldhammer.
Division of Pharmacology.
MER–29 Investigation (AF 1–942).

Along with Dr. Nestor of Division of New Drugs and Thomas M. Rice of the Cincinnati District, I visited the William S. Merrell Company in Cincinnati, Ohio on April 9 and 10 and copies of our memoranda of these visits have been directed to you. As will be noted in these memoranda, certain discrepancies between the original chronic monkey studies submitted in their new drug application and those found in their data notebooks have been disclosed. These discrepancies are not mistakes on the part of the William S. Merrell Company, but represent the submission of fraudulent and misleading data to FDA. The net effect of this misleading data was to make the drug appear less toxic in monkeys than was actually the case. This is particularly significant since at the time of our consideration of the NDA, representatives of the William S. Merrell Company presented strong arguments against the toxicity observed in rats and dogs in that a higher species, monkeys, which are closer to man than rats or dogs, showed no signs of toxicity upon chronic (16 months) administration of MER–29.

These discrepancies uncovered in our recent visit support the affidavit of Mrs. Jo Jordan in that fraudulent data was submitted to FDA on the monkeys administered MER–29 chronically.

On the basis of the affidavits of Mrs. Jo Jordan and Mr. Bruce Umberger (former employees of the William S. Merrell Company) and of the numerous discrepancies disclosed in Merrell's monkey study on MER–29, we strongly recommend that NDA 12–066 be suspended. In addition, we feel that sufficient evidence has been obtained to support prosecution of the corporation and the individuals involved and would recommend such action.

EDWIN I. GOLDENTHAL, Ph. D.

United States of America
Department of Health, Education, and Welfare

FDC–D–71

In the Matter of MER/29 (triparanol) capsules. New Drug Application No. 12–066

WM. S. MERRELL COMPANY, CINCINNATI, OHIO, APPLICANT

SUSPENSION ORDER

Wm. S. Merrell Company, Cincinnati, Ohio, the applicant for and the holder of effective New Drug Application No. 12–066 applying to MER/29 (triparanol) capsules, having requested the suspension of the effectiveness of said application, on the ground that clinical experience shows the drug is unsafe for use under the conditions of use upon the basis of which the application became effective, and thereby having waived Notice of Hearing as provided by Section 505(e) of the Federal Food, Drug, and Cosmetic Act, prior to such suspension;

The Commissioner of Food and Drugs, by virtue of the authority vested in the Secretary by the provisions of the Federal Food, Drug, and Cosmetic Act [Section 505(e); 52 Stat. 1052; 21 U.S.C. 355(e)] and delegated to the Commissioner by the Secretary (20 FR 1996) finds that clinical experience shows that MER/29 (triparanol) capsules are unsafe for use under the conditions of use upon the basis of which the application became effective;

Wherefore, on the foregoing finding of fact and the request of the applicant, the effectiveness of New Drug Application No. 12-066 applying to MER/29 (triparanol) capsules is suspended, effective May 22nd, 1962.

Dated May 22, 1962, at Washington, D.C.

G. P. LARRICK,
Commissioner of Food and Drugs.

THE WM. S. MERRELL CO.,
Cincinnati, Ohio, December 1, 1961.

DRUG WARNING—MER-29 (TRIPARANOL)

DEAR DOCTOR: In cooperation with the United States Food and Drug Administration, we are writing to inform and caution you concerning adverse effects, including some unpublished reports, associated with the use of MER/29 (triparanol). Although comparatively few serious clinical injuries have been reported to date, their possible significance is emphasized by findings from animal studies.

Cataracts.—Four cases of cataracts in humans are reported in patients who have received MER/29. One of these cases occurred in a patient receiving the recommended dosage of 250 mg. of MER/29 daily. Cataract and corneal opacities have also been produced with MER/29 in animals. Slit lamp examinations are necessary for early detection of developing cataracts. For this reason such examinations are indicated prior to and periodically during therapy. Before this problem came to our attention, approximately one thousand persons being treated with MER/29 were patients of ophthalmologists. Most of them have had careful eye examinations, including use of the slit lamp, before and during drug therapy. Results on these patients will be reported to you as soon as they are available.

Hair Changes.—There have been many cases of hair loss, either baldness or thinning of hair, changes in hair color and texture, and loss of body hair. Such hair changes may be related to the skin changes discussed below as well as to the eye changes described above. It is recommended that MER/29 therapy be discontinued promptly at the first evidence of hair or skin changes to minimize progressive effects possibly including eye injury.

Ichthyosis and other skin changes.—There are reports of skin reaction ranging from dryness, itching, and scaling to severe exfoliation, and ichthyosis. Some of these changes were also associated with hair loss and cataracts. It is recommended that MER/29 therapy be stopped immediately if such skin changes occur.

Depression of Adrenocortical Function.—Adrenocortical function depression as shown by reduced output of adrenal steroids has been produced by MER/29 in animals, and in man at high dosage levels. This effect has not been ruled out in humans at recommended dosage levels. Appropriate precautions should be observed if MER/29 is employed in patients with suspected borderline adrenocortical function or in patients who are subjected to stress.

Other Adverse Effects.—Other adverse clinical effects reported include 4 possible cases of leukemia and scattered cases of abnormal liver function tests, impotence, diminished libido, vaginal smear alterations, nausea, vomiting and urine test changes simulating protoinuria. At a level of 25 mg/kg per day of MER/29 deaths have occurred in some dogs within 35 days, with liver damage in some animals. It has caused abortion and prevented conception in rodents, diminished spermatogenesis in dogs, stopped egg laying in chickens, and was assumed to cause acute intravascular hemolytic episodes in some dogs in one study.

The side effects of all types reported to us to date total substantially less than one percent of the patients treated. This includes a number of patients who have been treated with MER/29 in clinical research studies for continuous periods of more than a year, including a few in excess of three years.

In view of all reports concerning adverse effects, it is recommended that MER/29 be used early in patients who can be maintained under very close supervision and frequent observation. Dosage should never exceed 250 mg. per day.

Further studies are under way to assess more fully the incidence and seriousness of adverse effects, with a view to a re-evaluation of the conditions and indications for use of MER/29. We will appreciate any information you may contribute from your clinical experience with MER/29.

Sincerely,

CARL A. BUNDE, Ph. D., M.D.,
Director of Medical Research.

U.S. Government Memorandum.

WM. S. MERRELL CO.,
Cincinnati, Ohio, February 13,1962.

To: Bureau of Field Administration.
From: Cincinnati District.
Subject: MER 29; NDA 12-066; NDA 13-320.

For your information in connection with your consideration of the status of this new drug, the following interesting sidelight was recently encountered:

Mrs. Jo Jordan, who is the wife of a member of the same car pool of Inspector Rice, formerly worked at the Wm S. Merrell Company under Dr. King. She worked about two years ago during the time when the research was being done on the Mer 29.

Mrs. Jordan suspected that Dr. King falsified the records on the animal studies concerning the Mer 29 to make the reports look good.

After about one year working in the animal testing laboratories under Dr. King, Mrs. Jordan resigned her job because of dissatisfaction with the way Dr. King was running the work.

She feels very strongly that Dr. King was dishonest in his dealings with her and had no qualms about doctoring up the results of the studies.

THOMAS M. RICE,
Supervisory Inspector, Cincinnati District.

U.S. Government Memorandum.

WILLIAM S. MERRELL CO.,
Cincinnati, Ohio, February 27, 1962.

To: Bureau of Field Administration.
From: Cincinnati District.
Subject: Mer 29.

In response to your memo of February 23, 1962, Mrs. Jordan was interviewed the evening of February 26 and the following information was secured.

Mrs. Jo Jordan presently resides at 3825 Trebor Dr., Cincinnati 36, Ohio. She was somewhat reluctant to discuss the events which occurred while she was working at this firm, but agreed to do so provided the information was kept strictly confidential.

Mrs. Jordan is a graduate of Holmes High School in Covington, Kentucky. Following this, she worked one year in a hospital in the field of nursing, and worked with Dr. C. J. Hudson, who is an oral surgeon for six years. She worked as a technician at Wm. S. Merrell Co., of Cincinnati, Ohio for approximately 2 years during 1957 and 1958.

She was under the direction of Dr. William J. King, during the latter part of this period, and it was during this time that she was engaged in the study in toxicology on Mer 29 using monkeys.

Mrs. Jordan's duties included bleeding the monkeys, running blood counts, assisting with autopsies, making up capsules of Mer 29 and placebos for the control groups, assisting with dosing both control groups and drug groups by poking the respective capsules down the throats of the monkeys, weighing food the monkeys ate, weighing the monkeys periodically, checking the monkeys reactions, preparing the graphs following autopsy, etc.

She recalls that Mer 29 was used on this toxicological study for a number of weeks. There were three or four monkeys in the drug group and a similar number in a control group.

Mrs. Jordan carefully weighed up the capsules containing the Mer 29 for the drug group, and prepared similar capsules containing sugar for the control group. The capsules of sugar were poked down the throats of the con-

trol group in the same manner as the Mer 29 was poked down the throats of the drug group so that the same irritation would be present in both groups.

At the close of the study, Mrs. Jordan had to work up graphs depicting the observations and took these to Dr. King. He asked which were the control monkeys and which were the drug monkeys. Dr. King's superior, whose name was not specifically recalled at this time, but which starts Dr. Vaughn or Dr. Van, decided to throw out a drug monkey and replace it with another control monkey which was never on the drug prior to autopsy. Mrs. Jordan said the one monkey that was thrown out at the end of the experiment and was never autopsied was doing very poorly after being on the drug. She said you could tell by the expression of the monkey, his actions, the expression in his eyes and his disposition. This monkey had become somewhat mean and acted angry. Mrs. Jordan believes that if this monkey had been left in, the results would have been very unfavorable. She said this monkey was definitely sick, that the eyes did not look right, and that the monkey laid on the bottom of the cage. She said because of the decision to take this monkey out of the drug group, that it was necessary for her to work up the charts three different times.

She said that Dr. King went along with the decision of his superior 100% and ordered all of those who worked on the monkeys never to mention it. The workers were told that this was the way the company wanted it and just to forget it.

Mrs. Jordan said that the following individuals were also in on this experiment, and all of these individuals are no longer employed at Merrells.

1. Dorthy Miner: This individual is now in Florida and her address is not known. Her job was primarily preparing and staining slides.
2. Mary Ann Stephens: She is now married and her married name is not known. Her duties involved drug work, but she did not work directly with the monkeys.
3. Mike: Mike's last name is not known. This individual quit and went back to school. His primary duties were taking care of the monkeys.
4. Bruce Umberger: This individual is now living in Columbus, Ohio, but his exact address is not known. This individual did the same work as Mrs. Jordan. One of his duties was to weigh the monkeys that Mrs. Jordan was unable to catch.

Mrs. Jordan also knows that on a number of occasions the capsules of Mer 29 were not actually given to the drug monkeys because they became very leery and were difficult to catch and hard to force the capsules down their throats. She knows that the reports were simply marked to the effect that the drugs were given, but since she is the individual who made up the capsules for the experiment, she knows exactly how many she made and knew that all of them were not used which were supposed to have been used.

Mrs. Jordan stated that Dr. King was an alcoholic and frequently was drinking on the job. Personally he owed money to Mrs. Jordan at the time she resigned her position because he did not repay her for supplies purchased for some of the experimental work. She resigned because she became "fed up" with the manner in which Dr. King was operating this research facility.

THOMAS M. RICE,
Supervisory Inspector.

U.S. Government Memorandum.

WILLIAM S. MERRELL CO.,
Cincinnati, Ohio, March 14, 1962.

To: Bureau of Field Administration; Attention: D. C. Hansen.
From: Cincinnati District.
Subject: Mer 29.

In response to your memorandum of March 7, 1962, we have now interviewed Mr. Bruce I. Umberger, Columbus, Ohio, and have secured from him the enclosed signed affidavit. This three page affidavit was worked up the evening of March 12, 1962. Inspector Rice interviewed Mr. Umberger alone. The affidavit was finally completed, sworn to by Mr. Umberger, and signed shortly after midnight so the affidavit is dated March 13, 1962. Prior to signing the affidavit, Mr. Umberger was formally sworn by having him hold up his right hand and swearing that the affidavit he was about to sign was true.

Following Mr. Maraviglia's phone conversations with you on March 13, 1962, Mrs. Beulah L. Jordan was again interviewed the evening of March 13, 1962. Inspector Rice interviewed her in the presence of her husband, Mr. Carson F. Jordan. During this interview a four page affidavit was drawn up, sworn to, and signed by Mrs. Jordan, and this is also enclosed. Prior to her signing this affidavit in the presence of her husband and Inspector Rice, she was sworn by having her raise her right hand and swearing that the affidavit she was about to sign was true.

Mr. Umberger is presently the assistant manager of the Broad-Lincoln Hotel, 631 East Broad Street, Columbus, Ohio. He also resides at this same address. He was employed at the Wm. S. Merrell Co., Cincinnati, Ohio, in the Toxicological Laboratory from September 1957 to September 20, 1959. Mr. Umberger is single, and was in the Army for three years subsequent to his graduation from Annville High School, Annville, Pa., in 1954.

Mr. Umberger left the Wm. S. Merrell Co. in order to register for college in the Ohio State University College of Veterinary Medicine. He recalls that he left the firm Friday, September 20, 1959, because he had to matriculate at Ohio State University on September 25, 1959. Mr. Umberger had planned to continue through school under the G.I. Bill, but because one of the checks was delayed he was forced to withdraw after two quarters because of financial problems.

Mr. Umberger was not dissatisfied with his job at the Wm. S. Merrell Co. and would be interested in going back to work for them. He is not certain at this time whether or not he would be able to do this since he left the firm at a rather inopportune time.

It was learned in the subsequent interview with Mrs. Jordan that Mr. Umberger got along very well with Dr. William M. King. Incidentally, Dr. King's name was incorrectly reported as "Dr. William J. King" in our memorandum of February 27, 1962.

With regard to the Mer 29 toxicity studies on monkeys, Mr. Umberger knows that the experiment ran approximately 18 months. He knows that it involved from 6 to 8 monkeys of which 3 were in the "drug" group, and the remaining 3 or 4 were in the "control" group. He knows that 3 control monkeys and 3 drug monkeys were carried through the entire experiment, while one each of the control and drug monkeys were autopsied approximately 6 or 7 months after the start of the experiment.

His duties included conditioning the monkeys for 6 weeks to 3 months before they were placed on the experiment. This included assisting in treating the monkeys for dysentery if this was needed, and in holding the monkeys when they were given penicillin shots and tested for TB. He also, weighed, handled, and observed the monkeys during their period of acclimation to make certain they were healthy animals and entirely suitable for the program. After the monkeys were placed on test, he helped hold the monkeys when they were given the capsules so that the capsules could be pushed down their throats. In order to dose a monkey, it was sometimes necessary for Mr. Umberger to hold the monkey's hands behind the monkey's back with one hand while Umberger forced the monkey's cheeks between the monkey's upper and lower jaw with his other hand. In this way the capsules could be placed in the back part of the monkey's mouth and pushed down the monkey's throat so the capsules would have to be swallowed. The monkey's throat was then massaged to make sure the capsules actually were swallowed.

During the course of this experiment on Mer 29 Mr. Umberger carefully observed the monkeys and helped in making notes and observations. Mr. Umberger recalled that these observations were recorded with a carbon copy in a book together with the recordings of the drug and placebo doseages and the weights of the monkeys. In the subsequent interview with Mrs. Jordan, she revealed that this duplicate record in the bound book was kept in this fashion for the rat studies on Mer 29, but that the records for the monkey studies were recorded in ink in a loose leaf 3-ring black notebook.

Laboratory records were retained in the laboratory. The monkeys were kept track of by having numbers tatooed on their stomachs, and thus some of the control monkeys could be used in later experiments. The laboratory records then would have a complete history of every monkey and would have the history of previous or subsequent experiments.

Mr. Umberger was very much interested in the monkeys, and was skilled in caring for them and training them. During the course of the experiment he

trained the monkeys to jump from their cages into a box for weighing, and after being weighed to jump back into their cages. The monkeys were weighed weekly.

Mr. Umberger noted that toward the end of the experiment one of the male drug monkeys developed an inability to land in the box when he jumped from the cage as if he did not see properly or was sick. He also had to help this monkey back into his cage after weighing. In subsequent weighings Mr. Umberger had to help this monkey into the box and back into the cage. Mr. Umberger also noted that this monkey got to the point where he would not react normally when he put his hand on his head. Normally a well monkey would be very much aware of any attempt to place a hand on his head and would have drawn away, but this monkey got to the point where he would not do this. Mr. Umberger stated that this monkey was initially a well and active monkey when placed on the Mer 29. After this the monkey first developed a higher degree of activity. This was eventually followed by the monkey becoming very much less active than normal. Mr. Umberger noticed this sub-activity first started when the monkey began chewing on his inner cheek. Mr. Umberger does not recall specifically the weight of this monkey, but it was not a particularly large monkey. He estimated that this monkey weighed from 12 to 16 pounds.

Mr. Umberger got to know the monkeys very well during this period the experiment was in progress because he took a particular interest in the work and was usually in the room with the monkeys by himself. At the close of the experiment he assisted with the autopsies of the monkeys. He understood that this completed the study. He did not participate in working up the final data. He does not recall anything particularly unusual about the autopsy of the monkeys, but he does not recall specifically that the sick monkey mentioned earlier was autopsied.

The remarks with respect to the actions of the sick monkey and the fact that he failed to land in the box when he jumped from the cage would have been recorded on the laboratory records, according to Mr. Umberger. During the first part of this experiment his supervisor was Mr. James Knox Smith, and he trained Mr. Umberger in the care of the monkeys and insisted that any observations of this kind be properly recorded. Mr. Smith left the firm a few months prior to Mr. Umberger's leaving. Mr. Umberger said that Mr. James Knox Smith left the firm because he was offered a chance to start up a new toxicity laboratory at the Reichert Company in Los Angeles, Calif. He said this firm is a subsidiary of Rexall. Mr. Umberger said that Dr. William King replaced Mr. Smith. He said Dr. King was a pathologist that was just out of school. Mr. Umberger said he did not know for sure that the sick monkey was included in the final data. Since he had not participated in working up the final data submitted there would have been no reason for the firm to confide in Mr. Umberger that there had been a substitution.

Mr. Umberger's observations about this sick, male, drug monkey were made because of his general interest for the welfare of all the animals which were used in all studies. These observations did not appear to be particularly alarming to him from the standpoint of toxicity and he is quite certain that this monkey continued to be dosed until the termination of the experiment.

Mr. Umberger also recalls that toxicological studies were made on dogs. He does not recall anything specific or unusual about these studies but believes there were at least two experiments on dogs, with Mer 29. His duties included conditioning the dogs prior to placing them on test, and weighing, feeding and generally caring for them. He knows that approximately 6 dogs were in a "drug" group and approximately 4 dogs in a "control" group. He also assisted in the autopsy of the dogs. He does not recall anything unusual about the autopsies of the dogs.

Mr. Umberger also participated in Mer 29 studies on white rats. These also were considered routine and he does not recall anything unusual or specific about these studies. He had approximately the same duties with respect to the white rat studies that he had with the dog and monkey studies. He does not recall the length of time the dog and white rat studies required.

Mr. Umberger remembered that two women technicians helped with the experiment with monkeys on Mer 29. These were as follows:

Mrs. Carol Root: Mrs. Root left the firm early in the experiment. There was some doubt in Mr. Umberger's mind as to whether or not Mrs. Root was actually present at the start of this experiment on monkeys.

Mrs. Jo Jordan: Mr. Umberger said that this woman's name was really Beulah,

but that everyone called her "Jo". He said that Mrs. Jordan also left the firm several months before he did.

In the interview with Mrs. Jo Jordan, it was determined that her correct name is Mrs. Beulah L. Jordan. Mrs. Jordan is the wife of Carson F. Jordan, and they currently reside at 3825 Trebor Drive, Cincinnati 36, Ohio. Mr. Jordan works in the engineering department of the Telephone Co. He is the one who rides in the same car pool with Inspector Rice. He was present at the time of all the interviews with Mrs. Jordan at the time of her being sworn, and signing the submitted affidavit. The Jordans have an unlisted phone number, and it is 891–6365.

Mrs. Jordan was employed as a technican in the Toxicological Laboratory of the Wm. S. Merrell Co., Cincinnati, Ohio for approximately 2½ years from the fall of 1956 to the early summer of 1959. During this time she assisted in the toxicological study on Mer 29 using monkeys. She now recalls that this experiment ran approximately 16 to 18 months, and it involved 6 to 8 monkyes of which 3 or 4 were in a "control" group and 3 or 4 were in a "drug" group. She now recalls that 3 "control" monkeys and 3 "drug" monkeys were carried through the entire experiment, while one of each group was autopsied after approximately 6 or 7 months.

Her duties included bleeding the monkeys, running blood counts, assisting with the autopsies, making up capsules of Mer 29 and placebos for the respective drug and control groups, assisting with dosing both control groups and drug groups by pushing the respective capsules down the throats of the monkeys, making notes about the food the monkeys either ate or refused to eat, weighing the monkeys weekly, checking the monkeys' reactions, preparing weights graphs after each week and after autopsy, and weighing each organ at autopsy.

During the course of experiment notes of observations made were recorded in ink in a loose leaf 3-ring black notebook, together with the recordings of the drug and placebo doseages and weights of the monkeys. This notebook was always retained in the laboratory and was never turned in to the firm's record office. This was a continuing record of any animals used, and since most of the control animals would not be autopsied they may be used in later experiments. Each of the monkeys was assigned a number so that a complete history of each monkey would be in this laboratory notebook.

In the case of the monkeys the food eaten was not weighed because the eating habits of the monkeys were such that they would not necessarily eat any given weighed out amount. Estimates of the food eaten however were made, and any observations of the eating habits were entered on a separate sheet and maintained in a separate loose leaf notebook. This was also always retained in the laboratory.

During the first part of the experiment on Mer 29 Mrs. Jordan was under the direction of Mr. James Knox Smith, but toward the end of the experiment he was replaced by Dr. William King. Mrs. Jordan noted that toward the end of the experiment one male monkey was sick and was doing very poorly, and had lost considerable weight. She recalls that at the end of the experiment he probably weighed no more than 8 or 9 pounds, and had lost approximately 5 pounds or more during the course of the experiment. Also this sick male monkey had become somewhat mean and acted angry during the experiment.

Originally he had been a healthy active monkey. After being put on the drug he first became more active than usual, but as time wore on he became very inactive and lay on the bottom of the cage. She knew from the expression in his eyes and his disposition that he was very ill. She knew that he was the only monkey that could not jump from his cage into the box for weighing and back into his cage after weighing. During the first part of the experiment this monkey could also do this very easily. She knew that on one occasion this monkey tried to jump in the box and missed the box entirely.

At the close of the experiment it was her duty to work up the weight graphs and show them to her superior, Dr. King. He in turn discussed this with his superior, Dr. E. F. Van Maanen. Dr. Van Maanen, with the concurrence of Dr. King, then decided to throw out the sick male drug monkey mentioned above from the experiment and substitute another control monkey in his place which had never been on Mer 29. The male monkey substituted weighed about 18 or 20 pounds. This would be about 10 pounds more than the sick monkey for which he was substituted. Apparently this monkey had originally been about the same size as the sick monkey for which he was substituted, that is he originally was the same size as the sick monkey originally was at the start of the experiment. After

this decision Dr. Van Mannen called Mrs. Jordan into his office and instructed her to make this substitution in working up the weight charts. Because of this decision it was necessary for her to make up the charts three different times. Although Mrs. Jordan was present during the autopsy of all of the monkeys and the substitute monkey used in her charts, the sick male drug monkey was never autopsied in her presence. She knows that the weight charts would have been very much different had data from the sick male monkey been retained in the final reports. She knows that this sick monkey had a weight loss from approximately 13 pounds at the start of the experiment to approximately 8 pounds at the close of the experiment.

Mrs. Jordan resented being asked to make this substitution and render a false report, and refused to sign her charts. Dr. King ordered her to never mention the substitution. She was told that this was the way the Company wanted it and to forget it. She was told that this order had come from higher up and there was nothing she could do about it but obey the order and do as the "higher-ups" wanted.

Mrs. Jordan also knows that during this experiment the capsules of Mer 29 were not given to the drug monkeys as they should have been on a number of occasions. She has no record of how often this was, but knows this did happen sometimes over a weekend. This came about because other people in other groups would be called in to work relief shifts in place of the regular employees of her group on a weekend. She was the one who weighed up the capsules and prepared them specially for each individual drug monkey. She prepared these Mer 29 capsules for a week at a time. She prepared just enough capsules to last one week until the monkeys were weighed again, after which it might be necessary to change the capsule to conform to the monkey's new weight in terms of milligrams per kilo body weight. In her routine the monkeys would ordinarily be weighed on a Friday, but the new calculations would not be made until Monday. Thus she made up the capsules on a Monday, and made enough so that there would be one capsule left to dose the following Monday morning until the new calculations could be made. She noticed that sometimes there would be 2 or 3 capsules remaining on Monday morning indicating that the monkeys had not been dosed on Saturday or Sunday as they should have been. She knows that during the experiment the monkeys on the drug became difficult to catch for dosing and became very "leery" of anyone who tried to catch them and dose them. She believes that this would explain why the weekend relief employees may not always have been able to catch and dose the monkeys. She knows that the charts were always marked as if the capsules were given however.

Mrs. Jordan also participated in similar studies on dogs and white rats involving Mer 29. She had similar duties in respect to these studies but she noticed nothing unusual about the conduct of these dog and white rat studies. She also participated in the autopsies of dogs and white rats, and worked up the weight charts at the close of these experiments. She knows that in the case of the rat studies duplicate weight records were kept in the laboratory by means of recording the data in a bound book with a carbon paper between two pages. This was not the case, however, with the monkey and dog studies.

She reported that other employees who helped with the monkey studies were as follows:

Bruce Umberger: This employee was still with the firm a few months after she left but is no longer with the firm now. She knows that he lives in Columbus, Ohio. She knows that his duties included conditioning and handling the monkeys prior to the start of the experiment. She knows that he helped autopsy the monkeys at the close of the experiment, and during the studies he helped weigh, dose, observe, and care for the monkeys. He was very much interested in the monkeys and spent a great deal of time with them, and he helped catch the monkeys and was working with them all the time. She knows that he had nothing to do with working up the final data at the close of the experiment on the monkeys, and thus she does not believe that he would have known of the substitution of the control monkey for the sick, male, drug monkey. She knows that Mr. Umberger also did similar work with respect to the studies on the dogs and the white rats.

Dorothy Miner: This individual is also no longer associated with the firm and Mrs. Jordan knows that she left the firm one month to a month and a half after she did. Dorothy Miner is presently in the State of Florida but Mrs. Jordan does not know her exact address. She knows that she was employed during the Mer

29 studies on monkeys. Her job was primarily the preparation and staining of slides. These were simply from the organs supplied to her at autopsy, and she would not necessarily know that a substitute monkey had been supplied for the sick, male monkey. Mrs. Jordan however did mention this at one time to Dorothy Miner, but she is not certain whether or not Dorothy Miner would have paid any attention to this sort of comment or remembered it as she was prone to drink heavily, frequently drank the test alcohol in the laboratory, etc.

Mary Ann Stephens: This individual is now married and her present name and address are not know to Mrs. Jordan. Mrs. Jordan knows that her duties primarily involved making blood counts on rats, and she does not believe that she had very much to do with the monkey studies and doubts that she knew that there had been a substitution. She knows that this individual did not work directly with the monkeys, and that she has also left the firm.

Mike: Mrs. Jordan does not know this individual's last name. She knows that he worked for the firm during the last part of the Mer 29 studies on the monkeys and he assisted Bruce Umberger in caring for the monkeys, which was his primary job. She knows that he also helped weigh the rats on the Mer 29 studies. She knows that Mike was very good with the monkeys and while he was present she was sure that the monkeys were properly dosed and cared for.

She said that he liked a good time and would frequently come in late on a Monday morning after being out all weekend. She was sure that if Mike were one of the individuals on duty on a weekend that the monkeys would be properly dosed, but it was during the times when neither she nor Mike were on duty on a weekend that she noticed the discrepancies in the number of remaining Mer 29 capsules.

Mrs. Jordan finally resigned her position with the firm at the conclusion of the Mer 29 studies on the monkeys because of her dissatisfaction with the way the work was being run by Dr. King. She refused to sign her final work charts which she had to work up at the insistance of Dr. King using the substitute monkey. Although Dr. King had ordered her not to tell about this substitution, she was not sworn not to tell.

Mrs. Jordan and her husband are high class public spirited people. Mrs. Jordan is understandably very much distressed about this whole affair and was initially reluctant to sign the enclosed affidavit. She finally did willingly swear to and sign the affidavit, however, because of her realization of her duty as a public minded citizen to the general public.

Mrs. Jordan was told that I personally did not know what the final outcome of this investigation would be, but I assured her that it was of vital importance, and that the matter was being given very careful top level consideration.

THOMAS M. RICE,
Supervisory Inspector.

Enclosures:
4-pg. affi. of Beulah L. Jordan.
3-pg. affi. of Bruce I. Umberger.

AFFIDAVIT

STATE OF OHIO,
County of Hamilton:

Before me, Thomas M. Rice, an employee of the Department of Health, Education, and Welfare, Food and Drug Administration, designated by the Secretary, under authority of the Act of January 31, 1925, 43 Statutes at Large 803 (5 U.S.C. 521); Reorganization Plan No. IV, Secs. 12–15, effective June 30, 1940; and Reorganization Plan No. 1 of 1953, Secs. 1–9, effective April 11, 1953, to administer or take oaths, affirmations, and affidavits, personally appeared Mrs. Beulah L. Jordan in the county and State aforesaid, who, being first duly sworn, deposes and says:

My name is Mrs. Beulah L. Jordan. I reside at 3825 Trebor Drive, Cincinnati 36, Ohio.

I worked as a technician in the Toxicological Laboratory of the William S. Merrell Co., Cincinnati, Ohio, for approximately 2½ years from the fall of 1956 to the early summer of 1959.

During this time I assisted in a toxicological study on Mer 29 using monkeys. This experiment ran approximately 16–18 months. It involved 6 to 8 monkeys

of which 3 or 4 were in a control group, and 3 or 4 were in the drug group. Three control and three drug monkeys were carried through the entire experiment, while one of each group was autopsied after approximately 6 or 7 months.

My duties included bleeding the monkeys, running blood counts, assisting with the autopsies, making up capsules of Mer 29 and placebos for the drug groups and control groups, assisting with dosing both control groups and drug groups by pushing the respective capsules down the throats of the monkeys, take notes about the food the monkeys ate or refused to eat, weighing the monkeys weekly, checking the monkys reactions, preparing weight graphs each week and after autopsy, and weighing each organ at autopsy.

Notes of observations made were recorded in ink in a loose leaf 3 ring black note book, together with the recordings of the drug and placebo dosages and weights of the monkeys. This note book was always retained in the laboratory, and was never turned in to the firm's record office. The estimate of food eaten by the monkeys and the observations of eating habits were entered on a separate sheet and maintained in a separate looseleaf note book which was also always retained in the laboratory.

During the first part of the experiment, I was under the direction of Mr. James Knox Smith, but toward the close of the experiment he was replaced by Dr. William King.

Toward the end of the experiment one male drug monkey was sick and doing very poorly, and weighed approximately 8 or 9 pounds. He had lost approximately 5 pounds or more during the course of the experiment.

This sick male drug monkey had become somewhat mean and acted angry. He had been a healthy, active monkey at the start of the experiment. After being on the drug he first became more active than usual, but later because very inactive and lay on the bottom of the cage. The expression in his eyes and his disposition indicated he was very ill. He could not jump into the box from his cage for weighing, and back into his cage as the other monkeys could. During the first part of the experiment, this monkey could also do this very easily. Later on one occasion when he tried to do this he missed the box.

At the close of the experiment I worked up the weight graphs, and showed them to Dr. King. He in turn discussed them with his superior, Dr. E. F. Van Maanen.

Dr. Van Maanen, with the concurrance of Dr. King, decided to throw out the sick male drug monkey mentioned above, and substitute another control monkey in his place which had never been on Mer 29. The male monkey substituted weighed about 18 or 20 pounds, or about 10 pounds more than the sick monkey for which he was substituted. Dr. Van Maanen then called me into his office and instructed me to make this substitution in working up the weight chart. Because of this decision, I had to make up the charts 3 times. The sick male monkey was never autopsied in my presence, but the substitute control monkey was autopsied in his place. The weight charts would have been very much different, had the data from the sick male drug monkey been retained in the final reports because of his loss of weight from approximately 13 pounds at the start of the experiment to approximately 8 pounds at the close of the experiment.

Dr. King ordered me to never mention the substitution. I was told this was the way the company wanted it and to forget it. I was told that the order had come from higher up.

Also during this experiment, I know that on a number of occassions the capsules of Mer 29 were not given to the monkeys as they should have been. This would happen over a week end, when people in other groups would work relief shifts in the place of regular employees of our group. I knew this because I was the one who weighed up the capsules for each individual drug monkey for a week at a time, and prepared just enough to last 1 week until the monkeys were weighed again and the calculations were made in terms of the monkey's new weight. My routine was to have 1 capsule left for Monday morning, but sometimes there would be 2 or 3 capsules remaining. During the experiment the monkeys on the drug became difficult to catch for doseing, which would explain why the week end relief employed may not have always dosed the monkeys. The charts, however, were always marked as if the capsules were given.

I also participated in similar studies on dogs and white rats invovling Mer 29. I had similar duties in respect to these studies. I noticed nothing unusual about the conduct of these dog and rat studies. I participated in the autopsies of the

dogs and rats on these studies, and also worked up the weight charts at the close of these experiments.

In the case of the rat studies, duplicate records were kept by means of recording the data into a bound book with carbon paper, but this was not the case with the monkey studies, and dog studies.

Other employees who helped with the monkey studies were:

Bruce Umberger: He was still with the firm a few months after I left, but is no longer with the firm. He now lives in Columbus, Ohio. His duties included conditioning and handling the monkeys prior to the start of the experiment. He helped autopsy the monkeys at the close of the experiment. During the studies he helped weigh, dose, observe, and care for the monkeys. He helped catch, weigh, and dose monkeys. He had nothing to do with working up the final data at the close of the experiment on the monkeys. He also did similar work with respect to the studies on dogs and white rats.

Dorothy Miner: This individual is also no longer associated with this firm, and left 1 to 1½ months after I did. She is presently in Florida, but I do not know her exact address. She was employed during the Mer 29 studies on monkeys. Her job was primarily the preparation and staining slides. These were simply from the organs supplied her.

Mary Ann Stephens: This individual is now married and her present name and address is not known. Her duties primarily involved making blood counts on rats. She did not work directly with the monkeys. She has also left the firm.

Mike: I do not know this individuals last name. He worked for the firm during the last part of the Mer 29 studies on monkeys. He assisted Bruce Umberger, and his primary duties were to take care of the monkeys. He also helped weigh the rats on Mer 29 studies.

I resigned my position with the firm at the conclusion of the Mer 29 studies on the monkeys, because of my dissatisfaction with the way the work was being run by Dr. King.

BEULAH L. JORDAN.

Subscribed and sworn to before me at Cincinnati, Ohio, this 13th day of March 1962.

THOMAS M. RICE.

AFFIDAVIT

STATE OF OHIO,
County of Franklin:

Before me, Thomas M. Rice, an employee of the Department of Health, Education, and Welfare, Food and Drug Administration, designated by the Secretary, under authority of the Act of January 31, 1925, 43 Statutes at Large 803 (5 U.S.C. 521); Reorganization Plan No. IV, Secs. 12–15, effective June 30, 1940; and Reorganization Plan No. 1 of 1953, Secs. 1–9, effective April 11, 1953, to administer or take oaths, affirmations, and affidavits, personally appeared Bruce I. Umberger in the county and State aforesaid, who, being first duly sworn, deposes and says:

I am Bruce I. Umberger, 631 E. Broad St., Columbus, Ohio. I am Assistant Manager of the Broad-Lincoln Hotel, 631 E. Broad St., Columbus, Ohio.

From Sept., 1957 to Sept. 20, 1959 I was employed at William S. Merrell Co., Cincinnati, Ohio, in the Toxicology Laboratory. During this time, I assisted with a number of experiments. One of these was designed to study the toxicological effects of Mer 29.

This experiment ran approximately 18 months. It involved from 6 to 8 monkeys of which 3 or 4 were in the "drug" group, and the remaining three or 4 were in the "control" group. Three control and 3 drug monkeys were carried through the entire experiment, while one of each were autopsied approximately 6 or 7 months after the start of the experiment.

My duties included conditioning the monkeys for 6 weeks to 3 months before they were placed on the experiment. This included assisting in treating the monkeys for dysentry if needed, and holding the monkeys when they were given penicillin shots and tested for TB. I also weighed, handled, and observed the monkeys during their period of acclimation to make certain they were well and suitable test animals.

After the monkeys were placed on test, I helped hold the monkeys when they were dosed so the capsules could be pushed down their throats.

During the course of this experiment, I carefully observed the monkeys and made notes and observations. These observations were recorded (with carbon copy), in a book together with like recordings of the drug and placebo dosages and weights of the monkeys. The monkeys were weighed weekly. The original pages from the book were taken out and sent to the firm's record office. The carbon copies of the pages were retained bound in the book in the laboratory.

During the weighing, I trained the monkeys to jump from the cage into a box, and after weighing, to jump back into the cage. Toward the end of the experiment I noticed one of the male drug monkeys developed an inability to land in the box when he jumped from the cage as if he didn't see properly or was sick. I also had to help him back into his cage after weighing. Also he did not react normally when I put my hand on his head, as he normally would have drawn away.

This initially active monkey, when placed in Mer 29 had at first developed a hyper-activity. This was followed by a sub-activity. I noticed this sub-activity first started by his chewing on his inner cheek. Ths monkey weighed 12–16 pounds.

I got to know the moneys well during this period, because I took particular interest in this work, and I was usually in the room by myself with them.

I assisted with the autopsies of the monkeys at the close of the experiment, and it was my understanding that this completed this study. I did not participate in working up the final data. I do not recall anything particularly unusual about the autopsy of the monkeys autopsied, but I do not recall specifically the autopsy of the sick monkey mentioned earlier.

It was normal procedure for me to set up the autopsy table.

During the first part of the experiment, my supervisor was Mr. James Knox Smith, but he left the firm a few months prior to my leaving, and he was replaced by Dr. William King.

I was assisted during the latter part of the experiment by Mike Piel who helped me dose, weigh and care for the monkeys.

Two women technicians who helped with the experiment were Mrs. Carol Root and Mrs. Jo Jordon. Mrs. Root however, left the firm early in the experiment. Mrs. Jordon also left the firm several months before I did.

These observations made by me on this sick male monkey were made because of my general interest for the welfare of all the animals which were used on all studies. At the time of their occurrence these observations did not appear to be particularly alarming to me from the standpoint of toxicity and I think the drug was continued until the termination date of the experiment.

I also recall that toxocological studies were made on dogs with Mer 29. I do not recall anything specific or unusual about these studies, but I believe there were at least two experiments on dogs. My duties included conditioning the dogs prior to placing them on test, and weighing, feeding and generally caring for them.

Approximately 6 dogs were in a drug and approximately 4 dogs in a control group. I also assisted in autopsies of the dogs. I do not recall anything unusual with the autopsies of the dogs.

I also participated in the Mer 29 studies on white rats. Nothing unusual is recalled about the white rat studies.

I do not recall the length of time the dog & white rat studies required.

BRUCE I. UMBERGER.

Subscribed and sworn to before me at Columbus, Ohio, this 13th day of March 1962.

THOMAS M. RICE.

U.S. Government Memorandum.

To: Administration.

From: Cincinnati District.

Subject: Memorandum of telephone conversation, April 12, 1962, between Mr. E. R. Beckwith, Executive Vice President, William S. Merrell Co., at Cincinnati, Ohio and Thomas M. Rice, Supervisory Inspector, Cincinnati District.

I called Mr. Beckwith today for the purpose of inquiring as to the raw data charts the firm was duplicating for us in line with our visits to the firm on April 9 and 10 in connection with the MER 29 Investigation.

I reminded Mr. Beckwith that they had promised to secure copies of these charts for us as soon as possible, and I again emphasized that we were anxious to get these copies as they were needed in the evaluation.

Mr. Beckwith stated that they were trying to get a complete picture of the whole situation, and that they would collect and duplicate the charts as soon as possible. He said because of the change in personnel about the time these charts were prepared, the data was scattered, and it was taking some time to get all of the pieces of information together.

I suggested that if the firm was unable to get the originals of the pages we wanted, that we would be happy to attempt to photograph the carbon copies in the bound notebook. Mr. Beckwith assured me that they would make every effort to get the material together as soon as possible and would notify me when it was ready. During the conversation, it was also verified that the information they were getting for Dr. Nestor relative to the clinical studies would be sent directly to him in Washington.

THOMAS M. RICE.

U.S. Government Memorandum.

WILLIAM S. MERRELL CO.,
Cincinnati, Ohio, April 17, 1962.

To: Administration.
From: Cincinnati District.
Subject: Mer 29 investigation, and recall; refusal to supply data.

During a visit to the firm today by Supervisory Inspector Thomas M. Rice and Inspector Charles W. Gressle, inquiry was made as to the copies of the raw data bound notebooks and copies of the original pages from these notebooks sent to the library, which had been promised to us at the time of our visits to the firm on April 9th and 10th. This was first discussed in the presence of Dr. George O. Sharp, Mr. Fred Lamb, and Mr. Ed R. Beckwith, Executive Vice-President. The point was not resolved at the time of the discussion with these three gentlemen, but the point was again raised with Mr. Lamb and Mr. Sharp later on during the same visit.

Mr. Lamb was advised that our record showed that we had made this request in detail at the time of our visit of April 9th and 10th and that both numbers and page numbers were set forth in detail. Mr. Lamb claimed that he did not recollect that the pages were written down in detail, and he produced a confidential memorandum of the visits which did not show that the pages were given. I pointed out that this was at variance with my recollection, and pointed out that Mr. Lamb personally was in the group of individuals during the final conferences when these pages were enumerated specifically. I also pointed out that at the time we were in Dr. King's office, Mr. Lamb had been called by Mr. Murray to seek permission at our request when we had requested that the notebooks be loaned to us so that we could make copies of the pages ourselves. I pointed out that at this time Mr. Lamb refused to deliver the books to us on the grounds that it was against company policy, but that he promised to have the pages we desired duplicated for us. Mr. Lamb made a point that this request was not made in writing, and that he did not consider it was a promise, but rather that he had said he would try to get them for us. I pointed out that we had given a Notice of Inspection at the time of our visit on April 9th, and that we had given another Notice of Inspection at the time of our visit today. Mr. Lamb made a point of the fact that the notices we had given related to Section 704 of the Act, and no where in this section did it state that it was mandatory that records of this type be given during an inspection. I pointed out that I considered such records an integral part of an inspection of a new drug product.

I also pointed out that Mr. Beckwith had been called again about April 12th to ask why the copies had not been supplied us.

Mr. Lamb made a point of stating that he was not refusing to provide this information as an individual, but he did not "run the company". He said that he did not want the record to show that he or the firm were refusing our request, but that inasmuch as discussions were being held at the Washington level in regard to the whole matter, and the fact that the firm had already instituted a recall, he did not see why it was necessary to produce these records for us. He said he felt it was a decision that he personally could not make, and it would be up to the attorneys at the Washington level to make this decision.

It ultimately developed that Mr. Lamb called some undisclosed individual believed to be an attorney presently conferring with our people in Washington. As a result of this call be reported that he would be unable to give me copies of the notebooks because he did not have them, and they were not on the premises at this time. He said he was embarrassed to have to report this, but he did not know that they had been sent to an attorney in New York City. He identified this attorney as Mr. Andrew Graham. At this point Mr. Lamb said that he would give us the copies if he had them and they were under his jurisdiction as an individual. He then said he would make every effort to get the desired copies for us and that I should call him again Thursday, April 19, 1962.

I told Mr. Lamb that it was my position that as of now I had been refused by the company because they had promised to produce these charts at the time of our visit of April 9th and 10th and now a week later I still had not been provided the charts.

At this time I again gave Mr. Lamb the numbers of the notebooks and pages, copies of which we required. These were as follows:

Notebook 770 Pages 40 and 78.
Notebook 799R Pages 16, 45, 59 and 75.
Notebook 848R Pages 16, 56, 75 and 100.
Notebook 904R Pages 18 and 19.

Again I emphasized that we desired copies both of the originals which had been removed from the notebooks and found in the library, and copies of the carbon copies remaining in the bound notebooks.

Mr. Lamb tried to make a point that this was now the first time that he was receiving this specific request.

See also another memorandum under today's date captioned "Mer 29 Recall" in which the details, present status, and enclosures concerning the recall are discussed in detail.

THOMAS M. RICE,
Supervisory Inspector.

U.S. Government Memorandum.

WILLIAM S. MERRELL CO.,
Cincinnati, Ohio, April 24, 1962.

To: Administration; Attn: Division of Regulatory Management.
From: Cincinnati District.
Subject: Mer 29.

In response to the phone conversations between Mr. Maraviglia and Mr. Goldhammer of April 18 and 19, 1962, William M. King was finally interviewed by Mr. Maraviglia and Mr. Rice at his residence, 431 Deanview Drive, Cincinnati, Ohio, the evening of April 24, 1962. Dr. King's phone number is VA-1-6435. We had been attempting to locate and interview Dr. King since Thursday, April 19, 1962. It was determined that Dr. King had been visiting his father and family in Johnson City, Tennessee over the Easter holidays. King has six children, and he had returned to Cincinnati so that his children might enter school again on April 25th.

King has been on "involuntary" vacation since Monday April 16th. He was told by Mr. Beckwith that he needed a vacation, and that he should not come back to work until he was called. At the present writing, King does not know his status with the firm. He plans to phone the firm on April 25th to find out what his status is.

King talked fairly freely with us, and although we doubt if he gave us all of the facts, the following information was supplied which ties in generally with information from other sources, and sheds some light on heretofore unknown facts.

He admitted that his Ph. D. degree has not been completed at this time. He said that the granting of his degree was awaiting rewriting of his thesis. His graduate work was being carried on at the University of Minnesota where he was teaching pathology. Prior to his work at the University of Minnesota, he graduated from St. Thomas College, St. Paul, Minnesota. He had transferred to Thomas from St. Louis University. He said that his adviser at the University of Minnesota had certified that all of his work was completed on his Ph. D. degree, and that it would be granted in absentia when his thesis was finally accepted.

King emphasized throughout the interview that Dr. Van Maanen was responsible for all data in the final form which was submitted to the Food and Drug Administration. He said that Dr. Van Maanen was the only man who could have ordered the addition of Monkey 51 in the middle of the study. King was of the impression that this was the only serious mistake in the studies. King stated that Dr. Van Maanen is not a citizen of the United States. He said that he had a Ph. D. degree from the University of Utrecht in Holland, in organic chemistry, and also had a Ph. D. degree from Harvard University in pharmacology. He said that Dr. Van Maanen had been with the firm since 1954 or 1955. Dr. Van Maanen is Director of Biological Sciences. He in turn is the subordinate of Dr. Werner, who is a vice president of the firm and Director of Research. King said that Dr. Werner was about ready to retire and did not know what was going on and relied entirely on Van Maanen for anything of this nature.

King said that he joined the firm in September, 1958 and took over where Mr. Smith left off in April, 1959. Thus, there was an overlapping during the time when both King and Mr. Smith were present in the firm, and both were present at the time of the termination of the monkey studies. King played down his knowledge of the raw data and said that he knew nothing about the discrepancies until the visit of Dr. Nestor, Dr. Goldenthal, and Supervisory Inspector Rice. He pointed out that Monkey M51 was added to the studies on June 23, 1958 several months prior to the time when he came with the firm. He said this order could have been given by only one person, and that would have been Dr. Van Maanen. He said that he had done a great deal of "digging" to try to find out what had happened and he was under the impression that the weights of monkey M51 had been taken from the weight records prior to June 23, 1958 when the monkey had not been on Mer 29, and that these weights had been used on the charts submitted with the NDA. He said that after the tenth month of the experiment, the weights of Monkey M51 were correct on the charts submitted and that dosing had been performed as indicated after that time.

King feels that Mer 29 is a safe drug if used properly, but blamed the doctors for not dosing properly.

King had a number of records he had taken from the firm. He said that he had been requested to prepare a summary for the firm's attorneys to explain all of the discrepancies. He was not willing to let us have copies at this time, but said that he knew most all of this by memory. We asked if he would be willing to sign a statement for us and he indicated that while he would not sign such a statement at the time of this interview, he would probably be willing to do so after he had resolved his status with the firm. He gave us to understand that he was dealing 100% above board with us and giving us the true facts as he knew them.

In respect to the female Monkey F49, King said that the records showed that this monkey had been taken off the drug on March 14, 1958 for some reason and restarted on the drug again on April 7, 1958. Except for this period, this monkey was on the drug continuously from 9/9/57 until February 19, 1959. On February 19, 1959, the drug was withdrawn again. It was after that time that the greatest weight loss developed. He said in trying to figure out what was wrong with the monkey, he believed that the monkey had gastro enteritis. He said that the monkey was not autopsied until March 5, 1959. He said that the responsibility for taking this monkey on and off the drug would fall directly on Dr. Van Maanen. He also said that the decision to wait for autopsy until March 5, 1959 on this monkey would also have been Dr. Van Maanen's responsibility.

King showed us a yellow sheet of paper which he said proved the dates of autopsy on the various monkeys because he had the weights of the organs recorded there. He also said that the actual dates could be checked because the dates were fixed on the slides, and were also fixed on the tissue in the paraffin blocks which were taken at the time of autopsy. King furnished us from his report he had written for the attorneys the following actual dates of autopsy.

Monkey	Number	Sex	Autopsy date
Control monkey	39	Female	Mar. 5, 1959
Drug monkey	49	do	Do.
Do	34	Male	Feb. 26, 1959
Control monkey	35	do	Do.
Do	33	do	Feb. 19, 1959
Drug monkey	51	do	Do.
Do	25	do	Mar. 14, 1958
Control monkey	48	do	Do.

King also spoke of another monkey which he gave as number 35 which had been on compound 5066 which he said was an analogue of Mer 29. He was under the impression that Control Monkey 35 Male had actually been on this drug prior to being used as a control animal.

In explaining why all autopsies were not made the same day, King said that this was because they were freezing tissue at the same time, and it would thus be impossible to prepare and freeze the tissue for all of the monkeys on any one day.

He mentioned that it was obvious the firm was looking for a scapegoat. He said that he couldn't care less, because he could always get a job.

One interesting sidelight was that he told us he had copies of all the pages of the notebooks for us the afternoon that Dr. Nestor, Dr. Goldenthal and Inspector Rice were at the firm (April 9), but he was told not to turn them over to us.

King admitted that he personally prepared all the microscopic sections of the tissues and examined them himself at the end of the study, and he personally had autopsied the drug monkeys 49, 34, and 51. He could not explain why there was no raw data on the autopsy of monkey 34 in the notebooks, but felt that the records he had of the weights, the fact that they actually had the tissues in paraffin blocks, etc. proved that the money was in fact autopsied on 2/26/59.

King stated that the second edition of the brochure sent out with Mer 29 made no mention of his findings on female monkey 49 which he had reported. He said that he had observed morphological changes in the ovaries and had so reported these on his autopsy reports. He said that it was Dr. Van Maanen's decision to leave out this information so that investigators supervising clinical studies on Mer 29 wouldn't know about it.

King mentioned that Mr. Holthaus, who he has as his assistant, was not in this department at the time these Mer 29 studies submitted with the NDA were going on. He said that he was, however, in the endocrinology department and had transferred to his department later. He identified him as the individual he asked to get the raw data when it was asked for at the time of our visits on April 9 and 10.

King stated that he had searched for the original records of weights and observations made out by the technicians. He admitted that these were kept in loose-leaf fashion on a clip board and these were the original sheets on which the weights were recorded. He said that these weights would have been transcribed into the bound notebooks by the technicians. He identified these technicians as Umberger and Jordan. It appears significant that this corroborates Mrs. Jordan's statement that the original observations and weights were recorded on a loose-leaf type sheet on clip boards. It would appear that any information regarding illnesses observed, any substitutions, etc. would have been on these original sheets which according to King cannot now be located.

Incidentally, King admitted to us that he had been severely reprimanded by Mr. Beckwith and Mr. Lamb for turning over the weight charts to us at the time of our visit on April 9th, and also for letting us examine the bound notebooks.

One other point in respect to Monkey F49, according to King was that there was a weight loss of 1.1 kilograms on this monkey while it was on the drug. He said this weight loss was shown on the chart submitted with the NDA to Food and Drug Administratoin, but the serious loss of weight after the drug was withdrawn was not shown. He tried to play down the significance of the weight loss by telling us that it was common for monkeys to lose a great amount of weight just as children do when they become dehydrated.

King refused to have us look at or copy any records in his possession at this time. He said the company would have a "fit" if they knew he had them. He said he had to remain "loyal" to the firm within the bounds of "intellectual honesty", and until he knew definitely what his status was with the company, he would not sign anything or allow us to make copies of anything in his possession.

At the termination of the interview, he said he was getting in touch with the firm tomorrow to find out where he stood. We told him we were giving him an opportunity to cooperate fully with the government to supply us with the real facts as he knows them. We told him that we would be getting in touch with him again in the next day or two. He professed that he wanted to cooperate, but wants to know his true status with the company first. We then left his residence.

On April 25, 1962, while Mr. Rice was at Merrell on an assignment concerning Kevadon, Mr. Lamb made a remark indicating that he knew about our visit to

King the night before. He told Rice, "I hear you were out working late last night with Mr. Maraviglia", or words to that effect. He did not say how he knew about this, but obviously King must have told him.

We intend to see King again soon.

THOMAS M. RICE,
Supervisory Inspector.
T. C. MARAVIGLIA,
Director.

U.S. Government Memorandum.

WILLIAM S. MERRELL CO.,
Cincinnati, Ohio, May 4, 1962.

To: Administration; Attn: Division of Regulatory Management.
From: Cincinnati District.
Subject: Mer 29.

In response to Mr. Goldhammer's phone conversation of 4/18/62 with Mr. Maraviglia, we were requested to develop every possible source of information in connection with the Mer 29 investigation.

To this end, Inspectors Brodsky and Rice interviewed Bruce Umberger at Columbus, Ohio the night of May 3 and 4, 1962. This interview was conducted at the Broad Lincoln Hotel, Columbus, Ohio where Umberger is currently employed as the assistant manager. The following information was developed.

Mr. Umberger has not been contacted by Merrell since Inspector Rice's interview with him on March 12th and 13th, 1962. Umberger did not contact anyone from Merrell in connection with Mer 29 or this investigation. Umberger did take a trip to Cincinnati a few weeks ago subsequent to the interview of March 12th and 13th to visit relatives. During that visit, by chance he met Mr. Herb O'Bannion (correct spelling not known). Mr. O'Bannion performed janitorial services at Merrell's and his duties included cleaning the monkey cages, waxing the floors etc. Mr. O'Bannion was encountered in Mt. Healthy, and no mention was made of Mer 29.

Up until our interview with Mr. Umberger, he was not aware that the recall had been instituted. He had heard from his brother that there was something reported about Mer 29 in the paper, but he did not seem to know exactly what the trouble was. Mr. Umberger said the recall information was not published in the Columbus papers in so far as he knew.

Umberger was appraised of the present recall and the seriousness of the problem, the fact that the adversary actions had developed including cataracts, etc. He was told that this visit was being conducted for the purpose of determining complete facts surrounding the investigation of Mer 29 by the company. We told him that the reason for our visit with him at this time was to secure factual information which he had part in obtaining in connection with these studies.

We showed Umberger photo copies of the several pages of the bound raw data notebooks. We also showed him copies of the four-page charts and Fig. 8 composite graphs. Umberger recognized these as data drawn up from information compiled by Jo Jordan, Carole Root and himself. We made a special point in being very careful not to show Mr. Umberger any data or information which appeared in the NDA. We had him review these data carefully in order to clarify and refresh his memory regarding certain information contained therein, so that he might explain the significance of these entries.

We asked him about the signatures at the bottom of the pages, the unsigned pages, and the dates and weights recorded on the charts and graphs. He explained the following:

1. Missing signatures at the bottom of the pages may have been an oversight on the technician's part. He said that whoever made entries on the pages signed the pages. If more than one technician made entries on anyone page, both technicians signed the page. If only one individual made entries on a page, then that individual signed the bottom of the page. Umberger stated that the monkey weights and dosages were originally recorded at the time of weighing and dosing on laboratory worksheets which were kept in loose leaf fashion in a three ring black notebook in the laboratory. These data were later transcribed in duplicate into the bound raw data notebooks. The original pages from the bound notebooks, would then be torn out and sent to the firm's records library, while the

carbon copies remained in the bound books. From these data, he would prepare a rough graph showing weight information over the period of time the experiment was conducted. From this rough graph, a neater and more accurate graph would be prepared. Umberger carefully scrutinized the individual graphs and charts and affirmed that these had been prepared from the raw data recorded on the pages of the bound notebooks. He stated that these graphs were the types of data he helped compile. He said that the printing and dates, and some headings on these graphs were not done by him, but that these were in part his. He explained that sometimes Jo Jordon or Carole Root would prepare the final graphs and charts from his rough charts because they could do a neater job. He indicated however that the information contained therein appears to be information actually compiled by Jo Jordan, Carole Root and himself.

2. From the graphs and raw data, Umberger was able to deduce that the sick monkey reported in previous memorandums was number M34. There had been some speculation that the sick monkey might be female monkey M49.

Umberger was very positive that this female #49 was not the sick monkey he had been referring to because this particular female monkey was a pet of his, and he had his picture taken with this monkey and was very familiar with it. He also recalled that female 49 had bitten the end of a finger off the small sick male monkey. This was referred to by him in his affidavit of 4/13/62 as the "sick male monkey".

3. Umberger was able to identify the "sick" monkey as male #34 for the following reasons:

(*a*) He was sure the sick monkey was a drug monkey and was a small male animal.

(*b*) He was sure it was not a control monkey.

(*c*) He was sure it was not a female monkey.

(*d*) He was sure this animal had been used in the entire study, i.e. was not started late in the study, was not sacrificed prior to the completion of the entire experiment, and was used as a drug monkey to the end of the entire study.

These facts, Umberger stated, ruled out all of the monkeys except male 34 because there were only ten monkeys on the study and from the data the status of each of the ten monkeys is as follows:

No. 39 was a female control monkey.

No. 49 was a female and he remembers this well because it was his pet, he had his picture taken with it, etc.

No. 40 is a female and was not present at the termination of the study. This animal had not been on drug 5066 and there are no further entries on this monkey after 3/13/58.

No. 25 was sacrificed before the completion of the study. It was a male animal on 5052 or Mer 29 for only the first approximate six months.

No. 48 was a male control animal sacrificed early in the study.

No. 51 was a male animal on 5052, but this animal did not start the study. It was inserted on 6/12/58 and was somewhat larger than monkey 34 during the closing months of the experiment.

No. 35 was a male monkey that was on 5066 at the start of the study, but later this monkey appeared as a control monkey.

No. 36 was a male monkey was on 5066 and this monkey was sacrificed before the completion of the experiment.

No. 33 was a male control monkey.

No. 34. This is the only animal which could have been the sick monkey, because it was a male monkey on the drug from the start of the finish of the entire experiment. It had about the same weight remembered by Umberger to be that of the "sick monkey".

4. Umberger noted discrepancies on autopsy dates for monkeys #33 and 51 in the notebook data. These discrepancies showed 2/19/59 and 3/4/59 as autopsy dates for these monkeys. Since the weight graphs and charts show weights for these monkeys subsequent to 2/19/59 and 3/4/59 as autopsy dates for these monkeys. Since the weight graphs and charts show weights for these monkeys subsequent to 2/19/59, Umberger believes that the 2/19/59 date is not the correct date of autopsy. He said that weights would not be taken after autopsy and recorded.

Umberger stated that blood samples are taken before autopsy by Mary Ann Stevens. If there was a crowded autopsy schedule, the blood might be taken a

day or two before the autopsy. This could establish which is the correct date of autopsy because samples of blood are not taken after autopsy. He explained that Mary Ann Stevens learned under Mr. Knox Smith and that she was the type of employee that would not make any false entries as to dates that was taken from animals on any data she helped to prepare. Umberger stated that Mr. Smith had told all technicians that if they were always truthful in their entries, they had nothing to worry about when they signed their names to a report. Knox Smith had always emphasized that only the truth should be recorded.

5. Umberger said that monkey # 35 was used as a drug monkey on 5066 according to the notebook data at the beginning of the study. He said this animal could have been used as a control for the 5052 study later in the study as it appears on the graphs and charts. He said that since it is recorded on the charts, it must have been used starting 6/12/58 as a control. Umberger further stated that this information should have been shown in the raw data notebook as a control, but that whoever made the entry for # 51 as a test animal on 5052 must have simply overlooked entering monkey 35 in the book as a control.

6. Umberger was unable to explain why no autopsy information was recorded for monkey 34 and monkey 35 in the raw data notebook. He believes the only explanation is that Dr. King may have had the data. He noted that in the raw data notebook for monkeys number 51 and 53 such an entry was made that Dr. King had the data. Later on entered in the notebook for animals 51 and 33. Umberger felt that in the case of monkeys 34 and 35 for some reason their entry into the raw data notebooks had been overlooked.

Following our interview with Umberger, a three page affidavit was prepared attesting to the above information. This was signed by Umberger after he swore with his right hand raised that the information contained in the affidavit is "the truth, the whole truth, nothing but the truth, so help me God." The oath was administered by Inspector Rice and witnessesd by Inspector Brodsky.

Umberger was asked if he would be willing to testify to the above statements if the need should ever arise. He stated that he would be willing to testify to anything he had signed his name to, but only to the true facts. He then asked us what he should do if he were contacted and questioned by representatives of Merrell. We told him that while it would be up to him to use his own judgment, we strongly suggested that he holds completely to the truth. We indicated that if he were contacted by any representative of Merrell, we would appreciate his contacting us. He indicated that he would do this.

One final interesting point should be reported in connection with monkey 34 as follows. Mr. Umberger told us that monkey #34 for which no autopsy result appears in the raw data notebook was in fact autopsied. He remembers this because he asked at the autopsy why the monkey behaved abnormally; i.e. why did it miss the box at the time it attempted to jump when being weighed. Umberger told us that he was advised that the monkey had a "reverse heart attack." Umberger could not further explain or elaborate on what this meant.

This may be significant since clinical studies in the NDA mention that in several instances, patients died, but this was attributed to the type of patients being given the drugs. These were explained away because they felt the patients such as had heart conditions would have died any way.

Note that the autopsy report on monkey 34 submitted with the NDA indicated nothing abnormal about the heart whatsoever.

PHILIP BRODSKY,
THOMAS M. RICE,
Inspectors.

Enclosure—Affidavit.

AFFIDAVIT

STATE OF OHIO,
County of Franklin:

Before me, Thomas M. Rice, an employee of the Department of Health, Education, and Welfare, Food and Drug Administration, designated by the Secretary, under authority of the Act of January 31, 1925, 43 Statutes at Large 803 (5 U.S.C. 521); Reorganization Plan No. IV, Secs. 12–15, effective June 30, 1940; and Reorganization Plan No. 1 of 1953, Secs. 1–9, effective April 11, 1953, to administer or take oaths, affirmations, and affidavits, personally appeared Bruce I. Umberger in the county and State aforesaid, who, being first duly sworn, deposes and says:

I am Bruce I. Umberger, 631 E. Broad St., Columbus, Ohio. I am assistant manager of the Broad-Lincoln Hotel, 631 E. Broad St., Columbus, Ohio.

This reaffirms my affidavit which I gave to Inspector Rice on March 13, 1962.

After reviewing copies of pages from the bound raw data note books Numbers 770R, pages 40, 78; 779R, pages 16, 45, 59 & 75; 848R, pages 16, 56, 75 & 100; and 904R, pages 18 & 19; the 4 page chart titled "Monkeys Chronic Oral Toxicity Mer 29 Body Weights"; and Fig 8, shown to me by Inspectors Rice and Brodsky today, the following is recalled by me as factual to the best of my knowledge and belief.

1. The monkey referred to in my affidavit of March 13, 1962 as the "Sick Male Drug Monkey" was monkey #34. I recall this for the following reasons:

(*a*) I clearly recall the "sick" monkey to be a male drug monkey.

(*b*) I clearly recall the "sick" monkey was a monkey that both started and finished the studies.

(*c*) There were only ten monkeys in the studies; namely, 3 female and 7 male as follows:

F39—control
F40—on 5066
F49—on 5052 (Mer 29)
M25—on 5052 (didn't finish study)
M48—control (didn't finish study)
M51—on 5052 (didn't start study)
M35—on 5066 at start—later a control monkey
M36—on 5066 (didn't finish study)
M33—control
M34—5052 (Mer 29)

All of the above, except M34 are ruled out because they are either female, control monkeys, didn't start studies or didn't finish the studies because they were sacrificed prior to the termination of the studies.

(*d*) I clearly recall the "sick" monkey was one of the smallest monkeys on Mer 29 and my estimate of the weight of this monkey agrees with the weights from all of the data reviewed, which was supplied by Inspectors Rice and Brodsky.

2. The information shown on the copies of the pages from the bound raw data note books mentioned above, represents data supplied jointly by Carole Root, Jo Jordon and myself. This material was transcribed from data obtained by us in the laboratory and originally written on loose-leaf data sheets at the time the data, such as weights were obtained. These data are correctly shown, in substance, in the copies of the bound raw data note books, the 4 page chart, and Fig. 8, mentioned above except for the following:

(*a*) No weight and dosage entries were made between 3/13/58 and 4/3/58 in the raw data books, but were entered on the charts.

(*b*) Weights for all monkeys completing the Mer 29 study are shown on the charts through 3/5/59, but the bound raw data notebooks show M51 and M33 autopsied on 2/19/59.

3. Any data projected showing additions or deletions from those recorded in the aforementioned bound raw data books, the 4 page graph, and Fig. 8 are not true representations of the data submitted in which I participated.

BRUCE I. UMBERGER.

Subscribed and sworn to before me at Columbus, Ohio, this 4th day of May 1962.

Witnessed by Philip Brodsky.

THOMAS M. RICE.

U.S. Government Memorandum.

WILLIAM S. MERRELL CO.,
Cincinnati, Ohio, May 5, 1962.

To: Administration; Attn: Division of Regulatory Management.
From: Cincinnati District.
Subject: Mer 29.

This is a continuation of the Mer 29 investigation. Please refer to the Confidential Administrative memo of 5/4/62 by Inspector Rice and Brodsky.

After returning to Cincinnati the evening 5/4/62 after concluding our interview with Bruce Umberger in Columbus, Ohio, Inspector Rice phoned Mrs. Jo Jordan

to arrange for an appointment in order to try to obtain certain additional information and explanation with the help of the raw data book pages and charts. At this time, Mrs. Jordan agreed to the appointment, and an appointment was se up for 1:00 PM Saturday May 5, 1962. During the the conversation, she mentioned at the time she was working for Merrell she had been required to sign a statement that she would never reveal any information which came to her attention while in the employment of Merrell. She was fearful that if she spoke further with us that she might open herself to suit by Merrell for revealing information. At any rate, she did not appear to be to alarmed and agreed to the appointment.

The morning of May 5, 1962 at about 10:30 AM, Mrs. Jordan's husband, Carson Jordon phoned Inspector Rice at his residence. He first said they would be busy the afternoon of the appointment. He then went on to say they would be busy all day, that they would be busy from now on, and he then ordered me never to call his phone number again, or to come out to see him at his house. He said that the reason for this was that it upset his wife too much, and he was very fearful of the consequences to her. He said I could call him at his office, but never to call her again.

The afternoon of May 5, 1962 Inspector Brodsky and I then proceeded to the residence of Mrs. Gladis Gebert, 401 E. Vine St., Reading, Ohio.

After introducing ourselves and presenting Mrs. Gebert our credentials, we explained we wished to talk to her in connection with an investigation we were conducting of the William S. Merrell Co. Mrs. Gebert said this sounded interesting and that she would be glad to speak with us about it.

We asked her about the circumstances involved in her leaving the firm and when and why she had left.

Mrs. Gebert said she worked at the firm from 1953 through the summer of 1956. She knew she had left the firm sometime after July 4, 1956, but before the fall of 1956. She said she left because she "couldn't stand to work down there any more". She said she worked as a technician under Knox Smith. She took care of animals including monkeys. She dosed, weighed, made observations in connection with animal studies. Mrs. Gebert said that Mr. Charles Thompson was in charge of the department. Under him were two sections in this research unit. Knox Smith was in the rear of this unit, and under him were the following technicians in addition to Mrs. Gebert.

(1) Ann Estep. This is Ann Estep Dover now residing at 314 Cleveland, St. Bernard, Ohio. Her phone is PL 1-8183. According to Mrs. Gebert, this woman drew the blood and did the blood studies on virtually all of the experimental work in this laboratory.

(2) A woman by the name of Pat. This Pat married Fritz Holthaus who is presently working with Dr. King at Merrell. At this time, Holthaus was not in this department.

(3) Dorthy Meyer. This woman took care of the tissues. She later was discharged sometime after Mrs. Gebert left the firm. Dorthy Meyer is now in Florida.

(4) Tom Beaver. This individual was quiet, calm, honest, "kept his mouth shut", made up formulae, and may still be with the firm. At least Mrs. Gebert said he was still there two years ago. She said Beaver is honest and would give truthful information.

(5) Tom Cashman. This individual according to Mrs. Gebert, was brought in to take her place. He came in shortly before she left. She knew nothing about this individual.

Also under Mr. Thompson was a second branch headed by a Dr. Brown. This is a woman whose first name was not recalled. This individual is no longer with the firm, and was either discharged or left the firm prior to the time of Mrs. Gebert's termination of employment.

It is apparent that Mrs. Gebert left the employ of the firm prior to the Mer 29 Oral Toxicity studies on the monkeys.

Mrs. Gebert, however, did have some very definite impressions about the manner in which business was being conducted at this firm, and felt compelled to tell us all about this "intrigue" which she was withholding within and had been wanting to tell someone for a long time. Mrs. Gebert emphasized that these things could not be proved, but they are true, and felt that the "whole place needed an expose". She said that Dr. Brown and Mr. Thompson were having a "war". Employees in the middle were forced to take sides. Dr. Brown was busy setting peo-

ple against each other. She said people in authority were mixing up data in data books. She said "You couldn't be honest and work there". At this point, Mrs. Gebert mentioned that Ann Estep was a "crooked, foul mouthed person in cahoots with the crowd". She told us that she lives in St. Bernard and did the dirty work for Knox Smith. She said her brother-inlaw runs a bar in St. Bernard. That Estep's brother-in-law ran a bar in St. Bernard was later confirmed during our interview with Ann Estep Dover. Mrs. Gebert said that she was attempting to stay out of the controversy, but later she was drawn into it and was fired. Prior to her being discharged, she actively took sides and tried to call to the attention of Mr. Thompson what was going on. She said Smith and Brown were working together against Thompson. She said they had no principles, and they tried to influence Dr. Werner who was above all of these individuals against Mr. Thompson by spreading rumors regarding illicit sexual activities between Thompson and the female employees. Mrs. Gebert did not think there was anything to this, but rather Thompson was a fatherly type individual who treated the employees or thought of his employees as his children. Later, there were rumors of familiarities between Dr. Werner and Dr. Brown (female). Eventually, Brown was released. She said that both sides in this feuding attempted to accuse opponents on the opposite side of illicit sex relations with employees. She again emphasized that Ann Estep "messed up" studies for Knox Smith.

She said as a result of this jealously, intrigue, lack of principle, and down right interference with experiments that she would suspect anything put out by this firm.

During her conversation, she said that several high principled individuals left the firm because of the atmosphere and the way things were bing run. One was Dr. Jake Stuke. She said that he was an endocrinologist, and finally left the company to take a job with another firm in Kalamazoo. She was certain the firm Dr. Stuke joined after leaving Merrell was Up John. Another high principled individual was Dr. Leonard Lerner. She said he left to go with another drug firm in New Jersey. She said this was the "worst dog eat dog, cut throat, cheating, lying place she ever worked at". She said she was "a wreck from this confusion and went to two psychiatrists". Her impression was that the people she was working with were capable of fixing tests to improve their own status and making money. She believes that Knox Smith with the help of Estep, would have data fixed in the record books.

It should be noted that Mrs. Gebert's employment with the firm was terminated because she was "fired". This came about or at least came to a head because a vicious monkey had been turned loose in a room with her. This monkey was known as No. 13 and she believed Knox Smith deliberately turned the monkey loose in this room, This monkey had bitten the animal room attendants. Knox Smith said that he had been turned loose accidentally, however, she accused Smith of doing it purposely.

Again it should be emphasized that all of the above is information Mrs. Gebert cannot prove, but because she felt so strongly about it, and wanted it off her mind she felt compelled to tell us.

We next interviewed Mrs. Ann Estep Dover, 314 Cleveland Ave., St. Bernard, Ohio.

Mrs. Dover worked with Merrell from June, 1944 through May, 1958. From 1944 through 1950 her duties were in the factory in the packaging department, etc.

From 1950 through May, 1958, she worked in the department of Pharmacology. Her duties involved working with the animals and included feeding, weighing, dosing, and especially doing blood work in connection with the animals, particularly monkeys. The blood work on the monkeys consisted of examining the blood for red blood count, white blood count, hemoglobin, hematocrite and differential counts. She actually withdrew the blood from the monkeys herself. This information was recorded directly onto 3'' x 5'' cards in the laboratory. Following this, she transcribed them into bound notebooks. While this mainly was done fairly soon after the studies, it might have been as much as one or two weeks before the transcriptions were made into the bound notebooks. The notebooks were kept in the laboratory. The entries were made in duplicate and the original copy was torn out of the book and sent to the firm's records library. The carbon copy of the reports remained in the bound notebooks. All entries were signed by the technician doing the work.

Mr. J. Knox Smith was her immediate supervisor. Mr. Charles R. Thompson

was the supervisor of Knox Smith. Thompson left before Mrs. Dover left the firm. Mrs. Dover left the firm because of pregnancy.

It was revealed that Mrs. Dover received a long distance telephone call from Knox Smith in Los Angeles on April 27, 1962. Mr. Smith had told her that she might have visitors. Mr. Smith was checking on names of former employees under him when he worked at Merrell's. Mrs. Dover stated that during and subsequent to her employment with Merrell, she had been very friendly with Mr. and Mrs. Knox Smith, and as a matter of fact, they correspond frequently.

Mrs. Dover stated that she was aware of the fact that she had worked on Mer 29 when she was with the firm. She said that she made graphs, and had access to data bound in the notebooks and the rough graphs, and her duties involved entering data into bound notebooks and making rough graphs in connection with her work. We showed her some of the raw data which she would have had access to at the time she worked at the firm. She said that she took blood and made studies on the blood on both control animals and drug animals on the experiments. These studies included animals on 5066 as well as on 5052 and the control animals. She said that any animals on these studies would be in the raw data books, and that the entries would have been made in her own handwriting, she would have signed the pages, and if confronted with this raw data, she would be able to swear that this data was in fact the true facts representing her original work. She confirmed that if she were confronted with data which were different from the data recorded in the raw data notebooks in her own handwriting and signed by her that she would emphatically say that the other data was false and her data was true.

Mrs. Dover said that also working in this department at the time she was there was Dorothy Meyer whose last name now is Sekins. Mrs. Sekins has left the firm and is now living in Florida. Mrs. Sekins was still employed by the firm after Mrs. Dover left the firm. Mrs. Sekins did the tissue work primarily.

Another employee in the department while Mrs. Dover was working there was Mrs. Carole Root. She was the wife of a Merrell employee in the sales department whose name was Charles A. Root, III. The Root's are presently living on Carolina Ave. in Kingsport, Tennessee. As far as Mrs. Dover knows, he is still with Merrell's. Mrs. Dover saw the Root's last July while on vacation in the Smokies. Carole Root had the job of dosing, feeding, and weighing monkeys. Note that Carole Root's name appears on many of the pages in the first part of the monkey studies in the raw data notebooks.

Another employe in the department during the time Mrs. Dover was with the firm was Bruce Umberger. He left the firm to go to Ohio State University. He has been in touch with Mrs. Dover whenever he comes to Cincinnati, and called her about a year ago. Other memos contain full information on this individual.

Another employee in the department was Mary Ann Stevens. This is Mrs. William Stevens who lives in Mt. Healthy, Ohio. Her husband is dead, and as far as Mrs. Dover knows, she may still be working with the firm.

Another individual working in the department was a female technician whose first name is Jo. She does not know her last name, but her husband's first name is Carson. This is, of course, Mrs. Jo Jordan, whom we have previously interviewed. This individual was employed at Merrell at the same time that Mrs. Dover was employed there.

Mrs. Dover in response to a question stated that she recalled nothing out of the ordinary in connection with these monkey studies.

It might be interesting to note that Mrs. Dover stated that the firm has not been in touch with her concerning this matter, except for the phone call from Mrs. Smith.

There was one interesting observation which Mrs. Dover made without our mentioning it which ties in with information secured from Mr. Umberger. This was that she recalled that one of the monkeys bit a finger off a second monkey. She did not seem to know whether or not the whole finger had been bitten off, but at least she knew one of the monkeys had bit the finger of another. This would tend to confirm the fact that this incident occurred sometime while the monkeys were on tests, and it would of necessity have had to occur between September, 1957 and May, 1958 in order to have both Umberger and Dover observe this incident, since Umberger did not join the firm until September, 1957, and Dover left the firm in May, 1958.

THOMAS M. RICE,
PHILIP BRODSKY,
Inspectors.

U.S. Government Memorandum.

WILLIAM S. MERRELL CO.,
Cincinnati, Ohio, May 30, 1962.

To : Administration ; Attn : Division of Regulatory Management.
From : Cincinnati District.
Subject : Mer 29.

On the evening of 5/28/62, Supervisory Inspector Rice again interviewed Mrs. Jo Jordan in the presence of her husband Carson Jordan as planned, and reported in our memo of May 26, 1962.

A photocopy of Mrs. Jordan's affidavit of 3/13/62 was given to her at this time as a result of her request.

Mrs. Jordan had agreed to allow only 30 minutes for this interview, but because she became more cooperative, the interview continued for nearly two hours.

While Mrs. Jordan would not permit our copying or borrowing Dr. Bunde's letter and no further affidavits were taken, the following points were developed during this interview.

1. Mrs. Jordan is still undecided as to whether or not she will see any representative of Merrell. She has been very much irritated by their use of private detectives, fake credit bureau calls, and inquiries from the neighbors, and contacts with her and her husband's employers. She is still extremely upset, nervous and on occasion nearly hysterical as a result of the entire matter. It is something she has been unable to cope with and she fears she may lose her present position as a result of this.

2. Mrs. Jordan has decided she will tell the truth if she does talk to the Merrell representatives.

3. Mrs. Jordan will cooperate with FDA and give truthful answers in the event she is called as a witness. At one time when she was so extremely upset about the whole matter, she had wanted to have nothing further to do with it.

4. Mrs. Jordan was shown the copies of (1) the pages from the monkey raw data books (located April 9, 1962), (2) the 4 p. chart "Monkeys Chronic Oral Toxicity Mer 29 Body Weights," (3) the chart "Figure 8, and (4) the chart "Figure 7" supplied us with the NDA, since she had access to all this material and had helped prepare it. She was able to clear up some of our questions as follows :

(*a*) the copies of the pages we have from the monkey raw data books are correct and have not been altered as far as she can tell. She recognized her writing and signatures. She now believes she took these books into the monkey room and made direct entries.

(*b*) the sick male drug monkey she referred to in her affidavit of 3/13/62 was M 34. (Note this agrees with Bruce Umberger's recollection). She knew it was a small male drug monkey on 5052 (Mer 29). It could not be 49 since it was female, and it could not be male 51 because it was added in the middle of the experiment and was a large monkey. M 25 could not be the one as he had been sacrificed early. M 34 is thus the only possible monkey it could be.

(*c*) she now believes she was mistaken as to the amount of weight loss of M 34, but now recalls that he was sick and did poorly and failed to *gain normally* over the experiment as the other monkeys in the same weight bracket did. This monkey did lose weight from 8.5 Kg on 12/18/58 to 8.1 Kg on 2/19/59, the last entry.

(*d*) She confirmed that M 34 was the one that couldn't see properly and was mean. He became withdrawn and just sat in the corner of the cage. He couldn't jump in and out of the box when being weighed and was the one that missed the box when he tried to jump into it.

(*e*) She recalled F 49 was Umberger's pet and was called "Forty-niner." She now recalled this female drug monkey was sick toward the last and lost a dramatic amount of weight.

(*f*) She recalled male drug monkey M 51 also lost weight toward the end and was somewhat sick.

(*g*) She further confirmed that M 34 was not autopsied in her presence. This is the reason no record of this was found in the raw data book. She could not explain what happened to this monkey after 2/19/62.

(*h*) She confirmed that the 4 p. chart "Monkeys Chronic Oral Toxicity Mer 29 Body Weights", and Figure 8 were correct graphs based on the actual weights

as recorded in the raw data books, except for the discrepancies in the autopsy dates and possibly some graph entries toward the end. She was inclined to think that the weights at autopsy were used in the last week or two for some of the animals autopsied prior to 3/5/59 to carry the chart out to 3/5/59 for all animals.

(*i*) She said Dr. Van Maanen was the one that told her to falsify the chart (fig. 7.) turned in with the NDA. He had her cut off the final several weeks shown on Figure 8 which showed the dramatic loss of weight of F 49. She had to make this chart over 3 times. He was the one who supplied the weights to be used for M 34 in the final charts. Note that the curve for M 34 on Fig. 7 does not agree with Fig. 8 or the raw data books, or the 4 page chart although the weights are in the same general range. Dr. King went along with these falsifications 100%.

(*j*) Mrs. Jordan noticed that there was no reference anywhere of monkey M 52. She was under the impression that this monkey had some connection with this experiment, but could not recall exactly. It is possible that the weights of this monkey were the ones supplied her by Dr. Van Maanen to be included in Fig. 7 supplied with the NDA, and perhaps this is the monkey whose autopsy results were used in place of M 34.

(*k*) Mrs. Jordan said that Dr. Van Maanen had insisted on her showing M 51 on Figure 8 as having been on Mer 29 for the entire experiment rather than for only the last 8 months. Also he insisted on her showing M 35 as a control monkey for the experiment for the entire time. She knew that this monkey had been on 5066 during the first part of the experiment. Note the weight for this monkey goes up rapidly on the charts, after the raw data books have no further record of the 5066 dosing on 3/13/58. There are no records of weights of this animal as a control and no records of any kind in the raw data books after 3/13/58 for this animal.

(*l*) Mrs. Jordan said that because of the cost it was common practice for this firm to use monkeys for a number of experiments. Thus, monkeys previously used as drug monkeys might wind up as controls in a later experiment. Normally all drug monkeys had been used as controls in previous experiments. 51, 49, 34 and 33 were fairly old monkeys while 35 was fairly young. She did not recall the ages of the others.

(*m*) Mrs. Jordan stated that she had written on a form at the time of her resignation her reasons for resigning as not wanting to be a party to falsifying records as she was required to do by Dr. King. The firm now claims this form of hers is missing, and she suspects Dr. King took it. She does not recall in how much detail she spelled out the falsifications on this form.

(*n*) Mrs. Jordan recalled there were some very suspicious looking rats on the Mer 29 studies, but she knows of no record falsification. She did recall that about ⅓ of the Mer 29 rats died. We do not have our copy of the NDA here to check this point as we have sent it to you, but it is our recollection that deaths of rats of this order were not reported. This point should be checked out.

(*o*) Mrs. Johnson did not recall that any of the dogs on Mer 29 died while she was there, and knew of no falsifications in the record.

(*p*) The firm has now asked Mrs. Johnson about other irregularities concerning Dr. King. She has been given to understand he has been fired because of improper relations with the female employees, and for dishonest fiscal practices and that Dr. Van Maanen is on extended leave. Mrs. Johnson said on one occasion, Dr. King had her pick up supplies in her personal car. After some delay, Dr. King paid her by personal check at the rate of 4¢ a mile for this company business. She later found out that Dr. King had collected 7¢ per mile from the firm for this. The firm has now asked Mrs. Jordan to put in her claim to the company for this difference which she is entitled to.

(*q*) Mrs. Jordan reaffirmed that Dr. King had sent a number of slides to the University of Mississippi for reading, confirmation, or interpretation.

(*r*) Mrs. Jordan is now convinced that the falsification of records not not known by the officers of the firm above Dr. Van Maanen, and that the entire falsification picture was their joint responsibility.

(*s*) Mrs. Jordan does not know the whereabouts of Dorothy Miner except that she believes she is running a motel and restaurant in Florida. She seemed certain that it was *not Coral Gables.* She believed she may now be married to a man whose first name is Frank, who she was living with. (His last name was not known, but this is apparently Frank Sekins). Her only clue was that

he was an officer in the VFW, when it was located on Ridge Ave. in Cincinnati, Ohio.

We will attempt to locate Dorothy Miner Sekins address from the VFW. We also will contact Dr. Van Maanen as soon as we are able.

THOMAS M. RICE,
Supervisory Inspector.

U.S. Government Memorandum.

WILLIAM S. MERRILL CO.,
Cincinnati, Ohio, June 19, 1962.

To: Division of Regulatory Management.
From: Cincinnati District.
Subject: Mer 29.

In response to Mr. Robert C. Branderburg's phoned request of 6/14/62, Supervisory Inspector Rice and Inspector Brodsky interviewed "Dr. Grady" who was named as "our consultant veterinarian" by Merrill.

This individual was found to be Dr. K. S. Grady, operator of Northern Hills Animal Clinic, 9211 Winton, Cincinnati, Ohio, and he was interviewed at his office on 6/18/62. He indicated he was expecting us to call.

Dr. Grady advised that he is a consultant for the firm, and has been under contract with the firm for about one year. He is paid a yearly stipend plus per diem when calls are made. Prior to this time he was called only as needed on a few occasions.

He emphasized that he had nothing to do with dosing or running tests, and didn't necessarily know which animals he was examining or which experiment they were on. He was primarily consulted in connection with the health of the animals, and except for a few instances, his work was confined to dogs.

In response to a question, he said he might have on occasion been asked an opinion as to how to treat a sick monkey or two.

Dr. Grady said he had maintained no records of the examinations he had made of these animals for Merrell, and had no record of when these examinations had been made. He explained that he usually went to Merrell once a week at his convenience which was usually Tuesday, Wednesday, or Thursday. During these visits, he spent approximately 3 to 4 hours and examined the animals (primarily dogs) as requested on an individual basis and dictated his findings to a Merrell secretary. These animal summaries he explained, consisted of one or two page reports with 3 or 4 sentences on each animal. These reports were never signed by Dr. Grady. He hay have seen some of them after typing on subsequent visits. He probably could recognize these reports, but could not vouch for their accuracy at this time since he had not normally signed them or retained copies. He said most of the reports were taken by Dr. King's secretary whose name was "Bonnie". He believes she is still with the firm. All of his work was done during the time Dr. King was present. He had never worked with Knox Smith, but had met him. He did have a few contacts with Dr. Van Maanen, but most of his contacts were with Dr. King. He said that Fritz Holthause was Dr. King's assistant, and he should have knowledge of any of his dictated reports.

He stressed the point that when the firm received shipments of monkeys, and beagles, he picked them up and examined them at his clinic merely from a health standpoint.

The examination of the monkeys was a chest X-ray only. He did no routine examinations on the monkeys and he did not receive or examine rats. Dogs other than the beagles were not examined.

Sometime prior to June 1961, before Dr. Grady's first contract with the firm, Dr. Grady was called in because the firm had on hand a number of sick dogs. His examination revealed hepatitis. The dogs were treated with hepatitis and distemper shots and were given antibiotics, fluids, and supportive B complex therapy. He was unable to recall the date, but he remembers he didn't have enough serum on hand to treat this large number of animals, so it was necessary to secure the serum from the American Cyanamide Warehouse. He recalls this was on a Friday, and it should be possible to determine this date from the warehouse if needed.

Dr. Grady stated that subsequent to his contract (June 1961) he made specialized examinations primarily on dogs eyes, once a week for a period of 3 to 4 months. He noted abnormalities in several of the dog's eyes, and he observed that these abnormalities developed slowly through various stages or progressions

until some of them were diagnosed as cataracts. The firm made photographs of some of these eyes, and he worked at these but was not asked to study them. Some of the dog's eyes showed fingernail like opacities.

Some of these same dogs also had severe dermatitis problems.

He pointed out these findings to responsible individuals of the firm through his reports, and discussions primarily with Dr. King. Although he did not know at the time he noted these abnormalities, he later found out that the dogs under study were being dosed with Mer 29.

He did not know if any of these dogs died. He recalled dog identification numbers of dogs he examined in the 140–150 series. Some may have been as high as 165. He does not know but what some of these dogs were on Kevadon and there could have been several Mer 29 experiments for all he knew. He did recall that he heard some of the dosages were 10 mg/kg., 20 mg/kg., and 40 mg/kg body weight.

He also was requested to look at a few rats that had dye opacities, but he does not know what studies these rats were on.

He recalls that at least one Mer. 29 dog had one eye removed, and he had been consulted as to which eye to remove. He assumed slides had been prepared from this eye.

Dr. Grady said he has not been consulted since the suspension of Dr. Van Maanen and Dr. King.

Dr. Grady said he had gone to Merrell, but on finding that Dr. King and Dr. Van Maanen were not there, he called Dr. Warner who advised that they had been suspended .

In speaking with Merrell personnel, Dr. Grady was not given any instructions as to what to say if contacted by Food and Drug.

Prior to leaving, Dr. Grady assured us that he wanted to cooperate with us completely and that if he recalled anything of significance, he would get in touch with us.

THOMAS M. RICE.
PHILIP BRODSKY.

U.S. Government Memorandum.

WILLIAM S. MERRELL CO.,
Cincinnati, Ohio, June 20, 1962.

To: Administration : Attn : Division of Regulatory Management.
From : Cincinnati District.
Subject: Mer 29.

In response to Mr. Robert C. Brandenburg's phone conversation with Supervisory Inspector Rice of 6/19/62, Inspector Meyring and Supervisory Inspector Rice interviewed Dr. Frank A. Nantz, M.D. 240 Doctor's Building, Cincinnati, Ohio, on 6/20/62.

Dr. Nantz advised us that his first contact with the firm developed because of his friendship with Dr. Isaac Ruchman who was employed in the department of virology at the firm. He has been a friend of Dr. Ruchman for 10 to 15 years. During this period, he has visited with Dr. Ruchman and other members of the staff at the firm, and has been called out to the firm for several occasions for purposes other than those connected with Mer 29. He has never had any formalized relationship with the firm, and has never had any compensation for his contacts including those contacts which resulted as a result of work on Mer 29.

Dr. Nantz is an M.D. and an Ophthalmologist, and in his regular practice he has been interested in research connected with the lowering of cholesterol. As a matter of fact, Dr. Nantz told us that he had been doing some research on sitosterol for Lilly.

After Mer 29 became available, Dr. Nantz was naturally very much interested in this new drug and as other doctors, he began prescribing it.

In November, 1961, as a result of his previous relationships with the firm, Dr. Van Maanan called him and asked him to come out and take a look at some dogs who were on a high level Mer 29 study.

He apparently went out to the firm and examined these dogs eyes on Thursday, November 9, 1961. While he was out at the firm, he was also asked to review a clinical description of four patients who had been on Mer 29. He did not see these patients, but the firm wanted to know whether or not there was a relationship between the cataracts in the dogs eyes and the cataracts in the patients eyes.

Because the firm wanted an immediate opinion, Dr. Nantz wrote a letter to the firm explaining his off hand opinion, and this is apparently his letter of November 10, 1961, addressed to Dr. Van Maanen. Dr. Nantz could not remember the exact date of his visit or the letter, but knew that it was in November or December. The dates supplied here were the dates provided from Mr. Brandenburg in his phone conversation with Supervisory Inspector Rice of 6/19/62.

Dr. Nantz verbally told the firm apparently Dr. Van Maanen, that he did not believe there was any relationship between the cataracts in the dogs and the patients because of the very high levels of Mer 29 in the dog study opposed to the lower levels being taken by the human patients. In his letter, he recalls that he did believe the cataracts were the result of the Mer 29 because of the high levels in dogs. but he believes that he finally mentioned in this letter that he could not say whether or not there was any relationship between the cataracts in the patients and those found in the dogs.

Subsequent to his first trip and letter, Dr. Nantz made additional trips to the firm to examine the dogs' eyes. He does not recall exactly how many trips were made or when they were made, but he did make in the neighborhood of six trips extending over a four month period. The last time Dr. Nantz has been out to the firm looking at the dogs' eyes was approximately one month ago.

As far as Dr. Nantz knows, these dogs have not been sacrificed as yet, because the firm promised to call him when the dogs were sacrificed so that he could observe histological technics and examine sections of the lenses.

When Dr. Nantz was out at the firm, he was shown slides of eye tissue sections of dogs which were fed Mer 29 and sacrificed prior to his visit. Dr. Nantz had never examined the eyes of these dogs while the dogs were alive from which the sections were taken.

Dr. Nantz knew that the dogs he had examined and who were apparently still alive now had been on a large dose of Mer 29 for approximately six months. He said that these dogs apparently developed the cataracts rather rapidly after the six months' period, and that the formation of the cataracts was quite variable from dog to dog. He said that in some cases, the abnormalities of the lenses tended to recede even while the dog was on the drug, and then after being retained on the drug, the opacity would continue to progress and develop.

Dr. Nantz also stated that there were skin disorders or rashes which developed on the dogs who developed cataracts. He stated that the rash developed prior to the cataracts as far as he could recall.

Dr. Nantz recalled that there were other dogs on another drug which may have been related to Mer 29. He did not know how many months the dogs were on the other drug, and at this time he is not certain as to whether cataracts were observed in these dogs on this other drug.

Dr. Nantz recalls that a second letter was written to the firm about February 20, 1962. The reason for this letter was that he had been asked by Dr. Bundie to come out to the firm to meet a well-known opthomologist from Des Moines, Iowa, who had made a special trip to Merrell to examine the eyes of the dogs on Mer 29. Dr. Nantz was about ready to depart for a professional meeting and vacation in New Orleans, and since this request came the day before he was to leave, he was unable to go out to the firm and meet this doctor, but he did write an informal letter to Dr. Bundie explaining what he had already seen, and this letter enumerated specific points he had observed in technical terms for the use of this doctor. This letter was much more detailed than the letter he had written in November to the firm.

Dr. Nantz and his secretary searched his files to see if they could find copies of these letters or any other correspondence, but they were unsuccessful.

Dr. Nantz promised to continue to search for any correspondence and to look at home, and if he was able to locate any correspondence with the firm in this connection, he would advise us, so that we could secure such correspondence.

At this time, Dr. Nantz recalled that he wrote only the two letters to the firm.

Although Dr. Nantz has not seen any cataracts in his own practice on Mer 29 patients, he inferred he changed his mind since his original letter, or original opinion that there was no connection between Mer 29 and cataracts in humans.

THOMAS M. RICE.
JAMES A. MEYRING.

United States District Court for the District of Columbia

Holding a criminal term

Special July 1963 Grand Jury sworn in on July 2, 1963

THE UNITED STATES OF AMERICA

v.

THE WM. S. MERRELL COMPANY, RICHARDSON-MERRELL, INC., HAROLD W. WERNER, EVERT F. VAN MAANEN, WILLIAM M. KING

Criminal No. 1211–63; Grand Jury No. Original; Violation: 18 U.S.C. 1001

The Grand Jury charges:

On or about July 24, 1959, within the District of Columbia, the defendants, The Wm. S. Merrell Company, a body corporate, Evert F. Van Maanen and William M. King, wilfully and knowingly made and used, and caused to be made and used, in a matter within the jurisdiction of the Food and Drug Administration of the Department of Health, Education and Welfare, an agency and Department of the United States, a false writing and document knowing the same to contain false, fictitious and fraudulent material statements and entries, in that the defendants knowingly and wilfully filed and caused to be filed, on or about July 24, 1959, with the said Food and Drug Administration, in Washington, D.C., a new drug application, designated as NDA 12–066, for MER/29 (Triparanol), a new drug then subject to the provisions of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and which was then a matter within the jurisdiction of the said Food and Drug Administration, containing certain reports of investigations made to show whether or not the said MER/29 (Triparanol) was safe for use, that is, the results of toxicity studies in animals, in which the defendants knowingly made and caused to be made false, fictitious and fraudulent material statements and entries, to wit:

1. The report of the six-week subacute toxicity study in rats on 37.5 and 75 mg/kg per day regimen of MER/29 contained statements and entries that four out of eight female rats on a daily regimen of 75 mg of MER/29 per kilogram of body weight had survived six weeks of experimentation and study, and it set forth figures and amounts showing the body weights and organ weights of said four surviving rats, their food consumption during the six-week study period and statements and entries showing that the hematologic values of rats administered MER/29 during the six-week study period were within normal limits and similar to the hematologic values of the control rats (i.e., rats which were a part of the study but not administered any of the drug MER/29), all of which statements and entries the defendants knew to be false, fictitious and fraudulent in that all of the female rats on the 75 mg/kg per day regimen of MER/29 had died before the completion of the six-week study and no final organ weights, body weights or blood values were obtained covering the entire six-week period, and that in certain of the remaining rats adverse blood effects consisting of changes in leukocytes, granulocytes and lymphocytes had been observed but were not reported.

2. The report of the twelve-week chronic toxicity study in rats on 25 and 50 mg/kg per day regimen of MER/29 contained statements and entries showing that hematologic and blood determinations were within normal limits, said statements and entries being false, fictitious and fraudulent in that, as the defendants well know but did not report, a marked increase in leukocytes and reticulocytes and a number of vacuolated and binucleated forms of lymphocytes had been observed in rats to which MER/29 had been administered.

3. The report of the chronic study in monkeys covering the period from on or about September 9, 1957 to on or about March 15, 1959 contained statements and entries that

(*a*) rhesus monkey designated as No. 51 in the study had been administered MER/29 at a dosage of 40 mg/kg per day for a period of six months and thereafter at a dosage level of 20 mg/kg per day for an additional ten months, which was false, fictitious and fraudulent, as the defendants well knew, in that rhesus monkey No. 51 had not been administered a dose of 40

mg/kg per day at any time during the course of said study, and had not been administered the dose of 20 mg/kg per day for the time specified but for a less time, to wit, approximately seven months and 26 days;

(*b*) monkey designated as No. 35 had been a control monkey for the entire period of the study and had been administered placebos for the entire 16 months, which was false, fictitious and fraudulent, as the defendants well knew, in that said monkey No. 35 had been administered another drug which was an analogue of MER/29 for the first six months of the study and had not been used as a control monkey during that period;

(*c*) the oral administration of MER/29 to test monkeys had caused no significant effect on the body weights of the monkeys receiving MER/29, which was, as the defendants well knew, false, fictitious and fraudulent, in that test monkeys Nos. 49 and 51 had each suffered significant loss of weight during the latter part of said study;

(*d*) microscopic examination upon autopsy showed the liver and gall bladder organs of female monkey No. 49 to be normal, which was false, fictitious and fraudulent, as defendants well knew, in that such examination disclosed that monkey No. 49 had an enlarged gall bladder, several small necrotic areas in the liver and many adhesions between the lung and chest cavity;

(*e*) microscopic examination upon autopsy of monkey No. 51 showed a normal heart organ, which was false, fictitious and fraudulent, as the defendants well knew, in that the said examination of the heart of monkey No. 51 revealed a condition described as possible left ventricular hypertrophy, and

(*f*) during the aforesaid chronic study, the MER/29-treated monkeys and the control monkeys showed similar hematologic values, and the morphology of the peripheral blood was similar in both the MER/29-treated monkeys and the control monkeys, which were false, fictitious and fraudulent, as the defendants well knew, in that various blood dyscrasias such as vacuolated and binucleated lymphocytes, and lymphocytes with irregularly-shaped nuclei had been observed in the blood smears taken from monkeys receiving MER/29 but not in those taken from the control monkeys.

Second Count

1. At the times mentioned herein, The Wm. S. Merrell Company had submitted to the Food and Drug Administration a New Drug Application, and amendments thereto, for a new drug known as MER/29 (Triparanol), said application stating and representing that attached thereto were full reports of all investigations that had been made to show whether or not the drug was safe for use.

2. During the period from on or about February 17, 1960 to March 31, 1960, within the District of Columbia, the defendants, The Wm. S. Merrell Company, a body corporate, Harold W. Werner, Evert F. Van Maanen and William M. King, knowingly and wilfully concealed and covered up, and caused to be concealed and covered up, by trick and scheme, material facts in a matter within the jurisdiction of a Department and agency of the United States, in that during the period above-mentioned and at the place aforesaid, the defendants caused to be submitted to the Food and Drug Administration of the Department of Health, Education and Welware, as an amendment to the New Drug Application of The Wm. S. Merrell Company for MER/29 (Triparanol), a new drug then subject to the provisions of section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) and which was then a matter within the jurisdiction of the Food and Drug Administration of the Department of Health, Education and Welfare, certain reports purporting to be full reports of the results of all investigations which were made by The Wm. S. Merrell Company to show whether or not said drug was safe for use, said defendants knowingly and wilfully withholding, and omitting to include therewith, reports of the results of certain investigations, and data and information obtained therefrom, which had been made to show whether or not the drug was safe for use, and failing to disclose the fact that certain investigations had been made, and that adverse and toxic effects had been observed in animals to which the drug had been administered, said investigations being more particularly described as follows:

A. An investigation made by The Wm. S. Merrell Company, begun on or about June 23, 1959 with three female monkeys, to study the effect of dosages of 10

mg/kg per day of MER/29 upon the ovaries of such animals, in which it was observed (a) that one monkey had ovarian changes in the form of an increase in the number of ovarian follicles which did not appear to have matured to a state of ovulation, (b) that one monkey had developed severe leukopenia and agranulocytosis, and (c) that two monkeys had a depressed granulocyte count, atypical lymphocytes and high leukocyte counts.

B. An investigation made by The Wm. S. Merrell Company in which four female monkeys were started on a toxicity study on or about September 15, 1959 for the purpose of determining the effect of an administration of 5 mg/kg per day of MER/29 on ovarian morphology, at the end of which investigation no evidence of recent ovulation was found.

C. A recovery toxicity investigation made by The Wm. S. Merrell Company with female rats, started on or about January 10, 1958 to determine the etiology of abnormal blood changes, in which it was observed that eight out of ten rats being administered a dosage of 50 mg/kg per day of MER/29 had died as of January 27, 1958, and the surviving two rats whose dosage as of that date was reduced to 25 mg/kg per day of MER/29 had died as of February 3, 1958.

D. A recovery toxicity investigation made by The Wm. S. Merrell Company with female rats started on or about January 30, 1958 to determine the etiology of abnormal blood changes which had been observed in previous toxicity studies, the results of which showed that rats being administered MER/29 developed abnormal blood changes in the form of binucleated lymphocytes, blood dyscrasias and an increase in reticulocytes.

E. A toxicity investigation in male and female rats which was conducted during the period between July 1959 through October 1959 by The Wm. S. Merrell Company to determine the effect of MER/29 on fertility and gestation, such rats having been administered 5 mg and 15 mg/kg per day of MER/29, in which it was observed that doses of 15 mg/kg per day reduced the conception rate when given prior to and during cohabitation, and

F. A toxicity investigation in male and female rats at dosages of 10 and 25 mg/kg per day of MER/29 which was conducted between on or about July 7, 1959 and October 1959 by The Endocrine Laboratories of Madison, Inc., Madison, Wisconsin, pursuant to a contract with The Wm. S. Merrell Company to determine the effect of MER/29 on fertility and gestation, in which it was observed that there was a reduced conception rate among rats receiving doses of 25 mg/kg per day of MER/29 during pregnancy, the size of the litter was reduced and there was an increase in rate of the deaths of the young during the 24-hour period after delivery.

Third Count

1. The Grand Jury realleges all of the allegations of the first paragraph of the Second Count of this indictment.

2. On or about February 17, 1960, within the District of Columbia, the defendants, The Wm. S. Merrell Company, a body corporate, Evert F. Van Maanen and William M. King, in a matter within the jurisdiction of the Food and Drug Administration of the Department of Health, Education and Welfare, an agency and Department of the United States, knowingly and wilfully made and used, and caused to be made and used, a false writing and document knowing the same to contain false, fictitious and fraudulent statements and entries, in that on February 17, 1960, the defendants caused to be submitted to said Food and Drug Administration, at Washington, D.C., on behalf of said The Wm. S. Merrell Company, as an amendment to its New Drug Application for MER/29 (Triparanol), a new drug then subject to the provisions of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and which was then a matter within the jurisdiction of the Food and Drug Administration, a writing containing reports of investigations that had been made to show whether or not the drug was safe for use, such writing containing the following false, fictitious and fraudulent statements and entries, to wit:

(*a*) The report of a six-month study in mongrel dogs receiving a dosage of 25 mg/kg per day of MER/29, which contained false and fraudulent statements and entries that three of the dogs had died early in the experiment and that two of the remaining dogs had maintained their body weight during the course of the study, when in truth and in fact, as the defendants well knew, the dead dogs had been replaced by three additional dogs and all of the dogs in the study had lost body weight.

(*b*) The report of a three-month study with five beagle dogs receiving a dose of 40 mg/kg per day of MER/29, which contained false and fraudulent statements and entries, as follows;

(1) that microscopic examination of dog No. 69 had disclosed a reduction of the number of mature spermatocytes in the seminiferous tubules and a paucity of spermatozoa in the vas, when in truth and in fact, as the defendants well knew, no spermatocytes were so found and vitally important portions of the gonads had undergone marked tubular and interstitial atrophy;

(2) that between the sixth week of the study and its conclusion dog No. 69 had gained weight when in truth and in fact, as the defendants well knew, it had lost weight;

(3) that the evaluation of the dog study was difficult because of the existence of concomitant diseases in The Wm. S. Merrell Company's dog colony and particularly the outbreak of distemper in October 1959, when in truth and in fact, as the defendants well knew, the original study which started on October 21, 1959, had been discontinued on October 30, 1959, and a new study begun on November 3, 1959, with different dogs, which had not contacted distemper during the aforesaid outbreak.

(*c*) The report of a four-month study in three adult mongrel dogs receiving a dose of 10 mg/kg per day of MER/29, which contained false, fictitious and fraudulent statements and entries, as follows;

(1) that the administration of MER/29 at a dosage of 10 mg/kg of MER/29 did not affect the peripheral blood values of these dogs and that the hematologic values for dog No. 57 during the study showed the initial and final hemoglobin in grams per 100 cc as 11.8 and 14.2 respectively, and the initial and final hematocrit percentum packed cells as 34 and 40 respectively, when in truth and in fact, as the defendants well knew, the initial and final hemoglobin values for dog No. 57 remained at 9.0 grams, and the initial and final hematocrit values for dog No. 57 were 27 and 32 percentum respectively;

(2) that although dog No. 58 showed an intial weight loss when the drug administration was started, it showed a gain for the remainder of the study so that the loss amounted to approximately one kilogram (2.2 lbs.), when in truth and in fact, as the defendants well knew, dog No. 58 had lost 3.7 pounds during the last week of the study.

Fourth Count

On or about February 8, 1960, within the District of Columbia, the defendants, The Wm. S. Merrell Company, a body corporate, Harold W. Werner and Evert F. Van Maanen knowingly and willfully made, and caused to be made, false, fictitious and fradulent statements and representations of material facts in a matter within the jurisdiction of a Department and agency of the United States, in that on said date The Wm. S. Merrell Company submitted to the Food and Drug Administration of the Department of Health, Education and Welfare, at Washington, D.C., a letter dated February 4, 1960 enclosing a revised brochure for MER/29 (Triparanol), a new drug then subject to the provisions of section 505 of the Federal Food, Drug, and Comestic Act (21 U.S.C. 355) and which was then a matter within the jurisdiction of the Food and Drug Administration, in which letter was falsely and fraudulently stated and represented that a caution statement reading, "Since cholesterol plays an important role in the development of the fetus, the drug should not be administered during pregnancy" had been inserted in the brochure "purely on theoretical grounds", when in truth and in fact, as the said defendant well knew, investigations and experiments had been conducted by said The Wm. S. Merrell Company, and by an independent laboratory pursuant to its request, the results of which disclosed that the administration of the drug to animals had resulted in adverse and deleterious effects upon the ovarian cycle, the rate of conception, the size of litters and the ability of the offspring to survive.

Fifth Count

1. At the times mentioned herein, the William S. Merrill Company had submitted to the Food and Drug Administration of the Department of Health, Education and Welfare, a New Drug Application, and amendment thereto, for MER/29 (Triparanol), a new drug then subject to the provisions of section 505

of the Federal Food, Drug & Comestic Act (21 U.S.C. 355), and had submitted as a part thereof, reports of investigations that had been made to show whether or not the drug was safe for use, said reports being submitted in an effect to persuade the Food and Drug Administration to permit said New Drug Application to become effective.

2. Among such reports was one reporting the results of a three-month toxicity study in rats being administered doses of MER/29 at the rate of 20 mg/kg per day and 40 mg/kg per day, in which it was reported that corneal opacities had been observed in the eyes of eight out of twenty rats which had been administered 40 mg/kg per day in the course of the investigation, such rats having been autopsied at the time of the report.

3. Said three-month toxicity study of the effect of the administration of MER/29 to rats at dosage levels of 20 mg/kg and 40 mg/kg per day was only one part of a continuing investigation which had been set up to continue for a period of one year; as of February 24, 1960, following the submission of the report pertaining to the three-month investigation, corneal opacities had been observed in the eyes of live rats being subjected to such continued investigation, corneal opacities being observed in 2 out of 38 rats used as controls, and in the eyes of one out of 35 rats being administered MER/29 in doses of 20 mg/kg per day, and in the eyes of 22 out of 36 rats being administered MER/29 in doses of 40 mg/kg per day.

4. On or about March 2, 1960, at Washington, D.C., the defendant, The William S. Merrell Company, a body corporate, knowingly and wilfully concealed and covered up, and caused to be concealed and covered up, by trick and scheme, a material fact in a matter within the jurisdiction of a department and agency of the United States, in that it knowingly and wilfully concealed and covered up and caused to be concealed and covered up in a matter within the jurisdiction of the Food and Drug Administration of the Department of Health, Education, and Welfare, to wit, the New Drug Application by The William S. Merrell Company for MER/29 (Triparanol) a new drug then subject to the provisions of section 505 of the Food, Drug and Cosmetic Act (21 U.S.C. 355) the fact that corneal opacities had been observed in the eyes of rats to which MER/29 was being administered at doses of 20 mg/kg per day and 40 mg/kg per day, by the trick and scheme of submitting to the Food and Drug Administration a letter dated February 29, 1960, from The William S. Merrell Company pertaining to said drug in which it was stated, with respect to corneal opacities in rats which had previously been reported in the amended New Drug Application for drug MER/29, that "Corneal changes have now been found in the control animals." but which omitted any statement that additional corneal opacities had been observed in the eyes of live rats to which MER/29 was being administered for experimental purposes during the month of February 1960, as alleged in paragraph three of this count, and that the control animals were different from those which had been used in its previously reported three-month study. Violation of 18 U.S.C. 1001.

Sixth Count

On or about March 7, 1960, within the District of Columbia, the defendants, The Wm. S. Merrell Company, a body corporate, Evert F. Van Maanen and William M. King, in a matter within the jurisdiction of a Department and agency of the United States, knowingly and wilfully concealed and covered up, and caused to be concealed and covered up, by trick and scheme, material facts, in that at the aforesaid time and place during a meeting with representatives of the Food and Drug Administration of the Department of Health, Education, and Welfare to discuss the toxicity of MER/29 (Triparanol), a new drug then subject to the provisions of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), for which a New Drug Application had been filed with said Food and Drug Administration, and which was then a matter within the jurisdiction of the Food and Drug Administration, the defendants did submit to said Food and Drug Administration a document and writing entitled "Summary of Toxicity Studies" and did discuss the results of animal and clinical investigations of MER/29 which The Wm. S. Merrell Company had made to show whether or not the drug was safe for use, but the defendants wilfully and knowingly failed and omitted to make known, either in said summary or in their oral conversations, the fact that The Wm. S. Merrell Company was then conducting a chronic toxicity study in rats in which during the month of February 1960

corneal opacities had been observed in rats receiving dosages of 40 mg/kg per day and 20 mg/kg per day of MER/29, and that in two dogs which had received 40 mg/kg per day of MER/29 for three months, observations had been made that one dog appeared to be blind and an opthalmoscopic examination revealed an opacity of the crystalline lens and that the retina was not visible, and that the other dog appeared to have an eye infection and an ophthalmoscopic examination revealed a slight opacity of the crystalline lens and that the retina was not clearly visible. Violation of 18 U.S.C. 1001.

Seventh Count

1. On or about June 29, 1960, Dr. Frank J. Talbot, Medical Officer of the Food and Drug Administration of the Department of Health, Education and Welfare, wrote to The Wm. S. Merrell Company advising that Lauretta E. Fox had reported that certain test rats which had been administered MER/29, a new drug then subject to the provisions of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), had developed an opaque cornea and lens in the eyes during an experiment and requested that The Wm. S. Merrell Company comment upon such study.

2. On or about July 25, 1960, within the District of Columbia, the defendants, The Wm. S. Merrell Company, a body corporate, and William M. King, in a matter within the jurisdiction of a Department and agency of the United States, knowingly and wilfully made and used and caused to be made and used a false writing and document knowing the same to contain false, fictitious and fradulent material statements and entries and knowingly and willfully concealed and covered up, and caused to be concealed and covered up, by trick and scheme, material facts in that they caused to be submitted to the Food and Drug Administration of the Department of Health, Education and Welfare, at Washington, D.C., on or about July 25, 1960, in response to the reequest mentioned in paragraph 1 above, a memoradum, dated July 22, 1960 prepared by the defendant William M. King, concerning the Lauretta Fox study in which it was falsely and fraudulently stated that "thousands of rats have been involved in many different experiments with MER/29 here in our laboratories,"; that "in only one group of animals in one experiment and at only one time did we observe eye changes," and that "We have no evidence from our experience or from the literature that MER/29 would in itself, produce such changes", said defendants then and there well knowing that in addition to the eight corneal opacities, previously reported to the Food and Drug Administration in February 1960, at least three out of 35 rate being administered MER/29 since that date at a daily dosage of 20 mg per kg of body weight, and at least 25 out of 29 rats being administered MER/29 since that date at a daily dosage of 40 mg per kg of body weight, had developed corneal opacities, and that in a dog study completed in February 1960 opacities of the crystalline lens had been observed in two dogs which had received 40 mg/kg per day dosage of MER/29 for a period of three months, which facts were not disclosed in said memorandum but were knowingly and wilfully omitted therefrom and concealed from said Food and Drug Administration.

Eighth Count

1. On or about October 6, 1960, Dr. Frank J. Talbot, Medical Officer of the Food and Drug Administration of the Department of Health, Education and Welfare, inquired of The Wm. S. Merrell Company concerning the effect of MER/29, a new drug then subject to the provisions of section 505 of the Federal Food, Drug, and Cosmetic Act (18 U.S.C. 355), upon the eyes of rats and concerning the rat studies of Lauretta Fox.

2. On or about October 12, 1960, within the District of Columbia, the defendant, The Wm. S. Merrell Company, a body corporate, in a matter within the jurisdiction of the Food and Drug Administration of the Department of Health, Education and Welfare, an agency and Department of the United States, knowingly and wilfully concealed and covered up and caused to be concealed and covered up by trick and scheme a material fact, in that at the aforesaid time and place the defendant did conceal and cover up and cause to be concealed and covered up in a matter within the jurisdiction of the Food and Drug Administration, the fact that in October 1959, The Wm. S. Merrell Company had initiated a toxicity study concerning the effect of MER/29 on rats which study was to be divided into three parts, one of three months', one of six months' and one

of twelve months' duration, and that, during the period between February and on or about October 10, 1960, examinations had been made of the rats' eyes which disclosed that the number of corneal opacities was increasing in rats receiving a daily dose of 20 mg/kg and 40 mg/kg of MER/29 and that by September 1960 nearly all of the rats remaining on the study of the 40 mg/kg per day dosage had developed some degree of blindness; said material facts being concealed and covered up by the trick and scheme of submitting by letter to the Food and Drug Administration at Washington, D.C., dated October 10, 1960, in response to its inquiry as set forth in paragraph 1, a carbon copy of a letter to Lauretta E. Fox dated September 29, 1960, in which it was falsely stated and represented that the results of Lauretta Fox' study, indicating involvement of the cornea and lens of the rats' eyes, "are most surprising to us," and that "Our pathologist states that he has never seen such involvement of the lens", The Wm. S. Merrell Company wilfully and intentionally omitting, in its letter to the Food and Drug Administration and in the carbon copy of the letter to Lauretta Fox enclosed therein, to disclose the true facts which it well knew, as set out above, concerning the existence of its continuing toxicity study in rats and the observation of corneal opacities in the eyes of rats during the period from February to October 1960.

Ninth Count

1. On or about September 23, 1960, Dr. Frank J. Talbot, Medical Officer of the Food and Drug Administration of the Department of Health, Education and Welfare, requested The Wm. S. Merrell Company to incorporate in its labeling a discussion of the effect on pregnant rats of large doses of MER/29, a new drug then subject to the provisions of section 505 of the Food, Drug, and Cosmetic Act (21 U.S.C. 355), and stating that the labeling for MER/29 should include a contraindication of the drug in women of the childbearing age, and also that, if the drug were prescribed for such women, a pregnancy test should be made every three months.

2. On or about October 10, 1960, within the District of Columbia, the defendants, The Wm. S. Merrell Company, a body corporate, Harold W. Werner and Evert F. Van Maanen, knowingly and wilfully concealed and covered up, and caused to be concealed and covered up, by trick and scheme, material facts in a matter within the jurisdiction of the Food and Drug Administration of the Department of Health, Education and Welfare, in that at the time and place aforesaid the defendants concealed and covered up, and caused to be concealed and coverd up, the fact that The Wm. S. Merrell Company had conducted various investigations in animals to ascertain the effect of the administration of MER/29 upon the ovaries of female monkeys and upon the fertility and gestation of female rats and the effect of said drug upon the offspring of female rats to which it had been administered, said investigations being more particularly described as follows:

(*a*) An investigation made by The Wm. S. Merrell Company; begun on or about June 23, 1959 with three female monkeys, to study the effect of dosages of 10 mg/kg per day of MER/29 upon the ovaries of such animals, in which it was observed that one monkey had ovarian changes similar to the changes observed in the ovaries of a monky on a previous MER/29 toxicity study.

(*b*) An investigation made by The Wm. S. Merrell Company in which four female monkeys were started on a toxicity study on or about September 15, 1959 for the purpose of determining the effect of an administration of 5 mg/kg per day of MER/29 on ovarian morphology, at the end of which investigation no evidence of recent ovulation was found.

(*c*) A toxicity investigation in male and female rats which was conducted during the period between July 1959 through October 1959 by The Wm. S. Merrell Company, to determine the effect of MER/29 on fertility and gestation, such rats having been administered 5 mg/kg and 15 mg/kg per day of MER/29, in which it was observed that doses of 15 mg/kg per day reduced the conception rate when given prior to and during cohabitation.

(*d*) A toxicity investigation in male and female rats at dosages of 10 and 25 mg/kg per day of MER/29 which was conducted between on or about July 7, 1959 and October 1959 by The Endocrine Laboratories of Madison, Inc., Madison, Wisconsin, pursuant to a contract with The Wm. S. Merrell Company to determine the effect of MER/29 on fertility and gestation, in

which it was observed that there was a reduced conception rate among rats receiving doses of 25 mg/kg per day of MER/29 during pregnancy, the size of the litter was reduced and there was an increase in rate of the deaths of the young during the 24-hour period after delivery.

Said concealment and covering up being effected by the trick and scheme of submitting to Dr. Frank J. Talbot, Medical Officer of the Food and Drug Administration, a letter dated October 7, 1960, from The Wm. S. Merrell Company in response to his request set out in paragraph 1, in which letter it was stated that "while high doses of MER/29 interfere with conception in rats there is no evidence that this is a clinical problem," and by substantiating this statement with memoranda and references to studies and medical literature which showed that other well known and widely used drugs had similar effects upon rats, but wilfully omitting and failing to disclose and make known the existence of the aforesaid MER/29 animal studies and the results thereof.

Tenth Count

From on or about October 26, 1961 to on or about December 1, 1961, within the District of Columbia, the defendants, Richardson-Merrell, Inc., a body corporate, Harold W. Werner, Evert F. Van Maanen and William M. King, for the purpose of and with the intent to influence the Food and Drug Administration of the Department of Health, Education, and Welfare, an agency and Department of the United States, in the exercise of its function of passing upon and approving the issuance of a warning letter by said Richardson-Merrell, Inc., to the medical profession concerning MER/29 (Triparanol), a new drug subject to the provisions of section 505 of the Food, Drug, and Cosmetic Act (21 U.S.C. 355), and its function of determining whether administrative action calling for the suspension of the effectivenes of the New Drug Application for MER/29 should be instituted, knowingly and wilfully concealed and covered up, and caused to be concealed and covered up, by trick and scheme, material facts in a matter within the jurisdiction of said Food and Drug Administration, in that, following the receipt, on or about October 18, 1961, from said Richardson-Merrell, Inc., of a report that MER/29 had caused eye injuries to humans, the Food and Drug Administration requested said Richardson-Merrell, Inc., to furnish complete data in its possession concerning adverse and toxic reactions resulting from MER/29 therapy in humans and animals, including all information concerning eye changes in humans and animals with reference to both corneal and lenticular changes; that thereafter between on or about October 26, 1961 and on or about December 1, 1961, certain officers and employees of said Richardson-Merrell, Inc., met from time to time with representatives of the Food and Drug Administration at Washington, D.C., to discuss the safety of MER/29, the preparation of the warning letter and the question of whether the drug should be withdrawn from public use; that during the course of the aforesaid discussions and by means of letters addressed to said Food and Drug Administration at Washington, D.C., said defendants did present and submit, and cause to be presented an submitted in purported compliance with the aforesaid request, certain data, reports of investigations and other information pertaining to adverse and toxic reactions of the said drug in animals and humans, including information concerning eye changes in animals and in humans, which said defendants falsely and fraudulently led the Food and Drug Administration to believe constituted all of the aforesaid reports of investigations, date and information pertaining to eye changes in humans and animals possessed by defendent Richardson-Merrell, Inc., said defendants well knowing that they had failed and omitted to report and make known the following material facts, to wit:

1. That said defendant Richardson-Merrell, Inc., had in its possession data and information obtained by its former subsidiary, The Wm. S. Merrell Company, from an investigation which that company had conducted as to the safety of the drug between on or about October 26, 1959 and on or about November 1, 1960, during which period said drug was administered to rats at 20 mg/kg and 40 mg/kg per day and which rats developed eye opacities in a quantity and degree greater than those reported to the Food and Drug Administration on February 17, 1960;

2. That said defendant Richardson-Merrell, Inc., was then conducting an investigation, which began on or about April 19, 1961, to determine the effect of MER/29 upon the eyes of rats, during the course of which MER/29 and MER/29 plus Vitamins and Cholesterol was being administered to rats at a dosage of 40 mg/kg per day and in which eye opacities were observed first to

have developed in June, 1961, and to have continued to increase in number and develop in degree to the point that on or about November 15, 1961 eye opacities had developed in all female rats being administered MER/29 and MER/29 plus Vitamins and Cholesterol at a dosage of 40 mg/kg per day, and opacities had developed in the eyes of 20 out of 24 male rats being administered MER/29 and MER/29 plus Vitamins and Cholesterol at a daily dosage of 40 mg/kg while none of the control rats had developed any eye changes in the aforesaid study.

Eleventh Count

On or about October 26, 1961, within the District of Columbia the defendants, Richardson-Merrell, Inc., a body corporate, and Evert F. Van Maanen, in a matter within the jurisdiction of a Department and agency of the United States, knowingly and wilfully made and used, and caused to be made and used, a false writing and document knowing the same to contain false, fictitious and fraudulent statements and entries, in that at the time and place aforesaid, the defendant Richardson-Merrell, Inc., for the purpose and with the intent of influencing the Food and Drug Administration of the Department of Health, Education and Welfare in the exercise of its function of passing upon and approving the issuance of a warning letter by said Richardson-Merrell, Inc., to the medical profession concerning MER/29, a new drug subject to the provisions of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), submitted to the Food and Drug Administration of the Department of Health, Education and Welfare a report from E. F. Van Maanen to Dr. Werner, dated October 24, 1961, entitled "Chronic Study with MER/29 In Dogs Progress Report," said progress report containing the following statements and entries which the defendants knew to be false, fictitious and fraudulent, to wit:

1. A statement that on or about October 18, 1961, the fundi of the eyes of dogs Nos. 158, 166 and 171 appeared normal, when in truth and in fact, as the defendants well knew, there was an inability to visualize the fundus of the left eye and difficulty in visualizing the fundus of the right eye of dog No. 158, in dog No. 166 spoke-like striations persisted bilaterally, and in dog No. 171 striations were seen at the innercanthus aspect of both eyes.

2. A statement that on or about October 18, 1961, the eyes of the surviving dogs Nos. 148, 149 and 169 which were being administered MER/29 plus Vitamins and Cholesterol were all normal, when in truth and in fact, as the defendants well knew, on or about October 18, 1961, these dogs had developed the following eye changes:

(*a*) *Dog No. 148.*—Striations had been observed at the inner-canthus aspect of both eyes deep to the cornea.

(*b*) *Dog No. 149.*—Left eye showed slight fluorescent reflections at 9 o'clock.

(*c*) *Dog No. 169.*—Striations had been seen in the left eye extending inward ½ mm. at 9 o'clock and in the right eye at 3 o'clock.

Twelfth Count

1. Between December 22, 1961 and December 29, 1961, The Wm. S. Merrell Company, Division of Richardson-Merrell, Inc., had pending before the Food and Drug Administration of the Department of Health, Education, and Welfare a supplemental New Drug Application for MER/29, a new drug then subject to the provisions of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), which proposed changes in statements in the brochure of said drug pertaining to the safety of the drug and possible adverse and toxic effects arising from its use. During the aforesaid period there were submitted to the Food and Drug Administration at Washington, D.C., as a part of said Application, reports of investigations made to show the safety of MER/29, and data and information pertaining to the possible adverse and toxic reactions of the drug, said Richardson-Merrell, Inc., representing that said reports of investigations, data and information were full and complete and constituted all of the data and information in its possession relating to the safety of the aforesaid drug and possible adverse and toxic reactions due to the drug in both animals and humans which it had observed or was reported to it.

2. On or about December 29, 1961, within the District of Columbia, the defendants, Richardson-Merrell, Inc., a body corporate, Harold W. Werner, Evert F. Van Maanen and William M. King, for the purpose and with the intent of influencing the Food and Drug Administration in the exercise of its function

of determining whether to permit the aforesaid supplemental New Drug Application for drug MER/29 to become effective, knowingly and wilfully concealed and covered up and caused to be concealed and covered up by trick and scheme material facts in a matter within the jurisdiction of the Food and Drug Administration of the Department of Health, Education, and Welfare, an agency and Department of the United States, in that by a letter dated December 28, 1961, said Richardson-Merrell, Inc., made a submission to the Food and Drug Administration of results of investigations, made to show whether or not the drug was safe for use and pertaining to the changes in the aforesaid brochure and representing thereby that it had submitted full reports of all such investigations as of that date, said defendants well knowing that as of December 28, 1961, there were certain reports of investigations, conducted by itself and by its former subsidiary The Wm. S. Merrell Company and data and information concerning the adverse and toxic reactions of MER/29 therapy in animals in the possession of Richardson-Merrell, Inc., which had not been submitted and the existence of which was concealed from said Food and Drug Administration, to wit:

(*a*) An investigation made by The Wm. S. Merrell Company, begun on or about June 23, 1959 with three female monkeys, to study the effect of dosages of 10 mg/kg per day of MER/29 upon the ovaries of such animals, in which it was observed (a) that one monkey had ovarian changes in the form of an increase in the number of ovarian follicles which did not appear to have matured to a state of ovulation, (b) that one monkey had developed severe leukopenia and agranulocytosis, and (c) that two monkeys had a depressed granulocyte count, atyptical lymphocytes and high leukocyte counts.

(*b*) An investigation made by The Wm. S. Merrell Company in which four female monkeys were started on a toxicity study on or about September 15, 1959 for the purpose of determining the effect of an administration of 5 mg/kg per day of MER/29 on ovarian morphology, at the end of which investigation no evidence of recent ovulation was found.

(*c*) A recovery toxicity investigation made by The Wm. S. Merrell Company with female rats, started on or about January 10, 1958 to determine the etiology of abnormal blood changes, in which it was observed that eight out of the ten rats being administered a dosage of 50 mg/kg per day of MER/29 had died as of January 27, 1958, and the surviving two rats whose dosage as of that date was reduced to 25 mg/kg per day of MER/29 had died as of February 3, 1958.

(*d*) A recovery toxicity investigation made by The Wm. S. Merrell Company with female rats, started on or about February 30, 1958 to determine the etiology of abnormal blood changes which had been observed in previous toxicity studies, the results of which showed that rats being administered MER/29 had developed abnormal blood changes in the form of binucleated lymphocytes, blood dyscrasias and an increase in raticulocytes.

(*e*) A toxicity investigation conducted by The Wm. S. Merrell Company between on or about October 26, 1959 and on or about November 1, 1960, during which period said drug was administered to rats at 20 mg/kg and 40 mg/kg per day and which rats developed eye opacities in a quantity and degree greater than those reported to the Food and Drug Administration on February 17, 1960.

(*f*) A toxicity investigation in rates conducted by Richardson-Merrell, Inc., which began on or about April 19, 1961, to determine the effect of MER/29 upon the eyes of rats during the course of which MER/29 and MER/29 plus Vitamins and Cholesterol was being administered to rats at a dosage of 40 mg/kg per day in which it was observed that on or about November 15, 1961 eye opacities had developed in all female rats being administered MER/29 and MER/29 plus Vitamins and Cholesterol at a dosage of 40 mg/kg per day, and opacities had developed in the eyes of 20 out of 24 male rats being administered MER/29 and MER/29 plus Vitamins and Cholesterol at a daily dosage of 40 mg/kg while none of the control rats had developed any eye changes in the aforesaid study.

A True Bill:

_____,
Attorney of the United States in and for the District of Columbia.

_____,
Foreman.

RICHARDSON-MERRELL INTER-DEPARTMENT MEMORANDUMS AND CORRESPONDENCE

[Inter-Department Memo, Oct. 7, 1958]

To: Dr. H. W. Werner (3).
From: Medical Research Department.
Subject: MER–29—HEMATOLOGY (Dr. Van Maanen's memorandum of 10/6/58 to Dr. McMaster).

The decision not to release blood smears from our toxicological studies to our hematological consultant, Dr. Jane Deaforges, represents a serious handicap in the MER–29 studies. As you know, Dr. McMaster and I have a moral and medical obligation to use MER–29 safely. Accordingly, we are both anxious to find out more about the blood changes which have been reported in experimental animals.

The second point is that if the changes in question are of no importance, it might be that we would have been justified in not describing them in the brochure. This I would question but now that they have been described in the brochure, they are known to all of our potential investigators. We have routinely come up against unwillingness to administer MER–29 to human beings because the significance of those findings is not well understood. To some extent we have overcome this resistance, and actually we have succeeded in giving MER–29 to some human beings. Despite this we are encountering continued resistance to studies on MER–29 because of the blood smears.

It is comforting to know that during the brief period of time that relatively large doses of MER–29 have been given to a patient in Rochester, Minnesota, the characteristic changes have not appeared. If they do appear, I will direct your attention to the last paragraph in Dr. Van Maanen's memorandum and suggest that we will probably not obtain the smears for study in our Biological Research Department, on the grounds that the animal hamatologists are not sufficiently versed in clinical homatology to interpret the human smears properly.

R. C. POGGE, M.D.

[Inter-Department Memo, May 5, 1959]

To: Drs. Blohm, Holtkamp, King, Kuhn, and Ruchman.
From: E. F. Van Maanen.
Subject: MER–29 Brochure.

Yesterday, it was rudely brought to my attention that the Medical Research Department is not too happy about certain items in our MER–29 brochure. Furthermore, the Medical Research Department complained that the latest information on MER–29 obtained in our laboratories was not included in the brochure. I have to admit that they are right on both accounts and I would like to remedy this situation as soon as possible.

I would like to request the respective Department Heads to go over their sections in the MER–29 brochure and to weed out extraneous material, such as windy descriptions of methods and results which were negative and are not contributing anything to clinical investigators. At the same time, add new material, particularly those experiments which indicate the safety of the compound as well as its mechanism of action.

In the toxicity section, I would like to request Dr. King to delete all material on the funny lymphocytes. I wonder also whether the roticulocyte change in the rate experiment needs the emphasis it has. Naturally, we should include our new chronic toxicity studies in monkeys.

To my knowledge, neither the Pharmacology Department nor the Microbiology Department has anything new to add to the data. I would appreciate it, however, if both Department Heads would go over their sections and suggest constructive changes.

Dr. Carkhuff has found recently that MER–29-citrate solution (as well as the strong hydrochloric acid solution of the base) changes rapidly upon standing.

The infrared spectrum indicates that MER–29 dehydrates to the ethylene (WSM–4594). This compound was tested by Dr. Blohm and, surprisingly, has no cholostarol-lowering effects. I do not think that this finding alters all our biological observations, since most of our results were obtained with the base. However, our cardiovascular results were obtained solely with the citrate salt. I would appreciate, therefore definitive information whether the hypotensive effects relate to the ethylene or ethanol.

Even though I know that you are all very busy. I would like to suggest that revisions of your sections be in my office by May 15.

[Inter-Department Memo, May 6, 1959]

To: Dr. K. D. Carkhuff
From: Medical Research Deparment
Subject: Intravenous MER–29 1 mg./cc.

Many thanks for outlining the reasons for the difficulty, if not impossibility, in preparing an intravenous form of MER–29.

You will recall that during our conversation concerning this subject, it was decided that we should, as least temporarily refrain from telling Dr. Hollander or any other person outside the Merrell organization that MER–29 undergoes rather rapid acid hydrolysis. As soon as the patent situation concerning the ethylene derivative has been clarified, we shall decide what further steps to take with regard to the possibility of using an extemporaneous sort of intravenous preparation.

R. H. McMaster, M.D.

[Inter-Department Memo, May 20, 1959]

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

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

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

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

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

R. H. W.

[Inter-Department Memo, July 17, 1959]

To: Mr. E. P. Anderson.
From: Frank N. Getman.
Subject: MER–29.

PERSONAL & CONFIDENTIAL

DEAR ED: Following up our conversation this week, Woodward and Werner are proceeding with plans to be sure our clinical work gets well wrapped up during the current calendar year. I told you how we had unsuccessfully tried to get Carlossi, Sterment and Holland. We now have under consideration two retired clinical research men from ethical companies—if they are able, and if their companies will permit it under their pension plan, our problem will be solved; otherwise, we will be in touch with you to see if we can borrow John Scanlan on a part-time basis. Woodward and Werner have been advised of his workload but also of your willingness to have him help us if we can confine the area to the cost.

Of course the big end of this job is getting positive proof of how well the product works and how. In addition, we want to be in a position to follow through with personal contact and on all adverse reports to get the facts. For example, we have had reports from two clinicians that of the first two patients they placed on MER–29 one died at the end of a week from a coronary. This is not written to alarm anyone as we are confident it was independent of the drug and if these patients might have been cured. However, on the surface of the record, you can see how bad this looks, and we need detailed case histories. There are also some toxicity questions found in laboratory animals which need to be carefully resolved.

Summing up briefly, we appreciate your offer of help but will not impose upon you unless we feel it is very important for the benefit of the Enterprise.

———— ————.

[Iuter-Department Memo, July 27, 1959]

To: Mr. Philip Ritter, III.
From: Frank N. Getman.
Subject: Let's Start Selling.

Jumping to any conclusion on the basis of only a few days' sales would be completely erroneous—and particularly when it is in the middle of a vacation period.

However, this is the year when we have every reason to believe Merrell should break into the truly "big time." We will do it only if we get off to a fast start and continue building throughout the year. On this basis, I have been somewhat disappointed over July results since, with the month nearly over, we have an increase of less than 8% against a budgeted increase of 24% and MER/29 is running less than ⅔ our budgeted figure.

Since I will not be here next week when you return from vacation, I took the liberty of having a short meeting with those of your sales executives who were in the city on Tuesday, the 26th, trying to get their opinion on why sales of our over-all line are lagging as well as MER/29. My only purpose was to start them thinking in order that they would be in a better position to give you recommendations when you return.

Let's take a close, critical look at the way we are stimulating the field force on MER/29. Very frankly, I have seen almost nothing going out of here in the way of good sales promotion ideas. The last revision of the detail was not very outstanding in my regard. It still seems pretty complicated for the GP, with a lot of long terms where shorter words would work. This is one that we discussed, and I find that no change was made in the closing which asked to put 10 patients on it. Why 10? To me it makes sense to ask a doctor to try a drug on two, three, or possibly five patients, but if we're going above that, why not ask for all of them? What do you think of a closing that says in effect, "I am sure that you will want to place all of your post-coronary and coronary prone patients on MER/29."

Admittedly, the above is only one single, short suggestion, but I think we ought to take a fresh look at our whole campaign on MER/29 with the idea of retaining the essential flavor of the introduction, but getting much more positive in order to motivate doctors to write scripts.

[Inter-Department Memo, Aug. 14, 1959]

To: Dr. J. S. Scanlan—Vick. New York.
From: E. F. Van Maanen.
Subject: MER–29—Effects on Monkey Ovaries.

DEAR JOHN: Dr. King informs me that you have two prints of sections from monkey ovaries. One represents a control monkey, the other, a monkey treated for 16 months with MER–29.

As you know, we are in the middle of identifying these changes. At the moment, we are not certain whether these are produced by MER–29 or whether they represent an idiosyncrasy of a monkey. Because we are not sure yet what these changes mean, we would appreciate it if these pictures would have a very restricted distribution. It may be very harmful, for instance, when clinicians start interpreting our results and later we would find that these changes were an anomaly. On the other hand, we feel obliged to inform you as well as our Medical Research Department about these findings but do not think that these should have wide outside distribution until we have identified the problem.

At the same time, we are very much interested to know whether females during the reproductive period do ovulate in the presence of MER–29.

[Inter-Department Memo, Aug. 19, 1959]

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

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

R. C. POGGE, M.D.

[Inter-Department Memo, Aug. 20, 1959]

From: John S. Scanlan.
To: Dr. E. F. Van Maanen.
Subject: MER–29—Effects on Monkey Ovaries.

You may rest assured that the pictures of the monkey ovaries which I received from Dr. King have received indeed a restricted distribution. Whilst in my possession they were shown only to Dr. Lloyd in Syracuse. However, I did discuss the matter with Gerry Mersen, although even he did not see the photographs.

This may well be a question of making a mountain out of a mole hill, however, we should not leave any stone unturned. How is that for a mixed metaphor?

No doubt Dorsey has informed you of the results of our discussions with Dr. Lloyd.

Kind personal regards,

JOHN S. SCANLAN, M.D.

[Inter-Department Memo, Feb. 16, 1960]

To: Dr. E. F. Van Maanen.
From: W. H. King.
Subject: MER–29 Monkey Ovarian Studies.

Four adult cynamologue female monkeys were given MER–29 in a dose of 5 mg/kg/day. Two additional monkeys that were sacrificed in the course of bilateral nephrectomies for the department of Microbiology furnished control ovary sections. Monkeys No. 80 and 87 were continued on the drug for six weeks, at which time they were autopsied. Monkeys No. 83 and 89 were given MER–29 for

the same six-week period, but were held without additional drug therapy for an additional six weeks and then sacrificed. The following summarizes the results of the study:

Of particular interest in this study is the fact that MER–29 given in dose of 5 mg/kg/day for six weeks did not produce the characteristic adrenal changes observed in the monkeys that had received MER–29 at a dose of 20 mg/kg for 16 months.

In a dose of 5 mg/kg/day for six weeks, MER–29 does not significantly affect the number of primary follicles, maturing follicles or matured follicles in the ovary of the monkey. However, in studying serial sections from both ovaries of the four monkeys so treated, no evidence was found of recent ovulation. By this, we mean that there were no corpora hemorrhagica observed, nor were there any evidence of recent corpus lateum formation. Although we cannot be sure that ovulation did not occur, there was no morphologic evidence to show that ovulation did occur in either of these monkeys.

There was no quantitable changes observed between the two groups of monkeys. Those ovaries examined at the end of six weeks of administration were very similar morphologically to those ovaries that had been off the drug for six weeks before the ovaries were examined.

Conclusions: 1) MER–29, at a dose of 5 mg/kg in the monkey, does not affect maturation of the primate ovary. 2) There is negative evidence to suggest that MER–29 administration of this dose prevents ovulation.

MARCH 26, 1960.

JOHN G. FREEMAN, M.D.,
Nebraska Psychiatric Institute,
Omaha, Nebr.

DEAR DR. FREEMAN: I hope eventually to be able to get caught up on my accumulated correspondence which has resulted from chronic absence from the office. I hope you will excuse the delay in acknowledgement of your kind letter of March 11 and the accompanying data sheets on the patients to whom you and your associates are administering MER/29.

The nicely detailed information you have given us will be of considerable value in our compilation of the assay of cholesterol response and side effects to be expected from MER/29 administration. I might add that most of the side effects you have reported have been unusual ones in that they have not been reported by other investigators. I refer specifically to patient V. H. who apparently developed a leukopenia while taking MER/29 and to patient M. H. who complained of blurred vision and headache after eight to ten weeks of therapy. I shall naturally be interested in any follow up information you may acquire in these instances. Patient I. W., who complained of edema and eye-watering during his first course of MER/29, will also be of interest, especially since he has been restarted on the medication. In reading down through the list, I notice also that patient R. S. had a leukopenia during two periods of administration of MER/29 and that patient I. W. was again forced to discontinue the drug because of watery eyes and edema.

Is it possible that the side effects such as those noted above could have been coincidental with the administration of drugs other than MER/29 concurrently? I would most certainly not ask such a question as this had there been similar reports from elsewhere. On the other hand, if these are indeed potential side effects of MER/29, I think we need to be completely aware of them and to assess them as carefully as possible. I shall look forward to your further reports when you feel them to be justified.

Sincerely yours,

R. H. MCMASTER, M.D.

NEBRASKA PSYCHIATRIC INSTITUTE,
THE UNIVERSITY OF NEBRASKA COLLEGE OF MEDICINE,
Omaha, Nebr., April 7, 1960.

Re: MER–29

R. H. MCMASTER, M.D.,
Department of Medical Research,
The Wm. S. Merrell Co.,
Cincinnati, Ohio

DEAR DR. MCMASTER: Following is a more complete description of the side effects noted in three patients, about which I have written you earlier:

I.W.—(*Edema*)

9–7–59 Medication started.
11–17–59 Eyes started to discharge and were swollen shut.
11–18–59 Medication discontinued.
12–24–59 Medication restarted.
1–4–60 Eyes red and discharging again. This continued in some degree until his death.

A.C.—(*Heart trouble*)

5–25–59 Eyes red and watery until end of study.
6–3–59 Study ended.
9–7–59 Started on medication again.
9–15–59 Eyes were discharging along with other complications and medication was discontinued.
12–16–59 Re-started on Mer-29.
1–21–60 Eyes discharging.
2–1–60 Eyes were discharging more along with other complications, and medication was discontinued for last time.

A.W.

4–20–59 Started on medication.
6–1–59 Eyes were a little red and discharging on last week of 6 weeks study.

Sincerely yours,

JOHN G. FREEMAN, M.D.,
Research Psychiatrist.

[Inter-Department Memo, Apr. 19, 1960]

To: Dr. R. L. Stromont
From: R. H. McMaster, M.D.
Subject: Hyman Engelberg, M.D. (Cedars of Lebanon Hospital, Los Angeles, California in the amount of $500.00)

Dr. Engelberg has made a verbal request for $500.00 to support his continued study of the effects of MER/29 on the lipoprotein fractions as assayed by the Codman technique using the ultracentrifuge. The results with the first two or three patients in whom this technique has been tried have been rather equivocal if not completely negative. Dr. Engelberg, however, is of the opinion that before any conclusions can be drawn, the experiment should be extended to include a larger group. He does not wish to subject these private patients to the expense of having these rather elaborate laboratory studies down and feels that The Wm. S. Merrell Company should foot at least a part of the bill. He believes that $500.00 will cover the costs for cholesterol determinations and the separation of the high and low density lipoprotein fractions by ultracentrifuge in another ten to twelve patients.

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

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

APRIL 29, 1960.

JOHN G. FREEMAN, M.D.,
Nebraska Psychiatric Institute,
Omaha, Nebr.

DEAR DR. FREEMAN: As you will note, my ability to correspond adequately is still suffering considerably from chronic absence from the office in connection with the MER/29 development program. Accordingly, I again apologize for the delay in acknowledging receipt of your report of April 7 on patients I.W., A.C., and A.W.

I must confess that I am still at a loss to account properly for the apparent high incidence of conjunctivitis in patients in your series who are on MER/29

therapy. At last count, there were well over two thousand patients under clinical study with MER/29; and to the best of my present knowledge, and certainly in terms of reports we have received, yours are the only patients who have offered this complaint. This certainly is not to say that the complaint must necessarily be unrelated to MER/29 therapy. In fact, patients I.W. and A.C. suggest a very definite relationship in that discontinuation and restarting of the drug resulted, first, in clearing of the conjunctivitis and then in its reappearance. It is true that we have had reports, amounting to perhaps 2% of all patients, suggesting that MER/29 is capable of producing an allergic type dermatitis. This has been variously reported as simple pruritus to actual urticaria or dryness or scaliness of the skin. It is not inconceivable, therefore, that the conjuctive could become a shock tissue.

I shall look forward to hearing from you again from time to time and will keep you posted as new developments occur which may be of interest to you also.

Sincerely yours,

R. H. McMASTER, M.D.

SAN DIEGO, CALIF., *May 15, 1960.*

The WM. S. MERRELL CO.,
Cincinnati, Ohio

DEAR DR. MCMASTER: I have just received very good news. My cholesterol count just taken is 200 Mg.%. That is excellent! My count was 220 to 325 Mg.% and never under 220 before I started on Mer 29.

I have had some reports back from the different people in 50's age bracket, who are taking 1-250 mg. Mer 29 per day and after 2 to 3 months they have had itching eyelids, little (crusts) in inner corner of eyes. Also one had a 20- vision and says that he is getting a slightly blurred vision which clears up and then re-establishes itself when the drug is discontinued and then resumed.

I have a lady acquaintance who took it for 5 months and who had always had a good firm head of hair. However it began to fall out quite heavily and upon discontinuance of MER 29 it became firmly embedded and healthy.

In your research, have you had any experiences like these? I have ⅔ of a bottle of MER 29 left. If you would kindly send us enough for balance of year would greatly appreciate it. I was one a day plus a few extras each month in case I was invited out to dinner or clubs where I cannot control my diet.

I trust your family is well and enjoying life.

I shall be writing up to Butte, Montana for some more Tamales shortly. If you enjoyed these I will send you some more or if you can think of anything else I should enjoy sending it.

Respectfully yours,

Dr. R. J. MCNAUL.

[Inter-Department Memo, May 17, 1960]

From: Marion W. Smith.
To: Dr. R. T. Stormont.
Subject: Policy Re Licensing MER-29 Analog and Analogs Generally.

I talked to Frank Getman this morning and we agreed as to the policy and procedure we should follow in connection with the question of licensing our MER-29 analog.

The facts seem to be that the animal work performed to date indicates some questions as to the toxicity of the analog in the lower animals (just as MER-29 itself does), but the work with monkeys indicates it may even be better than MER-29. Although a lot more animal work would have to be done to tie down better the question of toxicity, action of the product, etc., before marketing it, this could be done simultaneously with the clinical work. In view of the tremendous importance of MER-29 and this analog, it probably will be decided that Merrell should follow through with the additional animal work and the clinical work on this analog in order to prove out its relative inferiority or superiority and thus have it available as a substitute in the event MER-29 gets into trouble, or perhaps introduced later as an improved product.

In the past, our policy with respect to the licensing of the analog of a successful

product has been that, when we do not feel justified in doing the extensive animal and clinical work needed to prove out its value and when we could use the analog advantageously for trading purposes with a pharmaceutical house who does excellent screening work of this kind, we would be willing to give such a pharmaceutical house an exclusive (except as to us) license on the analog for a reasonable royalty in the licensee's home country, provided the complete pharmacological and clinical data is made available to us. If our hunch is that the analog probably isn't much good, we might be willing to give such a license merely on the basis of hoping to improve our relationship with the licensee sufficiently to be given an opportunity of licensing some future products that might develop. On the other hand, if our hunch is that the analog might be pretty good (but still not good enough to justify doing the work ourselves) we would, of course, insist on getting something more specific in return. The reasoning behind this policy is that since we do not feel justified in doing the necessary pharmacological and clinical work ourselves, we really might be getting something for nothing except the possibility of having one competitor in the country involved in the event the analog proved to be equal or superior to the original product.

This established policy does not quite fit the present situation, since we probably will consider this analog sufficiently important to do the additional work to prove it out in any event. However, if we could get something sufficiently worthwhile for it from an outstanding foreign concern . . . such as an exclusive license in the U.S. to a product which looks extremely good, or a firm contract to have first refusal over a period of years to all their future new products, or on future new products in an important field in which they are working . . . then we might be willing to give them such a license. This, of course, is a matter of bargaining and judgment in the light of the specific situation involved.

So you see, Bob, we really should not give a clear answer at this time to the question whether we would be willing to give such a license to Rhone-Poulene. As we agreed before you left, I suggest that you go ahead and see Mr. Monnet in June as you have planned, double check as well as you can the quality of their pharmacological and clinical work which as you know has not been up to the quality one would expect from a concern of their size and standing, and feel out Mr. Monnet as to what he would be willing to give us in return for such a license. Than we can decide what to do in the light of such facts as you can develop.

I am going to give George Garlach a copy of this statement of policy in order that he may try out the same type of trading with some of his outstanding German contacts on his next trip.

Incidentially, I am having the visa situation checked in France. I understand we already have a French visa on Mer–29, but I don't know how much data will be needed to obtain a visa on the analog. Until we get this, we must be very sure not to disclose to anyone the structure of the analog.

Hope your trip is progressing successfully and pleasantly.

Best regards,

MARION W. SMITH.

[Inter-Department Memo, July 22, 1960]

To: Mr. G. G. Totten.
From: R. H. Woodward.
Subject: Mer/29 Safety,

I am attaching our recent mailing over Dr. McMaster's signature in which I have circled certain words which, it seems to me, "gild the lily" to a great extent. I honestly do not believe they add to the sales impact of the * * * or of the thought, but I do think they are likely to irritate people who feel that a drug of the potential possessed by MER/29 and a drug which has not yet been used long in a commercial sense may have certain toxic effects and when we claim that it is free from such effects, I believe we are asking for criticism.

It seems to me that copywise, you can be just as strong without throwing in the adjectives that become obnoxious to some people.

This is all meant as constructive suggestions for your consideration, Gil, as I know that writing copy is a job which everyone feels he is an expert and can do better than the guys who have the responsibility.

[Inter-Department Memo, Aug. 3, 1960]

To: H. W. Werner.
From: F. J. Murray.
Subject: Mer–29.

I called Frank Talbot at the FDA to discuss the status of our liver function follow-up studies on MER–29. Talbot did not seem particularly worried about the liver problem and while data should be made available to him as quickly as possible, there is no emergency situation.

Dr. Talbot expressed concern at our promotional literature and indicated claims appear to be getting excessive. He strongly suggests that we avoid stressing potential uses and stick to approved claims.

Talbot asked whether we have any more information on the spermatogenic offset of MER–29. He pointed out that there was an indication in our animal data that this might be a problem and he would like to know the effects of MER–29 on sperm count of young men taking the drug for extended periods.

Dr. Talbot stated that he has been annoyed by letters and personal visits by physicians complaining about MER–29. In each case the complaint has been based on reports of hepatitis with the original information coming from Dr. Corday. Dr. Pollock was one of the visitors. Talbot wrote Corday some time ago making complete details and has received no reply (we likewise have been unable to get details from Corday. Talbot plans to write him again and we state that since Corday has been unwilling to document his claims, Talbot must assume the reports of Hepatitis are just rumors.

[Inter-Department Memo, Sept. 20, 1960]

To: Medical Department.
From: Frank Belknap 13350.
Subject: MER–29 Alopecia.

During a recent discussion of MER–29 with Fred S. Badman M.D., 2746 N. 2nd St., Harrisburg, Penna., the doctor mentioned that he is and has been very interested in the product but in discussing the drug with some of his medical friends in the western part of our state, one a dermatologist mentioned that a side effect that some of his patients might experience complete alopecia even pubic hair. The doctor asked if I would check to see if such was the case or whether it may be strictly a rumor.

FRANK BELKNAP.

[Inter-Department Memo, Oct. 5, 1960]

To: Drs. E. F. Van Maanen, H. W. Werner.
From: T. R. Blohm/mc.
Subject: Publication of Toxicology Studies on MER/29

There seems to be a general acceptance of the idea that MER/29 is reaching a sales volume which is worth protecting. According to all the information we can get, MER/29 will soon be challenged by one or more thyroid products. Our strategy in combatting this competition will be based on the danger associated with thyroid medication in cardiac patients. In order to be effective, we must be able to point to a clean bill of health on the same score. For this reason, I believe it is more important than ever that our safety data on MER/29 got in print. Of course, publication of this information will also spike the "liver toxicity" rumors which continue to circulate, and will render less effective certain private communications from bureaucrats to the effect that MER/29 "must be toxic." We also have data showing that desmosterol cannot be excessively atherogenic, since no arterial lesions were found in any of our chronic animals.

I realize that Dr. King is pushed to the wall with studies on potential new products, but I believe this is of sufficient importance to receive a high priority. Dr. King concurs with me on this.

[Inter-Department Memo, Oct. 5, 1960]

To: Dr. R. H. McMaster.
From: R. H. Woodward.
Subject: Irving S. Wright, M.D.

In your trip report for September 15–16, it is surprising to note that Dr. Wright is unwilling at this time to provide us with a copy of the manuscript which he has already submitted to CIRCULATION. I realize that this circumstance is unavoidable at times but in view of our relationship with Dr. Wright, the monies which we have expended to support the man and his work, and the importance of our knowing in advance what such a man will say; all indicate that we should still make some effort to get hold of this manuscript.

This points up the need, it seems to me, in any of our clinical research projects, and particularly where a grant is involved, to reach an agreement in advance on the availability of data and manuscripts prior to publication. I am sure that we will never get top investigators to agree to publish or not to publish results based upon Merrell wishes, but I do think we should strive for agreement on the basic principle that at least we have an opportunity to review and offer constructive criticism of papers prior to submission.

I realize we are dealing with one of the outstanding men in cardiology in the case of Dr. Wright and perhaps all of this is totally beyond our control. Dependent, however, upon how firm he was in refusing you, I wonder if we might still go back and ask for a copy of the manuscript.

OCTOBER 12, 1960.

FRED S. BADMAN, M.D.,
Harrisburg, Pa.

DEAR DR. BADMAN: Our representative, Mr. Frank Belknap, has informed us that you wish to know if MER/29 causes alopecia totalis. It is true that we have received reports (now totaling 8 cases from different geographic sources) of thinning of the scalp hair, but not total alopecia. In two other instances hair grew on previously bald heads in postmenopausal females. We are not sure what these results mean but the investigators reporting the cases have chosen to regard them as specific drug idiosyncrasies occurring in an insignificant incidence.

Thank you for your interest in MER/29.

Sincerely yours,

ROBERT H. MCMASTER, M.D.,
Associate Director of Clinical Research.

OCTOBER 25, 1960.

MRS. EVA E. LOUGHRAN,
Pontiac, Mich.

DEAR MRS. LOUGHRAN: We appreciate your letter of October 22, in which you report that you have had excellent results in reducing your cholesterol level with MER/29. We also noted with interest your report that during the past few weeks you have experienced loss of hair, and your doctor requested that you discontinue use of MER/29. You ask for advice on this matter.

Unfortunately, we are unable to answer your letter directly, since the etiology of falling hair can be quite difficult to determine. Therefore, I would suggest that you discuss the matter with your doctor and have him correspond directly with me, giving me facts about your case history and concurrent medication. Through him we shall be happy to discuss this matter.

I am sure that you can appreciate our inability to answer your request, since the doctor-patient relationship is mandatory in any discussion of this type.

Sincerely,

R. H. MCMASTER, M.D.

FEBRUARY 9, 1961.

JAMOOL S. KUBARAK, M.D.,
Tomah, Wis.

DEAR DR. KUBARAK: Mr. Stan Jangek passed along to us an unusual observation, reportedly a result of MER/29 therapy. You told him about one of your patients who noted a "film" which tended to effect vision. Because of the unusual

nature of this report and since it has not come to my attention before, I am writing to you for additional information.

Actually, we would expect just the opposite to occur. We know of a paper soon to be published showing some improvement in vision in patients with diabetes and hypercholesterolomia. Although these reports are preliminary they are most interesting and will be followed.

Thank you for bringing this to the attention of Mr. Junck. We would appreciate hearing from you if you have more information.

Cordially,

JOHN B. CHEWNING, M.D.

[Inter-Department Memo, Feb. 13, 1961]

To: Department of Medical Research.
From: Wm. J. Phelan, #48727, Houston, Texas.
Subject: MER/29.

Please find attached a brief case report on each of three patients referred to Herman J. Schultz, M.D., Dermatologist, by their internists when dermatitis developed while on MER/29 therapy.

To conserve time and space on the individual reports I hereby list the doctors involved and their addresses

Herman Glantzberg, M.D., Internist
703 Hermann Prof. Bldg., Ja 3-5129
Patient: 40 years, male, Prof., Univ. of Houston

Harry Leland Kaplan, M.D., Internist
6448 Fannin Street, Ja 6-2051
Patient: 69 years, male, retired

Alfons Salinger, M.D., Internist
2212 Calumet Street, Ja 3-4643
Patient: 50 years, male, dentist

Herman J. Schultz, M.D., Dermatologist
806 Hermann Prof. Bldg., Ja 8-1521
Patients: Three list all above.

All but Dr. Salinger practice practice in my territory. Dr. Kaplan and Dr. Glantzberg have had their office staffs telephone all large drug stores during the past three days the message: "Do not refill or fill any of their MER/29 prescriptions until further notice."

Today I visited the offices and talked to Dr. Schultz, Dr. Kaplan and Dr. Glantzberg. Each of these men are quiet, stable doctors who assured me that they are interested only in more information on the possible MER/29 side effects of dermatitis, falling hair, color change of hair and loss of libido, and not in scare talk of the product. During my talk with each man I reviewed, as on all details, the detail card and promotional literature listing of side effects (nausea, headache, dermatitis) which are rare and have usually been associated with higher dosages than those recommended.

It is my understanding that Mr. McMaster talked with Dr. Glantzberg and Dr. Salinger today and may visit Houston next week on this and other matters. Mr. Bristol has requested that I forward the attached information, and while keeping the Houston Group informed, to restate that our detailing instructions are exactly as they have been since the release of the product, with no more or no less emphasis on side effects.

Best regards,

BILL PHELAN.

[Inter-Department Memo, Feb. 13, 1961]

To: Department of Medical Research.
From: Wm. J. Phelan, #48727, Houston, Texas.
Subject: MER/29 Patient Report of Dr. Glantzberg.

1. Age—40, Sex—M, Prof. Univ of Houston
2. Diag. Prim:
   Familial hypercholesterolemia, hyperlipemia
   Xanthoma plaques
   One coronary occlusion 7 years ago

3. Patient responded to MER/29 therapy. Reduced from 600 mg/% to less than 400 mg/%. Plaques were reduced. Before adjusting diet, etc. as high as 1,400 mg.
4. MER/29 dosage range:
   June & July 1960—1 cap daily
   Aug 1960—2 caps daily
   Sept. Oct. Nov—1 cap daily
   Dec taken off MER/29 when severe dermatitis and hair change occurred
5. Symptoms since December, 1960:
   1. Dry, flaky alligator type skin ichthyosis type with secondary infection, then yeast, mold, monilial type in crotch and inner thighs (before antibiotic
   2. Loss of scalp hair
   3. Hair color change from dark brown to light blond, also eyebrows, etc.
   4. Loss of libido
   5. Skin condition such that patient finds it almost impossible to move to move around and carry out usual work, etc.
6. Patient referred to Dr. Herman Schultz who happened to have two more patients whose dermatitis may have been touched off by MER/29. These two patients are profiled on attached forms.
7. Dr. G. had office call all important drug stores to not to fill or refill his MER/29 Rx until further notice.

On Tuesday, February 7, 1961, I suggested to Dr. G. that he call Dr. McMaster or other doctors at Merrell to report this seemingly severe dermatitis and hair problem that may or may not have been caused by MER/29.

[Inter-Department Memo, Feb. 13, 1961]

To: Department of Medical Research.
From: Wm. J. Phelan, #48727, Houston, Texas.
Subject: MER/29 Patient Report of Dr. Kaplan.

1. Age—69, Sex—M, retired
2. Diag. Prim:
   Chronic coronary insufficiency, rare anginal pain
   Elevated cholesterol
   One myocardial infarction seven years ago
3. MER/29 dosage:
   1 cap daily for only three weeks
4. Concurrent medication: Peritrate and nitroglycerin
5. Reason took off MER/29:
   1. Swelling in several places in skin of furuncle (boil) type
   2. Severe monilial mold type dermatitis in crotch and folds of arms and legs.

   Dr. K. reported that this patient had never had skin trouble before.
6. Patient was referred to Dr. Herman Schultz (Derm.) who told Dr. K. that he (Schultz) was presently treating two more patients whose severe dermatitis may have been caused by MER/29.
7. Dr. Schultz presented to Dr. K. an opinion that the sharp drop of chol. brought about by MER/29 may disrupt the fatty protective film of normal skin and leave the skin susceptible to many infections. This opinion was disputed by Dr. Glantzberg. Dr. G.'s patient was in somewhat the same difficulty and still had around 400 mg/% and had been on MER/29 for some six months.
8. At this point Dr. Kaplan also learned of the dentist being treated by Dr. Schultz (referred to him by Dr. Salinger) as "being close to death" in a hospital and had his office telephone all important drug stores to stop filling and refilling his MER/29 Rx until further notice.
9. Having spotted this note from Dr. K. in two different drug stores on Friday I called for and got an appointment to see him today and promised him that I would (or Cincinnati would) keep him informed of any similar severe dermatitis possibly caused by MER/29. Dr. K. told me that Dr. Julian Fractman (one of my pre-marketing men) was also concerned of this.

[Inter-Department Memo, Feb. 13, 1961]

To: Department of Medical Research.
From: Wm. J. Phelan, #48727, Houston, Texas.
Subject: MER/29 of Dr. Salinger.

1. Age—50, Sex—M, dentist
2. Diag. Prim:
   Coronary heart attack
   Elevated cholesterol
3. MER/29 dosage range
   Can be obtained from Harry Davis, #48767, who calls on Dr. Salinger.
4. Reason patient taken off MER/29:
   1. Severe generalized ichthyosis
   2. Loss of scalp hair
   3. Definite lightening of color of hair, eyebrows, etc.
   4. Virtual lack of beard now, needs to shave but once a week
   5. "Zero" libido
   6. Severe and extremely painful monilial mold type dermatitis in groin, armpits and folds of arms.
5. I found the above information from Dr. Herman Schultz, 806 Hermann Prof Bldg, while talking to him in his office today. This patient was referred to him by Dr. Alfons Salinger, 2212 Calumet. Since Harry Davis calls on Dr. Salinger routinely Harry had received a carbon copy of a letter written by Dr. Salinger to Merrell in Cincinnati dated January 30, 1961, concerning this patient. It is my understanding that Dr. McMaster talked to Dr. Salinger today by phone and also has the note Dr. Salinger wrote in January.
6. Dr. Schultz reported that the patient was "just not doing well at all" in the hospital. The patient did not seem to respond to usual procedures and medications for the dermatitis he has developed.

HOUSTON, TEX., *Feb. 16, 1961.*

WILLIAM S. MERRELL CO.
Cincinnati, Ohio

GENTLEMEN: It has come to my attention that several cases of severe alopecia have occurred in this area from the use of MER–29.

Today, one of my colleagues showed me a case in which there was extensive alopecia, change in the color of the hair, severe skin reaction with secondary monilia infection.

Do you have any additional information regarding these skin reactions? If you do, please advise me as soon as possible, as I have a number of patients taking this preparation.

Thank you for your courtesy.

Yours truly,

H. JULIAN FRACHTMAN, M.D.

[Inter-Department Memo, Feb. 17, 1961]

To: Dr. Robert S. Shelton.
From: Frank N. Getman.

DEAR BOB: I certainly did appreciate your kind letter on my recent promotion—and also greatly appreciate the advice and suggestions you have recently been giving Harold Werner on some of our more troublesome research projects. By staying with them, we are bound to come up with the answer.

The excerpt you sent me from the February 11 issue of *The Medical Tribune* made interesting reading as I hadn't yet had an opportunity to see that issue. As you are probably aware, that panel of experts is "anti" everything unless they have the idea for initiating the project. Their remarks are just about what you would expect.

From the comments of several of our people, however, I understand that you distributed this excerpt rather widely. We want all of our people to be informed and kept up to date, but in a field as controversial as atherosclerosis and the lowering of cholesterol, we try to pass on the information with a positive, objective appraisal from management. Accordingly, I would appreciate your going

back to the suggested distribution list described in my memo of December 29, 1958 so that the added distribution can be made with appropriate interpretation.

Mentioning the above reminds me that we haven't kept this list up to date although you may have been able to guess the proper substitutions. Carl Bunde should, of course, be substituted for Ray Pogge, and Jacobs should be deleted. Any ideas and evaluations for the acquisition of domestic products should go to Joe Murray with copy to Bob Woodward, and any ideas for acquisition of companies should go to Bob Woodward. The balance of the list remains as it was at that time.

F. G.

P.S.—As a conversation piece, desmosterol is giving us questions and creates an unwarranted, troublesome problem. Certainly, all the evidence definitely indicates it isn't harmful and, in fact, we theorize that it may be beneficial—I have found in talking individually to any of the ones who raise this question that he readily admits it is as likely desmosterol is beneficial as harmful. We are, however, not ignoring the question and active research continues. Any suggestions you have on how we could augment or speed up our program on getting added proof to show that desmosterol is not harmful would be appreciated. We remain as convinced as ever that the only intelligent way to tackle the problem of lowering cholesterol is by interrupting its biosynthesis as MER–29 does.

MAYO CLINIC, ROCHESTER, MINN.,
February 25, 1961.

ROBERT H. MCMASTER, M.D.
Associate Director,
The Wm. S. Merrell Company,
Division of Richardson-Merrell Inc.,
Cincinnati, Ohio

DEAR DR. MCMASTER: In reply to your letter of February 20, I can only say that you have underestimated us. You sent us two case report forms and we will need three more for we now have five cases with some effects on hair. I shall fill out the forms and send them on to you with the data such as is available at this time. You will probably want subsequent reports on some of these.

Again our best regards to you and your staff.

Yours truly,

R. W. P. ACHOR, M.D.

[Inter-Department Memo, Mar. 18, 1961]

To: Professional Service Department.
From: M. Tenenbaum No. 10251.
Subject: MER/29.

A pharmacist in my territory stated that when taking MER/29 for about a week or more his eyes started to tear and burn slightly. When therapy was discontinued these symptoms disappeared, but upon resuming MER/29 therapy he complained of the same problem.

Do you have any information as to why he might be getting this reaction if it is possibly from MER/29?

Thank you for your consideration.

Best regards,

MARV.

[Inter-Department Memo, Mar. 23, 1961]

To: H. W. Werner, Ph. D.
From: R. H. McMaster, M.D.
Subject: MER/29—Complaints of hair changes.

CONFIDENTIAL

Attached is a tabulation of complaints received to date of changes in the scalp hair associated with MER/29 therapy.

Fifty-one patients who have experienced hair loss have been reported by 31 physicians. Of these, 4 are males, 42 are females, and in 5 cases the sex is unreported. It will also be noted that regrowth has occurred in 10 patients, 9 female and 1 male, beginning as early as 10 days after discontinuation of therapy. In 2 additional female patients, regrowth occurred despite continued therapy. Color changes have been reported in 3 males and 2 females of the group, and change in texture (usually dryness and brittleness) has been reported in 5 females and 1 male. No consistency in relationship with other medications can be defined from this tabulation. Dose relationships, where reported, are also of no particular help.

As addendum to this tabulation, the following paragraph from a letter of March 16 from Gordon McHardy, M.D., is of interest:

"Since your recent request in regard to hair thinning, I have gone over 200 of our cases who have been on MER/29 continuously over a period in excess of 12 months. In this series there was included the one patient of hair thinning on whom I reported to you and on whom we discontinued MER/29. Additionally, there were 6 patients in the group who reported a definite increase in hair growth. These, however, were all males. The increase in hair growth is obvious in 1 particularly obese individual who has grown a nice foreward flock of wavy black hair. We have encountered a second patient who has hair thinning, a female, age 52, who was on MER/29, 250 mg. daily for a period of only 42 days. During the same period, this patient had received intra-articular and oral corticosteroids. On noticing her hair loss, this patient 22 days ago discontinued MER/29 and has had a definite regrowth of new hair."

The 2 patients reported here by McHardy who have exhibited hair loss are included in the tabulation. However, the tabulation does not include the 6 males who grew hair in alopecic areas.

In view of Dr. McHardy's report, and the original reports of growth of hair in 2 elderly alopecic women by Kountz and Toro, we must also conclude that there are better classed as hair changes rather than simply as hair loss. It is, therefore, recommended that the words "changes in color, texture, or amount" be substituted for "loss" in the new brochure side effect statement. It is the feeling of the Department of Medical Research that there can be no doubt of the association of MER/29 therapy with these changes.

Enclosure [omitted].

[Inter-Department Memo, Mar. 24, 1961]

To: Mr. H. Smith Richardson, Jr.
From: R. H. Woodward.
Subject: MER/29—Complaints of Hair Changes.

CONFIDENTIAL

Before Frank left for vacation, we had initiated a review of reported thinning of the hair of people taking MER/29. It is our feeling that we are morally and legally bound to include our findings in the side effects statement in the FDA approved brochure—even though the reported incidence is only 51 cases of roughly 300,000 treated.

Attached for your review is a memo from Dr. McMaster setting forth the facts as we have them, together with a copy of a proposed letter to FDA by Joe Murray which has not yet been sent.

The reason for bringing this to your attention, Smith, is that we have made no changes to this point in any of our MER/29 literature, basically because we were afraid to "stir the pot" in Washington. We have heard from several sources that FDA at times has considered reopening our NDA file but, frankly, we do not know whether this is true. The risk we run in admitting this additional side effect must be realized, however, and weighed against our moral and legal obligations referred to earlier.

Frank and I both feel that the approach should be made. Further, we feel that to protect ourselves against possible damage suits, we should make the approach promptly. I though it well to inform you, however, so that you may express your own opinion since, after all, the future of MER/29 is of interest to you and to others in the Enterprise as well as to Merrell.

[Draft of Proposed Letter]

MARCH 24, 1961.

DR. FRANK J. TALBOT,
Food and Drug Administration, New Drug Branch,
Bureau of Medicine, Temporary Building "S"
Washington, D.C.

DEAR DR. TALBOT: Reference is made to our New Drug Application, 12–066, for MER/29 (triparanol). Our attention has been called to several reports concerning thinning or texture change of hair, and while it is difficult to access the importance of these reports (particularly since there have also been reports of increased hair growth), we feel some mention should be made in our literature. Accordingly, we propose to modify the last sentence under "side effects" in our existing brochure. This sentence now reads: "Isolated reports have been received of nausea, vomiting, temporary vaginal bleeding, and dermatitis." We would like to change this to: ". . . . temporary vaginal bleeding, dermatitis, and thinning of the hair."

If you have no objection to the proposed change, we shall plan to make it at the time of our next printing.

Sincerely yours,

F. JOS. MURRAY.

[Inter-Department Memo, Mar. 28, 1961]

From: Robert T. Stormont.
To: Mr. Smith Richardson, Jr.
Subject: MER-29—Complaints of Hair Changes.

According to Woodward's memo, the reported incidence of hair thinning in only 54 cases out of a total of approximately 300,000 cases who have received MER-29. This would mean that less than two people out of every 10,000 receiving MER-29 report some loss of hair. I wouldn't be at all surprised if two or more adult people out of 10,000 *not* receiving any MER-29 at all reported some definite hair loss during a few months period of observation. Furthermore, I wonder if there are any data on the incidence of hair-thinning associated with nicotinic acid therapy. Of course, it is quite probable that there are *unreported* cases of hair-thinning associated with MER-29 therapy, but I find it rather difficult to be convinced, on the basis of these data alone, that MER-29 is definitely responsible.

The observations of Dr. McHardy are also somewhat puzzling. In addition to two cases of hair-thinning he reports six cases of definite hair growth. Apparently, there have also been at least two other cases of hair growth associated with MER-29 therapy. I don't know what this means, but I find it difficult to believe that MER-29 is perhaps the long awaited cure for baldness.

We know that people observed spontaneous thinning of the hair or changes in its color or texture long before MER-29 was available. Furthermore, we know that a smaller percentage of people have experienced a spontaneous regrowth of hair. I don't wish to imply that there is no expectation for such phenomena. Systonic diseases accompanied by fever, thyroid therapy and certain hormonal imbalance states, undoubtedly, can result in alopecia or hair-thinning. Have all such known causative factors been ruled out in the MER-29 cases? I presume that they have in view of McMasters statement "that there can be no doubt of the association of MER-29 therapy with these changes."

I will now put on my other hat and argue on the other side. Hair loss doesn't occur spontaneously without any cause whatsoever. If we rule out known probable causes and are left just with MER-29, is there any other reason to believe that MER-29 could be responsible. The answer is probably affirmative in that MER-29 probably does have some endocrine effect. This is inferred from its chemical structure and the reports of vaginal bleeding associated with its use. Therefore, it is both possible and likely that those scattered reports of hair changes could be attributable to MER-29.

In summary, I would say that the weight of the evidence seems to indicate that MER-29 may produce some hair changes in a very small proportion of cases. However, I do not believe it is fair to say that this is proven beyond any doubt. Nevertheless, I am inclined to go along with the recommendations of the Merrell group as I am sure that at least one or more of the physicians who have observed this effect on the hair of several of their patients during MER-29 therapy will publish their findings in the near future. I don't particularly like McMasters sug-

gested phrase "changes in color, texture and amount," as this sounds rather frightening. After all, none of those cases developed green, pink or lavender hair, I hope. Therefore, I'm inclined to believe that Murray's simple phrase "thinning of the hair" should probably be sufficient. I believe it would be well also to stress the extremely low reported incidence of these hair changes.

ROBERT T. STORMONT.

[Inter-Department Memo, Apr. 7, 1961]

To: Dr. C. A. Bunde.
From: Harold W. Werner.
Subject: MER/29—Complaint of Liver Damage, Class I. No. 70 (Memo McMaster to "Too Many People" 4/4/61).

This memo should not have gone to Mr. Long and Mr. Ritter. In addition to reporting on what was learned, the memo needed to contain a final section describing what we did and, if there was any question to what we should do, making recommendations and carrying through to obtain needed action.

We do need to arrive at a point where positive action of the proper type is taken quickly and effectively.

P.S.—In a casual conversation with Mr. Long and Mr. Ritter please explain to them what is wrong with DeGraff's thinking and conclusions.

H. W.

THE WM. S. MERRELL CO.,
Cincinnati, Ohio, June 28, 1961.

JAMES C. MELBY, M.D.,
Department of Medicine,
University of Arkansas Medical Center,
Little Rock, Ark.:

Jim, I am sorry I could not see you again after our brief discussion following presentation of your paper. Dorsey Holtkamp told me that the many rumors and comments flying around frightened you and you had decided to discontinue your large-dose experiments temporarily.

I want to comment on this, and I hope you will accept this as an opinion based on having available many more data than any one or dozen investigators could have, and also, in part, from experience in tracking down some of these rumors, such as the one Seltzer was spreading. I also hope you can interpret this as being restrained to the extent of most of all wanting to protect our investigators from getting into any trouble, using MER/29 or any of our drugs experimentally. I find in most cases that I am more conservative and more cautious than our investigators.

Up to the present, we have had no evidence which could reasonably associate MER/29 therapy with hepatic toxicity, and this includes all cases treated by the large doses, such as you have used. I feel certain that if such toxicity were inherent in the drug, it would be obviously manifested by now and would occur with a very high incidence in the 2,000 mg/day patients, if it occurred at all in the 250 mg/day patients. As I told you early in your studies, caution and close observation is necessary, because our experience in the large doses at that time was very limited. Most of the clinical data on the larger doses did not exceed 500 or 750 mg/day, with the exception of some work done at the Mayo Clinic. Now, however, since your report last December, we have had many individuals asking for drug to use specifically for adrenal suppression in doses of 2,000 mg/day, and larger. Therefore, at present, I cannot tell you the number having received such a large dose, but it must be many times the cases you have studied. We still have no evidence associating hepatic toxicity with MER/29.

After MER/29 had been on the market for some six months or more, we began receiving reports of hair loss. These were isolated and mixed with reports of hair growth and color changes, so that it was difficult at first to decern a pattern or determine if the condition were truly drug-related. We immediately started a more intensive investigation of all complaints, using a definite form for obtaining uniform data, and soon concluded that, at least in some of the cases, the hair loss was related to MER/29 therapy. The higher incidence found by the Mayo Clinic group using larger doses confirmed this. However, their data were not made available to us until March 20 of this year. We immediately changed our literature to include this under side effects.

Before the drug was put on the market, dryness, or scaliness, or a rash-like condition had been reported in a certain number of patients. This was listed under the term dermatitis as a side effect in the original literature. We have heard of a few cases since, most of them recently, where this dermatitis has been of a very severe nature and in some instances referred to as ichthyosis. In the few which we were able to track down through the maze of rumors and have examined by dermatologists the term ichthyosis was found to be incorrect. Also it became apparent that some of these were not related to drug. At any rate, we are recognizing that if mild cases of dermatitis can occur, an occasional rare case will be severe. The two most severe cases which we have tracked down are the least likely to be drug-related. One was the case reported by Corday and which he has been ballyhooing around the country as if it had been an epidimc. This patient was on a least three other drugs known to produce allergic cutaneous reactions and had a previous history of neurodermatitis. The other one also had a history of neurodermatitis, and there is some question whether the dermatitis developing under MER/29 started before that therapy began.

We had further reports that MER/29 affected coagulation time of blood; some reports had an increasing coagulation time, some a decreasing coagulation time, and in some the comments were referred to prothombin time. Studies had been initiated in this direction before the drug reached the market and another was set up when the first reports came in. The data from these studies definitely show that MER/29 has no effect on any of the known factors related to the clotting of blood. There is a suggestion that it may actually decrease platelet stickiness, and this we are investigating further.

The only other complaint that we have received in more than six instances, which we use as our arbitrary number for being watchful, is the loss of libido. I defy anyone to make any sensible pattern out of these complaints. Almost 100 per cent of the complaints come from men, whereas about 80 per cent of the complaints on hair loss come from women. Some clinicians with more than 100 men on MER/29 have no complaints of loss of libido, whereas someone with 15 or 20 cases will report 2 or 3. One must always keep in mind that the majority of cases treated with this drug are middle-aged or beyond. Many have had recent infarcts and have fear of sexual activity as well as other activities, such as roller-skating or whatever you wish to choose. Again, we are not finding this complaint in those patients receiving the larger doses of drug, and if it occurs at all at the 250 mg dose level, it ought to be much more frequent at the higher doses, if it is a truth. I have a strong enough background in pharmacology to be suspicious of any drug action that deviates from some semblance of a dose-response curve.

The above is as accurate a summary and interpretation of our total experience with MER/29 toxicity as I can give you at this time. I will say that if you use the large doses you should exert extra precautions, especially in looking for the earliest manifestation of those side effects that now appear to be drug-related. Most specifically these are: a type of dermatitis, loss of hair, and change in hair color.

You are free to use this letter as you see fit, as it is only what I would comment to anyone asking me about the subject. We have somewhere around 3,000 case reports of unpublished data in our files and some 3,000 or more represented by published reports. In addition, Dr. McMaster and I have had personal interviews or frequent correspondence with at least 300 reliable investigators working with MER/29.

CARL A. BUNDE, Ph. D., M.D.,
Director of Medical Research.

[Inter-Department Memo, July 5, 1961]

To: Dr. H. W. Werner,
From: R. H. McMaster,
Subject: William Hollander, Boston, Consultation Fee.

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

Certainly we need his help and counsel.

JULY 7, 1961.

WILLIAM HOLLANDER, M.D.,
Sudbury, Mass.

DEAR BILL: It is my pleasure to enclose our check in the amount of $1,200. This represents our consultation fee for the six-month period beginning July 1 and ending December 31, 1961. You will hear from me separately concerning the expenses you have incurred during your recent speaking engagements.

With best personal regards,

ROBERT H. MCMASTER, M.D.,
Associate Director of Clinical Research.

JULY 5, 1961
$1,200.00

WILLIAM HOLLANDER, M.D.
Massachusetts Memorial Hospital
750 Harrison Avenue

Boston 18, Massachusetts

Consultation fee for advice and counsel on MER/29 research for the 6-month period, June 1 thru December 31, 1961.

R. H. McMaster 4407 02 1,200.00

AUGUST 4, 1961.

W. D. FEINBERG, M.D.
Building 14, Suite D, Medical Center,
El Paso, Tex.

DEAR DR. FEINBERG: Your Merrell representative, Mr. Theodore Rallis, has told us of the observations you have made in the case of one of your patients who is taking MER/29. I understand that concurrent with drug administration this patient complained of double vision and a peculiar loss of taste. This occured after six weeks of treatment, and complaints ceased upon discontinuation of therapy only to return three weeks later when therapy was resumed.

We are completely unable to provide you with information from other sources which might help you to explain these observations. This is the first instance of this sort about which we have heard. Also, nothing in the animal studies provides data which might shed some light on it. There is certainly a possibility that this patient is exhibiting an unusual sort of sensitivity to the drug and, in view of the experience, it would seem advisable that he should not use MER/29. Mr. Rallis enclosed your prescription blank listing these observations. I note that you have mentioned the patient had a Bell's palsy on the left side and am wondering if this, too, was related in time with the occurrence of the other symptoms. Any additional information you may care to provide would be most welcome.

We thank you for letting us know of this experience through Mr. Rallis.

Sincerely yours,

ROBERT H. MCMASTER, M.D.,
Associate Director of Clinical Research.

[Inter-Department Memo, October 1961]

To: Dr. H. W. Werner.
From: T. R. Blohm/mc.
Subject: Request for Radioactive MER/29 for Topical Use in Animal Eyes: Dr. R. M. Burnside.

Some months ago, Dr. R. M. Burnside, of the Dallas Medical and Surgical Clinic, Dallas, Texas, wrote to Dr. Bunde requesting some radioactive MER/29, to be used in determining whether or not triparanol penetrates into the eye structures of animals, when applied topically to the cornea. The request was turned over to me, and eventually bogged down in correspondence over the details of radioactive procedures. Now Dr. Burnside has renewed his request for this material, and we must decide whether or not to supply it to him.

As I understand it, if Dr. Burnside were successful in demonstrating penetration of triparanol into the internal structures of the eye, he would then proceed with a longer term study utilizing this mode of administration as an experi-

mental approach to the treatment of retinal arteriosclerosis. I think such a study at this particular time could be extremely dangerous to us. On the other hand, I don't see that we could prevent him from using unlabeled material if he were determined. I don't know how important this man's cooperation is to Medical Research's program, but I would certainly recommend doing everything reasonable to discourage him from carrying out this study. Since I must proceed one way or the other on the radioactive material, would you please let me have a decision on this?

[Inter-Department Memo, Oct. 5, 1961]

To: Dr. Werner (+2).
From: E. F. Van Maanen/shh
Subject: Fundus Camera for Eye Examinations.

Earlier this year we were confronted with a study using MER/29 in dogs in which the experimenters observed certain changes in the dog eye. We were invited to examine the dogs and they also showed us a sequence of color pictures showing the progression of the lesions which they had observed. No matter what could be said about the temporal condition of the eyes, the progression shown by the photographs was far more conclusive and indicative.

The person responsible for this study considers himself an export in canine ophthalmology. Considering the lack of competition, this is probably true. At the same time, this person was previously employed in the Toxicology Department of the Food and Drug Administration. His relationship with this branch of the government is still excellent. In order to substantiate his exclusive position, he is planning to write a monograph on the virtues of canine ophthalmology in drug evaluation. In view of the recent attitudes of the FDA, one can anticipate, therefore, that the FDA might require in the future ophthalmological reports from dog and monkey studies, particularly when it concerns revolutionary new drugs.

In view of the observations reported above, we started an extensive study in dogs and rats with MER/29 in which particular attention was given to ocular side effects. Except for slight keratinic changes in some rats, no major changes were observed until two weeks ago. At that time we invited the canine ophthalmological expert to examine our dogs. In most cases he gave them a clean bill of health. However, with two dogs he noticed some changes, but was not sure whether these were recent and whether they were drug-induced. Last week during the weekly routine dog examination, Drs. King and Grady were worried about ocular changes having occurred in one other dog since the previous examination.

Drs. King and Grady keep very careful records of their ophthalmological examinations. If no changes had occurred, this would probably be sufficient for our records. On the other hand, when changes do occur, the written protocol will not be sufficient for general judgment and for estimation of the progress of the lesion. Since much is at stake in this study and since tremendous efforts have been put into this study, I recommend that under these conditions we purchase a camera which can take colored pictures of the inside of the dog's eye. This will be important also for the development of other new cholesterol synthesis inhibitors.

[Inter-Department Memo, Oct. 17, 1961]

To: Dr. E. F. Van Maanen (+2).
From: W. M. King.
Subject: MER–29—Eye Changes.

Dog #173, a 8.5 kg male beagle was started on MER–29 on March 29, 1961. (40 mg/kg/day) On September 7, 1961, after twenty-two weeks of drug therapy, this animal developed a dermatitis, with a marked and progressive hair loss. These skin changes were particular noticeable on the ears. The skin on the ear showed a non-confluent macular rash, which the dog scratched. A skin scraping for mange mites on September 7, 1961, was negative. The ears were treated with Neomycin/Hydrocortisone ointment with poor results.

The eyes were examined on September 7 and September 14 by King and Grady; on September 20, 1961 by King and Wazeter (Merck, Sharpe and Dohme) and again on September 21, 1961 by King and Grady. Up to and including the ocular examination on September 21, 1961, no eye changes were observed.

On September 28, 1961, exactly six months after the onset of drug therapy, the following eye changes were noted:

There was bilateral hazyness deep to the cornea which made visualization of the fundus very difficult. Although not able to definitely localize this lesion it was the impression of the examiners that this change was in the anterior lenticular capsule.

At the examination on October 5, 1961, the dermatitis was severe and the animal completely blind. The eyes were similar bilaterally and the impression of the examiners was anterior lens cataractoid changes.

At the examination of October 12, 1961, no additional eye changes were noted, but the dermatitis continued to be widespread and severe.

In the rat study, at 40 mg/kg/day, twelve out of twelve males and six out of seven females have opacity in one or both eyes. In a similar group where vitamins and cholesterol are added to the drug diet, there are nine out of twelve males and eight out of twelve females with eye opacities.

In each case, the eye changes in the rats were preceded by hair loss and severe changes in the skin.

W. M. K.

[Inter-Department Memo, Oct. 19, 1961]

To: Mr. F. N. Getman.
From: F. Jos. Murray.
Subject: MER/29.

John Nestor of the FDA called at 8:40 a.m. today to advise they had given consideration to the letter we proposed to send to physicians on MER/29 side effects. Nestor raised the following points:

1) The FDA does not have sufficient pertinent facts to enable them to make a decision on the letter. It is their fear that side effects may be more extensive and more severe than stated in the letter, and it might, therefore, be misleading and lead the physician to a false sense of security.

2) The FDA wants all facts available to us on the cases of eye changes, including the actual case records. They also request a written copy of the letter we propose to send.

3) The FDA wants a statement from us to the effect that we have supplied all toxicity data in animals and man, including that available to us from outside sources. (The implications here are obvious and on pressing Nestor he offered as an example a comment that a Dr. Wong of Howard University visited us in April to describe results in chickens indicating interference with ovulation. Dr. Wong states we ignored the results, and Nestor declared this could be grounds for suspension of the NDA.)

4) Nestor stated he had discussed MER/29 with several experts and there is concern that there are numerous other serious side effects involved. These include: baldness, lenthyosis, impotence, interference with ovulation, induction of abortion, interference with adrenal function, and reticulocytosis together with hepolytic anemia as found by Page.

Dr. Nestor stated he had discussed the problem last night with Dr. Siegel and it is their feeling they have enough evidence to suspend the NDA. He also stated that their statistician has advised them that our claims for significant lowering of cholesterol levels are not true.

I told Nestor we would want to see him as quickly as possible but that we would have difficulty pulling together material to answer all these charges before next week. He agreed and indicated he would make himself available any day of the week. We are aiming at a conference on Thursday, October 26.

[Inter-Department Memo, Oct. 24, 1961]

To: Mr. W. R. Marschalk.
From: Frank N. Getman.
Subject: FDA action on MER/29.

Sherry Silliman and Fred Lamb have both advised me that a New Drug Application may not be suspended or revoked without a hearing—such hearings are not public. Apparently, however, the fact that a hearing is being called does become publicized.

Bengert is away for several weeks, but Silliman, of Norwich, said that the notice of hearing came after failure to reach agreement following a number of discussions with the FDA. According to him, news of the hearing was first published in Werble's "Pink Sheet," and he says Werble appears to have a good "pipeline" into the FDA. He added that the FDA does publish notices of hearings to be held. (I am asking the Legal Department to run this letter down.)

Going on with the Norwich case, the hearing technically is still in progress. All testimony on both sides was completed before the Examiner months ago. Briefs were filed in April, with no decision yet. Anticipating an adverse decision, Norwich plans an appeal to the courts. The product is still on the market and available to the physician. It has not been promoted in any way since the notice of hearing, and this was an agreement which Norwich made with the FDA. Naturally, sales have dropped drastically, but the product is still being prescribed by these physicians who have found it a very valuable drug. Norwich made its own publicity release to the public and to the stockholders after the notice of hearing had been received.

In the McNeil case, I know nothing more than what I have read in the "Pink Sheet," which stated McNeil sent out letters to MD's and drug wholesalers, setting in motion a "voluntary" recall program because of jaundice, hepatitis and liver damage reports. As far as we can tell, McNeil, after conferences with Food and Drug in which a hearing was probably threatened, took this action rather than go through a hearing.

In the White Laboratories' Entecqual case, the Government seized the drug on the basis that representations in promotional material for MD's differed materially from the labeling claims permitted by the effective New Drug Application—in other words, false and misleading labeling. Apparently this followed a failure to agree with the FDA on appropriate disclosure of side effects and also an appropriate dosage exclusion limitation for children—these negotiations going on while the NDA was in effect. Other actions such as multiple seizures or a suspension of the NDA were being considered by the FDA before White withdrew the drug from the market.

This background is furnished in view of the request that I provide, in advance, a company statement in the event of government action. I told Art Boschen this morning that in view of our lawyers' advise on advance release didn't seem necessary, but after tying the above factors together I am making the following suggestions:

In the event of rumor that the FDA is about to suspend the NDA

"We have not received notice of any such hearing, as provided in the law. We are not in a position to comment until we do—if we do."

In the event of receipt of notice of hearing

"The Wm. S. Merrell Company, Division of Richardson-Merrell Inc., has today received a notice of a hearing from the Federal Food and Drug Administration to determine whether its effective New Drug Application on MER/29 should be suspended. In our opinion such suspension would be unwarranted and unnecessary, and we believe that evidence presented at the hearing will sustain this position," stated H. R. Marschalk, president of Richardson-Merrell (or Frank Getman, president of The Wm. S. Merrell Company Division).

Let me know your final preference on who makes the announcement.

Admittedly, the letter announcement is extremely brief, but I am proposing it in this form for two reason—the first is that the less said, the better, as long as it adequately covers our position—and secondly, it is hard to give added reasons until we get the notice of hearing, which is similar to a complaint and outlines the reasons why the NDA should be suspended. If it should be a claim we withheld evidence, that would call for one type of statement, whereas if it were based on certain kinds of toxicity, it would call for another.

It seems to me this is as far as we can and should go at the present time, but I will welcome any comments or suggestions.

P.S.—Needless to say, our preparation for the Thursday meeting is going on at full speed.

OCTOBER 26, 1961.

DEAR DOCTOR: The purpose of this letter is to advise you of those cases where MER/29 therapy should be discontinued.

The types of cases where the drug is to be withdrawn more not apparent from the several thousand clinical cases studied during the two-year period prior to

marketing of MER/29. These cases have recently been observed following the widespread use of MER/29.

There have been a number of reports of hair loss, changes in color and texture of hair, and dermatitis. More recently, less opacities have been observed in four patients following severe dermatitis.

MER/29 should be immediately withdrawn if changes in hair or skin occur. Your patient should be informed to watch for hair or skin changes and directed to stop therapy and report to you if they should occur.

For your information, the dermatitic usually is a dry, scaly type which may be associated with mild itching. It regresses following discontinuation of the drug. In a few patients, this mild dermatitic has progressed into a more severe ichtyoid type which is the type in which the four cases of lonticular changes have been reported. This has only occurred when drug therapy has been continued for a period after the dermatitics appeared.

The hair loss consists of a diffuse thinning unlike aleposia oreata or totalio. In some cases, hair loss has become catonoivo; and in a few of these, the thinning has involved body regions other than the scalp. Regrowth of hair occurs after varying periods of time following discontinuance of therapy.

This letter is sent as part of our continuing policy of fully informing the medical profession about MER/29. Your adherence to the cautions presented here will permit you to use MER/29 effectively in your practice.

Sincerely,

CARL A. BUNDE, PH. D., M.D.,
Director of Medical Research.

OCTOBER 31, 1961.

W. FREUD, M.D.
Skokie, Ill.

DEAR DR. FREUD: I have heard recently from your Merrell representative, Mr. Steven Andre, who reports that two of your patients who are on MER/29 therapy have complained of "black spots before their eyes."

This is so unusual a report that I would like to ask you to provide us with additional details about these patients. In fact, we have never before heard of anything remotely resembling this. It would be important, for example, to know whether ophthalmologic examination has revealed anything of interest which may help to explain this phenomenon. It would also be important to learn whether these "black spots" are fixed or floating and whether the patients have experienced anything of this sort previous to MER/29 therapy. Also, have either or both of them had other possible side reactions—for example, dermatologic involvement? This would be important inasmuch as the eye and skin are both of ectodermal origin.

Any information you might be able to provide would be very much appreciated.

Sincerely yours,

ROBERT H. MCMASTER, M.D.,
Associate Director of Clinical Research.

WHITE PLAINS, N.Y., *July 8, 1964.*

BENJAMIN HERSH, Esq.,
Peekskill, N.Y.

DEAR MR. HERSH: At the request of Mrs. Elizabeth Ostopowitz I wish to send you the following report:

She was first seen in this office in September, 1963, complaining of difficulty in reading a newspaper in the three months prior. She stated that she took the drug known as MER 29 for seven or eight months following which there was loss of hair which has gradually returned.

Examination showed her vision limited to the counting of fingers in each eye because of cataracts. The lenses were diffusely involved with degenerative cortical changes including clefts and scattered opacities. There was no view of the fundus of either eye but light projection was accurate. The diagnosis of bilateral cataracts was made and considering the patient's age and the history it was felt that these cataracts were very likely related to drug ingestion.

On October 29, 1963 the cataract was removed from the right eye and on April 19, 1964 the cataract was removed from the left eye. In each instance the post-operative vision has been 20/20 and the patient is now wearing glasses which give her this vision.

A fee for these services is enclosed.

Yours very truly,

ARNOLD W. FORREST, M.D.

DECEMBER 28, 1959.

Dr. R. H. MCMASTER,
The Wm. S. Merrell Co.,
Cincinnati, Ohio.

DEAR DR. MCMASTER: I meant to catch you during the conference to tell you that I had decided it would not be advisable for me to accept your generous offer an honorarium for my contribution to the MER/29 conference. Because of my Government affiliation and also because I am currently a member of the Metabolism Study Section which may have to pass on grant applications in connection with projects involving your company, acceptance of an honorarium might be misunderstood by some. Therefore, I am returning your check with thanks. My expenses to this meeting were paid by the National Heart Institute.

I enjoyed participating in the conference and I believe it served a very useful purpose in bringing together people studying MER/29. The new information that we presented at the meeting represented primarily the work of the few weeks preceding the conference and so I had not had time to communicate with you about it before. There are several serious questions raised by these findings. First, we do not know yet whether 24-dehydrocholesterol is or is not atherogenic to the same extent or to a greater extent than is cholesterol. Second, we do not know yet whether 24-dehydrocholesterol has other biochemical effects that make it unsafe to treat with MER/29. I know that you are, of course, anxious to obtain FDA approval to market the drug but I do not feel that this would be wise in view of the new data.

What are your own thoughts on this matter? Have you any suggestions as to the kinds of information that should be sought in order to clarify the status of the drug?

Again, many thanks for your hospitality and for arranging a valuable conference.

Sincerely yours,

DANIEL STEINBERG, M.D.,
National Heart Institute.

[Inter-Department Memo, Feb. 18, 1960]

To: Those concerned.
From: Frank N. Getman.
Subject: Minutes of MER/29 meeting, February 17, 1960.

The following notes represent the pertinent questions raised and constructive suggestions made during yesterday's meeting on MER/29.

I. CLINICAL BACKGROUND

Morson requested breakdown on patients with pre-treatment cholesterol blood levels of over 250 mg.

Richardson, Jr.—what will be the doctor's reaction to Princeton Symposium? We feel that it will be the most terrific selling tool that Merrell has ever had, since it is a frank discussion of the product—we are telling both the good with the bad. (Getman.)

Morson pointed out that Hollander used the dosage of 750 mg. per day to reduce the tissue level of cholesterol and has wondered whether 250 mg. per day would do this.

Blohm answered that he believed it would, since higher dosage does not increase reduction of blood cholesterol levels. While we cannot prove beyond doubt that we reduce tissue levels at 250 mg. it has been universally accepted by our clinicians that tissue level reduction does occur at this dosage.

Dunning asked how long it would take to have established claims on peripheral vascular disease. It is possible that we will have this data in 6 months but we have problems in getting reliable objective methods and it could take years.

Morson asked whether we could get autopsies on patients who die while on MER/29 therapy. It was reported that all clinicians had been asked to do this.

Following a lengthy discussion on the clinical support on anginal pain, Getman pointed out that we will have a statistical breakdown on the response of anginal patients to MER/29. However, we do not plan to push angina initially. We have an important but complex story to tell on introduction and by early fall, if clinical work remains favorable, we will really push the use of MER/29 in angina.

Richardson, Jr. pointed out that it appeared to him that our claims on reduction of cholesterol were well supported whereas the other patient benefits were more nebulous. They might or might not occur with most patients. He wondered whether we should not establish it first and not make too strong a promise on the other patient benefits in order not to get doctors and patients disappointed. General agreement was expressed with this concept. However, we do not want to forget the promise of possible other patient benefits since our evidence to date certainly indicates that we are well justified in promising these possibilities.

In response to a question by Dunning on long term therapy, it was pointed out that approximately 500 patients have been on MER/29 for at least 9 months and about 150 for over 2 years. Many patients were on very high dosage (one on 3 grams a day for 14 months).

In answer to Mr. Richardson's request for more information on Desmosterol, the following was reported:

Two chemical papers have been published on it—it had not been considered important until the Princeton Symposium. The question that must now be answered is whether it is atherogenic and if so is it more atherogenic than cholesterol? Studies are going to be real tough since Desmosterol is not available. However, we are extracting it from MER/29 treated rats. We can be sure that it is not toxic in the human and if its atherogenicity were as bad as cholesterol, we would not be getting the patient benefits that we have experienced with MER/29.

Getman requested a report from Morson on MNOL's clinical experience with MER/29.

Morson reported that their work was very preliminary and that the only thing they had studied thus far was reduction in cholesterol. He stated they were following the same clinical protocol used in the U.S.

Getman pointed out that our feed-back from MNOL is too casual and asked that the methods be buttoned-up so that we can be assured of getting reports of MNOL clinical findings on MER/29 as well as other drugs clinically evaluated abroad.

Dunning suggested that a quarterly report would be of value in New York and a copy of which could be sent to Merrell. Morson will follow up on this and see that it is done.

II. Marketing

1. COPY PLATFORM

Richardson, Jr. pointed out that one of our stated objectives was to understate rather than overstate our claims on MER/29. He questioned whether our copy platform adhered to this objective. It was pointed out that we will, at times, make what appears to be strong claims but only when we can support these claims with published clinical data.

Dunning suggested that safety appeared to be an important selling point for MER/29 and should be given more prominence in our copy platform. This was agreed to and will be done.

Richardson, Jr. pointed out that in our copy platform we state that a large number of patients with angina would benefit from MER/29. He questioned whether this was an over-statement. This will be changed to read—"substantial number"—or the equivalent "some patients".

2. THE INTRODUCTORY AD

The 7-page introductory ad was thoroughly analyzed both as to copy content and layout. The following specific suggestions were made:

Dunning suggested that lack of toxicity be covered in the letter from Dr. McMaster.

Richardson, Jr. suggested that point #3 in the letter should be point #2.

Anderson suggested that we insert "excess" in front of "production" in 2nd sentence of letter.

Dr. Stormont questioned whether we could say—treatment of coronary artery disease as we do in the 1st sentence of the letter. He wondered if it might be confused as sole therapy—this will be checked out.

Dunning pointed out that we should always say inhibits "*excess* production of cholesterol"—this will be done.

Von Rosenstiel—p. 3 par. 2—why not paraphrase to get a stronger statement. This is a good point and we will rewrite it.

Chewning—shouldn't we also quote other authorities in addition to National Heart Institute? This will be checked out to see if we have other suitable authorities to quote.

Jacobs pointed out that p. 3 par. 5 does not give the dosage level used. This will be rechecked with the clinical paper.

Dunning wondered whether we couldn't use total numbers of patients and prepare our own charts. It was pointed out that we could not do this since we could not reference the data.

Von Rosenstiel wondered whether on p. 3 par. 4—the doctor will understand "conversion of acetate". This was a good point and the ad will be changed to read "decreases production of cholesterol in the body".

Anderson wondered if on p. 3 par. 4 we were making our statement strong enough. It was agreed that we probably were not and the sentence will be changed to read "acts by inhibiting * * *"

Richardson, Jr. pointed out that our ad shows reduction in conversion of acetate and he thought that we should also have one that shows reduction in cholesterol blood levels. This was agreed to and we can prepare one from p. 3 par. 5.

Von Rosenstiel pointed out that the fact that MER/29 does not reduce brain cholesterol is extremely important and should get greater emphasis.

Richardson, Jr. again raised the question that he was concerned that we might be over-claiming on patient benefit. He pointed out that our major proof was for cholesterol reduction and that safety was an important feature. However, our ad is devoted 50–50 to cholesterol reduction and other patient benefits with very little attention to safety. He said that our headlines concerning other benefits particularly bothered him. It was pointed out that we would give more prominence to safety although we didn't want to overdo it and that we would rework our headlines. However, we do not want to minimize the promise that MER/29 may, in some patients, in addition to reducing blood cholesterol, also result in beneficial effects on angina symptoms. Specific suggestions for doing this were made as follows:

Von Rosenstiel—pick headlines out of Hollander paper—the quote may go further than you want to but you can modify in body copy.

Getman pointed out that we were skeptical of riding one man's findings as headlines but we will recheck this possibility.

Stormont suggested that we modify our headlines on anginal patients by inserting "preliminary findings".

The layout of the ad was discussed and since we no longer plan to use the calligraphic man, we have quite a bit of free space on the border of our ad which could now be utilized for additional clinical quotes.

Dunning pointed out that in the summary section of the ad we might be in danger when we mention reduction of cholesterol in one week. This was agreed to and it will be changed to 2 to 3 weeks since there is no sense in running a risk when we don't have to.

Dunning also pointed out that on p. 7, item 2 thru 4 may not show up in 5 weeks—this will be changed.

The following additional general comments were made:

As an over-riding principle in our copy we should keep it as simple as possible since we don't know the extent of the average physician's understanding of

technical terms in this field. A section should be at the end of the ad covering availability and contra-indication such as "not to be used during pregnancy". This would also be a good section to include the things that MER/29 does not do. For example, it does not reduce brain cholesterol. The indications section of the ad should be reworked to correspond to the brochure which includes the most recent FDA changes in our basic brochure.

3. DIRECT MAIL

Anderson pointed out that the Princeton Symposium and the Western Union mailing were very unusual and he wondered whether we could capitalize on that with the rest of our mail. He was pointing to a desire for continuity in our over-all MER/29 image. It was pointed out that we were doing this with our gray and red color scheme and, of course, the calligraphic man would have appeared on all of our printed material and we are now looking for a substitute for the calligraphic man.

Von Rosenstiel suggested that all our mailings be designed to fit in the basic book on MER/29 which was delivered by Western Union. This may turn out to be an excellent suggestion and will be further evaluated.

4. SALES PROMOTION

(*a*) *The detail story*

Getman suggested that Dr. Wright's work on anti-coagulants be included in the safety section of our detail.

Richardson, Jr. suggested that we rewrite the section covering "speculation" since reduction in tissue levels is a fact rather than a speculation.

(*b*) *Supportive materials*

Richardson, Jr. suggested that a piece of literature for the doctor to give to the patient concerning MER/29 might be helpful in keeping the patient happy while waiting for results.

Chewning stated that we would like to get an article published in a magazine such as Today's Health and then make reprints available for patient distribution. The idea of a—patient booket—is worth further investigation.

Richardson, Jr. pointed out that since the majority of doctors feel that cholesterol is related to cardiovascular disease, it probably isn't necessary to go at great lengths during our detail to establish this importance. This important question will be re-appraised.

[Inter-Department Memo, Aug. 1, 1960]

To: R. H. Woodward (and others)
From: Frank N. Getman

Attached is the August Issue of Family Circle containing an article on "Now—many strokes can be prevented."

To me this is written in very simple, easily understood language on one form of cardiovascular disease.

It seems to me that it may be of assistance in helping us along with lay articles to be written on MER/29. It might also help in advertising and promotion, as I don't believe the average Co. yet understands our MER/29 story. Simplification should help.

Enclosure [omitted.]

TIMETABLE OF MER/29 PR PROGRAM

February.—Assist Marketing with submission of advertising copy for approval by the J.A.M.A. Advertising Committee, Dr. John Ballin, chairman.

March.—Effective NDA—begin 1) *press contacts* (see priority list attached) and 2) *clinical speakers service* (see plan attached).

March 1-4.—*Chicago Medical Society*, Lisan *exhibit*. Press release only.

March 18-25.—*American Academy of General Practice*, Philadelphia. Lisan (Hahnemann) *exhibit* should be brought to attention of press. It is proposed that this be done by Hahnemann PR director, Cy Lieberman. No major effort

will be exerted since the exhibit was reported at the Dallas A.M.A. meeting in 1959.

April 4–9.—*American College of Physicians*, San Francisco. Ralph V. Ford (Baylor) *paper* on MER/29. Alert ACP press staff; San Francisco and Houston papers; national news magazines, Drug Trade News and American Druggist; wire service medical editors. Report from San Francisco could be mailed to internists to reinforce the press story.

April-June.—Drug trade publications services with new product information and photo-features.

April 11–15.—*Federation meeting*, Chicago. National press conference will be held to take advantage of the coverage given this meeting by the best of the scientific press. Merrell *papers* by MacKenzie, King and Kariya will be presented. A clinical consultant will be invited to the press conference to give clinical interpretation of the scientific papers. Complete background release will be made, with timetable of future events to guide the press.

April 12.—*American Chemical Society*, Cleveland. Palopoli *paper* news release to press.

April 28.—*New York press conference*, to announce publication of the Princeton Conference. Participants: Drs. Wright, Page, Wilkins, Blohm. Conference will be held at Cornell University Medical College (alternate, New York Academy of Sciences).

The New York press corps would be invited to hear a report to the nation on heart disease and MER/29. A.M.A. and American Heart Association would be invited to send public information representatives.

Special mailing of the Conference publication will be sent to *Medical School libraries.*

May 2–4.—*Louisiana State Medical Society*, Baton Rouge. John T. Leckert (LSU) *paper*, Alert Baton Rouge and New Orleans papers; wire service medical editors.

May or later.—*New England Journal of Medicine.* Mellander paper to be published May or thereafter. Release from Merrell to all wire services, metropolitan newspapers, selected magazines and science writers.

June 13–17.—*American Medical Association*, Miami. Kountz (Washington University) and Lisan (Hahnemann) *exhibits* tentatively scheduled. Notify A.M.A. press staff for daily bulletin coverage; handout for press room.

Ruskin (Texas) has applied for a place on the program.

Check List of PR Contacts on MER/29

When NDA is effective, contacts will be made with editors, publishers and public information people to establish rapport and develop specific ideas for PR support for MER/29. Each contact represents a point of departure for a special working relationship and the PR "product" which will result.

1. Priority contacts to be made by Mantell and/or Chewning.

Modern Medicine: Interview insert, "Exclusive" interview with Princeton Conference participants.

Geriatrics: Editorial Comment.

J.A.M.A.: Special clinical communication.

U.S. News & World Report: Interview.

Time: Conference with medical editors.

Life: Conference with medical editors.

News Week: Conference with medical editors.

RN: Staff story on cholesterol.

American Druggist: Develop series of photo and news releases.

Drug Topics: Develop series of photo and news releases.

Drug Trade News: Feature stories and health column comment.

Saturday Evening Post: Feature stories and health column comment.

Look: Feature stories and health column comment.

Reader's Digest: Feature stories and health column comment.

Cosmopolitan: Feature stories and health column comment.

Ladies Home Journal: Feature stories and health column comment.

Red Book: Feature stories and health column comment.

Metropolitan newspapers: Selection guided by Princeton Conference participants list.

Also considered a priority job is the briefing of public information personnel at:

American Heart Association
American Medical Association
American College of Physicians
American Chemical Society
American Osteopathic Association
National Institutes of Health
Federated Societies

2. Important outlets for MER/29 news are the following groups or publications. These contacts will be developed as the plan unfolds or after the priority contacts are completed.

Scope
Medical News
MD News Magazine
Medical World
A.M.A. News
Today's Health
Argosy, Saga, etc.
Medical journals-Angiology
New York Times (Sunday column)
Family Circle

Drug and pharmacy publications (including Medical News Letter):

Business Week
Fortune
Chemical Week
Chemical and Engineering News
Wall Street Journal
McCall's
Good Housekeeping
Coronet
American Weekly, Parade and other syndicated features
FDC Reports

Syndicated health columns:

Alvarez
Berton
Bauer
Brady
Bundesen
Crane
Dean
Herschensohn
Hyman
Osborne
Steincrohn
Van Dellen

Science news editors (UPI, AP, NEA)
National Association of Science Writers

3. Special projects will be initiated at what seems to be the appropriate time. Examples:

Visits or communications with "sensitive areas" in the government.

Development of radio-TV coverage of the Princeton Conference press release of the monograph.

Coordinated PP program with the publisher of the Princeton Conference monograph.

Development of international medical meeting feedback for U.S. news release.

Special program (perhaps a small clinical conference) if indicated for Canada.

Insurance and industrial physician awareness of MER/29.

Presentation of awards or other evidence of recognition to Merrell scientists who developed MER/29.

Public education materials for MD to give to patient (perhaps a reprint from Today's Health, MD News Magazine, or a "reliable" national magazine).

PR MAILING LIST FOR MER/29

National Association of Science Writers	190
Medical journals:	
National	125
Local (county and State)	212
Hospital journals	15
Nursing journals	10
Drug trade and pharmacy	75
Newspapers	250
Canadian publications	42
Total	919

[From Sales Talk—News, Tips, Ideas, June 2, 1960]

EXTRA—MER/29 MAKES TIME

TIME MAGAZINE REPORTS ON MER-29

Time waits for no one—MER/29 is no exception. The "Medicine" section of the latest issue praises MER/29 in an article. "Cutting the Cholesterol." This issue will be in the hands of over 3 million persons. Publicity of this kind will send thousands of patients to their doctors asking about MER/29. Make sure they walk out of the offices with prescriptions.

[From Campaign Strategy—The Wm. S. Merrell Co.—Jan. 9 to Feb. 17, 1961]

USE MER/29 CLINICAL TRIALS TO PUSH "WAIT AND SEE" G. P.'S

YOUR ASSIGNMENTS THIS CAMPAIGN, JANUARY 9–FEBRUARY 17

In the doctor's office: MER/29.
In the hospital: MER/29 Cēpacol Lozenges (military).
In the drug store: Cēpacol lozenge/troche deals.
Also in the doctor's office: Idea sell, Tenuate Dospan, Simron.
Profitunities: OB products, TACE, Alertonic.

IN THE DOCTOR'S OFFICE

MER/29—MAJOR SELL

Objective: To persuade "wait and see" G.P.'s and internists to prescribe MER/29 now for at least three patients.

Materials: MER/29 patient trial kit (10 per man); new case history brochure (150 per man); supplementary materials: archives of internal Medicine Journal (Ruskin paper); direct mail and journal ad tear sheets.

It is no longer possible for you to "wait out" undecided doctors. The time for very definite forceful action is now. Such action is far and away your major responsibility this campaign.

"SICK PATIENTS FEEL BETTER" IS KEY TO CREATING DESIRE TO PRESCRIBE

By now you can identify the doctors not using MER/29. Yet, you know they should be. Very often, you know most of their reasons for not using it . . . cholesterol may not be atherogenic, desmosterol is a question mark, possible liver toxicity, doesn't work, doesn't do anything fast enough, costs too much. Doctor "X" hasn't started using it yet, Are any of these legitimate? No! From our viewpoint: we know they aren't true, we know what MER/29 can do for a person who needs it, and we know they have not stopped top MER/29 salesmen. There is no point in trying to overcome each of these objections. That's the long way around.

The quick way to get the non-prescriber using MER/29 is to use every resource you have at your command to show him that he will be benefiting himself and his sick patients in a giant way just as soon as he uses MER/29. That's any doctor's hot button . . . and you must come down on it harder than ever before.

Yes, MER/29 works by lowering cholesterol . . . doctors know this. Now, show them what they don't understand well enough yet . . . just how much MER/29 can benefit their patients!

And, you can show any given doctor five benefits of MER/29 therapy in 5 minutes.

Here are two powerful tools placed at your disposal for this important job:
1. A field tested structured presentation (with new selling aid).
2. The MER/29 patient trial program.

MER/29 STRUCTURED DETAIL

Doctor, when you are considering a course of therapy for a patient you must have good reasons for your selection. This is true in the case of MER/29. Knowing this and guessing that you have yet to decide in favor of MER/29, I would

like to summarize today, the important reasons why MER/29 should be a routine part of your treatment for patients with any manifestation of hypercholesterolemia.

First, MER/29 is a proven drug. It has been administered under controlled conditions to more than 2000 patients for periods up to three years. There is no longer any valid question as to its safety or lack of significant side effects. There is no longer any doubt about its ability to lower significantly the total sterol content of the human body.

But, here is what is most important. Here is the fact that recommends MER/29 for your routine use. You want to help sick people feel better while they are getting better . . . that is what is important to you. Mounting evidence makes it increasingly clear that MER/29, in some but certainly not all cases, affects for the better such manifestations of hypercholesterolemia as intermittent claudication, angina pectoris, myocardial infarction or ischemic ECG patterns.

As evidence of concurrent benefits obtained by lowering cholesterol in some patients, let me illustrate what I mean with some case histories which might parallel cases you see in your practice . . .

(Insert at least two case histories . . . local if you can and as many as you can . . . until he gets restless in his chair!!!)

These results are occurring not because of some temporary change, but as the Wilkins' group at Massachusetts Memorial Hospitals and others have pointed out, because MER/29 by lowering cholesterol may actually improve the adequacy of circulation.

Reports from all over the United States, to our Medical Research Department, underline that this must be the change that is occurring. We have had verified reports of improvement in anginal pain, less need for nitrates, greater tolerance to exercise, reversal of ECG patterns of a type that has never occurred before. In peripheral vascular cases, there are verified reports of lessened leg pain and ability to walk greater distances. I don't mean to infer that all . . . or even a majority of patients on MER/29 will get such results, but if you select patients whose history of hypercholesterolemia is relatively recent, there may be chances of such improvements occurring.

It will take time because the action of MER/29 is too basic to work superficially . . . but a number of these patients will volunteer, after a month or two, that the little gray capsule, taken once daily, is helping them and they're glad to be taking it.

Doctor, with such encouraging results a part of the background of MER/29, we feel it warrants personal evaluation by every physician who sees such patients. Using MER/29 need not mean doing extensive determinations when there are such direct benefits to be looked for. Because of this, I would like to recommend a course of action to you:

Select five patients from your practice with a recent history of some manifestation of atherosclerosis. As part of the therapy for these patients, initiate MER/29 one capsule daily for a minimum of two to three months. Be patient and have confidence in MER/29, and suggest to the patient that he cannot expect immediate improvement.

Then, after three months, judge MER/29 on the basis of the improvement your patients report to you. If you will do that, I'm confident you'll become one of the biggest users of MER/29 in this area—to the benefit of yourself and your patients.

FROM THE DESK OF PHILIP RITTER III

The above detail is as carefully worded, as carefully structured, as our original detail was. Again, as I did at French Lick, I ask you to follow this presentation word for word.

It represents the present ultimate in positive presentation of our basic MER–29 claims.

Please practice it until it becomes a part of your selling personality.

PHILIP RITTER III.

NEW MER/29 HOSPITAL EXHIBIT UNIT

The highly successful "Announcing MER/29" hospital exhibit unit has served its purpose and now goes into honorable retirement.

The new unit, which utilizes the permanent light box sent you with the old unit, will support your hospital exhibit detailing for the next 6–9 months.

The theme on the center panel, How MER/29 Differs from Other Cholesterol Lowering Agents, was selected because of the real need to stress the fundamental reason why MER/29 is superior. Of the products now on the market, only MER/29 has been clinically proved to lower the all-important tissue cholesterol.

The quotation on the right wing panel hits the "I'm not sure cholesterol is atherogenic" doctor right between the eyes.

"There is no question that coronary disease is more prevalent in individuals with an elevated serum cholesterol . . . A serum cholesterol below 180 mg. percent can be regarded as 'nonatherogenic,' a level above 250 mg. percent as constituting high risk."

Silber, E.; Pick, R. and Katz, L. N., Eds.: Circulation 21: 1193 (June) 1960.

This strong statement, published in a highly respected journal and written by well-known cardiologists, should go a long way toward convincing the "fence-sitters."

We expect to ship these units early in January. The light box provided with the original unit is to be used with this one too.

Continue holding MER/29 hospital exhibits as often as possible. Report after report proves they create MER/29 prescriptions in hospitals and drug stores.

[From Sales Talk—News, Tips, Ideas—Mar. 21, 1961]

SIMPLE QUESTION COUNTERS 90 PERCENT OF SIDE EFFECT QUESTIONS

We heard eight words the other day that neatly handle one of your biggest problems. When a doctor says your drug causes a side effect, the immediate reply is: "Doctor, what other drug is the patient taking?"

Even if you know your drug can cause the side effect mentioned, chances are equally good the same effect is being caused by a second drug!

You let your drug take the blame when you counter with a defensive answer. Know how to answer side effects honestly, yes, *but get the facts first:*

Doctor, what other drugs is the patient taking? Been doing it for years? Why didn't you tell us then?

BOWEN QUOTES ALEXANDER POPE TO CLOSE MER/29 DOUBTERS

Here's one that seems like a red hot idea for MER/29 . . . if it's your style. It's from Tim Bowen, Charlotte, N.C. Aimed particularly at the "wait and see" physician, Tim's close goes something like this (we got it third hand):

"Doctor, I can appreciate and admire your caution about any new drug, but MER/29 has been on the market almost a year now and was studied in thousands of patients for years before that. Its rate of use indicates that acceptance is broadening rapidly. Perhaps these words of Alexander Pope have some bearing to your consideration of MER/29: 'Be not the first by whom the new are tried, nor yet the last to lay the old aside'."

Lots of power there . . . can your style be bent just a bit to fit?

MER/29 PATIENT BOOKLET COMING . . . URGES PATIENTS TO STAY WITH IT!

"Patients won't continue on therapy" and "It costs too much" are really the same objection aren't they? To help doctors overcome these objections, you will soon have quantities of a booklet designed to accompany the first Rx and explain the rationale of MER/29. You will receive this valuable aid in April.

NEW LOOK FOR MER/29 STOCK PACKAGES

No doubt you've seen the new blue carton for MER/29 in many of your pharmacies. Soon all gray stock cartons will be replaced by "Merrell blue." The color coordinated Merrell "look" will lend prestige to the entire line of Merrell specialties on the pharmacist's shelf.

Note: MER/29 Complimentary Stock Packages will remain in gray cartons to carry out the color theme which pervades all MER/29 advertising and promotion.

MER/29 PATIENT TRIAL STUDY PAYING OFF ALREADY

We just had to buy a new file for the Orange Patient Trial cards—your response has been terrific. Here's a typical example of how the Study is helping get new prescribers. Chuck de Garmo, Los Angeles, writes that one of his "participants" is so enthusiastic about the program, he is going to increase it to about 25 patients. At the conclusion he plans to write a paper for publication. All but 3 of the patients will be paying for their MER/29. How many of your "on the fence" doctors are participating?

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