——— Mother—none of us—seek liability from your Company. It is our sincere hope that something can be done to prevent the recurrence of the tragedy to another. We feel strongly the utter lack of professional responsibility on the part of the doctor. Is it possible the man did not understand the potential effects or had insufficient advice concerning the drug from the company? Is it impractical to suggest that those to whom chloromycetin is available for administration should indicate, in writing, that they understand all of the undesirable effects the drug may produce in the human body during therapy, and after? If blood studies which are recommended during treatment could prevent a fatality, shouldn't they be mandated instead of merely recommended? Should the drug be withdrawn from a foreign market where the people entrusted with its administration may not be as professionally responsible as American doctors?

It is difficult to be objective and not allow emotions to be a part of this letter, since experiencing the tragedy of ———'s death. Her Mother, her sister and I, however, feel a compelling responsibility to write to you, the drug manufacturer to express our concern that other deaths may occur needlessly if a more responsible attitude is not taken by the maker of the drug, and the medical profession entrusted with its administration.

I will be pleased to receive a reply.

Very truly yours,

NAME WITHHELD.

Senator NELSON. This morning our witness is Dr. William C. Hewson, who is both a physician and a lawyer from Philadelphia.

Dr. Hewson, the committee appreciates your taking the time to come here and give your testimony today. I have read it and it is a very valuable contribution to the hearing record.

STATEMENT OF DR. WILLIAM C. HEWSON, PHYSICIAN AND LAWYER, PHILADELPHIA, PA.

Dr. HEWSON. Thank you, Senator.

Senator NELSON. You may proceed to present your testimony in any way you see fit. You may read it, and at any place in your statement where you feel it will be valuable for the record to extemporize and elaborate on any statement you make, the Committee will appreciate having your extended remarks. I assume you have no objection in the event that some questions occur to us during the course of your presentation.

Dr. HEWSON. Thank you, sir.

My name is William C. Hewson and I am a physician and a lawyer from Philadelphia. I attended undergraduate school at Temple University in Philadelphia and graduated from the Temple University School of Medicine in 1954. Following a year of internship at the U.S. Naval Hospital, Bethesda, Md., I served for 2 years in the Navy, following which I took a 1-year residency in the general practice of medicine. From 1958 to 1964, I was a general practitioner of medicine in West Chester, Pa., a borough of about 25,000 inhabitants, located about 25 miles west of Philadelphia and 20 miles north of Wilmington, Del. In 1964 I left the private practice of medicine to attend the law school of the University of Pennsylvania, from which I graduated in 1967. I am now associated with the Philadelphia law firm of Beasley, Albert, Hewson & Casey. That is the end of the credentials, sir.

Senator NELSON. Go ahead.

Dr. HEWSON. The marked overuse and misuse of the antibiotic drug, chloramphenicol (Chloromycetin), is now too well documented to be

gainsaid. This fact was more than sufficiently brought out by the distinguished experts who have testified previously before this subcommittee. The reasons behind this overuse and misuse pose a complex problem. I believe the blame falls on both the physicians and the pharmaceutical company involved—namely, Parke, Davis & Co., the holder of a patent on this drug until recently. This allegation of dual responsibility does not constitute a contradiction in terms, for the attribution of fault to one party need not exculpate the other. That may be a little inartistically put, but I think all I am basically saying is the fact that it is a prescription drug and that the physician makes the final decision as to whether to dispense it, does not create a mantle to protect the drug company completely. I think the rest of the statement elucidates that concept to some degree.

Even though a drug is available only on a physician's prescription, a drug house may be guilty of overpromotion of the product to the point of misleading the members of the medical profession as to both the indications for, and the restrictions on, its use. At the same time the ordering physicians may be aware to some degree of the potential untoward effects of the drug and yet prescribe it inappropriately, in disregard of that knowledge. In the California case of *Love* v. *Wolfe* and in our recent Philadelphia cose of *Incollingo* v. *Ewing*, both the prescribing physicians and Parke, Davis & Co. were found liable for the negligent administration of Chloromycetin to patients who subsequently died of aplastic anemia. That is from the effect of the blood on the bone marrow of these patients.

Senator NELSON. These were cases in which the prescription of the drug was not indicated.

Dr. HEWSON. That is correct. In both cases its use was for quite minor conditions.

Senator NELSON. What were the dates of the prescription of the drug—not the trial of the case—but when was the drug prescribed for the patient? In what years?

Dr. HEWSON. In Philadelphia it was prescribed in October of 1958, in July of 1959, and in January of 1960 for a little girl who was 4 years old in January of 1960. Then, there were additional prescriptions by phone, upon which I elaborate more later, during the months of February, March, and April of 1960. Then she came down with full-blown aplastic anemia in May 1960.

Senator NELSON. And in the *Love* case?

Dr. HEWSON. I believe that goes back to 1958, Senator.

Senator NELSON. Both of these cases were several years after knowledge was available as to the serious side effects of this drug.

Dr. HEWSON. Yes, sir. They both came well after the 1952 publicity and subsequent warning and they both came before the 1961 warning was placed on the literature accompanying the drug.

In the *Love* case the physician ordered courses of Chloromycetin for the plaintiff, Carney Love, for two conditions, first for infected gums and then for bronchitis.

Senator NELSON. Was there anything definite in the case to demonstrate that the drug was indicated for these cases because of the seriousness of the infection?

Dr. HEWSON. Senator, I do not have all the trial testimony of this

case. I have the appellate opinion only. They are not readily available to us. But, I do not believe so.

Senator NELSON. But they were found liable in any event.

Dr. HEWSON. There were no cultures taken to establish that it was a resistant infection.

In the *Incollingo* case a pediatrician prescribed Chloromycetin for Mary Ann Incollingo on three occasions for infected throat and tonsils; a second physician renewed Mary Ann's prescription by telephone on at least two occasions, without seeing the patient, for minor respiratory complaints. The two cases differed in that the prescribing physician in the *Love* case testified that he had been misled by the Parke, Davis advertising and detailing, while the initial prescribing physician in the *Incollingo* case stated that he was fully aware of the dangers inherent in the use of Chloromycetin and was not misled by the Parke, Davis promotional methods.

Mr. GORDON. If I am not mistaken, in the *Love* case the court held that the vigorous promotional campaign by Parke, Davis Co. canceled out any written warning that the firm may have given. Is that correct?

Dr. HEWSON. That is correct. That case was remanded once, has been up on appeal again and Parke, Davis' promotional methods have held that company in for something, I think, in the neighborhood of a $185,000 verdict. But it had been remanded for the second time to try the physician again. The two positions were not held to be mutually exclusive, and the doctor can be held negligent, also, despite the fact that Parke, Davis has already been deemed negligent for its promotional methods. In other words, he cannot hide behind the Parke, Davis promotional methods.

Mr. GORDON. Is it correct that the court held that proof of the sales of Chloromycetin expressed either in grams or dollars was relevant to show a motive or reason for the alleged promotion of the drug which is a definite issue in the case?

Dr. HEWSON. That is correct. That is an evidentiary problem—how relevant is the fact that they sold so much of the drug and so much of it was prescribed. It was held to be relevant in the sense that it might show a motivation or an intent to push the drug on the medical profession, to augment its sales.

Mr. GORDON. Thank you.

Dr. HEWSON. The renewing physician in *Incollingo* did testify that the drug company's promotional methods had misinformed him as to the proper use of the drug. In both cases the pharmacist who filled the prescription was exculpated. The rationale of those decisions, holding the prescribing physicians and the promoting drug company reprehensible, is not only acceptable but correct, in my opinion.

In *Incollingo* the alleged negligence of Parke, Davis & Co. was bottomed on the theory that the company had in effect, by its overpromotion of Chloromycetin, set the standard for the medical profession for the use of that drug during the period from its first introduction on the market in 1948 until its prescription for the plaintiffs decedent in 1958, 1959, and 1960. Because of Parke, Davis advertising and detailing methods, it was argued, physicians had been misled into using the drug indiscriminately, in disregard of the potential toxic effects of the antibiotic, for conditions where drugs of lesser toxicity

should have been used. Thus, the widespread, irresponsible prescription of Chloromycetin, although apparently accepted by a majority of the medical profession, was not reasonably prudent, or legally condonable, use of the drug. In other words, the general use of the drug was deemed not to be accepted legal use. The usual legal standard of the act of the reasonably prudent man under the circumstances was not met. These were not reasonably prudent physicians, nor was this reasonably prudent use of the drug. At least the jury so found.

Historically, Chloromycetin was first introduced in 1948 as a broad-spectrum antibiotic of great efficacy and minimal side effects.

Senator NELSON. It is still so advertised; is it not?

Dr. HEWSON. It is still very much so advertised, and I think every one has testified that it is a very effective drug, but that does not mean it should be used widely. There are other effective drugs, probably almost nearly so effective, and without the serious side effect of toxicity to the bone marrow.

Unlike the tetracyclines—Terramycin, Aureomycin, et cetera, which were also broad-spectrum antibiotics, Chloromycetin caused little gastrointestinal upset. Also, it was more effective in the treatment of certain diseases, such as typhoid fever. Sales of the drug increased markedly from 1949 to 1952. However, reports of aplastic anemia resulting from the use of the drug appeared during that time, and the Federal Food and Drug Administration asked the National Research Council to submit a report on the toxic aspects of this antibiotic. The National Research Council, which was composed mainly of eminent physicians, I believe, recommended that a warning be placed on Chloromycetin containers and the circular within. Parke, Davis & Co. followed the recommendation of the Food and Drug Administration; but the warning was required only on the circulars accompanying the injectable preparations, which are actually seldom seen by the prescribing physician. The injectable form of Chloromycetin is used in hospital practice for the most part; so that only the pharmacists were exposed to the FDA warning. The modified warning which Parke, Davis placed in most, but not all, of its promotional literature for Chloromycetin was weakened or diluted in at least five aspects from the recommended statement.

Senator NELSON. Are you saying that the injectable preparations are not used very often in physicians offices?

Dr. HEWSON. That is correct. The injectable preparation at that time had to be used every 4 to 6 hours and, even as a starting dose, it was not feasible to use it in office practice. A later preparation was to be used every 12 hours or even 24.

Senator NELSON. Is it still more commonly administered orally in office practice than it is by injection?

Dr. HEWSON. Oh, yes; very much more.

Senator NELSON. It is a tablet; is it not?

Dr. HEWSON. It is a capsule or a liquid pediatric preparation.

Senator NELSON. The package insert which contains the warning goes directly to the pharmacist at the drugstore; does it not?

Dr. HEWSON. Senator, from 1952 to 1961 there was no circular with the oral preparation. After 1962 it was required with the oral preparation, also; but that still goes to the pharmacist and he dispenses it without the circular enclosed, of course.

Senator NELSON. Well, are you saying after the drug was taken off the market in 1952 and then went back on to the market that the package did not include a package insert to the pharmacist between that period and 1962?

Dr. HEWSON. That is correct. First, I do not believe the drug ever was actually taken off the market and then the warning that was required by the FDA, and this was a Parke, Davis defense, too, stated that the warning was not required in the oral preparation and so was never put in until it was required by the FDA in 1961. The inference I get was that the FDA did not have the power or the authority to require it to be in the oral preparation until 1961.

Senator NELSON. There must have been some form of package insert that described the use of the capsule in the package to the pharmacist; was there not?

Dr. HEWSON. My understanding is that no package insert was required in the oral preparations. At least the warning was not required in that type, if there was one.

Senator NELSON. That puzzles me a little bit. It would seem to me that some insert would have to be in there to explain what the drug was used for even if it did not contain a warning.

Dr. HEWSON. Of course, this is a prescription drug, Senator, and a physician has to prescribe the use for it. The pharmacist, of course, should be aware of correct dosage, but in general it is on the prescription as the physician writes it.

Senator NELSON. So now, there is a package insert required and the package insert contains the warning; does it not?

Dr. HEWSON. Since 1961. Also the boxes, the small individual packages, had a one-sentence warning on it even as far back as 1952.

Senator NELSON. Now, if the doctor is not dispensing it himself out of his own office, how does he get the warning as to the side effects of this drug?

Dr. HEWSON. Well, first, most physicians do not dispense oral preparations of the drug in the office and they do not use the injectable form. I believe Parke, Davis did send out letters to 200,000 physicians in 1952 about the FDA investigation. Another source of information can be the advertising. Also, it can come from detail men. It can be from the Physicians' Desk Reference, which is sort of a bible to the practicing physician, although it really contains the literature on a drug as the drug company itself presents that information. It is really an advertising mechanism essentially. The wording does not come from an objective source. It comes from the drug companies. Probably the best and most reliable source is the objective medical literature, case reports, et cetera.

Senator NELSON. So the doctor who prescribes the drug does not regularly see the warning on a package insert because he does not see the package?

Dr. HEWSON. That is correct.

Senator NELSON. So, his source of information is medical literature and/or the advertising by the company and the detailing by the detail man; is that correct?

Dr. HEWSON. Correct. Yes, sir.

Mr. GORDON. Dr. Hewson, do you know of any cases where Parke,

Davis, either in letters to doctors or in advertising, adopted warnings on its own?

Dr. HEWSON. Oh, yes. After 1952, when the FDA warning was required on the package inserts and in the cautionary statements on the boxes, Parke, Davis did include a warning on most of its promotional literature, but not on all. This was not the same type—not the same warning, in effect, and certainly not in the same words that the FDA recomended.

Mr. GORDON. It was required by the FDA; was it not?

Dr. HEWSON. I do not believe so.

Mr. GORDON. Adopted on their own?

Dr. HEWSON. That is right. They did adopt it on their own but they did not adopt the FDA warning. Their warning, and that was one of our arguments in the *Incollingo* case, was considerably diluted or watered down, weakened. In at least five aspects we felt it was changed and our experts so testified.

Senator NELSON. Was the FDA warning just a suggestion to the company?

Dr. HEWSON. That is the way I read it, a recommendation, and they could only recommend it for the package inserts with the parenteral forms and for the enclosing boxes. Parke, Davis, itself, had to put it, of its own volition into its advertising, but they chose to present it in a changed form.

Senator NELSON. Did the law not authorize FDA to require warnings approved by them?

Dr. HEWSON. The warning which they put in their literature?

Senator NELSON. Yes.

Dr. HEWSON. No.

Senator NELSON. In their advertising, either?

Dr. HEWSON. I am sorry. That is what I meant by their literature, too. Yes; did not require them to put——

Senator NELSON. Are you saying the FDA——

Dr. HEWSON. We are talking about the period 1952 to 1961?

Senator NELSON. Yes.

Dr. HEWSON. Correct.

Senator NELSON. The FDA during that period did not have the legal authority to veto any specific advertising, so to speak, or to require any specific language in the advertising between 1952 and the Kefauver-Harris amendment in 1962; is that it?

Dr. HEWSON. I understand they had a recommendatory authority only. They did not have the legal power to require it.

Senator NELSON. Have you studied the law as to what authority they now have?

Dr. HEWSON. No. I know only of what it is from 1962 from reading the cases and listening to the Parke, Davis defenses.

Mr. GORDON. Can you tell us the five aspects in which Parke, Davis watered down, diluted the FDA warning?

Dr. HEWSON. Oh, yes. The FDA warning began with the statement certain blood dyscrasias have been associated with the use of Chloromycetin.

Senator NELSON. Now, this is the suggestion that FDA made?

Dr. HEWSON. That is correct. This is what was put on the boxes and in the circulars with the parenteral forms of Chloromycetin. The first

change that was made was that Parke, Davis started their warning with "Chloromycetin is a potent therapeutic drug" which, we argued, is a self-serving statement which tends to dilute what follows.

Also, in their warning they did not delineate the specific blood dyscrasias which were parenthetically enclosed in the FDA warning. In the part of the warning that referred to the taking of blood studies to determine bone-marrow changes, they added the phrase "as with certain other drugs," tending to equilibrate the toxicity of Chloromycetin with certain other unspecified drugs.

The FDA warning contained the words, relative to the required blood studies, "It is essential." The Chloromycetin warning deleted "It is essential."

The FDA warning was required to be placed at the top of the literature in the injectable circular. The Parke, Davis warning was usually placed well down in its advertising in relatively small print.

Following the 1952 investigation by the National Research Council and the ensuing warning, sales of Chloromycetin dropped precipitously. However, recovery was successful to the degree that the sales in 1960 were greater than the peak of any previous year. In 1960 enough Chloromycetin was sold to provide courses of therapy for nearly 4 million persons.

Senator NELSON. What is your estimate of the number based upon?

Dr. HEWSON. That, I believe, came from the Kefauver investigation.

Senator NELSON. I see.

Dr. HEWSON. There is literature on this. There are graphs which show these sales.

These sales were made despite the statements in leading journals from knowledgeable physicians and from American Medical Association councils that the drug should be used only for typhoid fever and other salmonella diseases or for diseases caused by organisms proven to be resistant to other, less potentially harmful, anti-infective agents. The increased incidence of staphylococcal infections in the middle and late 1950's account for but a small part of the resurgence in the use of Chloromycetin; for staphylocci had been shown to develop resistance to it, and other, more effective, and less seriously toxic antibiotics were developed to combat these bacteria. The enthusiastic promotion of Chloromycetin by Parke, Davis & Co. apparently played a significant role in the increased use of the drug.

The advertisements for Chloromycetin emphasize its great versatility and effectiveness, along with its ready tolerance and minimal side effects. And that applies to the advertising today.

This approach by Parke, Davis became evident soon after the FDA recommended the addition of the 1952 warning to the Chloromycetin literature. In Parke, Davis' "President's Letters," "Director's Letters," and "Ideas and Suggestions" to its promotional staff, as well as in its advertising, Parke, Davis asserted that the indications for the use of Chloromycetin were unchanged—this is after 1952—that it was still the most effective and versatile antibiotic, and that it was well-tolerated, with rare side effects. The statements inferred that the toxicity of Chloromycetin was akin to that of other drugs. Appeal was made to the doctor to base his evaluation of the drug on his past experiences with it. Detail men were to use a positive approach in

dealing with physicians and to discuss the untoward affects only if the physician raised the question. The fact that a causal relationship between the use of Chloromycetin and the development of aplastic anemia had not been scientifically proven was emphasized. This latter argument was set forth despite the summary of the FDA report of 1952 which stated that—

> From the data available from case records secured in this survey, it appears beyond a reasonable doubt that chloramphenicol, in certain susceptible individuals, causes blood dyscrasias, including aplastic anemia, thrombocytopenic purpura, granulocytopenia, and pancytopenia.

All of which are conditions of severe bone-marrow depression.

Similarly, in April of 1960 a report by the Subcommittee on Blood Dyscrasias of the Committee on Research of the American Medical Association published a cautionary reminder to the medical professions in the AMA Journal on the potential ill-effects of Chloromycetin on the blood-forming system. The report decried any possibility of a mere "chance association" in the case reports of aplastic anemia allegedly caused by Chloromycetin and concluded that there was no longer even a reasonable doubt that the drug could cause aplastic anemia. Making note of the widespread, indiscriminate use of Chloromycetin, the report called for judicious use of the antibiotic and stated that it should not be used prophylactically, in trivial infections, or in infections in which other, less dangerous antibiotics might be used effectively. This was the same year that Dr. Dameshek pleaded similarly to the profession in an AMA Journal editorial in which he reported four new cases of aplastic anemia (which he saw in 1 month, incidentally), as a result of Chloromycetin therapy for minor respiratory infections. It was also the same year, 1966, that enough Chloromycetin was sold and prescribed to treat nearly 4 million patients.

Such case reports and the inevitable conclusions therefrom must have, or should have, been known to Parke, Davis & Co. and to the medical profession in general. Yet, the Chloromycetin advertising was not altered until the second FDA warning became required in 1961. This warning was more specific, more forceful, and more detailed in its wording; and it was to be boxed and placed in a prominent position in the advertising. However, the tenor of the advertising and detailing did not change; emphasis was still placed on the broad-spectrum-type effectiveness of the drug, although its toxicity was documented in more detail. Obviously, as the huge sales of Chloromycetin since 1961 indicate, this change in the written advertising has not been an adequate deterrent to the indiscriminate use of this antibiotic. The small number of cases where Chloromycetin is specifically indicated can justify only a fraction of the doses prescribed. Undoubtedly, the fact that this unfortunate pattern for the clinical use of Chloromycetin has already become established plays a role in its continued administration (which serves to emphasize the importance of proper education of physicians in the initial period of a drug's availability); but more important, I believe, are the factors of drug detailing and physicians' inertia.

Mr. GORDON. When you talk about educating a doctor in the initial period of a drug's availability, have you any idea how this should be done and who should do it?

Dr. HEWSON. Well, certainly it is a crucial period because many of the side effects such as bone marrow aplasia do not show up for several

years or do not get well documented enough for everybody to become aware of it. Certainly, the most common source of information to the physician is the drug company through its advertising, through its detailing, and through the Physicians' Desk Reference.

Most desirable, of course, would be a more objective source of information, a less enthusiastic source, not so filled with accolades to its effectiveness but giving a more thorough discussion of its potential toxicity or its side effects and their incidence. I do not know whether the FDA could undertake this or whether some local type of educational system could be set up, but certainly the detailing and other advertising and promotion should be on a more objective basis.

Senator NELSON. Given the natural inclination of any company to increase its sales, is it really practical to rely upon a salesman of a product to accurately and scientifically inform the physician? It has not worked in this case.

Dr. HEWSON. No, I do not believe it is. Certainly, there is a large pecuniary interest involved. The detailing is done by nonprofessional men who are still basically salesmen. Even though maybe they may not realize it, they are dealing with life and death rather than with just sales of a product which is innocuous. These drugs are all potentially toxic and Chloromycetin more so.

Senator NELSON. When you consider that even as late as 1961, when the FDA quite belatedly, given all the information they had since 1952, insisted upon, under the law, a more specific warning; and given the fact that very distinguished hematologists such as Dr. Dameshek now of Mount Sinai Hospital were giving warnings to physicians, is it not clear that there is some rather dramatic breakdown in communications between the people who are informed about the drug and those who are prescribing it?

Dr. HEWSON. Yes. I think there is no doubt about that. I think the advertising, if we can use the term "overpromotion," may get the drug started on its misuse and then I think your communications, your chances to get through, probably are eliminated and I think the detailing can maintain the misuse and abuse. Despite the 1962 warnings, sales have stayed very high for chloromycetin and I think that speaks to what you have said and affirms it. But, from here on I go to the detailing and to the physician's role, which is more important than what the drug company puts down in black and white because the detailing is on a very personal, usually two-man level, in a closed room; and it is much more difficult to control. Then, of course, we must consider the role of the physicians who do make the final decision of whether the drug should be used; I think we have to look at them carefully—the role they have played and what they have done in this unrestrained use of the drug.

Senator NELSON. But, given the circumstance that the whole medical profession, that is, at least those informed about the drug, and AMA, and FDA, were well aware for years that the drug was being overprescribed—whatever fault there may be with the busy physician who is reading the clever advertising, and certainly there is some—is there not a grave responsibility that rests upon the medical profession itself, the American Medical Association, and the Government, the Federal Food and Drug Administration to remedy the situation.

Dr. HEWSON. Yes. I agree with you wholeheartedly, but I think the phrase you used, those who are informed, is the key to it. I think that certainly Dr. Dameshek and Dr. Weston, hematologists, good internists, stay well informed. They are academically oriented, but I do not think that speaks to the average physician. I think there is a communications breakdown. I do not think the AMA could communicate that well with the average physician, and certainly I do not think the drug companies would or could.

Senator NELSON. Is it not true that every major teaching hospital, at least, and every major first-rate hospital in every State of America for years has been very careful about the prescription of this drug and the prescription of it in such hospitals is at a much lower rate than it is outside of that hospital?

Dr. HEWSON. That is correct, and I think that goes along with my position—that the physicians out in practice, the ones performing the great amount, rendering the great bulk of medical care in the country, do not stay well informed, that your teaching hospital physicians are the vast minority of the physicians involved in giving medical care in this country.

Senator NELSON. But if that is the case, to remedy it then, do you not have to give to the FDA and the major medical societies some kind of a responsibility here for noting so if that is not done? Are you not going to have to have some change in their practices or legislation respecting this kind of a problem drug?

Dr. HEWSON. Yes. No doubt you would have to mitigate or obviate the influence of the over-promoting drug company and still you have to control on the other hand, the prescribing physician, the everyday average prescribing physician.

My own thought would be that the most workable solution would be to limit it to hospital practice where you could have a committee, even a one-man committee, determine when the drug should be used.

As for control by a governmental agency or though legislation, I am sure that could be tried. I do not quite know how they could exert a complete control and still leave the drug in the hands of everyday physicians. And this does not speak just of Chloromycetin. Certainly, I think your investigations will probably put Chloromycetin in its rightful medical place, at least I hope so; but this is 20 years since the drug came on the market and certainly we have to worry about the next Chloromycetin. And other drugs are certainly misued and abused, but the side effects are not so dramatic. When you get aplastic anemia your chances are 50 to 75 percent that you will die. The side effects of other drugs, such as anaphylactic reactions to penicillin, have a much higher survival rate. Or the side effects of a potent drug like cortisone; they are usually reversible on stopping the drug.

Senator NELSON. I note in reading Drs. Goodman and Gilman on chloramphenicol, they are quite specific in stating that it should be administered only in a hospital except in very special cases where there is an agreement between the patient and the doctor that the blood studies will be made, as I recall, once every 48 hours.

Dr. HEWSON. I am sure you have heard testimony to the effect, Senator, that these blood studies probably are not reliable, that the immediate depression of the bone marrow does not reflect that long-term

depression, that there are two actual effects, and the long-term one is just unpredictable. It shows up months later, ususally. And by then the damage that is there is probably irreversible, and whether or not you are going to survive depends on how much your marrow has been affected.

Certainly, if you see early changes you are going to discontinue use of the drug, but no one has proven that is an adequate preventative measure.

Senator NELSON. But all the experts do recommend regular blood studies during the administration of the drug, do they not?

Dr. HEWSON. I think so. But as a prophylactic measure this has not been proven. Certainly one would give the patient the benefit of the doubt; but, if you will notice, even the second FDA warning states that blood studies may not be adequate to prevent damage from the drug.

Senator NELSON. Go ahead.

Dr. HEWSON. In considering the physicians who have ordered Chloromycetin in patently excessive and unrestrained fashion, one must initially recognize that most of the medical care is rendered in the United States by physicians who do not limit their practice to one field of medicine. And, we might add, who are not in the academic-oriented environment of the teaching hospital or medical school. They are busy practitioners with limited time for reading and keeping abreast of the multiple fields of medicine which their practices encompass. They do not, and possibly cannot, take time to read the current medical literature or attend medical meetings and lectures. If medical journals are read, the advertising is often skipped over in order to peruse any articles of interest. A short talk from a detail man—Dr. Dameshek in his 1960 editorial refers to them as our medical profession's ubiquitous mentors. A short talk from a detail man is much more pleasant and feasible than a search of the literature to gather information about a particular drug. These sales representatives of the pharmaceutical houses are usually pleasant, personable individuals. They generally offer samples of drugs as an inducement to gain entrance to the physician's office. Although not professional men, they do come with the approbation of a large, respected company and with apparent firsthand knowledge of the drugs they detail. They offer an easily accessible source of information on new drugs.

Most physicians are undoubtedly aware of the positive, salesmanship approach of these representatives of the drug company. Their enthusiastic accolades to the drug being promoted are not accepted at face value by the physician, who undoubtedly takes this promotional technique into consideration when making the crucial decision of whether, on balance, the therapeutic effectiveness of the drug outweighs its potential deleterious effects in a given clinical situation. This difficult balancing decision is obviously impaired if the physician is not made adequately aware of the drug's side effects. The great disservice of the detail men is not in their exaggeration of a drug's beneficial uses but in their approach to its toxic effects. Commonly, the toxicity is not discussed thoroughly, is played down, or is not even broached. The otherwise uninformed physician is thereby grossly misled. Although he may recognize and allow for the affirmative ap-

proach of the detail man, the doctor may yet be instilled with unwarranted reliance if the toxic potential of the drug is not made known to him. The withholding of facts which may make the difference between life and death cannot be justified by the label of "sales promotion"; nor can the failure of the physician to seek complete data on a drug be accepted.

Mr. GORDON. What can you do about this?

Dr. HEWSON. Shall we go into that now? I think the remedy is the last part of the discussion. And it is the most difficult part, I agree.

Mr. GORDON. All right.

Dr. HEWSON. In my own experience as a general practitioner, I do not recall the Parke, Davis detail men ever discussing the relationship between administration of the drug and the development of blood dyscrasias, other than on one occasion when I asked about the present incidence. I was told that it was still quite rare. One of our experts in the *Incollingo* case stated that these detail men were so uninformed about the toxicity of Chloromycetin that he took it upon himself to give them a lecture on the subject. Another expert in the *Incollingo* case testified that he had been lecturing—he was a hematologist—he had been lecturing on aplastic anemia and the fact that he had four cases of it which he attributed to Chloromycetin. Several men, I believe three, from the administrative end of Parke, Davis came to visit him personally to ask what his data were and how well documented they were with the inference being that the relationship had never been proven.

Two of the physicians to whom I have talked stated that Parke, Davis detail men became at least annoyed when they were interrogated on the subject of blood dyscrasias from Chloromycetin. I have talked to one former Parke, Davis detail man who told me that he was instructed to discuss the effectiveness of the drug affirmatively and to approach the subjects of its side effects only if asked; then he was to relate only the incidence as given to him by the company and to refer any further questions to someone in Detroit. Of the many physicians that I have talked to with regard to these detailing methods not one has stated that the Parke, Davis man voluntarily brought the toxicity to the physician's attention. In my own practice I did treat the family of a Parke, Davis detail man, and on one occasion he told me that he was giving his child Chloromycetin, on his own, for a painful ear. Apparently he, too, was misinformed about the drug's potential toxicity.

The physician may be misled, then, by overpromotion in the detailing and the advertising of a drug (including the information in that old standby, the Physicians' Desk Reference, which contains the pharmaceutical house's promotional literature on its drugs) if he does not attempt to remain knowledgeable by referring to other more objective sources. Even if he becomes cognizant of the dangers of a drug, he may continue to prescribe it on the basis of his own safe experience with its use—a criterion which Parke, Davis has recommended.

Physicians who do not practice a limited specialty and who are away from the stimulating intellectual atmosphere of a teaching hospital are prone to become lulled into mechanical, unchanging treatment by the absence of unhappy results from its use.

Unfortunately, a drug is often in great popularity before an adequate test of clinical use and subsequent case reports clarify the dangers attendant to its administration. If the side effects are acknowledged, emphasis on the statistical relationship—1 case of aplastic anemia for every 400,000 courses of the drug, which was the 1952 estimate; and, then at the Kefauver hearings, it was 1 in 225,000; and now, I believe, the next reference is to that, of even 1 case for every 22,000 courses—may make that untoward reaction seem too remote to be of concern in a given case.

In addition, the pressure by patients for one of the antibiotic "wonder drugs" is not without its influence on many practitioners; for the lay mind has become imbued with the belief that these antibiotics are a panacea for all types of infections, major or minor, bacterial or viral. Many patients even know the name of the drug which helped them, or helped someone known to them, in the past.

The average physician, then, intelligent and well-trained, but still subject to human frailties, is not unaffected in his decisionmaking by such influences as the promotional activities of drug companies, the cajoling of his patients, and the apparent safety of statistics top weighted in his favor.

Any effective remedy to the problem of misuse and overuse of drugs must not only assure proper education of the prescribing physician but must also provide for prescription by physicians who will not be misled into improper use of the product. The method most likely to overcome the indiscriminate use resulting from overpromotion by the pharmaceutical house and from physician error is to confine its administration to the hospital environment, where it could be ordered only with the approval of a select physician, or a committee of select physicians, who would be most likely to be well aware of its indications, contraindications, and potential toxicity.

Since the only valid indications for the use of chloramphenical are limited to typhoid fever and other salmonelloses, and in other infections where drugs of lesser toxicity are shown to be ineffective, the relatively few patients with these conditions could easily be required to undergo hospitalization for treatment with the drug. The chronic state of typhoid fever, which requires prolonged treatment and would, therefore, be impractical for hospitalization throughout therapy, no longer requires treatment by chloramphenicol. I think this is akin to what we do now for cases where we think someone should undergo a therapeutic abortion or sterilization. Such a procedure requires the approval of a select committee, and I think it is more workable possibly than some administrative control.

Senator NELSON. Who would decide which of the drugs on the market should be placed in this special class and should be administered only in hospitals and/or with the approval of a committee of physicians?

Dr. HEWSON. Oh, I think that would well fall within the area covered by the FDA. I think they do the most studies on toxicity and use of drugs and indications and contraindications. It would not be a long list of drugs, I am sure.

Senator NELSON. Are you suggesting that the FDA, then, in consultation with experts in the medical profession, should be authorized

to agree upon what class of drugs should be placed in this special category?

Dr. HEWSON. Yes. I think the threshold decision of which drugs are to be placed in that category should come from the FDA, and I am sure they would make use of expert consultants from the profession.

Senator NELSON. They do not have that authority now.

Dr. HEWSON. I believe not.

To require a report on all cases of aplastic anemia or even of diseases treated by chloramphenicol from the individual physician would not be conscientiously followed, as our experience with venereal-disease reporting has shown. The procurement of more accurate evaluation of the incidence of blood dyscrasias following the use of chloramphenicol, as from hospital reporting, would be academically helpful but doubtfully help curtail use of the drug by the average practitioner, and probably would not be conscientiously followed. Placing the drug in the hands of the academically oriented, knowledgeable specialists, some of whom are available to virtually all hospitals, should be an effective, workable resolution of the problem.

That is the end of my statement, Senator.

Senator NELSON. If you are correct—and I assume you are—that the FDA presently does not have the authority to consult the profession and designate such a special category of drugs that should be administered only in hospitals or under specific circumstances, would you recommend that legislation be passed to authorize the FDA to do this?

Dr. HEWSON. I have never researched it, but I do not know of a drug being placed in such a category; so I just assume—it has never come up legally in my experience—that they do not have the power. Yes; I think it would be a most worthy addition to our control of drugs to authorize that power.

Senator NELSON. I do not know whether or not you read Dr. Dameshek's testimony.

Dr. HEWSON. Yes; I did.

Senator NELSON. Two weeks ago he made a similar type of recommendation. And so did Dr. Lepper. Both suggested that some kind of limitation of supervision over its administration be required.

Dr. HEWSON. Definitely. As I say, I feel it has to be controlled from both sides. I think the physicians have to be controlled as well as the drug company and its promotional methods.

Mr. GORDON. Dr. Hewson, on page 5 you referred to Parke, Davis' "President's Letter," "Director's Letters," "Ideas and Suggestions" to its promotional staff, et cetera. I wonder if you could give these to us for insertion into the record at this point.

Dr. HEWSON. Certainly. I have them with me.

(The documents referred to follow:)

MARCH 12, 1952.

Newspapers recently carried a story of two children's deaths allegedly as a result of antibiotic therapy. One of two products mentioned was Chloromycetin. Within 24 hours retraction was made based upon more thorough investigation.

Rich, et al., [Ann. Int. Med. 33:1459 (Dec.) 1950] described clinical, laboratory, and autopsy findings in a patient who developed aplastic anemia while on Chloromycetin therapy; Herrell of Mayo Clinic [Amer. Journ. Surg. 82:638 (Dec.) 1951] cites the Rich report, and not any experience of his own, as basis for his generalizations against the use of Chloromycetin; and Loyd [Antibiot,

and Chemother. 2:1 (Jan.) 1952] states in the title that his patient's aplastic anemia is "due to chloramphenicol" but in his conclusion is less positive, stating only the obvious, that it "appears that the blood dyscrasia followed prolonged administration of chloramphenicol". We are aware of some additional cases, some of which may be the subject of a report. In an exchange of letters on these, one of the authors who plans to publish stated "Admittedly proof that Chloromycetin caused the aplasia is lacking. The evidence is only circumstanial".

We will not criticize these reports and others which may appear from any viewpoint except to point out that they are based on the premise that as one event precedes another in time, there is a cause and effect relationship. One must realize that this is only the first step in such reasoning. The fact that a drug was administered prior to development of aplasia is by no means proof that the drug is the offender. At this time, there are absolutely no cases known to use in which such proof is existent.

We have had similar experiences with both Mapharsen and Dilantin when they were first introduced commerically and the same problems have been encountered with streptomycin, the sulfonamides, thiouracil and others; therefore, the present situation is not entirely unexpected. We are increasingly convinced of the clinical superiority of our product as demonstrated by the many millions of doses given throughout the world during the past several years. Clinical investigation of the effects of Chloromycetin on body cells and functions is continuing and several additional studies were recently initiated, but, to repeat, up to this date we cannot find any facts that will indicate that Chloromycetin causes aplastic anemia or agranulocytosis.

It is recognized that the publications referred to frequently give rise to inquires from your customers and that this problem is further complicated by the unethical tactics being employed by representatives of certain competitors. With respect to the former, it is recommended that you reply to such inquires in harmony with the comments contained in this letter. With respect to the latter, you may be assured that we will not stoop to combat this type of competition but will continue to detail Chloromycetin on its demonstrated merits.

The primary concern of Parke, Davis & Company has always been and always will be to develop and sell only drugs which will protect or promote health and to advance the cause of medicine. We are continuing to adhere rigidly to those precepts.

Sincerely,

H. J. LOYND, President.

PRESIDENT'S LETTER NO. 1—JUNE 6, 1952

The New York Times of May 23, 1952, carried a story under a Boston date line to the effect that Dr. Louis Weinstein, chief of the Infectious Disease Service, Massachusetts Memorial Hospitals, told more than 2,000 physicians attending the 171st annual meeting of the Massachusetts Medical Society that he knew of forty cases in the country in which chloromycetin had produced "very severe depression in the bone marrow".

That same day, at my suggestion, Dr. Gray wrote Dr. Weinstein asking him to produce whatever evidence he might have in support of the statement attributed to him.

Dr. Weinstein's reply is reproduced verbatim herewith:

MASSACHUSETTS MEMORIAL HOSPITALS,
JOHN C. HAYNES MEMORIAL,
DEPARTMENT OF INFECTIOUS DISEASES,
Brookline, May 26, 1952.

J. P. GRAY, M.D.,
Parke, Davis & Co.,
Detroit, Mich.

DEAR DR. GRAY: I have your letter of May 23rd inquiring with respect to the statement in the New York Times concerning my remarks on bone marrow depression produced by chloromycetin. In the first place, I have no manuscript of my talk since it was given mainly from notes. I did not make the statement that I *knew* of 40 cases. The statement I made was, "It has been said that there are somewhere around 40 cases of severe depression of bone marrow which have

come to the attention of various doctors in the country." I am fully aware of the reports in the references which you write me about. Most of the information that I based the *few* remarks that I made about chloromycetin at the Massachusetts Medical Society on was obtained from a discussion with Dr. Joseph F. Ross, the hematologist to the Massachusetts Memorial Hospitals. Some of the information which he gave me with respect to the instances of bone marrow depression is strictly confidential, and *none* of this was cited specifically in the talk that I gave. Dr. Ross himself has one patient who developed pancytopenia which was apparently related to chloromycetin. Dr. Ross tells me that he has knowledge of instances in which bone depression appeared to be produced by chloromycetin other than the case with which he had personal experience.

I might point out to you that I am rather surprised by the attention which my remarks on chloromycetin drew because this part of my talk occupied no more than about two minutes out of the total of twenty which I spent discussing the untoward effects of all the antibiotics. As a matter of fact, in discussing chloromycetin I pointed out that the few cases which have been reported should not keep physicians from using this drug in any instances where it was indicated but that in patients receiving chronic chloromycetin treatment, it would be wise to examine the blood once or twice a week. This is in agreement with the statement made in the article in the J.A.M.A. of last week in which were reported two instances of bone marrow depression which were thought to be related to chloromycetin administration. I pointed out at the meeting, also, that we have not and do not intend to give up using chloromycetin on my service at the Haynes Memorial Hospital in any instances where this agent was indicated.

I hope this gives you the information you would like.

Sincerely yours,

LOUIS WEINSTEIN, M.D.

(Dr. Gray has written Dr. Joseph F. Ross, mentioned in the above letter, but a complete report has not been received from him to date.)

* * * * * * *

If you are asked about the attitude and position of the Food and Drug Administration, I know you will be interested in this statement taken from the Washington Report on the Medical Sciences, Number 259, May 26, 1952:

"Dr. Henry Welch, chief of antibiotic division, pointed out that evidence clearly fixing culpability on chloramphenicol is still lacking, many of the two score affected patients having been on other drugs as well. He observed further that followup studies conducted at Gallinger and Childrens Hospitals in this city 'have disclosed no resultant anemias, also that the 40 cases reported nationally represent a statistically insignificant ratio of 1/400,000."

* * * * * * *

We are interested in facts, not rumors, and this letter is written with one purpose in mind, namely to give you factual information to present to any physician, pharmacist or hospital official who might bring up the question. In such cases, please show them this letter and make sure that it is read in its entirety.

Yours very truly,

W. J. LOYND, *President.*

[From the Journal of the American Medical Association, June 28, 1952, pp. 15839–15840]

BLOOD DYSCRASIA FOLLOWING THE USE OF CHLORAMPHENICOL

Chloramphenicol (chloromycetin®) has been accepted by the Council on Pharmacy and Chemistry for inclusion in New and Nonofficial Remedies. Its antibiotic properties are well known, and when the council accepted this product there was much evidence to demonstrate its therapeutic value. At the same time there then was little reason to believe that serious or fatal side-reactions would be demonstrated. Nevertheless, following a study of the chemical structure of the drug, the Council issued a warning at the time of acceptance even though there was meager evidence to prove that such a warning was necessary. Thus, on page 116 of New and Nonofficial Remedies, 1951, there appears the following statement:

"Changes in the peripheral blood or the blood-forming organs have been reported only during the use of choramphenicol. Mild hemolytic anemias,

granulocytopenia (no cases of agranulocytosis as far) and an arrest in the saturation of the forced elements in the marrow have been described."

Recently there have been additional reports of the effects of chloramphenicol on the blood and bone marrow. At least two types of reactions have been encountered. In one there is a transient depression of the formed elements in the blood, involving red cells, white cells, and platelets during therapy with the drug. This type of reaction has been very uncommon, and in the experience of one group well versed in the field of antibiotic therapy it has seemed to occur in patients who were receiving very large doses or the drug or in patients who had renal insufficiency. The blood of these patients returned to normal, or at least above pretreatment values, as soon as therapy with the drug was stopped, and no permanent deleterious effect was observed.

A second and more serious type of reaction that has been encountered is production of a true aplastic anemia. In the experience of one group, this anemia has occurred in patients who have previously received one or more courses of amphenical without untoward effect. When the drug was subsequently administered, even in small doses, a severe blood abnormality has appeared. Even deaths have been reported. Whether chloramphenicol continues to remain as one of the more useful antibiotics or whether it will be relegated to a place where its use will be confined to the treatment of patients with typhoid or serious infections for which no other therapy is available, remains to be seen. Further observations are in order. In the meantime, physicians should be on the alert for reactions following therapy with this and any other antibiotic, or in fact any of the newer drugs.

Few therapeutic agents, which are being introduced with ever increasing rapidity, are characterized not infrequently by their beneficial of life-saving qualities but also by their ability to cause injury or serious side-effects. A calculated risk is involved whenever one prescribes any medication. The physician is confronted constantly with the difficult task of determining whether the use of a given drug is likely to do more good for a particular patient than any possible harm. In spite of the vast amount of laboratory and clinical study that a new drug usually undergoes before it is placed on the market, subtle or insidious toxic effects, often of a serious nature, frequently are not recognized and brought to the attention of the medical profession in general until after the drug has been on the market for some time and has enjoyed widespread clinical use. A propensity to cause injury to the hematopoietic system is particularly likely not to be generally appreciated until a new drug has undergone extensive use for a considerable period of time. Physicians who observe hitherto unreported toxic effects or injuries attributable to a recently introduced therapeutic agent have the obligation or duty of bringing this information to the attention of the entire profession. If a physican does not have the time or inclination to prepare case reports of drug injuries for publication in a medical journal, he can perform a useful service by advising the office of the Council on Pharmacy and Chemistry of the pertinent facts in such instances. By this means the Council will be provided with necessary information that may serve as the basis for an early authoritative report or warning statement.

SUGGESTED DETAILS

CHLOROMYCETIN

Doctor, I am glad you asked me about the Chloromycetin "situation." Needless to say, we of Parke-Davis are also concerned.

We are particularly concerned about the increasing tendancy for newspapers and magazines to "practice" medicine. For, despite many fine bits of reporting by competent medical writers, too often articles are characterized by: careless or illogical deductions, lack of scientific understanding, use of material out of context, and lack of proper perspective.

(1–PP10)

Here is what Mr. John L. Bach, Director of Press Relations of the American Medical Association, recently had to say about this pertinent subject. (Repeat Bach statement).

Chloromycetin is among the important products that have run the gauntlet of newspaper evaluation. Perhaps the dramatic qualities of the antibiotic, itself, have contributed to this condition. A relatively few articles, however, have accused Chloromycetin of being associated with certain blood dyscrasias. On the other hand, intensive investigation by the Food and Drug Administration, carried on with the assistance of a special committee of eminent specialists appointed by the National Research Council, resulted in unqualified sanction of continued use of Chloromycetin for all conditions in which it had previously been used.

A sensible caution against indiscriminate use, which we have incorporated into our advertising and labeling, is a welcome addition to our literature and to the label on Chloromycetin products, and in our opinion, would be appropriate in those on any potent chemotherapeutic agent. Actually, such caution is an assurance that the full benefits of well-tolerated Chloromycetin will be available and free from misuse.

(2–PP10)

Here is the breakdown of the recent survey made by the Food and Drug Administration covering 539 patients. It should be borne in mind that this survey *was specifically made for the purpose of ascertaining, if possible, the degree of involvement of Chloromycetin* in the development of blood dyscrasias. You will notice that there are three categories, "A", "B", and "C". These three categories relate to: "A" those cases in which Chloromycetin was the only drug given; "B" those in which Chloromycetin was given in combination with other drugs; and "C" those cases in which Chloromycetin was not involved.

(3–PP10)

On this page, Doctor, we have reduced to percentage the salient points which we noted from the tabulation I have just shown you.

Several interesting factors are obvious from these data. The number of cases of blood dyscrasias found in this survey apparently associated with Chloromycetin alone is *only about 10 per cent of the total cases surveyed.*

In this survey *specifically intended to find the facts on Chloromycetin, 341 patients out of a total of 539, more than 60 per cent of the total were of cases in which this antibiotic was not involved.*

(4–PP10)

Are the broad-spectrum antibiotics important factors in the incidence of blood dyscrasias? Of course, it is logical to use Chloromycetin as an example, because it has been the subject of intensive and thorough investigation. An investigation, incidentally, in which Parke-Davis wholeheartedly cooperated. Here is a chart showing the increased use of Chloromycetin from the time of its introduction Notice the steady, continued and rapid rise which now amounts to many millions of doses, comprising several millions of courses of therapy.

(5–PP10)

Here, Doctor, we have plotted the mortality from *aplastic anemia as reported* by thirty States for the years of 1949, 1950, 1951. These figures, compiled by Parke-Davis from data obtained from the thirty States in which these figures were available for the three year period, revealed a specific mortality per 100,000 of 0.41 in 1949; 0.42 in 1950; and 0.43 in 1951.

(6–PP10)

Now, on this page we have plotted the two curves superimposed on the same set of coordinates: A. Chloromycetin curve; B. Mortality from aplastic anemia. The lack of parallelism leads to the impression that there is little relation between the two factors that, were Chloromycetin an important cause, would be expected to show parallelism at least.

(7–PP10)

Up through October, 1952, 59 published papers, reporting on experience involving more than 1700 patients, have presented data in which thorough blood studies had been made on each patient before, during, and following therapeutic courses of Chloromycetin. *Doctor, is it not significant, that in not one of these 1700 patients was there any evidence of blood dyscrasia following administration of the antibiotic?*

You may wonder about the results of laboratory animal studies. This type of investigation was started long before the commercial release of Chloromycetin. Only by the use of the antibiotic in exceedingly high dosages given parenterally was it possible to produce even mild reversible anemia in dogs. As you know, it is difficult to depress bone marrow function in animals. In studies aimed at detection of possible bone marrow toxicity, many procedures have been followed but with little success. Attempts were even made to depress further the function of bone marrow in animals previously subjected to repeated injections of known depressants. However, recovery ocurred upon transfer to Chloromycetin therapy. These and related studies, both laboratory and clinical, as well as of manufacture control, have continued uninterrupted throughout to the present time.

We ask for open-mindedness in approaching this subject. We assure you that Parke-Davis will take every means possible and exhaust every possibility in attempting to get at the solution of *this baffling problem of modern therapeutics, involving, obviously, not only Chloromycetin, but many other potent chemotherapeutic agents as well.* And we assure you also that the profession will be kept fully informed, as to the progress of this fundamental pharmacologic development insofar as Chloromycetin is concerned.

Before terminating this interview may I re-emphasize a fact which has not changed with the developments of the past year? *Chloromycetin continues to be the outstanding wide-spectrum antibiotic because of its well-tolerated nature and its high degree of effectiveness.*

(8–PP10)

Chloromycetin is definitely well-tolerated! Its relative *freedom from undesirable side reactions*, such as nausea, vomiting, headache, skin eruption, and enteritic symptoms frequently encountered in broad-spectrum antibiotic therapy, enhances its usefulness in clinical practice.

(9–PP10)

And, as you know, Chloromycetin is highly effective as a specific therapeutic agent. You know, of course, of its singular effectiveness in typhoid fever; it is recognized as the outstanding specific therapeutic agent in that entity, *not being equaled by any other known medicinal agent. Chloromycetin is highly effective in many other conditions:* in influenzal meningitis, in surgical infections, and *in many other conditions in which the etiologic agents fall within the extremely broad spectrum of Chloromycetin.*

Doctor, give Chloromycetin the trial that the evidence before you justifies; we encourage you to use the antibiotic in the most difficult clinical problems that you can find assuming that Chloromycetin is indicated. *Your carrying out adequate blood studies will asure your patient that every safeguard is being taken,* and you will have the opportunity thereby to prove to your own satisfaction, *on the basis of your own experience,* the truth about Chloromycetin. We are confident that, again, on the basis of your own experience, you will continue to include Chloromycetin as an integral part of your armamentarium, because it is the effective, potent, therapeutic agent that it has been found to be by physicians in all parts of the world.

IDEAS AND SUGGESTIONS

CHLOROMYCETIN

In using this detail (PP10) you should carefully follow the instructions contained in Mr. Walker's accompanying letter. Start your interview with the Chloromycetin Cream Detail (PP9). The special detail (PP10) should not be introduced unless the physician brings up the subject or unless you know that he has ceased prescribing Chloromycetin. Your efforts should all be directed in a positive direction designed to provide facts which will induce physicans to use Chloromycetin in the wide range of infections in which it is effective. These fundamental points should be stressed: (1) Chloromycetin has been proved clinically effective against many of the infections due to gram-positive and to gram negative bacteria, to rickettsia, and to certain of the viruses. (2) Chloromycetin is especially noted for its relative lack of irritation to the gastrointestinal tract and of other side effects often associated with broad-spectrum antibiotic therapy. (3) High blood serum levels, in general proportionate to size of dose, are readily attainable, and since the antibiotic is able to penetrate the blood-brain and other barriers, it provides broader clinical coverage.

It is suggested that you use a copy of the spectrum folder U 89–2 in lieu of literature for distribution when the occasion arises to give detail PP10. A new full-color blotter, portraying all of the product forms, will be supplied to you very shortly, as will a desk-top product information card. A deluxe product booklet is being made ready for the press at this time. Other promotion material is in process of preparation and will be released as soon as possible. The current literature on Chloromycetin Cream, T–68, is still applicable in detailing the physicians on that product form.

SPECIAL CHLOROMYCETIN DETAIL

This detail approach has evolved from a talk given by Mr. Walker at a meeting of New York State pharmacists at the Hotel Statler in New York City. Vincent Cioffi, of the New York Branch, first used the newspaper comments in detailing and he was able to report very substantial territorial gains by incorporating this feature in his presentation.

It should be kept in mind that the incidence of aplastic anemia is not known because statistics on this affliction are incomplete and inadequate. In the survey, among those who received the estimated 8,000,000 courses of therapy of Chloromycetin, aplastic anemia is known to have appeared in 139 patients. The ratio of 139: 8,000,000 gives a rate of 1.74 per 100,000 which probably is not much greater incidence than would be expected in a population of sick persons who had not received any Chloromycetin. In the survey also there were an additional 157 case records on patients who had aplastic anemia classified as group C (Chloromycetin not involved). (And it is to be remembered that these do not constitute all the cases of aplastic anemia that had occurred; these were collected in a survey directed primarily at Chloromycetin.) In other words there were a few more patients (157 as compared with 139) found in the survey who had aplastic anemia unrelated to Chloromycetin than there were those whose aplastic anemia was observed to have followed Chloromycetin therapy. Further, the incidence of this disorder is apparently on greater today than it was before Chloromycetin was introduced and came into widespread use on the basis of recorded deaths by States' Registrars of Vital Statistics for recent years.

Mr. Cioffi also stressed the possible importance of infection provoding a trigger mechanism for the production of aplasia. According to this theory, Chloromycetin, by eliminating the infection, allowed the patient to go on to such a development for which he was destined even before or without therapy.

This approach was based on a talk given at a local medical group meeting by Frank Schley, New York District Coordinator for the Department of Clinical Investigation. Mr. Schley commented as follows:

"A point of interest under investigation by certain hematologists at the present time is the significance of a lack of resistance to infection as a sypmtom of an impending blood dyscrasia. This very symptom may be the cause for which an antibacterial agent is ingested. In the past it has been said that infection is usually the cause of death in aplastic anemia. It is also recognized by hematologic authorities that bacterial and virus toxins have been incriminated as a trigger mechanism to initiate a blood disorder. Toxins produced by infections themselves are blamed by eminent hematologic authorities. Lawrence, while at the University of Rochester, produced severe neutropenia and leukopenia in cats by a viral agent."

Planned Presentation sheet 5–PP10 contains a curve plotted from reports of all recorded aplastic anemia deaths compiled by Parke-Davis personnel from data supplied by States' Bureaus of Vital Statistics. You will be interested in the complete totals: rates given represent specific mortality rates (aplastic anemia deaths per 100,000 total population, both sick and well), for the years cited:

	1948	1949	1950	1951
Average, 16 States reporting all years	0.3575	0.4057	0.4534	0.4667
Average, 30 States reporting1949, 1950, 1951 only		.4113	.4222	.4336
Average, 35 States 1950 and 1951 only			.4237	.4141
Average, 36 States reporting 1951 only				.3768

BIBLIOGRAPHY

We are also supplying to you for your background information a bibliography compilation entitled "Hematologic Aspects of Chloromycetin" which provides references and brief abstract of the contents of virtually all publications which have appeared beginning in 1948, in which there are references to hematologic aspects of Chloromycetin therapy. This compilation was prepared by the Department of Clinical Investigation by a staff under the direction of Miss Margaret Hanser. We expect to provide additional detailed bibliographic material of this sort as rapidly as it can be prepared.

"...it does not help the physician who prepared his paper with only a medical audience in mind. The doctor may be discussing a subject based on only a handful of cases; yet his experimental research may be important enough to present to the medical meeting even though he knows it is 'premature' in every sense of the word. In such a case, the physician is presenting his facts to his colleagues only and not to the public. For any organization to follow a general practice of mimeographing such a paper and passing it on to writers, without first weighing its impact on lay readers, is to do a disservice not only to the doctor who was invited to deliver the paper, but to the medical profession and the public as well."

Bach, J. L.: Doctor, Meet the Press, J. A. M. A., 149:1137 (July 19) 1952.

1-PP10 PRINTED IN U.S.A.

		No. Cases	No. Deaths	Percentage
A	Chloromycetin alone	55	23	42%
B	Chloromycetin and other drugs	143	82	57%
C	Chloromycetin not involved in development of dyscrasia	341	155	46%
		539		

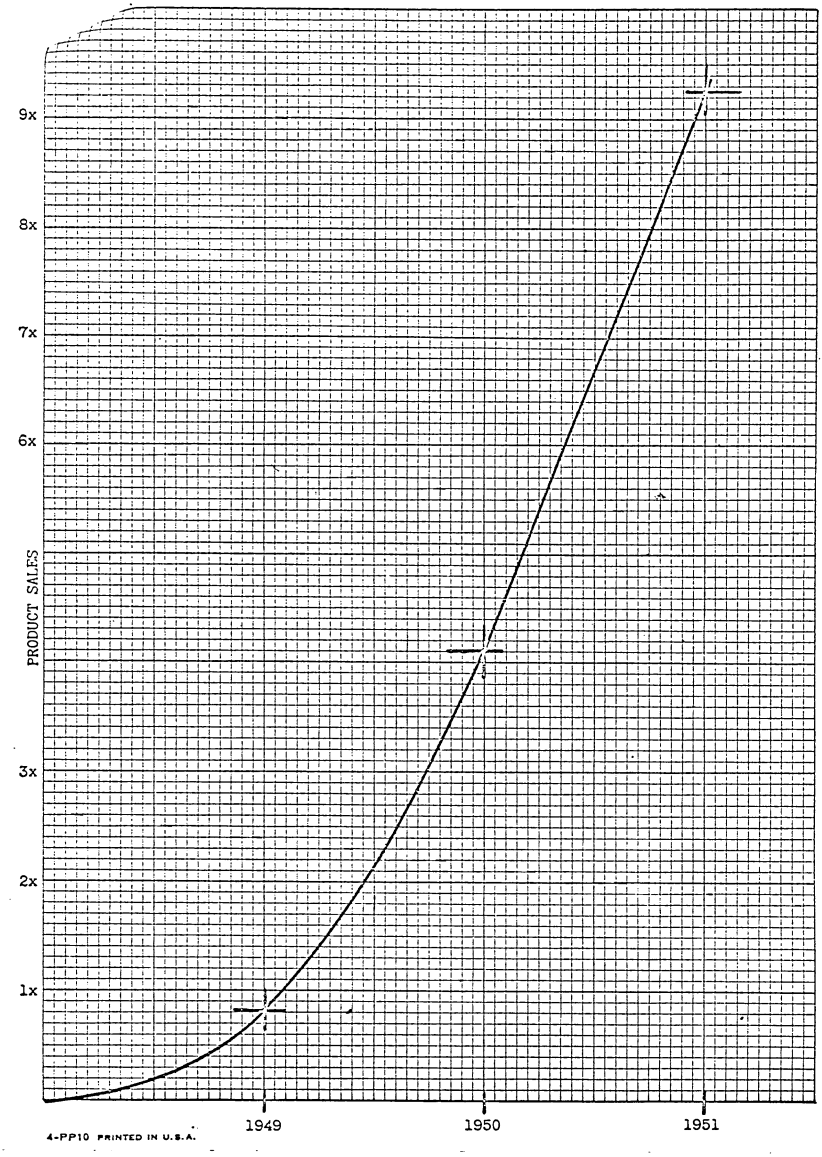
2-PP10 PRINTED IN U.A.S.

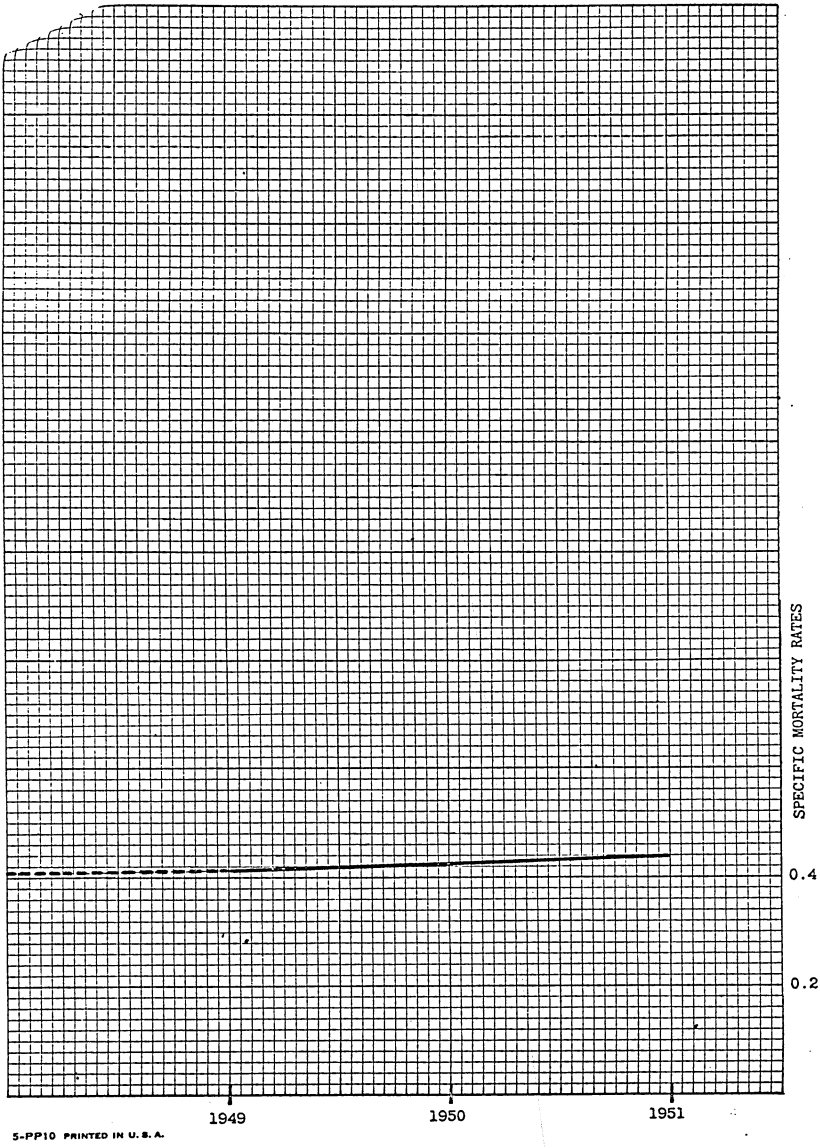
Chloromycetin alone $\frac{55 \times 100}{539} = 10.2\%$

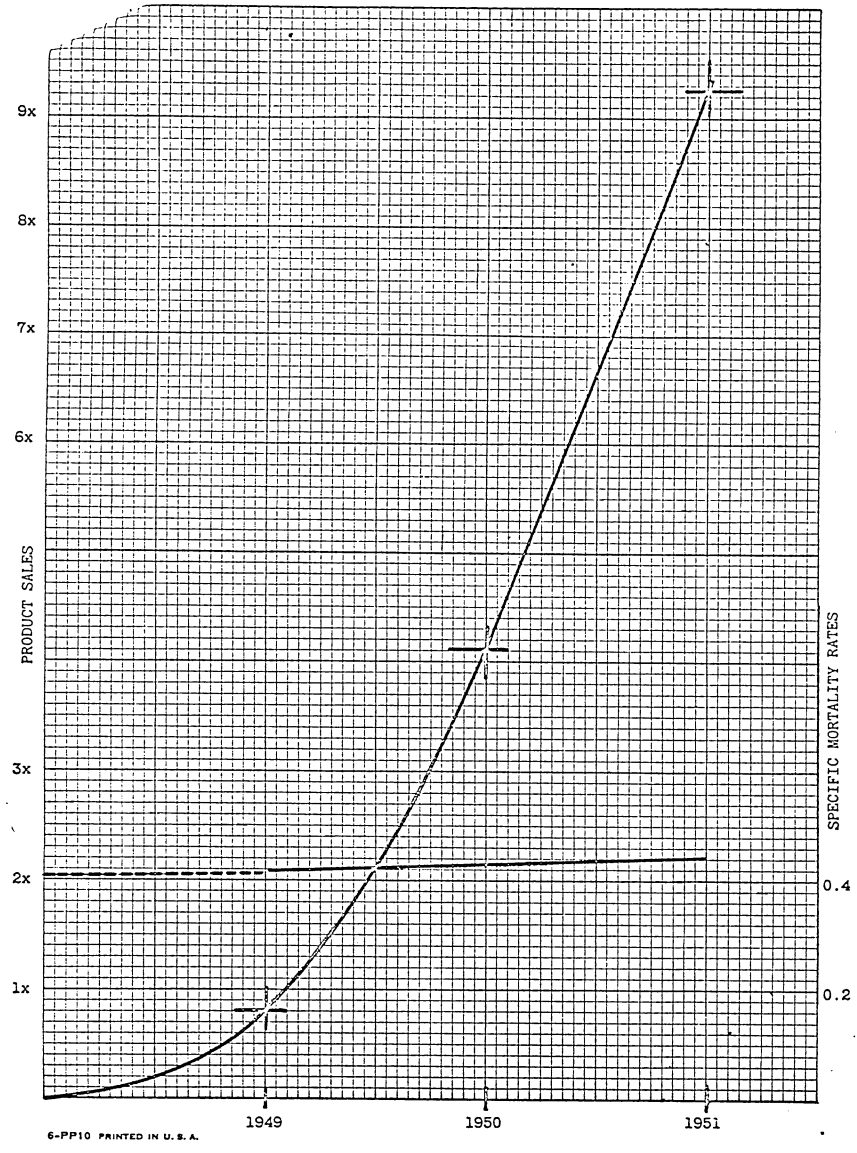
Chloromycetin not involved $\frac{341 \times 100}{539} = 63.3\%$

(these figures from survey by the FDA directed primarily at Chloromycetin)

3-PP10 PRINTED IN U.S.A.


9x
8x
7x
6x
PRODUCT SALES
3x
2x
1x
1949
1950
1951
4-PP10 PRINTED IN U.S.A.


SPECIFIC MORTALITY RATES
0.4
0.2
1949
1950
1951
5-PP10 PRINTED IN U. S. A.


9x
8x
7x
6x
PRODUCT SALES
3x
2x
1x
SPECIFIC MORTALITY RATES
0.4
0.2
1949
1950
1951
6-PP10 PRINTED IN U. S. A.

59 published papers

involving approximately 1700 case histories, each of which reported on thorough blood studies prior to, during, and following therapy.

Not one of these seventeen hundred cases revealed any evidence whatever of blood dyscrasia following administration of the antibiotic.

7-PP10 PRINTED IN U.S.A.

CHLOROMYCETIN

well-tolerated

broad-spectrum

antibiotic

8-PP10 PRINTED IN U.S.A.

CHLOROMYCETIN

highly-effective

broad-spectrum

antibiotic

9-PP10 PRINTED IN U.S.A.

PARKE, DAVIS & CO., DIRECTOR'S LETTER, UNITED STATES AND CANADIAN SALES DEPARTMENT, DECEMBER 22, 1952, LETTER NO. 3

To members of the professional service staff.

Gentleman: The summary of last summer's special survey by the Food and Drug Administration of the relationship of Chloromycetin to reported blood dyscrasias has been published in the December issue of "Antibiotics & Chemotherapy."

We are sending to you a quantity of reprints of this article for distribution to physicians. Attached to this letter is a specimen reprint marked to call your attention to *significant facts which should be kept in mind* when evaluating the contents.[1]

Here are some questions which you may be asked relative to this report together with factual answers which are vital to a full understanding of the points developed in the survey.

Question. What did the recent investigations show?

Answer. Several hundreds of case records, collected from hospitals and physicians throughout the country by members of the FDA field staff, were reviewed. Of 539 in which classification was possible, in only 198 (37 per cent) was there evidence that the development of blood dyscrasia was associated with the use of Chloromycetin either alone or in conjunction with other drugs.

Question. Was Chloromycetin the only drug administered in these 198 cases?

Answer. No. Chloromycetin was the only drug administered in 55 of the 198 patients. Other drugs had been given in the remaining 143 cases.

Question. What "other drugs" were involved?

Answer. These were numerous; in some instances they were mentioned specifically, but in most they were mentioned only by categories. Included were: analygesics, anticonvulsants, antihistaminics, antipyretics, antibiotics (other than Chloromycetin, of course), antimalarials, antibacterials, and other chemotherapeutic agents.

Question. What safeguards protect patients against blood distorders?

Answer. Judicious use of potent therapeutic agents in the hands of the physician; careful observation of the patient; avoidance, when possible, of prolonged or intermittent use; and adequate blood studies, especially during prolonged or intermittent therapy when required. There is no known method permitting determination in advance of those in whom blood dyscrasias are likely to develop.

Question. What were the conclusions of the official agency (FDA) regarding further availability and use of Chloromycetin as a result of the survey?

Answer. The F.D.A. concluded that serious blood dyscrasias following the use of Chloromycetin are uncommon. The report specifically stated that Chloromycetin is a valuable drug which, however, should not be used indiscriminately or for minor infections. When prolonged or intermittent administration is required, adequate blood studies should be carried out. Attention of the physician is invited to these points through a warning on the label and through a statement in the literature on Chloromycetin.

Question. What are the present indications for Chloromycetin?

Answer. *These are not changed.* Chloromycetin is effective and is indicated in a wide range of bacterial, viral, and rickettsial infections, including: urinary tract infections; brucellosis; bacterial and primary atypical pneumonias; pertussis; enteric fevers (salmonelloses, including typhoid fever); dysenteries (shigelloses); rickettsial infections (Rocky Mountain spotted fever, typhus fever, scrub typhus fever); acute gonorrhea; granuloma inguinale; and lymphogranuloma venereum.

Very truly yours,

GRAYDON L. WALKER.

PARKE, DAVIS & CO.,
June 16, 1954.

Letter No. 8

To all sales representatives:

An important highlight in the development of up-to-date information on the antibiotics was presented in a symposium on antibiotics held in Washington this winter. A number of papers dwelt on the matter of safety and efficacy of Chloro-

[1] Retained in committee files.

mycetin. We are sending a limited quantity of each of the pertinent reprints to you and marked specimens are attached to this letter.[1]

We have bracketed in red certain salient points that you should especially look for. We would add that a complete reading of each of these papers would be very helpful to you in getting a more complete picture of the situation. We would especially recommend, for example, a careful reading of Dr. Ethan Allan Brown's discussion of Dr. Perrin Long's article. Dr. Brown has put his finger on a number of points pertinent in modern-day antibiotic therapy.

We believe that you will agree with us that these papers indicate an increasingly broader acceptance and interpretation of the role of Chloromycetin in the treatment of infectious diseases. These reprints constitute additional verification of our continuing belief that Chloromycetin is truly one of the world's outstanding therapeutic agents.

Very truly yours,

GRAYDON L. WALKER.

FEBRUARY 18, 1960.

To: U.S. Branch Managers.

CHLOROMYCETIN

We still receive an occasional report indicating that one of our sales representatives has not followed instructions which have been issued on several occasions in the past.

Any discussion with a physician regarding Chloromycetin must, without exception, be in accord with good sound medical information which has been provided by the Promotion Department, or in our regular literature.

It is your personal responsibility to see to it that no salesman under your direction makes statements relative to Chloromycetin which cannot be substantiated in the literature or other officially approved promotion material. This is not a situation you can correct and then forget because you have the continuing problem of new sales representatives as well as regular sales representatives who may become a little careless because of the increase in specification and preference for Chloromycetin by physicians.

Please see to it that every man on your sales staff is advised again at this time and that the question receives appropriate emphasis at concentration meetings outlining again the importance of adhering strictly to sound medical information as covered in our literature or in other approved promotion material. We usually do not give much credence to anonymous reports and the most recent accusations did not provide specific names and places, but we do want you to make it clear to every man on your staff that we will not retain in our employ any sales representative who makes statements which cannot be backed up in approved medical literature or other promotion material.

We fully appreciate the situation in the field such as competition occasionally stimulating a re-hash of some of the old publicity about Chloromycetin often by individuals who have had little actual experience with the drug as contrasted with the many physicians who have prescribed thousands of doses with no untoward effects. However, the problem is in an area where it is difficult to prove anything and therefore, please establish a procedure to convey the above instructions to your staff at regular intervals since we wish to adhere to our usual conservative policy of presenting only medical facts that can be demonstrated beyond doubt.

Very truly yours,

GRAYDON L. WALKER.

[From the Journal of the American Medical Association, vol. 172, No. 18, Apr. 30, 1960]

COUNCIL ON DRUGS

REPORT TO THE COUNCIL

The Council has authorized publication of the following report.

H. D. KAUTZ, M.D., *Secretary.*

The Registry on Blood Dyscrasias sponsored by the Subcommittee on Blood Dyscrasias of the Committee on Research has received a number of case reports concerning the possible association of a blood dyscrasia with the use of chlor-

[1] Retained in committee files.

amphenicol. The subcommittee has concluded that it might be proper to caution the profession by publishing a reminder concerning the potential ill-effect of this drug on the hematopoietic system. It is hoped that publication of this information will render a service to the medical profession.

NORMAN DE NOSAQUO, M.D.,
Secretary, Committee on Research.

BLOOD DYSCRASIAS ASSOCIATED WITH CHLORAMPHENICOL—(CHLOROMYCETIN) THERAPY

With an increase in the receipt of reports by the Registry on Blood Dyscrasias in which chloramphenicol is associated with the development of a blood dyscrasia, it becomes important once more to review briefly the toxic effect of this drug on the blood-forming organs of sensitive persons. The paucity of recent publications in the American literature should not be construed to mean that the reports of chloramphenicol-induced aplastic anemia some years ago were merely a chance association. There have been numerous reports in more recent years of chloramphenicol-induced aplastic anemia in the foreign literature.[1] Between January, 1953, and January, 1960, the Registry on Blood Dyscrasias has received a total of 223 reports of pancytopenia; of these, 91 were cases in which chloramphenicol had been administered. Of the 91 cases, there were 34 instances in which chloramphenicol was reported as being the only drug given.

Severe reactions to antibiotics occurring in patients between late 1955 and early 1957 have recently been studied in a nationwide survey by Welch and colleagues[2] of the Food and Drug Administration, Department of Health, Education, and Welfare. This study reported on 31 patients with aplastic anemia associated with chloramphenicol administration, of whom 23 died. Of these 31 cases, only 8 had been reported to the registry. Although some of these patients may have received chloramphenicol in the presence of a developing aplastic anemia, this explanation seems improbable. It is important to note that, in the survey of the FDA, few cases of aplastic anemia were associated with the administration of penicillin, streptomycin, the tetracyclines, or a sulfonamide.

The Subcommittee on Blood Dyscrasias recognizes that chloramphenicol is a valuable and important addition to a physician's armamentarium. This is particularly true since it has been shown that certain strains of staphylococci resistant to penicillin and the tetracyclines are sensitive to chloramphenicol. The manufacturer has repeatedly directed the attention of the medical profession to the need for judicious use of the drug by a warning statement in the labeling and advertising of the product. Although the warning statement specifically cautions against the indiscriminate use of the drug or against its use for minor infections, an examination of the reports received by the registery reveals that the drug has been used in such conditions as upper respiratory infections, including the common cold, bronchial infections, asthma, sore throat, and tonsillitis, miscellaneous urinary tract and ear infections, undiagnosed low-grade fever, and even disseminated lupus erythematosus, gout, eczema, malaise, and iron deficiency anemia. It is incumbent upon a physician when he prescribes chloramphenicol that he carefully weigh the need for the drug in relation to the risk of possible serious toxic effects.

Although the subcommittee recognizes that chloramphenicol is a valuable antibiotic, it is also the opinion of the subcommittee that there is no longer a reasonable doubt that chloramphenicol may cause aplastic anemia. Periodic blood cell counts may be of some help; however, they cannot be relied on to detect signs of marrow toxicity sufficiently early so that chloramphenicol administration can be discontinued before an irreversible aplastic anemia develops. Therefore, judicious use of the drug must be the rule, and it should not be used prophylactically, in trivial infections, or in infections in which other, less dangerous antibiotics may be used effectively.

---

[1] (*a*) Visconti, P.: Sulla mielosi aplastica globale da cloramfenicolo: Contributo clinico, Riforma med. 70:1043–1046 (Sept. 15) 1956. (*b*) Cable,, J. V., and Reid, J. D.: Jaundice and Aplastic Anaemia Following Chloramphenicol Therapy, New Zealand M. J. 56:532–535 (Oct.) (*c*) Shaw, R. G., and McLean, J. A.: Chloramphenicol and Aplastic Anaemia, M. J. Australia 1:352–359 (March 16) 1957. (*d*) Louwette, R., and Lambrechts, A.: La toxicite sanguine du chloramphenicol, Rev. med. Liege 12:10–16 (Jan. 1) 1957. (*e*) Madsen, N. O.: Anaemia aplastica fremkaldt of chloramphenicol, Ugesk, laeger 119:489–491 (April 18) 1957. (*f*) Slamone, L.: Sull'emopatia da CAF, Riforma med. 71:494–498 (March 4) 1957.

[2] Welch, H.; Lewis, C. N.; Weinstein, M. I.; and Boeckman, B. B.: Severe Reactions to Antibiotics: Nationwide Survey, Antibiotic Med. 4:800–813 (Dec.) 1957.

[From the Journal of the American Medical Association, vol. 174, No. 14, Dec. 3, 1960]

CHLORAMPHENICOL—A NEW WARNING

In one month recently, I saw 4 new cases of aplastic amenia. Although they ranged in age from 3 to 63, and came from different sections of the country, they had one common denominator; chloramphenicol had been used in the recent past for minor respiratory infections. There was no history of the use of other antibiotics or potentially toxic drugs and since the anemia and the other manifestations appeared a few months after the last administration of chloramphenicol, it seemed clear that this drug was responsible for the marrow aplasia.

In our recently studied series of aplastic anemia (seen within the past 3 years) 8 of 30 had received significant amounts of chloromycetin, almost invariably for minor infections. Of the most recent 10 cases of aplastic anemia, 5 had followed therapy with chloramphenicol. The tragic thing about all these seriously ill cases, most of whom died, is *that the drug need never have been given.*

It is becoming increasingly clear that chloramphenicol, an excellent broad-spectrum antibiotic, has antimetabolic effects, as well—that is, it may injure the intrinsic "machinery" of certain rapidly proliferating cells, notably of the bone marrow. Thus, Rubin and associates, using radioactive techniques, demonstrated a depressant effect of chloramphenicol on erythropoiesis; this occurred in 5 of 15 subjects receiving ordinary doses and in all of 4 cases with cancer who were given unusually large doses of the drug.[1] In another study by Saidi and Wallerstein[2] 10 of 22 cases treated with chloramphenicol for various infections developed striking vacuolization of nucleated red cells in the bone marrow, associated with a maturation arrest phenomenon and marked reduction in blood reticulocytes. The possibility is present that these temporary changes could go on to complete or partially complete destruction of the bone marrow providing (a) that sufficient drug was used or (b) the patient became sensitized in some manner and was given a second course of drug therapy at another time. It is thus conceivable that both an immediate or direct effect as well as an indirect or hypersensitivity mechanism maybe responsible for the marrow reactions seen.

Following the introduction of chloramphenicol in 1948 and the reports of the first cases of aplastic anemia between 1950 and 1952, many editorials and reports of special *ad hoc* meetings appeared. Evidently the medical profession was profoundly influenced; in any event, the sales of chloromycetin declined sharply, reaching their lowest level in 1954. This lull was short-lived. By 1958, there was a five-fold increase in the sales of the drug and by 1960, enough chloramphenicol was being distributed, and presumably used, in the United States to supply 3,732,416 persons with 10 Gm. courses of drug! (These data were supplied through the kind cooperation of Dr. Harry Carnes, Parke Davis & Co., Detroit, Mich.)

To those of us who see cases of aplastic anemia following the use of various possible etiologic agents, chloramphenicol stands out as the most important single historical factor. To be sure, evaluation of histories and even of statistics relating to both the incidence of aplasic anemia and of chloramphenicol as an etiologic agent is difficult. Nevertheless the importance of the chloramphenicol-aplastic anemia relationship persists, and one must naturally be concerned with the possibility that an increased incidence in aplastic anemia may result as use of the drug increases so rapidly. Is the pharmaceutical house which introduced and popularized the use of chloramphenicol to be taken to task? This seems unfair for there can be no question that this respected company has gone to every effort for ferret out statistics of case reports to carry out experimental work in various animals and even to note the effects of marrow transplantation in chemically induced aplastic anemia of monkeys.

Is it the physician, then, who is largely responsible? In a way he is, for without his prescription, the drug would not be administered. Certainly, if he regards chloramphenicol lightly, to be dispensed like aspirin, for every minor cold and respiratory infection, he is not without blame. But are there certain mitigating factors? Some say that a person ill is a person to be treated! The urge to make a person comfortable and to cure his illness as quickly as possible is an urge each of us has. It follows then that a good antibiotic of the broad spectrum

---

[1] Rubin, D.; Weisberger, A. S.; Botti, R. E.; and Storaasli, J. P.: Changes in Iron Metabolism in Early Chloramphenicol Toxicity, *J. Clin. Invest.* 37 : 1286–1292 (Sept.) 1958.

[2] Saidi, P., and Wallerstein, R. O.: Effect of Chloramphenicol on Erythropoiesis. To be published.

variety and which can be readily administered is something to be used at every opportunity. This is part of the mores in this affluent society of ours. We have potent medicines; the patient is ill; we must treat! The days of simple herb medicines and of simple galenicals have long since passed. More often than not, the newer synthetics, most of them composed of molecules with benzene rings and nitrogen, NH, NH_2, or NO_2 groupings—are used, and all of them, it should be said, are potentially harmful.

What then can be done? A few suggestions may be offered: (1) Physicians must be warned, and in no uncertain terms by means of articles, editorials, meetings, announcements; not once, but repeatedly that chloramphenicol is not only a potent antibiotic but apparently an antimetabolite as well, having effects not only on bacteria but on the bone marrow. (2) By some means, whether by regulation or by self-discipline, promiscuous use of the drug should be avoided and its use restricted to impelling circumstances, i.e., for conditions in which no other antibiotic is currently effective. One realizes that this is more easily said than done, knowing the physician's individualistic nature. (3) The patient and the patient's family must be warned, either by the physician or by the druggist that this is a powerful drug; that it should be used only once; that its repeated use may result in serious blood reactions; that it should not be kept in the bathroom cabinet and used again if an apparently similar disorder supervenes. (4) The manufacturing drug house should instruct its detail men, our ubiquitous mentors, not to minimize the dangers of the drug, and to emphasize its value for certain specific conditions, and not for the whole gamut of infectious diseases. The journal advertising could be made more forceful regarding the necessity for guarding against use of the drug indiscriminately, and especially in minor infections, or in repeated courses; or off the bathroom closet shelf.

It might be wise for the patient or his family to have some knowledge of what antibiotic is being used in a given case. Perhaps we physicians might also consider, at least for many of the acute, self-limited infections, the more conservative course (radical by present-day standards) of giving no potent medications at all, but rather such symptomatic care as aspirin, fluids, and the like. After all, the body defenses are usually capable of handling most acute upper respiratory infections.

In any event, something must be done to reduce the incidence of grave insult to the bone marrow produced by some of the antibiotics. The practicing physician would do well to think twice before prescribing a potent antibiotic and to ask himself "Is this drug really necessary?"

WILLIAM DAMESHEK, M.D.,
Boston, Mass.

[From the Journal of the American Medical Association, Mar. 17, 1962]

COUNCIL ON DRUGS—REGISTRY ON BLOOD DYSCRASIAS

REPORT TO THE COUNCIL

In 1952, the Council on Drugs became concerned with the problem of hematotoxicosis from the ever-increasing number of therapeutic agents. The Council's former Committee on Research recommended that a Registry on Blood Dyscrasias be formed; and after a 2-year pilot study, the Registry was permanently established. Reports are tabulated for each 6-month period, and the summary tabulation is distributed to medical schools, hospitals, medical societies, and collaborating physicians.

With expansion, the need for a résumé of the tabulated information has become apparent. The reports received by the Registry for the period January 1 to June 30, 1961, were used for this purpose. The information must be considered raw data, since reports are received from many sources and no follow-up is possible.

The résumé is intended to provide concise information regarding common associations between drugs and blood dyscrasias, to acquaint physicians with the existence of the Registry, and to encourage them to report cases of blood dyscrasia in which drugs or other chemicals may be the suspected cause.

Résumé of Reports Received by Registry on Blood Dyscrasias January 1 to June 30, 1961

In the period from January 1 to June 30, 1961, 138 new cases of blood diseases suspected of having been caused by drugs or chemicals were reported to the

Study Group on Blood Dyscrasias of the American Medical Association. These included cases which were published in the American medical journals during the same period. Forty-eight cases noted in foreign medical journals are reviewed separately.

These findings increase the total number of cases reported since 1955 to 1,504 and the total number of drugs and chemicals reported to be associated with the development of blood dyscrasias to 411. Because of the large number of drugs involved, it has become increasingly difficult to evaluate the data and establish firm etiological relationships between specific drugs and specific blood disorders. However, certain previously unsuspected hematological side effects of drugs may be recognized much earlier if data are gathered from all over the country. Therefore, the Study Group on Blood Dyscrasias feels that it is important to continue to act as a clearinghouse for all suspected instances of hematological side effects which may arise from the use of drugs.

In order to transform the accumulated data into useful information, the Study Group has recommended that a brief analysis of the reported material be prepared. A copy of the complete tabulation is available upon request from the Council on Drugs.

An anlysis of the new cases added to the tabulation during the first 6 months of 1961 does not justify any sweeping conclusions or condemnations. The drugs appearing in the tabulation are those which are known to have produced toxic reactions and which continue to cause trouble when used, or are those drugs which are widely used.

A total of 163 different drugs and chemicals were associated with the 138 cases reported to the Registry during the period in review.

A.—Ninety-eight drugs were associated with one case each. Of these, only imipramine hydrochloride (Tofrānil) requires special mention. This drug was introduced, in 1959, for the treatment of depression. Since that time, it has been reported as a possible causative agent in 9 cases of leukopenia, 2 of which were fatal. However, only one additional case has been reported in the first 6 months of 1961.

B.—Thirty-one drugs were associated with 2 cases each. The potentially toxic effect of quinidine (Asarum, Conchinine, Conquinine, Pitayine, Quindate) on platelets is emphasized by the fact that 2 patients developed thrombocytopenia after the administration of quinidine, the only drug used.

C.—Twelve drugs were associated with 3 cases each. Dexamethasone (Decadron, Deronil, Gammacorten), a synthetic analogue of hydrocortisone, was reported to be associated with 2 cases of pancytopenia and 1 case of leukopenia. This drug is mentioned because it had not previously been associated with the development of blood dyscrasias. However, in all 3 cases, other drugs known to be potentially toxic were administered concurrently; thus, it seems dubious that dexamethasone was the offending agent.

D.—Eight drugs were associated with 4 cases each. A definite cause-effect relationship could not be established in any of these cases because of the variety of blood disorders induced and the many other drugs used concomitantly.

E.—Fourteen drugs were associated with 5 or more cases each:

Acetophenetidin (Phenacetin)—8 cases
Acetylsalicylic Acid (Aspirin)—15 cases
Chloramphenicol (Chloromycetin)—56 cases
Chlorothiazide (Diuril)—7 cases
Chlorpromazine (Thorazine)—11 cases
Diphenhydramine (Benadryl)—6 cases
Diphenylhydantoin Sodium (Dilantin Sodium)—5 cases
Meprobamate (Equanil, Meprospan, Meprotabs, Miltown)—7 cases
Novobiocin (Albamycin, Cathomycin)—5 cases
Penicillins—17 cases
Phenobarbital (Luminal)—10 cases
Promazine (Sparine)—5 cases
Sulfisoxazole (Gantrisin)—6 cases
Tetracycline (Achromycin, Panmycin, Polycycline, Tetracyn)—18 cases

As in previous tabulations, the drug associated with the highest number of blood dyscrasias in this period is chloramphenicol. It was the only drug administered in 23 of the 56 new cases reported to be associated with the use of chloramphenicol; in 28 of the remaining 33 cases, it had been employed in conjunction with drugs not known to cause blood dyscrasias. These results support

the contention that chloramphenicol has a definitely toxic action on the bone marrow; therefore, it is mandatory for the physician to be aware of the potential toxicity of this otherwise valuable antibiotic.

Senator NELSON. Doctor, we appreciate very much your taking the time to come here today. Your testimony has been very valuable to the record. I want to thank you very much.

Dr. HEWSON. It is a privilege to be asked, Senator.

Senator NELSON. That will conclude the hearings until tomorrow morning at 10 a.m.

(Whereupon, at 11:05 a.m., the hearing was recessed, to reconvene at 10 a.m., Wednesday, February 28, 1968.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, FEBRUARY 28, 1968

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

The subcommittee met, pursuant to recess, at 10:15 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson, and Long of Louisiana.

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

Senator NELSON. We will now open the subcommittee hearings.

We have as a witness Mr. Edgar F. Elfstrom, publisher of the Daily News Tribune in Fullerton, Calif.

We will also hear testimony from Dr. Watkins, of California, and Dr. Franklin Farman, of Lakewood, Calif.

I have asked the gentlemen to join each other at the witness table, and if you have any comments or additions to make to the testimony of any one of the other witnesses that you think would be helpful for the record, just feel perfectly free to interject the remarks.

I will ask Mr. Elfstrom to proceed with his statement. I assume that you have no objection to an interruption for a question if something occurs to us in the course of your testimony.

Mr. ELFSTROM. Not at all.

Senator NELSON. Will you proceed with your statement?

STATEMENT OF EDGAR F. ELFSTROM, PUBLISHER, DAILY NEWS TRIBUNE, FULLERTON, CALIF.

Mr. ELFSTROM. At the outset, I want to say that I consider it a privilege to appear before you. And I assure you that I am grateful for having been asked.

Senator NELSON. I want to say on behalf of the committee that we realize that you gentlemen have come all the way from California to testify, and we know that it imposes a considerable sacrifice and burden in time upon each of you. And we are appreciative that you are willing to take the time to come here and testify for the record in this hearing. We appreciate it very much.

Mr. ELFSTROM. Thank you.

Our family is one of the legion of victims of a Chloromycetin tragedy. Our youngest daughter, a 19-year-old healthy, happy college

student, was given this potent antibiotic, first for a sore throat by a general practitioner, and subsequently some months later for a minor urinary infection by a urologist which, expert medical advice has informed us, would have cleared up without medication if left alone.

She was given more than 100 capsules of the drug intermittently over a period of some 6 or 7 months, and was hospitalized with aplastic anemia some months after the medication was discontinued. She passed away after 3 weeks of such intense suffering that it is beyond description, a nightmare Mrs. Elfstrom and I shall never forget as long as we live.

We did not know the name of the antibiotic that had been prescribed for her, or anything about it, until just before her death when we set out to learn what had caused a youngster who had been the picture of health all her life to succumb so quickly.

Among other things, we learned she had never been given a blood study by any of the physicians who had treated her despite the fact the warning in effect then specifically called for such studies. In a meeting held with the grievance committee of our Orange County medical society, we heard these men say they did not know the meaning of "intermittent therapy" which the Food and Drug Administration said was especially dangerous.

We also heard the president of our medical society say local doctors knew so little about the drug that they had asked an official of Parke, Davis who was attending a meeting in San Francisco at the time, to come down to Orange County to tell a group of physicians about the drug. Incidentally, this official did not appear. He said he had to return to his office unexpectedly; the consensus here was that when Detroit found out about the proposed meeting they ordered him to return immediately.

After several such frustrations Mrs. Elfstrom and I decided we would dedicate ourselves to doing something about warning the public, the innocent public I hasten to add, of the hazards of this drug and about the way its indiscriminate use was being promoted. If our memory serves us correctly, one of the well-known men of medicine who testified during the hearing conducted by the late Estes Kefauver in this very room, said "its sale was being pushed like soap."

Our research has developed a mountain of material, so much in fact that it has more than filled a four-drawer legal-size file case. Included among the many medical articles and reprints that warn of the drug's potential danger are countless letters from distraught parents and relatives who have lost loved ones following Chloromycetin therapy for such minor infections as the common cold, sore throats and other upper respiratory ailments for which antibiotics are not effective, mosquito bite, acne, infected gums, sore fingers, mumps, earache, and so forth. Here are excerpts from just a few——

Senator NELSON. These are letters that you have received?

Mr. ELFSTROM. Yes, sir.

Senator NELSON. And you have copies of the letters?

Mr. ELFSTROM. Yes; they are in our files.

Please add our daughter's name, Susan Alma Staggs, age two and a half, to the statistics you are gathering. She received Chloromycetin in August, aplastic anemia was diagnosed in October, and she passed away in Children's Orthopedic Hospital on December 8. God speed you on to the success of this mission—from a Washington family.

Senator LONG. May I ask if that is Washington, D.C., or the State of Washington?

Mr. ELFSTROM. The State of Washington.

My grandson, a boy of sixteen, was ill and we called in a man who was said to be one of the leading specialists in the country. This doctor prescribed Chloromycetin for the boy and it killed him—from the associate publisher of a group of prominent daily newspapers.

My daughter, Pamela, passed away due to the Chloromycetin she was given. Only people like you and I know what we have all gone through. We all appreciate what you are doing. Maybe all of us in some small way can contribute to the ban of this terrible drug—from a Colorado mother.

Barbara was a beautiful, chubby little girl with a head of blonde curls and blue eyes. She was the picture of health. We know nothing but that this awful drug took her life—from a New York mother.

My two and a half year old daughter, Elizabeth, died August 17 of aplastic anemia. The previous September she had been administered Chloromycetin by a pediatrician who had attended the child since birth, for a sore thumb, two months later for a cold, and two times more for a sty, never taking a blood count. I have lost all interest in everything. I can not speak about what my baby went through, all in vain, but I want you to know there is someone who knows how you feel about your loss and understands—from a Long Island mother.

My daughter Isabel died on August 14 of aplastic anemia, caused by Chloromycetin prescribed for an ordinary cold on two occasions within a year—from a New Jersey father.

I have wanted so often to write and thank you but my daughter's death (a 35-year-old government scientist) incidentally, she was from Washington here, although she died in California—came as such a shock that my health has not been good—from a California mother.

Other letters tell of the death of a 21-year-old college football player who was given Chloromycetin for acne, of a Navy Wave who was given the drug in a naval hospital, of a Massachusetts father who was given more than 50 blood transfusions in the veteran's hospital following the onset of aplastic anemia caused by the drug.

We have heard from physicians, too, who have had tragedies in their immediate families, such as this one from a doctor in Texas:

In February my seven and a half year old son died from aplastic anemia due in the opinion of five specialists, including the State's outstanding hematologist, who attended him, to the routine administration and dosage of Parke, Davis' Chloromycetin by me for an ear-throat infection on the advice of representatives of Parke, Davis who repeatedly assured me of its safety, and urged its use, routinely, in general practice. Almost simultaneously there were two other deaths in this area, a child and an adult which appear to be attributable to the same cause.

Senator NELSON. May I interrupt a moment? This is a letter from a physician in Texas who administered the drug himself?

Mr. ELFSTROM. Yes. Incidentally, I have a copy of his letter to me.

Senator NELSON. What is the date of his letter?

Mr. ELFSTROM. 1961.

Senator NELSON. 1961. This is some 9 years or thereabouts after the serious side effects of this drug were known to the company and to the medical profession; is that correct?

Mr. ELFSTROM. That is right. Dr. Watkins can tell you about that. I will find the letter in my file and give it to you.

Also, let me interject here that it seems that the younger the person the quicker the reaction follows. An older person usually hangs on for quite a while with the anemia. I have records of a case in Detroit where more than 200 blood transfusions were given to this man before he passed away, and of a woman down in Miami, Fla., who was given more than 180 blood transfusions before she passed away. But the younger the person, the quicker the reaction.

We could go on for hours telling about the countless tragedies that have come to our attention since we started to devote limitless time to the problem.

We are saddened by all of them because we know the suffering such tragedies bring. Some date back to the time of our disaster but many are recent as is this one from a father in Iowa who writes, in part:

We lost our almost 16-year-old daughter November 3, 1967, at Rochester, due to aplastic anemia caused by Chloromycetin, and my wife and I do not seem to know how to live with it.

I will not go into detail but our daughter was given 52 capsules for a sore throat in June.

Senator NELSON. Was she sent to Rochester for this treatment?

Mr. ELFSTROM. Let me go on, and I will explain it.

Senator NELSON. What I want to get at was whether it was administered at Mayo.

Mr. ELFSTROM. No. For instance, just last week we received a telephone call from this father, who said his wife, who had been teaching school, had to resign her position and he was afraid she was going out of her mind.

Just before I left California, I received a letter from this man that I would like to read into the record. It is dated February 21:

DEAR MR. ELFSTROM: Thank you very kindly for your reply to my letter. Your information is deeply appreciated.

"I am not a fluent writer, but I would like to furnish you with a résumé of our horrid experience with Chloromycetin, hoping perhaps it might prove to be of some value to you in Washington, D.C. I would also like to assure you that if we can personally help in any way, we would be most happy to do so. We will even come to Washington on February 28 if there is anything we can do to help.

Our 15-year-old daughter, Chris, was given 52 capsules of this drug in June and July of 1967 for a sore throat. Blood tests were not taken prior to or while she was taking this drug. A throat culture was not taken. My wife, daughter, or myself were not familiar with this drug. Chris was allergic to sulfa, but I do know there are many other antibiotics of a less toxic nature that could have been prescribed.

The first visible symptom was discovered by us the latter part of August, blood spots under the skin. We took her immediately to the same doctor who prescribed the drug and who had been our family doctor for 5 years—and he took the first blood tests. Her platelets were destroyed.

That is the congealing factor of the blood. If you don't have platelets, you will just bleed to death.

So he sent us to the Iowa City Hospital. Chris was checked very thoroughly, bone marrow, etc. They diagnosed "Thrombo cyto penic purpura" and commenced with high dosages of cortisone. She was there a couple of weeks and was allowed to come home. She kept failing so we entered the local hospital and in a few days were on our way back to Iowa City, where she had another bone marrow test and more blood tests. This time they thought she had leukemia; we decided to take her to Mayo Clinic. Three days of intensive testing and they diagnosed aplastic anemia; we had not even heard of this disease and felt a great relief. This was the first time we were alarmed about Chloromycetin.

We flew back home and in a few weeks she was again admitted to the local hospital for blood transfusions. Our local doctor was beginning to treat us different and even sarcastic, and in a subtle way wanted out from under the case.

One night at 12:30 a.m. she started bleeding profusely from her kidneys. I immediately called the doctor and he told me a little blood looked like a lot. I told him I knew better—he did not come to our home. The next morning about 7 a.m. I took a urine specimen to the hospital and in a few minutes he telephoned and alarmingly stated it was raw blood.

The internist at Iowa City was gone for the week, so I chartered a plane to Rochester where she was admitted to the Methodist Hospital, with Dr. Bayrd, a hemotologist, in charge.

Chris was given four or five platelet transfusions and four or five pints of blood. She died exactly 2 weeks to the day we entered Rochester, from an overwhelming infection on November 3, 1967.

In other words, when your antibodies are gone—these are the disease-fighting particles of your blood—and when they are gone, any infection can take over.

We allowed an autopsy hoping it might help some other victim. In a letter from Dr. Bayrd he termed her death "a monumental disaster and a great tragedy," and stated the drug should be used very sparingly.

We flew back home that evening; the doctor telephoned me; I asked him how many capsules of Chloromycetin he gave her. He reported 12 capsules and said "I'm sure that it didn't cause aplastic anemia," and that he was going to continue to use it. I have documented evidence that he prescribed 52 capsules.

Incidentally, there is a case in California of a six and a half year old girl that died from aplastic anemia at the City of Hope Hospital which you have all heard of. And when the father began to check into the reason for it, he asked the doctor what he had given here. He had changed on his record the name of the antibiotic to TAO. But the father had been smart enough to get to the pharmacy first, and he found out that she had had two prescriptions of Chloromycetin. I will go on with the letter:

I would like to ask the president of Parke, Davis several questions:

(a) If he or his wife watched one of their children die a little bit each day for 11 weeks with a disease that struck our daughter like rat poison, if he could still take pride in his promotional prowess?

(b) How would he or his wife answer this question from a 15-year-old daughter "Mommy what is happening to me," and "why is God doing this to me," on the day that she passed away?

(c) Could he go back to his office and watch the sales soar after watching his wife collapse on the hospital corridor floor?

(d) How would he go home and tell an 11-year-old son he no longer has a sister who never did one thing wrong in her life but trust doctors?

(e) Could he watch his wife turn from a happy, beautiful woman of 123 pounds deteriorate to 87 pounds and go back and step up the production of Chloromycetin?

(f) Could he spend 24 hours a day for 2 weeks with his daughter at Rochester, and return to the factory to see how sales are coming along?

My wife had to resign from teaching school this year. I taught school and was a superintendent of schools for 12 years. My point is that we are fairly well educated and yet allowed our daughter to die needlessly.

I did not intend for this to be so lengthy. Again thank you for your information and please give me the privilege of helping you, if you think I could. I am enclosing a picture of my daughter; perhaps the Parke, Davis president would like to study it for a while.

I want to show it to you.

(The photograph was displayed.)

Mr. ELFSTROM. I want to keep the photograph, but she is the picture of perfect health.

I will proceed with my statement.

Since 1961, there have been a number of bills introduced in the California Legislature designed to control the indiscriminate use of Chloromycetin. Several called for a warning on the label going to the patient, with different wording, and one restricted use of the drug to hospital administration. None of them passed, even though doctors and dedicated men of medicine testified in their favor, due to the vigorous opposition of Parke, Davis, the Association of Pharmacists, and the California Medical Association.

Following failure of the bills, resolutions were passed calling for hearings by committees from both the senate and the assembly, and

requesting the State department of public health to make continuing studies of the relationship of Chloromycetin to the development of aplastic anemia.

These studies by the department of public health, the only ones so far made anywhere in the world to our knowledge have revealed that instead of the incidence of aplastic anemia following Chloromycetin from one in 800,000 as was introduced in evidence in a lawsuit here in Washington, to one in 36,118 with an average dose of 4.5 grams, or one in 21,671 with an average dose of 7.5 grams per person.

When we first started working on the problem we tried to seek some cooperation from the Food and Drug Administration. But we just wasted our time. In fact, in one of his many communications to us, the then Commissioner, George P. Larrick, brushed us off with the statement:

> I am convinced, based on the views of FDA's medical staff and eminent medical authorities who are experts in the field of antibiotic use, that Chloromycetin is a valuable drug which saves more lives than it destroys.

Senator NELSON. When was that statement made by Mr. Larrick?

Mr. ELFSTROM. In a letter to me, sir.

Senator NELSON. What year?

Mr. ELFSTROM. 1962 or 1963, I have forgotten which, but I have a copy of the letter. Can you imagine this coming from the head of the FDA? Knowing what we did about the many tragedies that followed the indiscriminate use of this drug, this statement we considered an insult to our intelligence.

We did not fare any better with the Medical Director of the FDA, Dr. Joseph F. Sadusk, Jr., who, we observe, subsequently has been appointed a vice president of Parke, Davis. Strange bedfellows.

We understand this man tabled a suggestion made by his deputy to reopen the question of Chloromycetin labeling in 1966.

Senator LONG. Let me see if I get this straight. Do I understand that Dr. Joseph F. Sadusk, Jr., was a Medical Director of the Food and Drug Administration, and supported Parke, Davis in their conduct, and that he subsequently became the vice president of Parke, Davis?

Mr. ELFSTROM. That is right, sir.

Senator LONG. So he helped them with this activity and then took a job from them?

Mr. ELFSTROM. Draw your own conclusions.

Senator LONG. I would say that this was very effective public relations work on their part.

Mr. ELFSTROM. Dr. Watkins has some other information that you will find helpful.

We are happy to acknowledge, however, that the present Commissioner, Dr. James L. Goddard, and the current Director of the Bureau of Medicine of the FDA, Dr. Herbert L. Ley, have been cooperative and seem to be trying to find a solution to the problem.

We know organized medicine will vigorously oppose any change, insisting that its prerogative to prescribe for its patients—a captive audience in every sense of the word—should not be interfered with. But how it can stubbornly insist on no restrictions in the face of evidence that has been piling up for years now of the continued indiscriminate use of this antibiotic is beyond comprehension.

We don't know how many times we have heard the statement made

by the profession that the problem can be solved by education. We submit, this process of educating physicians in the proper use of Chloromycetin has been going on now for nigh on to 20 years and still abuses continue.

The other day a man who has devoted the past 10 years to seeking adequate legislation in California which would censor and/or reprimand physicians who carelessly and repeatedly violate the code of good medical practice, dropped by to see us as he also has been interested in the Chloromycetin problem. He said one of the physicians in his city had the audacity to tell him that doctors would have no worry about prescribing Chloromycetin if they carried plenty of malpractice insurance. This is unbelievable.

A physician here in our city who evidently was full of misinformation about the drug and the work we had been doing, said to a friend of ours that we should be behind bars.

In January of last year the CMA News of our California Medical Association, stated:

> No reasonable basis exists for enactment of a special legislative category to restrict the use of the drug chloramphenicol by licensed physicians in California.

And this was after release of the latest study of the department of public health which revealed an increase in the incidence of aplastic anemia following use of the drug as mentioned above.

We wrote the association, in part, as follows:

> If a layman can accummulate continuing and mounting evidence that this potent antibiotic is being prescribed for minor infections (in most instances without blood studies) contrary to the specific warning issued by the Food and Drug Administration, you must know it, too.
>
> Unless you can guarantee that members of the profession will pay heed to the FDA warning literally, you are going against the public interest by opposing legislation which would make such adherence mandatory.

In reply the executive director of the CMA concluded his letter with:

> Your concern is understood and appreciated, but your conclusions and suggestions do not agree with those of this association. The medical profession has had a long and honored history of striving to protect the public interest, and will continue to do so in the future.

We were pleased to note that the several eminent men of medicine who appeared before this committee 2 weeks ago agree that some restriction—legislation or directive—is necessary and advisable.

During the hearing on Chloromycetin conducted by the California Senate Factfinding Committee on Public Health and Safety, held in the State Building in San Francisco, Kenneth McGregor, the then vice president of Parke, Davis—who presented a prepared statement—was asked by one of the senators whether he would consider it bad medicine for a physician to prescribe Chloromycetin for a common cold or sore throat. Mr. McGregor hesitated for quite a while before he answered and then said it was a loaded question which he did not feel he should answer.

Despite the opposition that developed, our crusade, if one could call it that, has been endorsed by a number of well-known men of medicine who have encouraged us in a task they knew would meet strong opposition but which they felt needed exposure by someone outside the medical profession.

To name a few:

From Dr. Walter C. Alvarez:

I am so glad you are carrying on this fight. I think my old friend Dr. Meyer's suggestion of using certain drugs only on hospital patients is a good one. I plan to have another column on the subject which is stimulated by your good work.

I have received many sad letters from people who have told me of the death of a child or relative—due to the unwise use of Chloromycetin—often for a mild illness.

From Dr. Daniel Liebowitz, prominent bay area internist who was asked to testify at the San Francisco hearing:

You will have been of service to medicine if you can continue to spur legislation that will guarantee an adequate warning to patient, pharmacist and physician.

From the deputy director of our California Department of Public Health:

We do appreciate your deep interest in this matter and the highly effective manner in which you are exerting leadership in an effect to bring about an adequate solution.

From Dr. Karl F. Meyer, of the University of California Medical Center, San Francisco, whose reputation is worldwide:

We (referring to Dr. Maxwell Finland of Harvard University) both sincerely hope that you continue your efforts along the lines you have so auspiciously initiated.

Others included Dr. Chaucey Leake, professor of pharmacology of the University of California, San Francisco, who came to Sacramento in behalf of legislation to control use of the drug.

Another man of medicine whom we admire is Dr. Philip Condit, head of the division of infectious diseases for the California State Department of Public Health. He headed the Chloromycetin study for the department and he and his staff deserve much commendation for their painstaking devotion to seeking the truth.

In the California Senate hearing in Los Angeles he said:

Chloromycetin, an antibiotic recommended for use only in very serious infections, is killing people to whom it need never have been given.

In the current—February 1968—issue of the Reader's Digest, the Pharmaceutical Manufacturers Association has inserted an eight-page advertisement headed: "Medicines and Your Family's Health" which extols U.S. Patent 2,483,885, Chloromycetin. It states, in part: "The new drug, which was to prove effective against dozens of diseases, also caused occasional, and sometimes serious, side effects in some patients," minimizing its potential danger and saying nothing about the deaths that have resulted from its indiscriminate use.

It has been our understanding that since the passage of the Kefauver-Harris amendment to the Food and Drug Act, advertisements for prescription drugs must carry at least a summary of any warning required by FDA regulations. Here is a case in point where such a requirement obviously has been ignored. It is a full-page advertisement in the February 1968 issue of the Bulletin, a publication of our Orange County Medical Association, which states above a picture of a physician sitting at a hospital desk, simply "A Name You Can Count On When It Counts—Chloromycetin (chloroamphenicol)—Parke Davis"—and in small print "Complete information for usage available to physicians upon request."

Earlier this month Mrs. Elfstrom received a letter from a graduate student in biochemistry at one of our midwestern universities. Being

a member of the same church organization we are members of, she had just recently learned of our tragedy, and she wrote to tell us what she had been doing about Chloromycetin.

We were very much interested in what she had to say and we believe you will be also. In part, she wrote:

> During my undergraduate studies at the University of Colorado, I worked in a hospital laboratory. At this time, I witnessed the very needless deaths of several people—especially young people—because of this unreliable drug. Realizing the dangers of Chloromycetin, I decided to thoroughly research the drug and its actions for my thesis when I entered graduate school.
>
> During the past 12 months, I have worked with organ cultures of all types of blood marrow, including human marrow obtained from pathologists. I have used many different dosages of Chloromycetin on the cultures—have worked with rats, monkeys, and humans (in vitro—to the extent of using human blood marrow). Countless numbers of blood slides have been made and much work has been done with electron microscopy to determine changes within the various systems of the body.
>
> We feel at this time that we are on the verge of understanding the mechanisms of chloramphenicol that causes the blood marrow to cease its function. We are quite certain that it is caused by the extra radical compound that chloramphenicol has that other antibiotics do not.
>
> * * * Our next step is to prove that Chloromycetin is much more harmful than helpful and is grossly overused.

The Congressional Record appendix of January 30, 1961, page A583, contains this statement by Dr. John M. Adams, chairman of the Department of Pediatrics at UCLA:

> Contrary to the belief of many doctors, Chloromycetin has an effect which is harmful in varying degrees to the bone marrow of all persons who take it. This effect, which can become manifest as a lethal disease called aplastic anemia, is not limited to certain susceptible individuals but is a universal effect.

The time is long past due when the medical profession should be stopped from playing "Russian roulette" with this potent drug. And it is dedicated men like you, Senator, who can bring this about.

May God bless you, richly.

Senator NELSON. Thank you very much for your testimony, Mr. Elfstrom.

Mr. Gordon?

Mr. GORDON. I have just one question to ask you. How do they handle the use of chloramphenicol in the Los Angeles Hospital?

Mr. ELFSTROM. I understand in the General Hospital that each prescription for Chloromycetin that is written by the doctor in the hospital has to be countersigned and OK'd by the head of the services.

Mr. GORDON. They do have restrictions?

Mr. ELFSTROM. Even in the hospital.

Mr. GORDON. Even in the hospital.

Senator NELSON. Are either of you doctors personally familiar with the practice in the Los Angeles Hospital on the use of chloramphenicol?

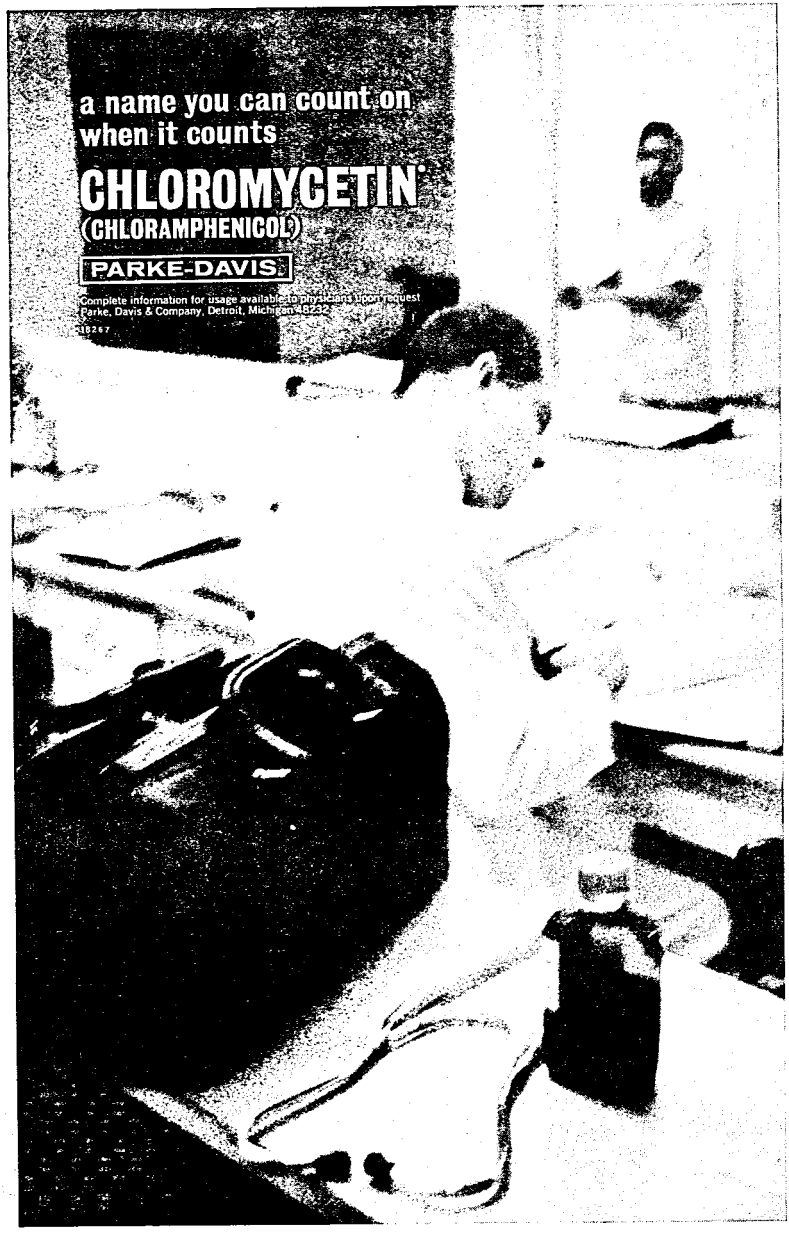
Dr. FARMAN. I used to be on the staff, but I am not at the moment.

Senator NELSON. Our next witness will be Dr. Albe Watkins, of La Canada, Calif.

Mr. ELFSTROM. Excuse me; for the record, I would like to submit the original of that advertisement. And this is a photocopy of that doctor's letter.

Senator NELSON. They will be included in the record.

(The material referred to follows:)


a name you can count on
when it counts
CHLOROMYCETIN®
(CHLORAMPHENICOL)
PARKE-DAVIS
Complete information for usage available to physicians upon request
Parke, Davis & Company, Detroit, Michigan 48232
18267

KOUNTZE, TEX., *April 3, 1961.*

EDGAR F. ELFSTROM,
Daily News Tribune,
Fullerton, Calif.

DEAR MR. ELFSTROM: Senator Estes Kefauver has suggested I write you concerning the following matter, with which I gather from his letter, you are already tragically familiar.

In Feb. 1961, my 7½ year old son died from aplastic anemia due in the opinion of the 5 specialists, including the State's outstanding hematologist, who attended him, to the routine administration and dosage of Parke Davis' Chloromycetin (Chloramphenicol) by me for an ear-throat infection *on the advice* of representatives of Parke-Davis who repeatedly assured me of its safety, and urged its use, *routinely,* in general practice.

Almost simultaneously, there were 2 other deaths in this area, a child and an adult which appear to be attributable to the same cause.

I am contemplating legal action against Parke Davis Co.; please advise me of your experience in this matter and how we who have had this terrible result in common may cooperate to the best interests of medicine and humanity.

Respectfully,

H. A. HOOKS, M.D.

Senator NELSON. Dr. Watkins.

STATEMENT OF DR. ALBE M. WATKINS, LA CANADA MEDICAL CENTER, LA CANADA, CALIF.

Dr. WATKINS. As Mr. Elfstrom has already stated, I, too, am greatly honored that you have accorded me, a California country doctor, this privilege of speaking before this august body.

Practicing physicians are directly influenced by representatives of pharmaceutical companies or by journal advertisements to the extent I would estimate of 75 to 80 percent of their prescriptions. The remaining 20 to 25 percent may be influenced by medical school or medical association lectures—many representatives of the former may be working on grants from these large pharmaceutical companies.

With reference to Chloromycetin (chloramphenicol), Parke, Davis in the early years completely omitted any report of toxicity for at least 16 to 18 months. This complete disregard of basic morality was directly responsible for my son's death. Later when forced to mention possible reactions they played down any such reports or insisted, as they did at conventions of AMA, that there was not any proof of the drug Chloromycetin causing death. They insisted other medications had been taken concurrently as iron, aspirin, etc., for a long time.

This drug was given me by a representative of Parke, Davis. And I have made it a habit when they come in to extol the virtue of the drug to ask them about the reactions first. And this man told me there were no reactions, this was a perfectly safe antibiotic. So I took the drug home and placed it in my medicine cabinet.

A few days later my son suffered a urinary tract infection, and I went to the cabinet and I looked at the drugs I had. I picked up a bottle of sulfa, and I said, I don't want to give him this, because this might depress his blood-making system, his hemopoietic system. Imagine that. And I looked at Auromycin and Terramycin, and I said, sometimes this upsets the stomach, and I don't want him to get sick with the drug.

And then I spotted the Chloromycetin. And I gave him the Chloromycetin, which caused his death several months later.

A druggist, about 2 blocks from my office asked me "How did you happen to give him Chloromycetin?" This was in 1952. And I said, "This was the one drug that I thought was harmless."

The pharmacist told me, "I told that representative 3 days before that that the drug was harmful, that a lady had died in Pasadena"—which was about 3 miles away from my office. So the representative of Parke, Davis knew at the time he gave me that drug, he deliberately lied to me that the drug was harmless.

And as I said, I went home and some days later gave it to my son, and that was the cause.

This representative of Parke, Davis was given a 3 months' leave of absence. He later sold his home and moved out of the area. I understand his health was not too good after that.

Parke, Davis has been one of the leading grant pharmaceutical companies, but by strange coincidence these grants always seemed to go where the criticism of their product, Chloromycetin, was the hottest, as to Dr. Doan, of the Ohio State University; University of Michigan; and many, many others. Mysteriously very little criticism of Chloromycetin continued from these schools after a Parke, Davis grant. A Dr. T. E. Woodward, University of Maryland, and many others receiving substantial funds were always very vociferous in their praise of the drug in the face of evidence of its toxicity.

It is my opinion that Parke, Davis was not nearly as interested in finding out why the drug was toxic as it was in stifling criticism.

A Dr. Smith, formerly of AMA Council of Drugs, which at that time was critical of Parke, Davis promotional tactics, was given an executive position with Parke, Davis, as was more recently a former FDA official. I think he is today president of Parke, Davis. There was a rumor Dr. Welch, former head of the Antibiotics Division of the FDA, had some financial interest in Parke, Davis.

While my own lawsuit was pending, a well-known ethical writer, David O. Woodbury, Scottsdale, Ariz., came into my office to inform me Parke, Davis' chief attorney from New York had contacted Mr. Woodbury in his New England home, flew up, and had breakfast with the only purpose in mind to find out about my character. Mr. Woodbury said he found it difficult to understand the gutter tactics of such a large, so-called ethical corporation.

There has never been adequate control of this drug or its advertising. The company was guilty of withholding all reports of reactions of the drug from the time of introduction until made to do so by AMA and FDA some 1½ to 2 years after its introduction. They engaged in a series of correspondence with the families of the victims, denying any reactions and trying to blame any such reports on other products like aspirin taken at the same time.

They were always very polite in expressing their sorrow at the loss of the child or the adult and were always glad, they said, to hear from the relatives of the victims at any future date. In my case, they were not so polite but accused me of vilifying their innocent officials.

They immediately, however, notified AMA and FDA of some reported reactions, reports which they had been withholding, for the first time after hearing from me because I told them I was writing to AMA and FDA concerning these reactions—reactions which they

had been sitting on for at least a year or a year and a half before receiving my letter. Their advertising during that period of time carried not one word of warning until they were forced to include this by both AMA and FDA.

This is the letter I wrote to Parke, Davis when I heard my son—they first thought he had leukemia, they had gone through the usual routine, many doctors diagnosed it as granulocytopenia-purpura or leukemia. And hematologists in those days were able to decide it was aplastic anemia.

This was the letter I wrote to Parke, Davis on May 5, 1952:

DEAR SIRS: This story is of the tragedy in one man's family due to his faith in a "reputable concern and the representatives thereof" concerning a product of theirs, a "harmless antibiotic." We know the drug is harmless because every few days we get a bulletin from the company which has plastered all over the outside envelope "No evidence of intolerance," "No untoward effects with these children." "No evidence of toxicity," "No clinical manifestations of toxic symptoms," etc. ad infinitum. We felt doubly sure that this drug was safe because we asked the salesman point blank about the gossip concerning its toxicity particularly from one prominent hospital—the Children's Hospital—I had heard two days before that there was some drug over there, and he wasn't quite sure, the man who told me, but he thought it might be Chloromycetin. But the salesman said no, it was not their drug, he didn't know anything about that.

And he denied that any criticism of his product existed. We now know that he was duly informed, as this drug house will know later.

We have—or had—by the time you receive this letter, four sons. Our third son unfortunately was born with a single kidney, and underwent plastic surgery 1 year ago on the ureter. He was getting along very well, watched his health like an adult, and participated in all usual activities of a ten year old. We were out of town for two days around the middle of February and unfortunately he developed a little Cystito-pyelo-nephritis, with a fever of 102 the day we returned. Being duly cautious of his health, I started to give him some penicillin, but thinking it was probably a gram negative infection decided sulpha or an antibiotic would be better. We decided not to give sulpha as it might depress his hemopoletic system (imagine) and we considered Terramyacin or Aureomycin might cause gastroenteritis—but then the thought recurred that we had another antibiotic which was entirely harmless and very effective. I might have done better had I taken a gun and shot him—at least he wouldn't have suffered.

We, as parents are an M.D. of some 16 years practice. My wife, a graduate nurse of approximately 18 years, and our children being our only possessions of value, are well cared for. We noticed approximately 10 days after his 3–4 days of this harmless antibiotic, our son was very pale and a blood count revealed a depression of all components of 50 per cent. A repeat two days later was further depressed and petechial hemorrhages started. Our life from here on has been as near a hell on earth as you can imagine. Here, a very intelligent, handsome little ten year old, who is so conscientious about his health he can't rest night or day, wondering why he is suddenly so ill, and bleeding, necessitating eight transfussions in as many days. He has had over 150 shots of penicillin, streptom ACTH. Vitamins, etc. Imagine, I didn't want to give him one shot of penicillin for his 102 fever.

I would like to see the directors of this reputable company sit by this little fellow's bedside, see his worried expression and try to explain to him what happened. I would like for the learned scientist who developed this "harmless drug" give him every one of his 150 shots, as I've had to do—lay awake night after night, watching his every movement, wondering why it had to happen and praying asleep and awake finding it was a bad dream, and James is as healthy and fine as ever.

This reputable old established company now knows this drug isn't harmless—as they have known for some time—we appreciate the company's asking for, and being granted the permission to notify all doctors of toxicity—only about two years too late, and the climate is getting little too hot, the truth is finally out. Think of all the money that has been made by this product between the first reports of the toxicity and now. Can such a leading pharmaceutical house be

ignorant of the undercurrent that has been gathered over the country from Mayo to Harvard, to Boston, to Johns Hopkins, to Salt Lake City, to Texas and California.

While James was sick, I wrote all over the country. I tried to find out about this, and I had letters from all these places I mentioned.

We naturally reported it to the AMA. This company can give me credit for not being afraid to speak. I have nothing to lose from here on out, to the government, or Pure Food and Drug, and we assure anyone interested, we are not finished. All of this is small recompense for the life of my beautiful, talented son—in convincing this company—(but not from warning them, that was done months ago) that the laws of Christianity apply as much to a corporation regardless of their wealth and influence as to the lowly man on the street.

If nothing more comes of it, we have lost our son, this company has lost more—for a dollar it has sold its honor and each individual in this concern, who is connected in this travesty of justice will remember it as long as they live and be judged accordingly thereafter.

After he died, I put the family and three little children in the car and took off. We didn't know exactly where we were going, but we thought we would end up at the FDA. I would drive 400 or 500 miles a day and stop at a town. And when we stopped in the evening, I would go through the classified phone book and call just any doctor and ask, "Have you heard of anyone having reactions to this drug?"

Coming across the United States, I picked up 15 cases from California to the FDA. When I finally arrived here in Washington on a Friday afternoon, Mr. Welch's secretary didn't want to let me in. I guess I didn't appear like a professional man. But I had driven all the way across the country, and I said, "I have come from California. I will sit here until he does let me in."

And he was very cordial to me. And he said I was the best agent he had. As a result of my coming across and acquainting him with the ones I had picked up across the country, they did the first survey.

I left Washington and went to Philadelphia and Boston. When I arrived in Boston some 3 or 4 days later, they had picked up 188 cases that they knew nothing about before I made this trip across here.

And then I made a similar trip. We drove 11,000 miles the first year, and 9,500 the second year. I tried to go to all the universities, I tried to see what was going on. I went to Johns Hopkins—I have a letter from Johns Hopkins, by the way.

In 1952 there was a directive from Johns Hopkins that for this drug to be allowed two or three doctors had to sign the order. And they were very careful in Johns Hopkins in 1952, they knew it was a dangerous drug.

Senator NELSON. May I interrupt for a moment? You mean before the drug could be administered in Johns Hopkins as early as 1952, that hospital's practice was to require the countersignature of another doctor on the prescription?

Dr. WATKINS. Yes, sir.

Senator NELSON. And the head of the service?

Dr. WATKINS. Dr. Conley was head of hematology. He was very kind to me. And he told me he had correspondence with Parke, Davis. I have other letters here——

Senator NELSON. I want to finish the point on the use of the drug in Johns Hopkins as early as 1952. Before it was administered, it was

required that more than one doctor sign the prescription or the order for the drug; is that what you were saying?

Dr. WATKINS. Yes, sir. They put out a bulletin. I have it here, at Johns Hopkins for all interns and residents to read.

Senator NELSON. Do you have a copy of it?

Dr. WATKINS. Yes, sir.

Senator NELSON. What did it say?

Dr. WATKINS. This letter was written to me on September 1, 1952.

Memorandum: Subject: Chloramphenicol.

At the request of Dr. A. McGehee Harvey, the following is submitted for the information of the entire medical staff of the Hospital:

Cases of aplastic anemia attributable to the administration of chloramphenicol are occurring throughout the United States with alarming frequency.

Observations to date suggest that two types of reaction may occur. Occasionally patients receiving this drug develop evidences of bone marrow depression during therapy. This may be manifested by leucopenia, granulocytopenia, thrombocytopenia and anemia. In our experience in this Hospital there is suggestive evidence that this type of bone marrow depression may be treated to the plasma concentration of the drug since most of our patients either had received large doses, or had evidence of renal insufficiency. In these cases the blood has returned to normal after the drug was discontinued.

A much more serious type of reaction concern the production of a real aplastic anemia. In cases of this type the occurrence of a blood disorder has apparently most often been associated with repeated administration of the drug, suggesting that a prior sensitization has occurred. In many of these patients relatively small doses of chloramphenicol have been used, and the blood disorder seems definitely not to be related to plasma concentration.

An outstanding feature of the aplastic anemia associated with the use of chloramphenicol has been the development of profound thrombocytopenia. In all of the fatal cases which have come to my attention, death has resulted from hemorrhage. Leucopenia and neutropenia occur, but present a less serious problem. Anemia in most of the cases apparently has been mild, except for that which can be attributed to hemorrhage. In a number of patients, death has not occurred for many months after the initial bone marrow depression. Efforts to bring about bone marrow regeneration through the use of ACTH, cortisone, and numerous other agents have been extremely disappointing. Observations to the present time suggest that unless recovery occurs soon after the drug has been discontinued, it is not likely to occur.

It seems not unlikely that as more individuals are sensitized by the use of this drug, the incidence of aplastic anemia may increase. For this reason, and because of the serious nature of aplastic anemia, I believe that the drug should be used with very great caution. I recommend that chloramphenicol be used only for the treatment of seriously ill patients suffering from infections not amenable to treatment with other antibiotic or chemotherapeutic agents. When chloramphenicol is used, blood counts should be performed. However, I doubt that the precautions of frequent blood examinations will eliminate the danger of the use of this drug.

That is very important, because they always said that you should get a blood count. But many people didn't show anything wrong with their blood count when they were taking it. This blood disease order came on months later, and a blood count did not help you at all.

"It seems not unlikely that by the time blood changes have occurred, the disorder may be irreversible."

This is by Dr. Edwin L. Crosby. I am sorry. I do not have that one. But Dr. Conley had to OK every bit of Chloromycetin that was used. And I personally talked to Dr. Conley, who was head of the department at that time. I am sorry, I thought I had that letter with me. My recollection is, I was in his study, and he told me he had to OK it every time it was ordered, that he had to pass on it. And they watch those cases very carefully.

Senator NELSON. Before it could be administered to any patient in that hospital?

Dr. WATKINS. Yes; they did daily blood counts on it.

On my two trips across the United States, stopping at nearly every university and inquiring in every good sized town, concerning reactions to Chloromycetin, I was convinced of many things.

No. 1, that every case investigated, the victim would in all probability have survived the original illness had they not been given any Chloromycetin.

No. 2, that I would not gain much information from my own profession. A doctor in Charleston, W. Va., Dr. William Thornhill, who had lost a 16-year-old son with five capsules was very helpful, but an internist in Colorado would have no part in helping me, saying "My daughter is gone. It was God's will."

A psychiatrist in Oregon would not even see me. In all, we had records of around 30 physicians who either died or lost a member of their family. I feel convinced that many victims have been signed out as leukemia, and any doctor who had lost a case through his ignorance and malpractice would not leave a stone unturned in an attempt to cover up his malfeasance.

This was way back in 1952. Doctors were particularly hard hit in those days, as I was, because we had great faith in Parke, Davis, we thought they could do no wrong, we thought if a Parke, Davis man came in our office and told us something was good, it was good. And that is the reason that this list we have here of doctors who have lost their life or their wife or one of their children were hard hit. And all of these, I think, have notified Parke, Davis. And this was previous to 1952.

Some doctors are always comparing the calculated risks of using this drug with anticancer drugs and other dangerous drugs seldom used, usually used in hospitals, and only used in almost hopeless cases. They do not try to understand this drug is used on relatively healthy innocent little children with mild pharyngitis or some similar disease. In my records of many deaths, most of these victims had sore throats or urinary infections, although quite a few were treated for acne.

You take a culture of someone with an infection in the hospital or throat or otherwise, and then you culture this on an agar medium. And Chloromycetin always comes back, it is always the drug, it is always the drug of choice, it is always No. 1. It is the one that the organism is sensitive to. Doctors were very much impressed with that until they became better informed.

Doctors are impressed with in vitro studies in which Chloromycetin is always shown to be the really effective antibiotic—they do not stop to think that carbolic acid in the agar plate culture would give a similar inhibiting, growth reading because it, too, is poisonous.

I think Chloromycetin is so toxic that it kills the germs in the agar plate. As I say, many other poisons would, too. But the thing we have to understand is that doctors are human. We are in a competitive profession, believe it or not. Every doctor is competing in the healing art, and he wants to make and perpetuate a good image of himself as a healer.

So naturally he wants to use the drug that is going to give results, because that is the way he gets his patients to come back to him.

The Government and the pharmaceutical industry must take steps to protect the public, which my profession has failed to do. Long before the reactions were common knowledge, all reputable drug companies knew Chloromycetin was a dangerous drug.

Before I knew it in 1952, other men came in and told me, representatives of other companies told me this. They so informed their salesmen but warned them not to make the profession or public aware, not to talk against a competitive product. After all, they, in turn, might be detailing something dangerous.

I told one or two companies in those early days, especially Eli Lilly in Indianapolis, that there should be a central policy-governing body to reprimand and inhibit the unprofessional conduct and unethical practices of a few—otherwise they would all fall victim to severe Government supervision of their entire industry.

The day is here, and many restrictions are already in evidence at this time. If, as Parke, Davis advises, this drug should be used for typhoid fever—where I am told it converts many acute cases into chronic carriers—and for rickettsial fever and salmonella, what do you think the gross sales would be since there are so few cases of these diseases in our country?

Do you know anyone that has typhoid fever or any of these diseases? As a professional, I haven't seen one case of typhoid fever in 10 years. Compare this gross figure of, say, approximately $100,000——

Senator NELSON. I believe you are talking about the cumulative sales over a period of time. I believe the sales were $70 million worldwide in 1966, and $45 million in the United States.

Dr. WATKINS. I am not sure. It seems to me like I have a recollection of the sales being close to $200 million.

Dr. FARMAN. $40 to $50 million.

Mr. ELFSTROM. In 1960 it was $60 million.

Dr. WATKINS. I thought it was very high in the fifties. I knew it was the most commonly used.

Senator NELSON. I am talking about the testimony as to current sales. I don't know what it was in previous years.

Dr. WATKINS. Compare this gross figure of, say approximately $100,000, if it were sold and used for diseases in which it might be of benefit, with a known calculated risk, to the millions grossed from the misdirected and criminal use of Chloromycetin.

I have a large, general practice averaging approximately 40 patients daily in the office, and numbering six to 12 patients in the hospital all the time. Although I have not ordered Chloromycetin for any patient in the last 16 years, and have not lost one patient with infection, I have had consultants on my cases use it. And never once, so help me God, have I seen a patient saved or benefited by the use of this drug.

You say, what happened to it? For instance, we had a case this year that had a subacute bacterial endocarditis. The man was supposed to be allergic to penicillin. We tried various things, and nothing worked. And my consultant had permission to use chloramphenicol. I was interested in saving his life. It was a calculated risk, he would have died anyway. We had him on it for a week. It did nothing for him. And then we had to take a chance. He was supposedly allergic to penicillin, but we tried penicillin. And the man got well.

I have talked to my colleagues and some believe they have on occasions seen good results, but I would feel in many of these cases another antibiotic would have done just as well. They resorted to Chloromycetin before I would have used it.

The statistics offered by Parke, Davis for many years of one death to 400,000 users were challenged time and time again by reputable men. We challenged them away back in 1952. In my little area of 15,000 people north of Glendale, north of Pasadena, and north of Los Angeles, when this happened to my son, we had four cases within a radius of 4 miles, four cases.

Now, you can magnify that over the whole United States. And they say one case in 400,000.

But the company aware of the discrepancy continued to advertise this ratio, because no one or no organization had the power to force them to be truthful and accurate. Now these odds have been reduced to what we estimated 12 years ago, and if the truth were known and these little victims were not signed out as leukemia or other similar blood diseases, then this ratio percentage of odds would be much further reduced.

This drug poisons in some degree every person who uses it. There is absolutely no way to prevent or to foretell where and when it will kill. The UCLA scientist said that. Everyone who uses this drug is poisoned in some way. Most of them recover. There is absolutely no way to prevent or to foretell when and where it will hit you. I mean this idea of a blood count every day does not mean very much. It might pick up some cases. But most of these cases have been recorded after they had the blood count, after they were out of the hospital when they first showed evidence, like my son did, weeks later.

Since most aplastic anemia cases die of brain hemorrhage can we not believe that many of the young and middle-age people who suddenly have a brain hemorrhage may have at one time been treated with Chloromycetin.

It is unbelievable that this drug has been allowed outside of hospital use for the past 15 to 16 years. Personally, I have little or no faith in its value over penicillin, tetracyclines, and erythromycins.

The abuses of this drug dates back to the time doctors were erroneously told as was I, that Chloromycetin was the only absolutely safe antibiotic. Parke, Davis deliberately lied to me at the time I was given the drug. Now all these years later, although doctors have been warned by advertising in medical journals, by lectures, by newspapers, by magazine articles, even by radio and television—still my profession continues to use Chloromycetin indiscriminately.

In my own small community of approximately 16,000 people, the drug is being prescribed. A few years ago, some really good friends and former patients called me in sheer desperation because their daughter whom I had cared for as a small child had been, without her parents' knowledge, given Chloromycetin for acne while attending the University of California at Santa Barbara. She was dying of aplastic anemia at the UCLA Medical Center and the family thought I might know, because of my interest in this drug, of some successful treatment. They could not believe that 10 years after our own tragic loss that they so well remembered that practicing doctors were still prescribing the

drug. This tragedy has been repeated time and time again, and will continue as long as the drug is not restricted in its use.

Would any of you gentlemen take the drug? Is there any doubt that if your doctor examined you in his office and said you needed an antibiotic, do you think you might just look at the prescription and ask your doctor friend what antibiotic he is giving you? The public deserves the same consideration and protection you, knowingly now, can afford yourself.

Senator NELSON. Thank you, Doctor.

Dr. WATKINS. I have one other letter here. This is from Dr. Wintrobe, who is, I think, head of hematology; he is a very well-known professor at Salt Lake City. This letter was written—I think it is the month of my tragedy; I wrote my letter on May 5.

Senator NELSON. What year?

Dr. WATKINS. 1952. And he had had correspondence at this time with Parke, Davis. He told them of the toxicity of this drug. I have another letter from a doctor—we were trying to inquire from someone that we had heard had died in Michigan. And here the doctor writes me and says he could not find out any information. He says the reason is the family is in a bad mental state, and he thinks if he inquires into this that it might upset them more.

That is what I heard all the way across the country. It was either God's will or he didn't want to upset the family any more.

Here is a letter written in 1953 from a M. D. Levin, Baltimore, Md. He says he thinks it is a dangerous drug. And he says, "My personal experience not only supports your statements"—he is writing this to a doctor who had written about it being harmful—"but I would confront them with the statement that I personally warned the manufacturer relative to this synthetic product quite a while ago."

This was in 1953, in September. They had adequate information.

And again I want to tell you how I appreciate the opportunity to come before you. And I feel that if something can be accomplished by this, that my son, Dr. Farman's daughter, Mr. Elfstrom's daughter, and probably hundreds of thousands of others probably will not have died in vain.

Senator NELSON. Counsel advises me that the figure I gave of $45 million in sales in 1966 were wholesale figures, so that it would be a higher amount on the retail level.

Dr. WATKINS. There is a little profit on it.

Senator LONG. I would like to question you about what you are saying here; that is, that assuming that this drug will kill, the number of deaths are far greater than anyone in this room knows. We lawyers used to joke about it. You take out title insurance. You think someone has good title to a piece of property he is selling, but we insure ourselves against our error, so that the insurance company will make good the loss in the event we make an error.

Lawyers always joke about it, saying that doctors have an advantage over lawyers; doctors can bury their mistakes—and they frequently do.

Now, in this particular case, just from my own practical experience, I know that doctors are very reluctant to admit they made a mistake.

Dr. WATKINS. Yes, very.

Senator LONG. Even if it were because someone lied to them or misinformed them, they are very reluctant to admit that they made a mistake.

I argued with my brother-in-law, who is a doctor, about whether I should pay a bill when a doctor improperly diagnosed the disease of a relative. And he advised me to go ahead and pay it, understanding what the problems are in medical practice. Being a doctor himself and the son of a doctor, he felt that I should by all means pay it.

I recall another case where a friend was suffering some malady, and a very reputable doctor advised him that this was a disease that was bothersome, but by no means serious, and advised him of what the treatment should be. Subsequently, he went to one of the outstanding clinics of the country, where his disease was diagnosed as cancer. The doctor who made the original diagnosis insisted, and stuck by his original conclusion right up to the point where they took out part of the body, and there was a great big piece of cancer. So, if he had stayed by the original diagnosis, the man would have been dead.

But there is no doubt about it, if your statement is correct—that these people die of this drug, that these figures—1 in 400,000—might be off by 2 decimal points. And I assume that you believe that that is quite possible?

Dr. WATKINS. Very definitely so; much higher than any estimate that has been made so far. For that victim the statistics are 100 percent.

Senator NELSON. Is there any place in FDA or anywhere else in the country where there is a record kept of all the known cases? Or is there any known procedure by which they are reported to any central place in the country?

Dr. WATKINS. Not that I know of, but there again you are going back to the physician. And I am loyal to my profession. I think it is the most wonderful profession on the face of the earth. But doctors are human beings, and they have the same weaknesses that anyone else has. And the average doctor is not going to admit a mistake if he can help it; I say the average. And for something as serious as this, if there is any way he can get out from under it, I think he will. I think it is proven.

Senator LONG. If he admits a mistake—and let's face it, doctors do make mistakes like anyone else—he is subject to the patients or at least the patients' relatives, going all over town and telling everyone they know that that doctor just killed that victim by prescribing the wrong drug. And that is a very grave injury to a doctor, I take it, to have that happen, when people go over the streets of his hometown saying that he killed somebody by prescribing the wrong drug.

Dr. WATKINS. That is true. I made a habit for years after this of going around to Parke, Davis at the AMA conventions and asking the reactions to this drug. They say, it has never been proven. I think they will tell you today that it has never been proven, they took aspirin or other things at the same time.

Senator LONG. The aspirin might have killed him.

Mr. ELFSTROM. That is what they told me.

Dr. WATKINS. It has never been proven. I have a letter from a doctor in St. Joseph, Mo., a very good friend of mine. And this was after the thing broke. And the salesmen were coming in and telling him

this. He said, "It might be of interest to know that Parke, Davis is now detailing this drug in this area. One was here in the past month, and I told him of your experience with the drug, and he denied that anything such as that was happening in the country."

Senator NELSON. What year was that?

Dr. WATKINS. This was in 1952. But this was long after all this broke, all this news broke, because my trouble happened in May, and they were forced to admit this trouble in June, I think, or July of that year. This was in December.

Senator NELSON. I take it from your testimony on page 5 that you believe that this drug should only be administered in a hospital. Do I understand you correctly?

Dr. WATKINS. It is my opinion anyone sick enough to take Chloromycetin is certainly sick enough to be in the hospital.

Senator NELSON. We have had testimony by previous medical experts here suggesting that it should be administered only in hospitals, and Dr. Gilman makes the same contention in his book on therapeutics, Goodman and Gilman, "The Pharmacological Basis of Therapeutics."

Would you suggest, then, that the FDA or somebody be authorized to require that this drug be confined to hospital use?

Dr. WATKINS. Absolutely, without any qualifications.

Senator NELSON. It has been suggested by some that this would be inconvenient, because some people are out in rural areas away from hospitals, and so forth. How do you evaluate that?

Dr. WATKINS. I would say that if, as they recommend, they have a blood count, if it is that rural, if it is that behind the times, they probably don't even have a means of taking a blood count of a patient. So I would feel today—this is America, and I think there are enough hospitals, I don't think there is any place where it would be impossible to get them into a hospital. I think it should be confined to them.

Senator NELSON. I notice that Goodman and Gilman say on page 1246, among other things, that chloramphenicol should not be used on an outpatient basis unless the physician and patient arrange and adhere to a definite followup schedule with visits at least every other day.

Dr. WATKINS. I agree with that. But there again, what is he going to do when he sees them, if he takes a blood count?

Here is a letter from the Mayo Clinic I would like to submit for the record but will read the last paragraph:

"The point that seems most important to me is the matter of sensitivity that develops to the drug and consequently the inability of following blood counts in order to avoid disaster in case the patient happens to be one of the sensitive individuals."

(The letter referred to follows:)

MAYO CLINIC,
Rochester, Minn., June 7, 1952.

ALBE M. WATKINS, M.D.,
La Canada Medical Center,
La Canada, Calif.

MY DEAR DR. WATKINS: Your recent letter to me has been held until I returned from a short vacation, consequently the delay in answering. I can certainly sympathize with you and know that any words we might offer are of little solace in view of the loss of your son.

I am quite sure that steps are being taken to both recognize and publicize the effect of Chloromycetin on the bone marrow and that in due time it will take its

proper place among our therapeutic agents, strictly in the field where it is required and where the risk of its use will have to be balanced against the need of its therapeutic ability. I have already presented at our Staff Meeting a report of ten cases of aplastic anemia secondary to Chloromycetin therapy. Six of these cases are already dead. This report will be published in the Proceedings of the Staff Meetings of the Mayo Clinic and I am sure that you receive these Proceedings regularly. If not, we should be very happy to send you a copy of this report. The cases, I believe, will be published in their entirety and there may be further follow-ups on the cases that are occurrent at the moment, by the time publication is complete. I could not, of course, supply you with the names and addresses of these patients for obvious reasons but the material in the Proceedings are, of course, open to all of the professions once they are published. Other hematologists, I am sure, are going to follow suit and publish their cases, in which Chloromycetin is the etiologic agent or at least the common denominator in these cases of aplastic anemia and I would think that within a period of six months many reports will be available and that Chloromycetin will have been put in its proper therapeutic niche. The point that seems most important to me is the matter of sensitivity that develops to the drug and consequently the inability of following blood counts in order to avoid disaster in case the patient happens to be one of the sensitive individuals.

I do appreciate your confidence in writing to me in this hour of trouble and while time will never erase your sorrow I do hope that it will soon lessen it.

Sincerely yours,

M. M. HARGRAVES, M.D.

Dr. WATKINS. The inability of the blood count, that is what he says, Dr. Hargraves, of the Mayo Clinic. This was back in 1952.

Senator LONG. Let me understand this, because apparently this company would contend that you are prejudiced, and there is no proof that this drug is what actually caused it, that these things might have happened anyway.

Now, do I understand it that reputable institutions like Johns Hopkins share your feeling that this drug may very well be causing these deaths, and that therefore, they would wish to use extreme care when this drug is administered? You say Johns Hopkins said that it should only be used when you have two doctors, is that right?

Dr. WATKINS. Yes. That is what Dr. Conley told me at Johns Hopkins in 1952.

Senator LONG. Are there other well known hospitals or organizations of doctors which have taken the same attitude toward this drug?

Dr. WATKINS. The Los Angeles County General does. That order has to be countersigned.

Senator LONG. So in Los Angeles County General they would insist that the order be countersigned?

Dr. WATKINS. Many hospitals have this requirement.

Mr. ELFSTROM. I think if you made a survey of all the hospitals in the country, you would find quite a few that have that requirement.

Senator LONG. So there are quite a few hospitals that have concluded that you are right about this matter; this is what has caused these deaths.

Mr. ELFSTROM. It is my understanding, Senator, that the Food and Drug Administration has this authority now to restrict the drug's use, to restrict the drug to the hospitals. In fact, they have the authority to take it off the market if they choose to. But we have never asked for that.

Senator NELSON. I am not sure as to what legal authority we have. Dr. Goddard will be testifying tomorrow. And this among other questions will be raised with him at that time.

I think I should say for Senator Long's benefit that the company does concede that in a certain number of cases, say, rarely, various blood dyscrasias do occur, including aplastic anemia. And they include that information, as they have been required to do since 1962, on the package insert, in their precautionary statement.

I think one of the problems is that despite the precautionary statement, a substantial number of the medical profession still continue to prescribe Chloromycetin for minor infections such as head colds and acne, and so forth and so on, whereas it should only be prescribed, according to the medical testimony we have heard, for typhoid fever and other groups of infections in which the disease is very serious, and for which there is no other antibiotic that will effectively do the job.

The tragedy is that it is being prescribed for all kinds of cases in which it is not indicated. But the company does not deny that.

Senator LONG. They have a patent, and they want to make a big profit every time it is used. And they get about 50 times what it costs them to manufacture it.

Dr. WATKINS. Here is a brochure that came out, I think, in 1959, from the company, and right down here at the bottom it says "This is using it on dogs"—"Anemia developed in various degrees in these animals."

And this is 1959.

Senator NELSON. What is the pamphlet?

Dr. WATKINS. It is Chloromycetin from Parke, Davis. They knew about it in dogs in 1959. Our tragedy was in 1952. His tragedy was in 1960.

Mr. ELFSTROM. I think in the testimony before Senator Kefauver's committee, which I followed very closely, there was evidence introduced that a Dr. Radomski, who was with the Food and Drug Administration at the time, had made a study of the drug on dogs, and had found some fatal effects from anemia. I think Dr. Radomski is now down at the University of Miami.

Senator NELSON. I think that is conceded scientifically.

One of the facts that we do not know is the precise incidence of blood dyscrasias, aplastic anemia, and so forth, because there has not been any really accurate statistical compilation. The statistics have always been guesses. As Dr. Watkins testified, it was once claimed that aplastic anemia would occur only once in 400,000 cases, and once in 200,000 cases, but there has not been a very scientific compilation of the statistics.

So I think it is conceded by the experts at least that these are all simply guesses. Is that not correct, Dr. Watkins?

Dr. WATKINS. Yes, sir.

Mr. ELFSTROM. In California, the department there states they can conservatively estimate the incidence as 1 in 21,000.

Senator NELSON. Of aplastic anemia? Are either of you doctors aware of evidence of other serious blood dyscrasias which aren't included in the statistics on aplastic anemia? In other words, are there other problems, other illnesses that occur as a consequence of this drug that do not result in aplastic anemia?

Dr. WATKINS. This has all evolved very slowly. You would not believe the difficulty we had in the early days of trying to prove it,

against the company's wishes, of course, and all that they were trying to say, that aspirin and other things would cause it. But as this man from Mayo says, this is a common denominator in all these cases that they got in the Mayo Clinic, and they had a lot of them in 1952, the common denominator that these patients had taken was Chloromycetin. Not all had taken aspirin or phenobarbital, but all of them had taken Chloromycetin.

So you had to do it the hard way. It has been a hard, uphill battle. And we said from the beginning that we thought many cases of leukemia were caused by the drug—either was actually leukemia or they were signed out as leukemia. As I told you at the beginning, it takes an awfully good hematologist to tell the difference between leukemia and aplastic anemia in the early beginning.

But there is a thought the Chloromycetin also causes leukemia, and I think there have been some published articles on that.

Mr. GORDON. In a recent issue of the New England Journal of Medicine there is an article by Dr. William Dameshek on this subject.

Dr. WATKINS. And I think once you prove that causing some forms of leukemia you are going to prove your statistics down to what it should be, that is all we want: honesty. If we had had an honest opinion in the beginning, the drug would have either been off the market or limited to hospitals. I honestly believe that the public would not have stood for this. But they had to really fight against a lot of opposition and money, because they really put the money around to the universities.

Senator LONG. Doctor, I am going to have to leave to go over to the Senate Chamber. And before I leave, I want to thank you for the testimony you have given here, and also to express my gratitude to Senator Gaylord Nelson for his efforts to investigate this matter, and the related matters involved.

I was once chairman of this subcommittee. When I became chairman of the Committee on Finance, Senator Nelson indicated to me that he thought he had the time and would like to devote his effort to investigate the whole subject matter, and where abuses existed, to try to do something about it.

I told him that at the time when he ran for reelection, he was not likely to get a single campaign contribution, and it would probably assure him of a well-financed opponent on behalf of this $4 billion industry.

But he has persevered, and I believe he is rendering a good service to the country as, for example, this matter and other disclosures that have been made in regard to abuses in the drug area.

After some disclosures I and others made in earlier years, we insisted that there be prosecution for conspiracy with regard to the tetracycline use by certain companies; that is, a price-fixing deal. And the Justice Department finally mustered the initiative to go ahead and prosecuted the cases. And they were found guilty.

And in this particular area, I am most impressed by what you said about this. And I hope that we can obtain effective action on this. And perhaps one way or another they can do something aobut it. And it may be to require that they put a label on that bottle and say in the opinion of many doctors, that this drug has been known to cause death. That is what you are saying, as I understand it.

Senator NELSON. We will now hear from Dr. Franklin Farman, from Lakewood, Calif.

Doctor, we appreciate your being here today.

STATEMENT OF DR. FRANKLIN FARMAN, LAKEWOOD, CALIF.

Dr. FARMAN. I wish to thank you, Senator Nelson, and Mr. Benjamin Gordon, for inviting me to the hearing. It is a very great privilege and we hope we will be of some aid to the committee.

I have a statement here that might fill in the background of this problem, as an introduction.

I am a specialist in urology, and I belong to the American Medical and the California Medical Associations, and the American Urological Association, and the American College of Surgeons.

I wish to relate our experience with the Department of Health, Education, and Welfare, the American Medical Association, and Parke, Davis & Co., and to point out some of the reasons why chloramphenicol should be restricted in its manufacture and use.

In June 1952, we lost our daughter—5 years old— through the administration of Chloromycetin—trade name—manufactured by Parke, Davis & Co. Her death was one of many similar cases of blood dyscrasias induced by the use of Chloromycetin which have continued to occur in the United States up to the present day.

I quote from Dr. Walter C. Alvarez, former Mayo Clinic clinician.

Mr. Elfstrom also quoted from Dr. Alvarez. I wish to quote Dr. Alvarez, formerly of the Mayo Clinic, again.

He stated in the Lincoln, Nebr. Evening Journal of November 24, 1952:

> The journal of the American Medical Association has had three articles telling of nine such deaths, due apparently to the taking of chloramphenicol. For these nine cases which are reported, there may well be hundreds more that were not reported.

Senator NELSON. In the case of your child, had you received any warning?

Dr. FARMAN. Not personally. She was treated by our pediatrician.

Senator NELSON. What was the nature of her problem?

Dr. FARMAN. She had an upper respiratory infection.

Senator NELSON. Am I correct that the drug is not indicated as a drug of choice for respiratory ailments?

Dr. FARMAN. It is not now, but in 1952 it was highly advertised for that. I will go into that later.

Senator NELSON. Go ahead.

Dr. FARMAN. This is true, even today—many cases of anemia and severe blood dyscrasia following the administration of Chloromycetin are not recognized or reported.

In June 1952 Mrs. Farman and I called personally upon the president of Parke, Davis & Co.—Mr. Harry Loynd—and asked him to remove Chloromycetin from the market.

Senator NELSON. You asked him to remove the drug from the market?

Dr. FARMAN. Yes. We were right in his office, and we asked him to remove it from the market, and stated the reasons why. This he refused to do although it had been proven that Parke, Davis & Co. had been warned by various physicians that Chloromycetin was a toxic dangerous drug.

At that time, 1951, Chloromycetin accounted for about one-third of their gross sales, $40 to $50 million, out of a total of $138 million gross. This figure jumped to $86 million in 1960—mostly domestic market.

Following our talk with Mr. Loynd, I went to Chicago and stated the facts to Dr. Austin Smith, then editor of the American Medical Association Journal. On June 28, 1952, Dr. Smith on the editorial page of the AMA Journal warned the medical profession of the United States in regard to the dangers of the use of Chloromycetin. In addition, several scientific articles appeared in medical literature in regard to blood dyscrasias resulting from the administration of Chloromycetin.

And they have continued to appear in the past 15 to 18 years.

In June 1953 Dr. Albe Watkins, of LaCanada, Calif., Dr. Patrick Corcoran, of Evansville, Ind., and I appeared before a committee of the American Medical Association in New York City. Through our efforts a resolution was passed by the house of delegates to the effect that greater control in advertising of dangerous drugs should be undertaken.

I might say that the passage of such resolution has very little effect, because it failed to curb hardly any advertising of the type that Parke, Davis particularly resorts to.

Mr. GORDON. May I interrupt here for just a moment?

A little further up on the page you say that on June 28, 1952, Dr. Smith, on the editorial page of the AMA Journal, warned the medical profession of the United States about the dangers associated with the use of Chloromycetin. Am I correct that this same Dr. Smith is now president of Parke, Davis & Co.?

Dr. FARMAN. Yes, he is. I think he took over the first of the year, or last year, which I hope is going to be a change in policy.

Now, maybe this problem will be solved voluntarily. We may not need the legislation.

Mr. GORDON. Thank you.

Dr. FARMAN. Following the AMA convention in New York, Dr. Watkins, Dr. Corcoran, and I called upon the Department of Health, Education, and Welfare in Washington.

We had a conference with Commissioner George P. Larrick, then Deputy Commissioner, and Dr. Henry Welch, head of the Antibiotics Division of the FDA.

Dr. Welch appeared to us to be quite evasive as to his department's responsibility. He seemed to feel they tested only for the purity of the product and not for the inherent danger of the drug itself or the claims of the manufacturer as to its safety and nontoxicity. It is a matter of public record that Dr. Welch was forced to resign his position in 1960, after having been exposed for cause by the Kefauver committee.

In March 1953 we entered suit against Parke, Davis & Co. through our attorney, Mr. Thomas Bewley, of Whittier, Calif., for the wrongful sale—including advertising—and manufacture of Chloromycetin. A great many other suits were brought against this company throughout the United States for similar reasons. All of these suits were settled by Parke, Davis & Co. without court trial, including our own. In many cases the settlement was the highest amount allowable by the courts

for the death of a child. In our own case the money is being used as a memorial for the benefit of children.

Since the Kefauver hearings Parke, Davis & Co. have added warnings by package inserts of the potential dangers with the administration of Chloromycetin. It was some time before these warnings were printed in fairly bold type which is easily readable to the medical profession.

I call to your attention the Food and Drug Administration directive for adequate blood tests during the entire administration of chloramphenicol which, incidentally, can be carried out properly only in hospitals. Chloromycetin is still produced, as far as I know, from dichloracetic acid, a known poison containing the nitrobenezene ring.

You will find on inquiry that Chloromycetin is not produced in the same manner as other antibiotics. The manufacturer has stated "in its chemical nature, chloromycetin is unrelated to any other antibiotic"—this is so; it is a synthetic drug produced from a toxic chemical.

In my own mind, I don't classify it as an antibiotic, it is a synthetic toxic chemical.

I think most of you are familiar with the antibiotics, and how they are produced. They are really produced from mold or other bacteria. And they have the ability to inhibit the growth of other micro-organisms that cause infection.

Dr. Watkins compared Chloromycetin to carbolic acid. Well, this is a synthetic drug. And it is produced from dichloracetic acid, which is a known poison.

I submit here an excerpt from my brief on Chloromycetin which was prepared for our attorneys in 1953.

(The material referred to follows:)

A long list of diseases are given by Parke, Davis & Co. in which Chloromycetin is indicated clinically. Among these are:

Bacterial Pneumonia
Boutonneuse Fever
Enteric Fever and Dysentery
Epididymitis
Gonococcus Infection
Granuloma Inguinale
Hemophilus Influenzae Infection
Herpes Zoster
Infectious Mononucleosis
Laryngotracheobronchitis
Lymphogranuloma Venereum
Measles
Mumps
Pertussis
Primary Atypical Pneumonia
Prostatitis
Psittacosis
Rocky Mountain Spotted Fever
Scrub Typhus
Surgical Infections
Syphilis
Trachoma
Tularemia
Typhoid Fever
Ulcerative Colitis
Undulant Fever
Urinary Tract Infections
Typhus Fever

81-280 O—68—pt. 6——30

Dr. FARMAN. They advocated in the early fifties some 28 diseases for which the drug could be used safely. This list has been reduced by pressure from the AMA and the FDA to about three, I mean typhoid fever and certain types of dysentery and meningitis. But very subtly Parke, Davis & Co. advertised its use for respiratory infection. Now, to my mind, this accounts for the great sale in the United States, because there are a lot of colds and other respiratory infections.

Well-known authors state that the administration of chloramphenicol always produces change in the bone marrow, some degree of anemia or blood dyscrasia such as aplastic anemia.

There are still being reported unfavorable reactions and deaths following the administration of Chloromycetin. One questions why this should be. It would seem the answer lies in the effect of advertising—to which not only the lay public but also the medical public is susceptible.

I know of no more tortuous death—as Mr. Elfstrom has brought out, and also Dr. Watkins—especially in children, than that of blood dyscrasias following the administration of this drug, Chloromycetin. It would seem this company should long ago have removed from the market voluntarily the manufacturing of this synthetic chemical agent.

If a physician desires to give Chloromycetin, it should be done under the most controlled condition of hospital administration and then only if the patient or his guardian is in full understanding and agreement. This is not taking the practice of medicine away from the doctor, it is only laying down the ground rules for good medical practice, protecting both the doctor, the patient, and the drug manufacturer.

I have another little statement. I could enter it now or later. It is a suggestion from a doctor as to the matter of control.

Senator NELSON. Go ahead right now. You are making a suggestion as to how the administration of this drug should be controlled?

Dr. FARMAN. Well, it deals with the cost of drugs, and brings it out; it is very short.

Senator NELSON. Sure. Go ahead.

Dr. FARMAN. The cost of prescription drugs sold over the counter could be reduced by limiting the profit—now, I know this is very difficult—of the manufacturer to a reasonable rate of return. It is my understanding that these manufacturers make a thousand percent, frequently, in the manufacture of drugs sold.

The manufacturer could lower overhead and pass the benefit on to the consumer of prescription drugs, and in the treatment of sick people.

Three, promotional activities and extravagant advertising should be eliminated as a means of the distribution of prescription drugs.

Four, in a sense, the large pharmaceutical firms have usurped the teaching of therapeutics after the doctor graduates from medical school.

Five, new products should be introduced through the State universities, or possibly State medical societies. The Council on Drugs of the American Medical Association has been helpful to the doctor.

Six, the so-called detail man should be restricted in his activities, or eliminated from the doctor's office. There is a better way to obtain reliable drug information.

Senator NELSON. Thank you, doctor. You also suggest, as other doctors testified here have, that the drug should be administered only in a hospital; do I understand you correctly?

Dr. FARMAN. Yes. A drug of this type—it is a toxic chemical, but there might be a few cases in hospitals where under proper supervision it could be administered safely. The trouble is, it is prescribed—the average general practitioner in the United States is too busy to be properly informed. They listen to the detail men, and they also read the drug ads. And so so they prescribe anything that is advertised to them.

But I feel that we are here—that is one purpose of our trip here, to get the FDA, or possibly Congress, to begin to pass legislation which is going to help the country.

Senator NELSON. It has been suggested in previous testimony here that there are various methods which could be used. One of the suggestions that was proposed is that perhaps the FDA could be authorized in consultation with the medical profession to designate certain very toxic drugs such as Chloromycetin as a special category of drugs, and determine the procedures under which they could be administered; that is, they may list whatever drugs are considered to be very dangerous such as Chloromycetin, and simply require that they be administered only in a hospital—or, as other testimony has been given, that you require that some of these drugs be handled in the same way that morphine is, for example.

Would you think that some general procedure such as this would be workable?

Dr. FARMAN. Yes, I do. I think we are coming to a point in the United States where we should do something helpful. I think the laws don't quite cover yet the food and drug industry properly. I am very much in favor of eliminating Chloromycetin from the market—if Dr. Austin Smith were here today, we could ask him just to remove the drug from the market and it would be very simple for you and the rest of us, and I think maybe he would do it. And then we don't have to pass legislation. It is not a drug that you need. There are many other safe drugs that you can use.

Of course, they won't claim that, and if you own stock in Parke, Davis, why you are interested in sales. But here we are dealing with a human element. And we think the time has come when concerted action should be undertaken—I mean both by the doctors and Mr. Elfstrom, the editor of the newspaper. It is hardly conceivable that this thing has been going for 18 years, since 1950.

Senator NELSON. Mr. Elfstrom.

Mr. ELFSTROM. I have a comment or two to make. I have quite a few articles in my newspaper about various disasters that have resulted from the indiscriminate use of this drug. And I am sure it has been read by most of the physicians in the community, many of whom are familiar with what I have been doing.

But a short while ago I got a telephone call from a druggist in a neighborhood town where we circulate quite heavily. And he said, "The doctors here are prescribing Chloromycetin like mad for the flu."

Senator NELSON. For the flu?

Mr. ELFSTROM. For the flu. And here, after not only the warning

that goes with the package, but all that has been in my newspaper, it is still being ignored.

Another thing, we have spoken of the torture of a Chloromycetin death. I hate to describe it, because it brings back memories that I try to forget. But the body gradually disintegrates. It gets ulcerated all over, and then bleeds to death. And to see a beautiful, healthy body deteriorate like that is just beyond description.

Senator NELSON. Dr. Watkins.

Dr. WATKINS. I would say a third of my son's body was gangrenous before he died, a third of it, black, smelly terrible. We could hardly stay in the room. A third of it.

A friend of mine came in and said, "How can you put up with this?"

And I said, "What can you do?"

And he said, "Why don't you put him to sleep?"

I said, "He may never wake up."

And he said, "How can you stand it?"

And so I put him to sleep, and he never woke up. A third of him was gangrenous.

Pursuant to what Dr. Farman said, here is a letter from a man in Baltimore—you see, this drug originally came from the soil of Venezuela. It was rather expensive to bring this soil in and extract this Chloromycetin, or the name of this particular antibiotic from it. So Parke, Davis developed this way of making it from this dangerous chemical that Dr. Farman brings up. He says:

> I personally warned the manufacturer relative to this synthetic product quite a while before any of the unfavorable results from its use came to our attention.

This was in 1953. So here is a man, a scientist, that warned them that this synthetic drug, which costs about 8 cents a capsule and sells for 60 cents—that is a pretty good profit—it costs a lot more to bring it in from the soil than to do it naturally.

Mr. ELFSTROM. Now, there is a peculiar circumstance in connection with my daughter's death. A few days before her death there was a woman in the hospital laboratory who came to us and said that they had a prayer circle in their church, which was down at Newport Beach, and they met the following day, and they would be glad to include our daughter in their prayers—which we were grateful for. And she also said that her husband, who was the minister of the church there, the Episcopal church, would be very glad to come up and offer what comfort he could, and would we like it. And we said, under the circumstances, we were in shock, we would like it, yes.

And he was a very dedicated man of God. He came up and he spent 2 days with us, and the last hours with our daughter. He witnessed her death, and how terrible it was.

His name was Rev. John Parke, and I didn't know it at the time. A few weeks after her death, we went down to see the Reverend and brought a donation for his church in our daughter's memory for the help that he had been. And we asked him if he could suggest any way that we could help others.

And he said, "I happen to be the grandson of Parke of Parke, Davis, who has long since been out of the company," but, he said, "I will be glad to write to the president of the company and explain to him what I have witnessed and urge that something be done about it."

He got a very diplomatic reply from President Lloyd that was noncommittal.

Mr. GORDON. Mr. Chairman, I want to make sure that all letters, articles, and other documents that have been referred to will be supplied for the record.

Mr. Elfstrom, would you please make sure that we get them?

Senator NELSON. The committee appreciates very much your coming all the way here from California. Your testimony is a very valuable addition to the record. And I am hopeful something constructive will result from it. We realize how much time each of you has put into trying to educate the public and the profession about the problem.

You have made an invaluable contribution even prior to your being here before the committee, and we thank you very much.

Mr. ELFSTROM. Thank you, sir.

Senator NELSON. We will adjourn until 10 o'clock tomorrow morning. Our witness will be Dr. James L. Goddard, Commissioner of the Food and Drug Administration.

(Whereupon, at 12:10 p.m., the subcommittee adjourned until Thursday, February 29, 1968, at 10 a.m.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

THURSDAY, FEBRUARY 29, 1968

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

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

Present: Senator Nelson.

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

Senator NELSON. The hearings of the Subcommittee on Monopoly will come to order.

This morning we have as our witness Dr. James L. Goddard, Commissioner of the Food and Drug Administration, U.S. Department of Health, Education, and Welfare.

Dr. Goddard, we are very pleased to have you back again to testify before the committee.

You may proceed as you see fit. I trust you would have no objection to interruptions for questions.

STATEMENT OF DR. JAMES L. GODDARD, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE; ACCOMPANIED BY WILLIAM W. GOODRICH, GENERAL COUNSEL, AND DR. HERBERT L. LEY, DIRECTOR, BUREAU OF MEDICINE

Dr. GODDARD. Thank you, Senator Nelson.

I would like to introduce my colleagues, Mr. William Goodrich, the general counsel for the Food and Drug Administration, on my left, and on my right, Dr. Herbert Ley, Director of the Bureau of Medicine.

Mr. Chairman, I appreciate the opportunity of appearing before your committee today to discuss the Food and Drug Administration's action and intentions in regulating the interstate distribution on the antibiotic drug, chloramphenicol.

The Nation has watched with great interest the testimony unfolding before this committee in the past weeks. The committee's hearings have brought renewed attention to important questions that concern us all: Is this a drug too dangerous to remain on the market? Should its use be restricted in some way? Are the FDA, the medical profession, and

the manufacturer of the drug taking all necessary steps to assure the safest possible use of the drug?

Before discussing these questions and alternatives, however, it may be useful to outline what has been done in the past. Chloramphenicol was first isolated in 1947 from a soil sample collected in Venezuela. It was found that liquid cultures of the organism, Streptomyces venezuelae, possessed marked effectiveness against several Gram negative bacteria and also exhibited antirickettsial and antiviral activity. Shortly thereafter the chemical structural formula was determined and the antibiotic was prepared synthetically. And, as you know, it was later patented by Parke, Davis & Co.

In 1948, chloramphenicol was produced in amounts sufficient for clinical trials and general clinical use. It was found to be of value in the therapy of a variety of infections, including epidemic typhus in Bolivia and scrub typhus and typhoid fever in the Malay Peninsula.

Mr. GORDON. How about the United States?

Dr. GODDARD. I am talking now about the early uses of it, where it was used against epidemics particularly.

On January 12, 1949, the Parke, Davis New Drug Application for Chloromycetin, that company's brand of chloramphenicol, was allowed by FDA to become effective.

This followed clinical trials in the United States on appropriate types of infections, Mr. Gordon.

In the summer of 1949, as the result of new legislation, chloromycetin was classified as a "certifiable antibiotic," subject to the batch certification provisions of the Food, Drug, and Cosmetic Act.

Senator NELSON. In the New Drug Application, did any of the experimental data submitted to FDA indicate the development of blood dyscrasias or other adverse side effects?

Dr. LEY. None, sir.

Senator NELSON. How long did they experiment with it?

Dr. GODDARD. Clinical trials, Dr. Ley, went forth over about 18 months?

Dr. LEY. From early 1948 until 1949, as I recollect, was the period that the clinical trials were in progress, both overseas and in this country.

Senator NELSON. These were first on animals, I take it?

Dr. GODDARD. It would have been animal work on toxicity, "LD 50's" and things of this nature would have been carried out. But the clinical trials were directed toward the patients with specific infectious diseases.

Senator NELSON. I notice in reading the literature, and some of the testimony, that the experts always strongly urged or state that it is necessary that continuous blood tests be made, and that as soon as any changes are indicated in the blood, therapy be stopped immediately.

You mean that in all these trials they saw no blood changes at all?

Dr. LEY. Senator Nelson, in some of the early work in the Malay Peninsula, I was involved myself personally. We studied at that time the early report in 1948, covering about 50 patients with scrub typhus, and two patients with typhus fever. We occasionally noted drops in white blood cell count in these patients, who frequently, by

the very nature of their disease, had low white blood counts. At no time in the early studies did these drops become of significant importance, so that we elected to terminate therapy.

Official recognition of the serious problems in terms of blood anomalies resulting from the drug was not made until about 1950 or 1951.

Senator NELSON. Do you mean to say that in the testing on animals, where the range of experimentation would be much more flexible, they did not try dosages of such a nature that demonstrated dramatic blood changes?

Dr. LEY. Yes, Senator Nelson.

In some of the animal studies which were conducted about 1950 or 1951, in dogs specifically, there were changes observed in the nature of temporary depression of bone marrow, anemias, which are quickly returned to normal after the drug was discontinued.

At no time, however, in dogs, as I understand the evidence, has an aplastic anemia been observed or described.

Now, our expert committee pointed out that any human being will respond with a temporary decrease in hemoglobin when given this drug. This normally disappears promptly after the therapy is terminated.

The estimate is that two grams a day will produce detectable temporary drops in hemoglobins in about 50 percent of the individuals receiving the drug.

Senator NELSON. You are saying, as I understood it, that these blood dyscrasias were noticed in 1950 and 1951. But I am saying what about the experimental data on animals submitted with the New Drug Application in 1949? Did the company indicate anything on blood dyscrasias at all?

Dr. GODDARD. No, sir.

Senator NELSON. They did not?

Dr. GODDARD. No, sir. In fact, it was not until 1953 that FDA itself carried out animal studies, dog studies, as a result of some of the problems being demonstrated in humans.

The early studies on this drug, of course, suffer all the problems that we have to live with in drug studies—as greater experience is gained in what we call phase 4, these adverse reactions then begin to become apparent.

But to my recollection and to Dr. Ley's recollection, there was nothing in the New Drug Application that indicated that the animal studies displayed any problems in the early stages.

Senator NELSON. Did I understand from the testimony that there were animal studies made prior to the application for marketing of the drug, and that those studies were submitted to the FDA at the time?

Dr. GODDARD. That is my recollection. We can dig that up again. But we have looked at it, and I recall that there were animal studies. I will have to look again.

Senator NELSON. Given a certain amount of this drug, a certain number of grams, the testimony has been that you get a blood dyscrasia, almost always, apparently. And I am just wondering why in the experimentation with animals, when they could use larger dosages

than in human experimentation, that they did not discover anything that would warrant the attention of the FDA at that time concerning the side effects of this drug.

Dr. GODDARD. Senator, let us reexamine the original NDA and see what that discloses. But I will also point out that the studies required at that time were not to the degree and depth that they have been since the 1962 amendments. They were not as sophisticated—the animal studies, I am speaking of—as they now are. So therefore it is quite possible that this was missed at that time.

(The subsequent supplemental information follows:)

STATEMENT OF THE FOOD AND DRUG ADMINISTRATION CONCERNING ANIMAL STUDIES CONTAINED IN THE ORIGINAL CHLOROMYCETIN NDA

Clinical use of Chloromycetin was originally proposed in NDA 6655. Sometime after the NDA was made effective, the drug was made certifiable.

A reprint of an article by R. H. Smith *et al.* (Chloromycetin: biological studies, J. Bact. 55: 425, 1948) was filed as part of the NDA. Although the bulk of the article deals with microbiological studies, the following animal experiments are reported:

1. Acute toxicity studies in mice (I.V., S.C. and P.O.) and dogs (I.V. and I.M.).
2. Subacute toxicity studies in mice (S.C. and P.O.), rabbits (S.C.) and dogs (I.M. and P.O.).
3. Absorption and excretion studies in dogs.

Senator NELSON. Go ahead.

Dr. GODDARD. When chloramphenicol was first introduced in 1949, it was widely heralded as a broad-spectrum antibiotic, effective against an impressive range of micro-organisms. It was also considered to be largely nontoxic. There was no indication at that time that the drug had any serious side effects.

Early in 1950, however, a few published reports drew attention to the possibility that chloramphenicol might cause serious and fatal blood dyscrasias. The 1951 edition of New and Non-Official Remedies warned that "changes in the peripheral blood or blood forming organisms have been reported during the use of chloramphenicol." An editorial in the Journal of American Medical Association, June 28, 1952, referred to additional reports of blood disorders. It went on to say—

A second and more serious type of reaction that has been encountered is production of a true aplastic anemia. In the experience of one group this anemia has occurred in patients who have previously received one or more courses of chloramphenicol without untoward effect. When the drug was subsequently administered, even in small doses, a severe blood abnormality has appeared. Even deaths have been reported.

In response to these reports, FDA conducted a nationwide survey of case records in hospitals and clinics in an attempt to evaluate the magnitude of the problem and to determine whether a cause and effect relationship existed between the drug and the disease. This survey produced records of 410 cases of serious blood disorders, of which 177 were definitely known to have been associated with chloramphenicol. In 61 cases choramphenicol was the only drug administered. In half of these 177 cases the blood disorders were fatal. They include aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia. In June 1952, the FDA referred the case histories obtained in the survey to the National Research Council (NRC).

Senator NELSON. When you say FDA discontinued the certification, did that remove it temporarily from the market?

Dr. GODDARD. No further batches of the product could be introduced into the market. It was not recalled at that time. What was in place, and was being used, was permitted to remain on the market.

Senator NELSON. Whatever was already in the marketplace could continue to be used?

Dr. GODDARD. At that time.

Senator NELSON. All the experts who have testified here on the administration of this drug, and have discussed the statistics of serious side effects, including death, were really unable to come up with anything approaching an accurate estimate of the number of deaths or serious permanent injuries which have left people ill for the rest of their lives.

Does FDA have any reasonably valid statistical information on how many people are being seriously and permanently affected adversely by the administration of this drug?

Dr. GODDARD. Senator, this is a problem, as you well know, not only with this drug, but with many other drugs. We do not have the kind of data base that would give us, with a high degree of assurance, reliable data on which to draw such conclusions.

Let me point out that the best study, in our opinion, is the one carried out by the California Medical Association. As a result of that survey, and study that they carried out, now some——

Dr. LEY. The survey was published in January 1967.

Dr. GODDARD. It was published in January 1967. We note that they find a fatality incidence of 1 in approximately 24,000 persons receiving this particular drug.

Senator NELSON. Fatal?

Dr. GODDARD. Yes, sir.

Senator NELSON. Now, how many had serious permanent side effects—what percentage?

Dr. GODDARD. I do not know that.

Dr. Ley, do you?

Dr. LEY. The chief figures in the report are aimed at fatalities. There are a number of other conditions which they mention, most of which I believe are reversible.

Senator NELSON. Well, what about instances where the drug suppresses the capacity of the bone marrow to produce blood by 20 percent, or 10 percent, which leaves the person ill the rest of his life, although he lives. Are there any statistics on that kind of result?

Dr. GODDARD. Senator, I would be happy to have our people go through the CMA report again, and provide that for the record, if I may. I do not recall it.

(The subsequent supplemental information follows:)

STATEMENT OF THE FOOD AND DRUG ADMINISTRATION REGARDING NONFATAL COMPLICATIONS REFLECTED IN CALIFORNIA MEDICAL ASSOCIATION STUDY

Our review of the California Medical Association Report does not disclose any non-fatal, drug related experiences with Chloramphenicol. The California study was based on a review of death certificates; therefore non-fatal complications of Chloramphenicol administration would not be reflected in the study.

Dr. LEY. I have rough figures here, of a total of 79, in addition to the fatalities, who experienced a leukopenia, and 79 who had a bone marrow depression.

Senator NELSON. From what?

Dr. LEY. From the chloramphenicol.

Senator NELSON. What statistics?

Dr. LEY. This is a summary from the California report.

Senator NELSON. One of the doctors who testified yesterday related that in his relatively small town of 16,000 people, he became aware of four cases of aplastic anemia at one time. And we have heard of similar situations through the mail that is coming into our office from little towns of 800, 900 people. I have five or six from my own State. These letters are from people who just notice something in the paper about these hearings and write.

It seems to me that the California study tends to give the physician a whole lot more security in prescribing this drug than the facts, as we know them, would justify.

You have a risk of one death in 24,000. How many cases are there of permanent injury?

Dr. GODDARD. As I said, Senator, I do not believe anyone has realistic figures on this. The incidence of nonfatal side effects which may be of long duration is probably higher than the incidence of fatalities, if the usual course of events is held to follow in this instance.

However, the British study, which we think has certain deficiencies, points out that fatalities occur as often as 1 in 10,000 patients receiving the drug. One has to be very careful in carrying out studies of this type, because aplastic anemia, as you well know, occurs from other causes—they may be idiopathic. And to simply relate all cases of aplastic anemia to chloramphenicol is not proper nor supportable. But nonetheless, I have to go back to my original statement and say that the CMA study is the best one we have seen so far.

Now, that does not mean that the incidence may not be higher. It simply reflects a lack of good data, Senator.

Senator NELSON. But why is our data so poor?

Dr. GODDARD. Senator, this is true in almost this entire field. We do not have good reporting. Hospital record systems vary throughout the United States. There is no requirement for reporting these kinds of episodes. It is done upon the initiative of a few physicians.

We have had great difficulty in getting good reporting in our adverse reaction reporting system, even in those instances where we paid the resident physician $5 for submitting a report. It is extremely difficult.

Now, as we progress with the usage of computers in hospitals to store patient data, the kinds of activities that are being carried out in Michigan by Dr. Virgil Slee's organization, and at a number of large hospital centers, it is going to be possible to extract much more significant information from existing hospital records.

But in the present situation, where we are totally dependent upon the physician assuming—upon his own initiative—the burden of sending a report to a firm, the FDA, or the AMA, we do not get good reports. The AMA in fact has discontinued its adverse reaction reporting system simply because of the lack of interest of participating

physicians. This in spite of reminder cards, tear-out cards in their weekly publication, the JAMA. And it is an extremely difficult subject to get at.

I am convinced that small increments are being made. We are making some progress. But the problem is not unique to chloramphenicol. We are constantly up against the lack of good data, whether you are talking about chloramphenicol, the sulfa drugs, whatever you will.

Senator NELSON. Well, I can appreciate that.

But it seems to me that you have to start some place. And chloramphenicol is not just another drug. As you know better than I, it is very, very limited in its recommended use. And, I guess, every hematologist in America is shocked at the indiscriminate prescription of the drug, and the unnecessary killing of innocent people. I understand you to say you would have to have drug reporting on all the drugs in the market from all the hospitals every single year if you want to follow such a procedure with chloramphenicol, and that it is probably unnecessary. But the medical profession has had long experience with the sulfas and penicillins and I guess has a pretty good idea about the problems there. At least the problems are not as serious as they are in the case of chloramphenicol, are they?

Dr. GODDARD. I would have to say that the fatal reactions to some of the drugs you have mentioned, although not as frequent, also constitute a serious problem.

Senator NELSON. Well, are you telling me, doctor, that the best clinicians in our great medical profession, who have the expertise, and the FDA could not sit down and select a dozen drugs that are not in a gray area at all, or a half dozen, on which we must have hospital reports and decide that reporting be required.

Why can't we do that? Why go on needlessly injuring and killing people. Almost all the cases we hear about deal with persons who should never have had the drug in the first place. And, Dr. Weston, Utah State Medical Examiner, said he had never seen a case of a person who died from aplastic anemia when the drug was really indicated. Every single one of them were cases in which the patient should not have received the drug, as I recall.

Dr. GODDARD. I would not question his testimony, Senator. But let me point out that in the California study, 7 out of 10 deaths that occurred, occurred in patients who received the drug for appropriate indications.

Senator NELSON. Yes. But how are the cases selected? If it were prescribed for an inappropriate case—acne or a head cold—there is a strong inclination on the part of the physician, when he finds out what he has done, not to report it. Any time it were given for a proper indication in a hospital, no doctor would hesitate for a moment to report that this was the result he got. So that is a loaded statistic, I think.

Dr. GODDARD. I would tend to agree with you, Senator. I am simply pointing out that it does occur in those patients who receive it for proper indications as well.

Senator NELSON. Well, I am assuming it does. As you are aware, Dr. William Dameshek is a distinguished hematologist who has seen many, many cases and has written on the matter in the AMA Journal. He

testified here the other day. Let me read from something he wrote in 1960 for the AMA Journal. Now it is almost 8 years later.

He states:

> By some means, whether by regulation or self-discipline, promiscuous use of the drug should be avoided and its use restricted to impelling circumstances, that for conditions for which no other antibiotic is currently effective. Among 30 cases of aplastic anemia he had seen within the previous 3 years, he said 8 had received Chloromycetin.
>
> Almost invariably for minor infections. Of the 10 most recent cases, five had followed therapy with Chloromycetin. The tragic thing about all of these seriously ill cases, most of whom died, is that the drug need never have been given at all.

He does not come up with the statistics that the California study does, and my guess is that this is true because the California study included all the cases that were reported because they concerned cases in which the drug was indicated, or at least a lot of them did.

Dr. GODDARD. Senator, let me make it perfectly clear—I am not trying to whitewash this drug, or the excessive use of this drug by the medical profession, or be in a defensive posture with respect to the Food and Drug Administration's certification of the drug. I am simply trying to point out there are instances where it is properly prescribed, and it will still cause problems.

The agency has, since 1952, made attempts to curb the excessive usage of this drug, and we will continue to try to reduce this to its proper level of usage.

I do not want you to get the impression that I am defending improper prescribing habits.

Senator NELSON. I did not intend to leave that impression. As a matter of fact, if you do not already know it, I have very high admiration for you. I do not think any previous Commissioner approaches you in the vigor with which you protect the public interest, and in your concern about it. I mean that in all sincerity.

But the cold, hard facts are that this issue is almost 20 years old, and not a damned thing has happened, except that we prescribe more, more, more. And we heard five witnesses last week who made guesses that 90 percent of the prescriptions are being given to people who should never have it—down to Dr. Mark Lepper's estimate that only one-third of 1 percent of all the cases who get it should get it. He is saying, then, that between 10,000 to 50,000 people out of 4 million who receive it should get it. Well, this is a disaster, a catastrophe. And I do not see how we can go on for 18 years saying we are doing everything we can.

We would be better off, actually, in view of what has happened, if we never gave the drug at all. It is doing more harm than good. But the least we can do is get good and tough about how it is used, and under what circumstances. Four million people take this drug each year—it is just preposterous. And I do not understand why we just do not get tougher than nails about it.

These warnings in the package insert, and in the journal advertisements, mean absolutely nothing. A representative of that company sat right here before me and acknowledged that they ran an ad in the British Medical Journal, February 1967, without a word of warning, while they ran one 7 days later in this country with the warning.

They said they did not have to run it in England because the law did not require it. I asked what about the underdeveloped countries? They said that England has a sophisticated system for medical protection. I presume we have a sophisticated one here. But 4 million people are getting Chloromycetin who should not be getting it. Then you get to the underdeveloped countries where there is no protection at all, and you can see what is happening.

All I am saying is that it is one thing if a warning has not worked for a couple of years, but we are talking about 2 decades. I think we have to do something dramatic about this now.

That is my whole point.

Mr. GORDON. Dr. Goddard, you referred to the California study. Now, as I understand it, this study for the first time indicated that the risks were higher than were known at the time that the drug was put on the market; is that correct?

Dr. GODDARD. That is correct.

Mr. GORDON. The California study came out in January of 1967?

Dr. GODDARD. That is correct.

Mr. GORDON. Did the Food and Drug Administration notify all the doctors in the United States about these new risk estimates?

Dr. GODDARD. No, we did not.

Mr. GORDON. Why not?

Dr. GODDARD. The California report itself, which was known to us at that time said, and I quote:

> No reasonable basis exists for the enactment of special legislative category to restrict the use of the drug chloromycetin by a licensed physician in California. Our data indicate that this antibiotic is being administered in accordance with good medical practice, and the risk use factor does not provide a sufficient basis to single out this drug for special legislation.

They did not—and there are a number of other statements here—they did not recommend any additional steps be taken at that time.

Senator NELSON. Who is "they" in this case?

Dr. GODDARD. CMA, California Medical Association—joint study group.

As you know, Senator, we have had a number of groups of qualified physicians meet on the subject of this drug over the years. The latest one met last week to advise us on what steps could be taken and should be taken. And the question of restricting the drug to hospital usage has come up in almost every one of these meetings. Also the question as to whether or not the drug should be withdrawn from the market. Both of these suggestions have been rejected by advisers who included people such as Dr. Dameshek, eminent physicians in their own fields of specialization who have detailed knowledge of the risks involved in the use of the drug.

Senator NELSON. I believe Dr. Dameshek is prepared to say that some very tough regulations should be made—possibly treating it as you do morphine, or confining it to hospital use. His posture on what we should do about this now is much stronger than anything the FDA is recommending.

Let me read what Dr. Dameshek said in testimony before us:

> The numerous warnings regarding indiscriminate use of chloromycetin have been practically without effect. It is now about time to consider more radical measures such as complete restriction of the drug for a few specific indications.

Should one stop its use altogether—this would surely be a wrong thing to do—because the drug is a potent antibiotic and has a well-defined usage. Should one simply continue with a warning statement in the advertising and in the package? These seem to have little if any value.

And then further in his testimony, he was willing to set up some procedure to strongly control its use.

Dr. GODDARD. Our ad hoc committee, which met Monday, also basically was in agreement with Dr. Dameshek. and Dr. Ley and myself certainly are.

We have a revision of the indications to be used, the package insert, which I have before me. We are going to discuss this with the company in the next few days. These indications markedly limit the indications for the usage of this drug.

Senator NELSON. For the package insert?

Dr. GODDARD. Yes, sir. But we are also going to take other steps which I mention in my testimony, which will not restrict this kind of information to dissemination through the package insert. As you well know, I think the package insert is an ineffectual way of getting at the transmission of information to physicians. This new information will also be required in PDR. It will be required in so-called reminder ads. These reminder ads now operate under an exemption from the Secretary which permits Parke, Davis to advertise this drug without any warning whatsoever. And so we do have steps that we propose to describe today that we think will have some impact. They may fall short of what you wish, but there are certain problems we feel need discussion.

Mr. GORDON. Dr. Goddard, I am not satisfied with the answer that I got to my question.

Dr. GODDARD. I wondered if you would be.

Mr. GORDON. Why didn't the FDA notify all the physicians in the United States about the new and additional risks which were revealed by the California study in January of 1967?

Dr. LEY. Mr. Gordon, in response to this, I have to draw upon the memory and recollection of other people who were there, because I was not there at the time.

The California study identified a level of risk between roughly 1 in 24,000 and 1 in 46,000 per death. This study was in essence within the broad limits already established for the drug by other studies. I am specifically referring to the study published in Britain in 1960, which identified a risk figure of somewhere between 1 in 10,000, and 1 in 100,000. As nearly as I can reconstruct the events that occurred at that time, the California study was weighed, evaluated, and considered not sufficiently different from existing information to require a special type of action at that time.

We are certainly——

Mr. GORDON. We are not talking about action here. It is a question of relaying the information to the physicians in this country.

The California study came up with a risk ratio of 1 in about 20,000. Before then the risk ratio was considered to be much lower.

Now, would it be your opinion that the doctors in the United States should know of these new and higher risks?

Dr. LEY. We certainly plan to include this, the study's estimate of risks, as a portion of the new labeling.

Mr. GORDON. This is new labeling, and you are planning to do it now. But it was January of 1967 when this report came out, almost a year and a half ago.

Dr. GODDARD. The answer is that it would have been better to have done it then. That is the only answer I can give you. I have no reason for it not being done, other than the judgment that was made at that time, that there was a general knowledge that the risk was between 1 in 10,000 and 1 in 100,000.

Mr. GROSSMAN. Doctor, that is a pretty wide gap, isn't it?

Dr. GODDARD. Yes, sir, and I think it reflects again the problem we have in not having available good data.

Mr. GROSSMAN. That is what I wanted to ask you. How do you feel about some kind of a coordinated national—nationally enforced reporting system. Is it possible to do something like this? In other words, it does not seem we are getting anywhere. On the point you raised before—some doctors report if you pay them $5, some others do not. This does not seem to be a very effective way of effectively finding information. I would like to find out how many people who got the drug and should have gotten it ended up with some problems, as well as those who should not have gotten it.

Dr. GODDARD. We would like to know that, too. But the development of an effective national reporting system is an extremely complicated problem, one that we have worked on. Dr. Ley may wish to speak to this. We have made some changes recently to try to get better drug data from a variety of sources.

I know of no way to enforce—from the national level—a reporting system.

Mr. GROSSMAN. What about regionally enforced, State enforced? In other words, isn't it time we tried something else—because the present systems just are not working.

Dr. LEY. I think two facts should be pointed out.

As far as the present legislation is concerned, the manufacturer is required to report to us all reactions reported to him. There is no requirement for any physician to report reactions to the manufacturer. But those that are reported, which are not any more than the top of an iceberg, must be reported to us.

Senator NELSON. How many have been reported to you by Parke, Davis?

Dr. LEY. Over the period from July of 1963 to the end of 1967, which is the end of our tabulation, a total of 93 hematologic reactions have been reported from Parke, Davis to us, of which 59 are reported as aplastic anemia.

Senator NELSON. That is really just a ridiculously useless figure. Everybody knows it is more than that.

Dr. GODDARD. Senator, in answer to the previous question, let me say I have also had some experience with the reporting of other diseases which is required by law. Reporting of syphilis is required by law—by the States. It is completely ineffective. You get about 1 case out of 11 reported by the practicing physicians. Even though it is a legal requirement.

Now, I do not know how we can do anything to get physicians to report adverse reactions to drugs when we cannot get them to report

something as important as syphilis, in terms of breaking the chain of transmission. We can eradicate this disease in this Nation very quickly, if we had good reporting.

Mr. GROSSMAN. Do you think it is because the individual doctor is afraid?

Dr. GODDARD. No. Well, there are all sorts of reasons.

One is that the demand for physician services has greatly increased. No question about it—most of the physicians are working 70 hours a week, and seeing, in the opinion of many experts, far too many patients—because of the demand for services. This is increased by the kinds of programs we are now engaged in. I do not visualize it getting better, because our supply of physicians is not increasing rapidly in this Nation.

The complexity of medical practice itself is increasing, so that the physician not only has to see more patients, but the kinds of things he has to do are more complicated. He has less and less time available for these kinds of activities which, frankly, he views as not being directly related to patient care, and therefore of a lower priority. And that is an understandable point of view. It is not perhaps commendable, but understandable.

And so I am not optimistic about this kind of reporting until we can institute the kinds of automated data systems. This will take 5 years at a minimum, and then and only then will we begin to get this kind of information—not just on this drug, but on many other drugs and many other conditions which would be valuable to us in our health efforts in this Nation.

Mr. GROSSMAN. Do I imply from your later testimony that you do not favor a drug review committee type of program, on a local level, where——

Dr. GODDARD. I think this would be absolutely wonderful. I have been preaching for a year and a half now to try to stimulate physicians and hospitals to have therapeutics committees in the hospitals which do more than consider the drugs to be included in the hospital formularies. Some hospitals do this. But they should begin to review the usage of drugs within the hospitals. Are they being properly used, what kinds of adverse reactions occur? Studies have been carried out by Cluff and others which show that a significant portion of hospital beds are being unnecesssarily occupied by people who have adverse reactions to drugs, and that proper attention here, as has occurred in the field of review of surgery within the hospitals, could markedly reduce the bed occupancy, and thus in effect obviate the need for new construction in some instances.

So I am very much in favor of therapeutics committees which review the use of chloramphenicol and other drugs in the hospital.

Mr. GROSSMAN. It might be easier as a reporting system, too, if you had four or five doctors—they would be more likely to report the results, because the responsibility is more diffuse.

Dr. GODDARD. It would have many beneficial effects if such operations were to be instituted in each of the majority of the 8,000 hospitals throughout the United States.

I feel very strongly that this would be a desirable step forward. And I would hope that the committee would consider requesting the Joint Commission on Accreditation to appear and to give their views

as to how feasible it would be to incorporate within the provisions the requirements for accreditation one which spoke to the question of the existence of a therapeutic committee within the hospital.

Mr. GROSSMAN. Thank you, doctor.

Senator NELSON. What is the authority of the Joint Committee on Accreditation? What is the source of their authority?

Dr. GODDARD. Senator, I think they have more leverage than authority. By denying certification, approval, to a hospital, they in effect shut off their supply of interns and residents, and this is a very crucial matter for those hospitals that use interns and residents to handle much of their caseload, much of the work that goes on.

And so there is an authority related to certification of the individual institution rather than an authority that comes from a State or Federal body. It is a voluntary program with participation by the hospitals in the United States. Not all of them participate—I do not recall the numbers, frankly, but it is a significant proportion of all hospitals that do.

Senator NELSON. Do we have any statistics on how many hospitals in America have therapeutics committees?

Dr. GODDARD. I will attempt to get them and supply them for the record, but it is a very small percentage at the present time.

Senator NELSON. Small?

Dr. GODDARD. I believe it is, in terms of the context we are talking about.

(The subsequent supplemental information follows:)

STATEMENT OF THE FOOD AND DRUG ADMINISTRATION REGARDING HOSPITALS WITH THERAPEUTICS COMMITTEES

Information obtained from the American Hospital Association, Chicago, Illinois, indicates that in September of 1967 there were 7,253 registered hospitals in this country. Of these, approximately 1,700 were accredited. To become accredited, a hospital must have a "Pharmacy and Therapeutics Committee," unless the hospital staff is less than 10. Even a smaller staff must have this activity, if not a committee. Therefore, about 23 percent of registered hospitals in this country have Pharmacy and Therapeutics Committees.

Dr. GODDARD. Now, many hospitals have committees which you might better call formulary committees, yes—these exist. But we are talking about a broader range of functions—the review of adverse reactions, the review of drug usage to see whether or not appropriate drug utilization is being carried out. This type of activity is not a common one.

Senator NELSON. Do most of our major teaching hospitals have a therapeutics committee in the sense you are talking about?

Dr. GODDARD. Most of the major teaching hospitals, Dr. Ley and I agree, would have such an activity.

Senator NELSON. Well, I think that is a good suggestion. The committee will consider inviting the Joint Committee on Accreditation to appear.

Continue.

Dr. GODDARD. The National Research Council established a committee of outstanding hematologists and internists under the chairmanship of Dr. John Holmes Dingle, professor of preventive medicine, Western Reserve University, to review and evaluate the chloramphenicol problem. On August 7, 1952, the committee reported as follows:

An ad hoc Conference was held on 6 August and reviewed all available data presented by the Food and Drug Administration and by Parke, Davis and Company.

The consensus of the Conference was as follows:

1. Certain cases of serious blood dyscrasias (aplastic anemia, thrombocytopenic purpura, granulocytopenia, and pancytopenia) have been associated with the administration of chloramphenicol.

2. Although this complication has thus far been uncommon, it is sufficiently important to warrant a warning on the label of packages of the drug and in advertisements of the drug and the recommendation that chloramphenicol not be used indiscriminately or for minor infections.

3. When prolonged or intermittent administration is required, adequate blood studies should be carried out.

4. In view of the paucity of information at the present time the Conference hopes that further study of serious reactions to chloramphenicol and other drugs will be promoted. The records of the Veterans Administration and military forces could be of great value in providing some of the desired information.

Senator NELSON. This was 1952?

Dr. GODDARD. That was 1952.

Senator NELSON. Has any formalized procedure been instituted to accumulate the statistics and records from the Veterans' Administration and the military forces respecting this drug?

Dr. GODDARD. There is no formal system; no, sir.

Senator NELSON. Well, here is a recommendation made in 1952.

Dr. GODDARD. We do know that the Veterans' Administration and the military forces have procedures within their own organizations controlling the use of chloramphenicol. But in terms of a formal system of transfer of information, no.

Mr. GOODRICH. The recording system that we have originated with this type suggestion for all drugs, and the contracting and reporting system was set up on that basis, utilizing primarily the veterans and other military hospitals as reporting sources.

Dr. LEY. And civilian hospitals as well.

Mr. GOODRICH. In the beginning they were essentially these two resource groups.

Senator NELSON. What kind of statistics do we now have from the military and from the Veterans' Administration on the use of this drug and on its side effects?

Dr. LEY. This effort has been implemented with considerable delay. Within the past year, we have pressed strongly for participation of the teaching hospitals in both the veterans hospital system and the military system in our hospital reporting program.

We are at this point in time in a position in which the majority of these teaching hopsitals are participating. This is a very slow procedure to stimulate when we cannot actually force participation of this sort.

Senator NELSON. Are you talking about military teaching hospitals?

Dr. LEY. There are certain military hospitals which are accredited for teaching purposes, and Veterans' Administration hospitals similarly.

Senator NELSON. How many are there in the United States?

Dr. LEY. Let me provide this information for the record, if I may. We can give you a complete statement on this reporting system.

(The subsequent supplemental information follows:)

STATEMENT OF THE FOOD AND DRUG ADMINISTRATION REGARDING FEDERAL HOSPITALS ENROLLED IN FDA ADVERSE REACTION REPORTING PROGRAM

(45 Hospitals—All Approved For Residences Except 3 USPHS Hospitals and 2 USAF Hospitals (approved for Internship Only)—As Marked With *)

(7) *Army*

Brooke General Hospital, Fort Sam Houston, Texas.
Fitzsimons General Hospital, Denver, Colorado.
Letterman General Hospital, San Francisco, California.
Madigan General Hospital, Tacoma, Washington.
Tripler General Hospital, Honolulu, Hawaii.
Walter Reed General Hospital, Washington, D.C.
William Beaumont General Hospital, El Paso, Texas.

(7) *Navy*

The U.S. Naval Hospital, St. Albans, New York.
The U.S. Naval Hospital, Philadelphia, Pennsylvania.
The U.S. Naval Hospital, National Naval Medical Center, Bethesda, Maryland.
The U.S. Naval Hospital, Portsmouth, Virginia.
The U.S. Naval Hospital, Great Lakes, Illinois.
The U.S. Naval Hospital, San Diego, California.
The U.S. Naval Hospital, Oakland, California.

(7) *Air Force*

Willford Hall Hospital, Lackland AFB, Texas.
Andrews AF Hospital, Andrews AFB, Washington, D.C.
Travis AF Hospital, Travis AFB, California.
Keesler AF Hospital, Keesler AFB, Mississippi.
*Scott AF Hospital, Scott AFB, Illinois.
Wright Patterson AF Hospital, Wright Patterson AFB, Ohio.
*Carswell AF Hospital, Carswell AFB, Texas.

V.A. (13)

Veterans Administration Hospital, Birmingham, Alabama.
Veterans Administration Hospital, Long Beach, California.
Veterans Administration Hospital, Wadsworth GM & S Hospital, Los Angeles, California.
Veterans Administration Hospital, Sepulveda, California.
Veterans Administration Hosiptal, Chicago West Side Hospital, Chicago, Illinois.
Veterans Administration Hospital, Dallas, Texas.
Veterans Administration Hospital, Boston, Massachusetts.
Veterans Administration Hospital, Bronx, New York.
Veterans Administration Hospital, Oklahoma City, Oklahoma.
Veterans Administration Hospital, University Drive Hospital, Pittsburgh, Pennsylvania.
Veterans Administration Hospital, Memphis, Tennessee.
Veterans Administration Hospital, Richmond, Virginia.
Veterans Administration Hospital, Wood, Wisconsin.

USPHS (11)

Baltimore, Maryland.
Boston, Massachusetts.
*Carville, Louisiana.
Detroit, Michigan.
*Galveston, Texas.
New Orleans, Louisiana.
Norfolk, Virginia.
San Francisco, California.
*Savannah, Georgia.
Seattle, Washington.
Staten Island, New York.

Senator NELSON. Dr. Goddard thinks it may be impractical to require hospital reporting. Maybe you cannot enforce reporting in the civilian hospitals, so we do not get very good statistics. But 16 years ago the ad hoc committee made a recommendation, and over that period we could have accumulated all kinds of statistics. Yet, we cannot seem to do anything about that.

The President of the United States and the Secretary of Defense could settle that in just about 5 minutes. Have you ever asked the Secretary of Defense?

Dr. GODDARD. Not to my knowledge.

Senator NELSON. Here is one arm of the Government worrying about the problems, and ad hoc committees making recommendations, and 16 years later these recommendations have not been implemented.

Now, it does not surprise me—I have seen lots of bureaucracies in my lifetime. But 16 years seems like a long time on an important matter.

Dr. GODDARD. I would agree.

Senator NELSON. Go ahead, Doctor.

Dr. GODDARD. Senator, just a followup point. Dr. Ley tells me they have been pushing this with the medical heads of the various military services, and VA, and it has been very slow. Dr. Ley feels somewhat more optimistic that they will give us this kind of information to a greater degree than they have in the past. So we have made the effort to get this kind of data from them.

Now, the chloramphenicol was to be marked following this meeting with the label warnings as follows:

Senator NELSON. Can you clarify for me the present legal authority that FDA has over prescription drug advertising?

Dr. GODDARD. In 1962 the Kefauver-Harris amendments gave us authority to regulate drug advertising. Then in 1963 we promulgated regulations which require drug companies to provide information to physicians through the various media that they use to advertise their products. They must present the information in fair balance, with the bad along with the good, and the information on advertised effects—important information required for prescribing. And that is the basic authority we operate under. I do not know the section.

Mr. GOODRICH. Section 502(n) as amended by the Kefauver-Harris drug amendments required that in the case of prescription drugs, the manufacturer, packer, or distributor must include in all advertisements which he disseminated or caused to be disseminated, the established name of the drug, the formula, such information about effectiveness, side effects, and contraindications as should be specified in regulations. The regulations have been promulgated, put into effect in 1963. They are in the process of being revised, elaborated, and improved at the present time.

Dr. GODDARD. We think improved. There is some disagreement on that, I might say.

Senator NELSON. You have stated the general basis of the law. The law then authorizes the FDA specifically to go how far? Does the FDA have the authority to say that, "You shall put exactly this language in this way in your package insert, in the advertising in medical journals and elsewhere?" Do you have that power?

Mr. GOODRICH. Yes, we do. We have had this authority on the package insert since the beginning of the new drug provisions. We have not had control over the claims of effectiveness. But all warnings essential for safe use has been wtihin our authority, under the new drug provisions since 1938—in the case of new drugs—and since 1945 for antibiotics, when the first antibiotic was brought under certification.

We have indeed specified in our antibiotic regulations, in the case of chloramphenicol, the precise box warning which now appears in PDR and in the labeling and in all the promotional material for this drug, except reminder advertising.

It is the very warning that Dr. Dameshek recommended, and that our committee recommended in 1960. And we are, we think, improving on it now with the benefit of another committee.

Dr. GODDARD. But, Senator, we do not control the text of every advertisement that is produced.

Mr. GOODRICH. But in the sense that he was asking, as I understood, if this became necessary, did we have the authority to do that. And the law says that the ad shall include such information about side effects, counterindications, and effectiveness as we shall specify in the advertising. Now, we started off with a system which required that the advertising limit its promotion within the claims authorized by new drug clearance or by antibiotic clearance. We could become more specific if that is necessary, and we have become more specific in the case of Chloromycetin.

Senator NELSON. So you do have the authority to specify exactly the language as to safety and effectiveness.

Mr. GOODRICH. Right.

Senator NELSON. So that if there is an exaggerated claim, you can simply direct the company to change the language; is that correct?

Mr. GOODRICH. The company has hearing rights and other protections that go with this. But we have the ultimate authority to resolve the question.

Senator NELSON. And before whom is the hearing conducted?

Mr. GOODRICH. Before a hearing examiner in our department, with judicial review in the courts of appeal.

Senator NELSON. Has there ever been a case where the drug company disagreed with what the FDA directed, and asked for a hearing? And, then, have there been cases where they asked for a hearing and later appealed the decision of the hearing to the courts?

Mr. GOODRICH. There have been cases in which there was a request for a hearing. There have been—in other settings, but not that particular one—appeals to the courts.

But in general, the companies have not exercised their hearing rights in developing labeling and promotion for drugs. They have become convinced, I believe, that no drug can gain a place in medical practice or retain a place except on its scientific merit. And therefore the——

Senator NELSON. Who is this?

Mr. GOODRICH. The drug industry. They could not really press a drug onto the market over the objections of the Bureau of Medicine where there were scientific reservations. And so the way the procedure works is that the differences are resolved through the new drug procedures, or through the antibiotic procedures.

Now, we, as you know, have required warnings to be sent out in "Dear Doctor" letters and other ways. We have not had a controversy over any of that activity so far. It is possible we will have sometime.

Senator NELSON. But of course they have successfully promoted chloramphenicol over and against the best expertise of the medical profession for 18 years.

Mr. GOODRICH. They have been required since 1952 to put on the warning which Dr. Goddard was just about to read you; in 1960 to strengthen that warning. And any promotion contrary to that warning would be a violation.

The company was allowed to use reminder advertising, and we are in the process of revising those regulations to discontinue that.

Now, as you know yourself, I am sure, from the Kefauver hearings, there was evidence that Parke, Davis used detailing pieces outside the labeling. We did contact the company about that. They assured us that that was unauthorized and contrary to company policy, and that they would instruct their staff accordingly.

Now, detailing is a difficult practice to deal with. But if we have evidence that a product is being offered orally, or in any other way, in excess of the authorized claims or without the required warnings or in derogation of the required warnings, we have the procedures to take action.

Senator NELSON. We will get to that a little later, because I want to ask you what you are doing about the most recent PMA ad in the Reader's Digest.

But what puzzles me about this is that we have required them to include this warning in their ads. Dr. Dameshek approved it, he advised me—apparently he was on the ad hoc committee.

Dr. GODDARD. Not on this one. He was on the one in 1960, 1961.

Senator NELSON. Yes. And so that warning was put on. And Dr. Dameshek's testimony is that it has been a total failure. So the fact is that everything that has been done has not worked.

Would you not agree that if Dr. Dameshek and the experts who testified here are correct, that somewhere around 90 to 99 percent of the cases receiving chloramphenicol should not, and that our methods of controlling advertising and cautioning physicians have been a colossal failure?

Dr. GODDARD. Yes—I think we would agree that the methods of informing the physicians and getting them to act on that information have been a failure.

Senator NELSON. We will get to your recommendations later. Go ahead.

Dr. GODDARD. The warning that was then required was:

Warning—Blood dyscrasias may be associated with intermittent or prolonged use. It is essential that adequate blood studies be made.

The following warning was to appear at the top of the package insert:

Certain blood dyscrasias (aplastic anemia, thrombocytopenic purpura, granulocytopenia and pancytopenia) have been associated with the administration of Chloromycetin. It is essential that adequate blood studies be made when prolonged or intermittent administration of this drug is required. Chloromycetin should not be used indiscriminately or for minor infections.

In announcing the reinstitution of certification for chloramphenicol, FDA said:

> The administration has weighed the value of the drug against the capabilities for causing harm and has decided that it should continue to be available for careful use by the medical profession in those serious and sometimes fatal diseases in which its use is necessary.

Senator NELSON. In what year was that done?

Dr. GODDARD. 1952.

The FDA characterized its experience as "an impressive reminder that highly potent drugs must be treated with extreme care and should not be employed unless there is a clearcut indication that they are needed."

The Kefauver Subcommittee on Antitrust and Monopoly subsequently reported that these warning measures were diluted by Parke, Davis instructions to its detail force, which the subcommittee said presented the report of the National Research Council as a blanket clearance of the drug.

Nonetheless, the use of the drug dropped off markedly after the new warning issued. This was a short-term reaction, however, and use of the antibiotic increased during the years that followed.

Senator NELSON. I realize you were not the Commissioner at that time. But I have read the Kefauver testimony, and I presume you have read it. It is a very impressive example of clever advertising language being used by the company to circumvent the statement of caution that was suggested by the FDA at that time, was it not?

Dr. GODDARD. Yes.

Senator NELSON. And as I recall the testimony before the Kefauver committee the company claimed that the drug had been completely cleared by the committee of the National Research Council or words to that effect.

Mr. GOODRICH. This was in terms of instructions to the detail force. Now, you will recall, Senator, that prior to the enactment of the Kefauver-Harris amendments in 1962, we had no right to obtain that information by inspection. We had no right to records of these drug companies. And we learned about this detailing through the material subpenaed by Senator Kefauver's committee.

Now, we did have one of our own physicians detailed improperly in 1959, and we, on the basis of our own experience, contacted the company immediately, calling attention to this misuse of a piece out of the literature to dilute the aplastic anemia warning. The company, from their president on down, gave assurance that that type detailing was not authorized.

Under the existing law, we do have the right to inspection to obtain records of this sort. And we have asked, within the last few days, what detailing pieces there were, and we are told that there are none—no specific detailing pieces.

Mr. GORDON. Yesterday one of our witnesses who is a physician, Dr. Watkins, testified that a detail man misinformed him about the dangers of Chloromycetin. Two days ago Dr. Hewson, from Philadelphia, testified that in his own experience as a general practitioner, he could not recall a Parke, Davis detail man ever discussing the relationship between administration of the drug and the development

of blood dyscrasias. Several doctors testified in the *Love* v. *Wolf* case, in California, that Parke, Davis' detail men told of the virtues of Chloromycetin and minimized its dangers.

Do you really accept the firm's assurance that the statement was both unauthorized and contrary to company policy?

Mr. GOODRICH. They supplied us with instructions that they had sent to their force, and they are a part of the record in the Kefauver hearings, as you know. All that correspondence is included in the Kefauver records. I would not mean to imply in any way that the detail men were not making these presentations. Indeed, the detailing of our own physicians showed they were. But we took steps to call it to the company's attention.

Now, the point of monitoring detailing is a very, very delicate point with us. We have no way, really, to monitor what goes on between the detail men and the physician in his private office.

We do have control over the printed and promotional material, so that the message will come through loud, clear, and repeatedly in the promotion about what the drug is for and what warnings should be observed.

Senator NELSON. It has not in the case of this drug come through very loudly or very clearly, obviously.

Mr. GOODRICH. Since 1960, there has been this warning, and the current PDR, if you look at it, has a black box warning right at the top of the column, which has Dr. Dameshek's warning. This discussion of Chloromycetin has been before the profession some time. Now, it is not effective, I know that, and I know that there is room for improvement. We are planning to do that.

Dr. GODDARD. It is probably the strongest drug warning that exists, Senator. And in spite of that it is still being misused. The warning does not work.

Senator NELSON. So where do we go from there?

I wanted to ask you a question.

The FDA has the authority to require and does require the package insert. Am I correct in that?

Dr. GODDARD. That is correct.

Mr. GOODRICH. And it has done so for Chloromycetin since the 1960 ad hoc committee. Up until 1961, I believe it was, we allowed package inserts to be made available on request. But in response to the 1960 ad hoc committee recommendations, one of the conditions was that package insert be included in all packages.

Now, there has been on the bottle, on the carton, on the bottle containing the capsules, a warning since 1962 about blood dyscrasias. This is the one Dr. Goodard just read:

> Warning, blood dyscrasias may be associated with intermittent or prolonged use. It is essential that adequate blood studies be made.

That has been on the bottle since 1952.

Senator NELSON. For capsules, not injectables.

Mr. GOODRICH. For all containers, yes sir.

Senator NELSON. But, the package insert in almost all cases goes to the gentleman who does not prescribe, that is, the pharmacist—so that does not help to warn the physician at all.

Dr. GODDARD. Except this. All the detailing material that the detail

man leaves with the physician is also considered labeling, and it must also contain that same warning promptly displayed.

Senator NELSON. Is he required to leave the material containing this warning with the doctor?

Dr. GODDARD. No, he is not.

Senator NELSON. If you require the package insert, why wouldn't it be helpful at least to require him to leave it with the physician?

Dr. GODDARD. If he leaves anything, the warning must be included. But he is not required to leave the drug or the warning upon the occasion of detailing. He may simply discuss the drug with the physician.

Mr. GORDON. It is the oral presentation, however, which is the most potent presentation, is it not?

Senator NELSON. Doctor, I have to go over to the Labor Committee to help them make a quorum for an executive session. We will recess for 10 minutes.

(At this point in the hearing a short recess was taken.)

Senator NELSON. We will now resume the hearings. Go ahead, Doctor.

Dr. GODDARD. In 1955 Parke, Davis requested a deletion of part of the warning statement. The firm's letter pointed out that some patients with blood disorders attributable to Chloromycetin had received only a few capsules. The company regarded the warning, which referred to prolonged or intermittent therapy, as a legal liability in litigation.

We rejected this proposal, and while strengthening the warning was suggested, the decision was made to continue the warning as recommended by the scientific committee.

In December 1959, one of our physicians, who was also in private practice, was visited by Parke, Davis' detail men who claimed that there was no more danger of blood dyscrasias with Chloromycetin than with any other antibiotic. The company was informed of this impropriety, and gave assurance that the statement was both unauthorized and contrary to company policy.

In April of 1960 the Council on Drugs of the American Medical Association made another report on blood dyscrasias associated with chloramphenicol. The report said that although the warning had been in use for a long time, physicians continued to use the drug indiscriminately for minor infections, including those associated with the common cold.

FDA asked the National Research Council in November 1960 to again consider the chloramphenicol problem in light of a new evidence accumulated since 1952. FDA wished to obtain the council's opinion as to whether chloramphenicol should be allowed to remain on the market, whether its use should be restricted to hospitals if it were to remain on the market, and what label changes the council would recommend if the drug was allowed to remain on the market.

The recommendations of the council were received by FDA in January 1961. The council concluded that, due to its therapeutic value, chloramphenicol should remain on the market; due to some of its proper indications for use, home treatment, as opposed to hospital treatment exclusively, was reasonable; due to its serious effects, further warnings and increased education of the medical profession were necessary.

In accordance with these recommendations, the labeling of chloramphenicol was revised in February of 1961 to include a prominent "warning box" containing the following information:

Warning—Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reaction may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective. It must not be used in the treatment of trivial infections such as colds, influenza, or infections of the throat; or as a prophylactic agent to prevent bacterial infections. Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia.

Mr. GORDON. Dr. Goddard, what is meant by "adequate"? Is this a scientifically fixed and precise term, or does it lend itself to individual interpretation?

Dr. GODDARD. In the phraseology used in 1961, adequate blood studies to be made during treatment, was subject to judgment on the part of the physician. We subsequently have changed this phraseology. Mr. Goodrich points out that this is why we pointed out specifically early peripheral blood changes, in that same context.

Senator NELSON. Is the warning used in 1961 still the warning that is used?

Dr. GODDARD. No, sir. It was subsequently revised, I believe—minor revisions were made in 1966, as I recall.

Dr. LEY. Change from "should" to "must" not be used.

Senator NELSON. One word.

Dr. LEY. Yes, sir.

Dr. GODDARD. "Chloramphenicol must not be used when other less potentially dangerous agents would be effective." That was the change.

Senator NELSON. I would like to read to you a section of the warning statement:

Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effect.

I suppose if you read that sentence to even a layman, he would say, "Of course it should be used only against organisms which are susceptible"; the sentence means nothing. And then the advertising continues to talk about its value as a broad-spectrum antibiotic. The PMA ad in Reader's Digest says it is useful against dozens of diseases. It seems to me that the sentence is at best useless, and may be harmful.

Dr. GODDARD. Of course, Senator, this refers to the use of sensitive testing—using the organisms obtained from the patient, cultured by disk, and then the antibiotics that are under consideration being used. That is what this particular sentence refers to.

Senator NELSON. You mean the sentence is saying that a culture should always be taken, and then a test of its effect on the organism made prior to administration?

Dr. GODDARD. That is what lies behind that sentence, Senator. Dr. Ley, do you wish to comment on this?

Dr. LEY. Yes. This is a point which we discussed at great length with our advisory committee this past Monday.

For certain very serious and acute infections, the physician should have the freedom to prescribe this drug where, if he has not given it, the patient would be much more seriously ill. We feel that the physician also has the responsibility to initiate such sensitivity testing at this time as well.

The example which weighed most heavily in our committee consideration was that of a youngster with a serious meningeal infection. If you delayed therapy until the sensitivity tests are available, such a child might suffer serious brain damage. The new labeling draft which we have considered with the committee makes provision both for the initiation of therapy, and requires the sensitivity test to be done concurrently. So that I believe this one looseness in the wording of the old indications and warning section is now corrected.

Senator NELSON. The next sentence is, "Chloramphenicol should not be used when other less potentially dangerous agents will be effective."

Dr. GODDARD. That was changed in 1966 to say "must not be used when other less potentially dangerous agents will be effective."

Senator NELSON. That is the one change made between 1961 and 1966?

Dr. GODDARD. That was the one change.

That is the one change as far as the box is concerned.

Senator NELSON. Go ahead.

Dr. GODDARD. Parke, Davis was required to mail the new prescribing information to all medical doctors and osteopaths in February 1961 with a statement that the prescribing information would accompany all oral and parenteral Chloromycetin products.

Between 1963, when our prescription drug advertising regulations were first adopted, and 1966, Parke, Davis advertised Chloromycetin by reminder ads, which carried no indications and no warnings. The regulations permitted this.

Mr. GORDON. Can you give us the reason why this type of ad should be exempted from carrying the warning?

Dr. GODDARD. There is a history of this which Mr. Goodrich is more familiar with, and may comment on.

But in general, it was felt that reminder ads, which are permitted under an exemption by the Secretary, serve a useful purpose.

Mr. GORDON. Why should it have been permitted?

Mr. GOODRICH. There is a type of advertising and promotion that is used in the drug industry which features only the name of the drug and the name of the company. It does not purport to offer to the physician any indications for use, nor to indicate in any way what the drug is for. It simply is a reminder of the name of the drug and of the company that makes it.

This type of advertising was defended by the drug industry at the public proceedings which preceded the establishment of the regulations. We concluded it was reasonable to allow reminder advertising, so long as no indications for use were made, or implied directly or indirectly, and so long as nothing was said about the drug other than its name and the name of the company.

Now, we are reexamining that policy in evaluating the new regulations. And as the statement indicates, we propose to change the regulations so that Chloromycetin could not be advertised by reminder ads.

Mr. GORDON. These reminder ads are designed to sell the drug, are they not?

Mr. GOODRICH. Of course, all advertising is intended for selling, and I do not accept the idea that they are not. But the argument is that these are institutional type reminders, and as long as they do not carry any information to the physician about how to use the drug, it is not necessary to have the warnings on them.

Mr. GORDON. Whose argument is that?

Mr. GOODRICH. This is the argument advanced by the PMA at the hearing in 1962, when the regulation was adopted.

Mr. GORDON. And you accepted the argument?

Mr. GOODRICH. Yes.

Mr. GORDON. Do you agree with it?

Mr. GOODRICH. I do not.

Mr. GORDON. Why hasn't something been done about it since 1952?

Mr. GOODRICH. Because I did not have the power of decision.

Mr. GORDON. I am not asking why you personally did not do anything. Why didn't the Food and Drug Administration do something about it since 1962?

Mr. GOODRICH. The Commissioner in 1962 and his advisers were persuaded that this was a practice that would not be abused and could be allowed.

We reinstituted consideration of it last fall when the regulations were up again. The same arguments were advanced, and tentatively accepted this time. But we did point out that the reminder ads were being abused by being used for drugs having more serious side effects, and this issue brings it to a head with Chloromycetin.

Dr. GODDARD. Let me also say, Mr. Gordon, that in my opinion we have had far more serious problems with drug advertising to contend with since I have been Commissioner than the reminder ads. And I have directed most of my attention to the extent I can be directly involved in this to the other problems of drug advertising, along with Dr. Ley and Dr. McCleary, who have done such an outstanding job trying to clean up medical advertising. There have been serious problems, in my estimation, some far more pervasive than the reminder ads as such.

Senator NELSON. Just for clarification of the record, what is permitted in the reminder ad?

Dr. GODDARD. Only the name of the company, Senator, and the drug that they are reminding the physician of. "Don't forget Chloromycetin, doctor, Parke, Davis."

Senator NELSON. They may not say in the reminder ad "broad spectrum antibiotic," any descriptive language like that?

Dr. GODDARD. No, sir.

Senator NELSON. So this is a reminder ad that complies with FDA regulations. It has a picture of a doctor and so forth, and says "A name you can count on when it counts. Chloromycetin, chloramphenicol, Parke, Davis, complete information on usage available to physician upon request," and so forth. That is a reminder ad?

Mr. GOODRICH. Yes, sir.

Senator NELSON. And they may not say more than that under the present regulations?

Dr. GODDARD. That is correct.

Senator NELSON. And I understand you are reviewing that now?

Dr. GODDARD. I would propose if the exemption is to be permitted to continue for Chloromycetin that the warning box be incorporated in the reminder ad itself, or the exemption be dropped completely.

Senator NELSON. Thank you.

Dr. GODDARD. Now, that of course has to go through the procedures that we described earlier.

Senator NELSON. Which?

Dr. GODDARD. Opportunity for public hearing, and review by the courts.

Senator NELSON. Yes. But have you made that decision as to the reminder ad?

Dr. GODDARD. On this drug, basically, it has been made.

Mr. GROSSMAN. Doctor, would that hold up for other drugs?

Dr. GODDARD. It could, if there was an indicated need.

We are reexamining the entire issue of reminder ads—not just this one.

In 1964 the company decided to advertise the drug promotionally. That means the more routine type of advertising. They met with our medical advertising group to consider how this should be done. Our physicians noted that the package insert had no "Indications" section, but instead described the broad range of antimicrobial activity of the drug. To correct this, an indications section was devised and other changes made to emphasize that the drug was only indicated for, and should be prescribed in accordance with, the important information in the "warning box." In 1966, the company made the requested changes and discontinued the reminder ad campaigns.

And I would add as a postscript that for a large part there may be still some reminder ads.

Dr. LEY. Few only.

Dr. GODDARD. The labeling was reviewed again in 1966 by the Acting Deputy Director of the Bureau of Medicine and the "box warning" was changed to say that the drug must (instead of should) not be used to treat trivial infections or in any other conditions except as described in the box.

Despite these label revisions, editorials in the Journal of the American Medical Association, and warnings in other publications such as the Medical Letter, the use of chloramphenicol has increased and continues to increase. Most of this use, we believe, is for medical conditions for which the drug is not indicated or for which it is expressly prohibited such as acne, the common cold, simple infections, and the like. We are disappointed by a current advertisement in the Reader's Digest by the Pharmaceutical Manufacturers Association, which describes chloramphenicol as a prime member of a "class of drugs that fights 100 diseases" and characterizes it as a "broad spectrum" antibiotic effective against dozens of diseases, causing only occasional and sometimes serious side effects in some patients.

Senator NELSON. Doctor, you state that the use of the drug continues to increase?

Dr. GODDARD. Yes, sir. As measured by sales, the amount that is being certified by the Food and Drug Administrtaion through batch-by-batch certification.

Senator NELSON. Do you, under your batch-by-batch certification, keep track, then, of total numbers of grams manufactured per year?

Dr. GODDARD. Yes. Total number of grams. Those figures are on the way. I have asked that they be sent up here, and I am told they should arrive here within 15 minutes.

Senator NELSON. You anticipated my question.

Dr. GODDARD. Yes. And also I can tell you that those figures will be delivered monthly to my desk from now on. That is another procedural change we have made—so I can more closely keep track, along with Dr. Ley, who has not had these figures in the past either, of the amount being certified.

Senator NELSON. And what period of time do the figures that you have requested from your office cover?

Dr. GODDARD. One year. 1967.

Senator NELSON. Do you have the statistics on prior years?

Dr. GODDARD. We could go back, I believe, and dig those out of the files, sir, and we will do so if you wish to have them.

Senator NELSON. I think it might be helpful to at least have a representative sampling every 2 years or so, since 1952, so we could see how many grams are marketed. Is it in grams that you keep the record?

Dr. GODDARD. Yes.

Senator NELSON. If you could supply that, along with the 1967 data so we can print it in the record at this point, I think it would be useful information.

Dr. GODDARD. Be happy to do so.

(The subsequent supplemental information follows:)

STATEMENT OF THE FOOD AND DRUG ADMINISTRATION REGARDING GRAMS OF CHLORAMPHENICOL CERTIFIED IN PHARMACEUTICAL PREPARATIONS

Year	Parke, Davis	Other firms (oral products only)
For use orally or by injection:		
1952	33,436,597	0
1953	5,943,165	0
1954 [1]		
1955	18,638,518	0
1956	27,320,359	0
1957	28,872,529	0
1958	40,593,884	0
1959	50,070,646	0
1960	54,606,330	0
1961	27,126,744	0
1962	34,934,914	582,650
1963	37,988,417	0
1964	32,619,478	250,000
1965	36,282,949	0
1966	43,542,769	3,673,908
1967	37,641,898	9,838,274
Intended for topical use:		
1952	68,496	
1953	87,777	
1954 [1]		
1955	96,978	
1956	100,756	
1957	88,968	
1958	92,232	
1959	104,332	
1960	119,993	
1961	62,955	
1962	99,614	
1963	88,120	
1964	98,563	
1965	99,835	
1966	95,435	
1967	155,006	

[1] Not available.

CHLORAMPHENICOL CAPSULES AND TABLETS CERTIFIED TO OTHER FIRMS

Firm	1962[1]		1964		1966		1967	
	Capsules	Grams	Capsules	Grams	Capsules	Grams	Capsules	Grams
Arco-Abello	273,600	68,400						
Labs. Atral	2,000,000	500,000						
Castillon Labs	42,000	10,500						
Continental Labs					920,000	230,000	9,400,000	2,350,000
Davis-Edwards							600,000	150,000
Instituto Luso Farmaco					[2]926,500	231,625		
Lepetit	14,000	3,750						
McKesson Labs					9,857,942	2,464,486	15,190,253	3,797,563
PharmUSA					2,989,465	747,366	14,062,842	3,515,711
Rachelle							100,000	250,000
Zambon			1,000,000	250,000				

[1] None certified in 1963 and 1965.
[2] Tablets.

Senator NELSON. Now, on the Reader's Digest ad—I read it through very carefully two or three times. I note that you are disappointed in it.

Dr. GODDARD. Yes, sir; I am disappointed in this because for the past year and a half we have been watching with some concern the incursion, if I can use that word of the pharmaceutical manufacturers individually and collectively in the lay media, in terms of an indirect form of advertising. And it gives us concern.

We have noted and alerted them to this, and expressed our concern in meetings with them, because it seems to us that this is a logical step that they might consider taking. In fact we have had some past cases that have given us so much concern that we have called the company to task in an individual case.

This simply is another example of moving beyond the ethical advertising in medical journals, and bringing the message directly to the public. And we view this as something rather serious.

Senator NELSON. It had always been my understanding—you may correct me if I am wrong—that in prescription drug advertising, the sole constituency of the company is the medical and paramedical, if that is the case, people in the profession. The companies have never gone to the lay media, so to speak, to advertise a prescription drug, because the person there does not make the decision, presumably, about what he should get. Is that correct?

Dr. GODDARD. That is correct. That is the assumption that our regulations first formulated in 1963, were based on.

Senator NELSON. I do not know whether you have noted it, but I have received letters, and have, on a half a dozen occasions, picked up institutional-type pharmaceutical on the radio. You can hear it every morning here, if you turn your radio on at the right time, and every evening going home.

Is that a new development in this field?

Dr. GODDARD. Mr. Goodrich has followed this over the years. To my knowledge it is a fairly recent one. The whole field—for example, we picked up some ads on oral contraceptives that we were concerned about, because they represented to us at least a first step into the field of advertising directly to the user.

Now, one of the things physicians do not like, and understandably so, is to have the patient come in and say, "Doctor, I want such and such

a drug." Now, there is enough of this occurring already. In my own private practice of medicine years ago I had patients come in and say, "I need a shot of penicillin." And some of them flatly told me if I would not give it to them, there was another doctor down the road that would, and he did.

So I let him do it.

But the promotion of drugs to the public I find very distasteful and an unfortunate step forward. I am saying we are seeing signs of this occurring.

Now, it is quite proper that the public have early information, because they are keenly interested, on new developments in medicine. The press does an outstanding job on this. And it is indeed a fine balance between what represents promotion of the specific product, whether it is for a new treatment for arthritis, which involves so many millions of people, or this type of publication, which is an ad by, not a company, but by an organization made up of companies.

Senator NELSON. I suppose there is some kind of qualitative distinction between an institutional-type ad which promotes the industry as a corporate citizen in a public ad vis-a-vis an ad that picks a specific drug and promotes it in the public media. Is that correct?

Dr. GODDARD. Yes, sir; that would be true.

Senator NELSON. Now, this is a case here, in the Reader's Digest, where the PMA selects chloramphenicol, and on page M–3 they print a special section, as they did on a previous occasion, as you are aware.

Dr. GODDARD. Yes, sir.

Senator NELSON. And this ad does have "advertisement" printed on each page now. The line at the top is, "There was nothing anyone could do to stop them from dying until the American doctor came down from the sky with a new drug." Then it goes on to say the things you mentioned in your prepared remarks.

We have a copy of a letter here, signed by Mr. Stetler, from the Pharmaceutical Manufacturers Association, addressed to "Dear NARD Members"—National Association of Retail Druggists.

Dr. GODDARD. I know the association, Senator.

Senator NELSON. I knew you were familiar with it.

Dr. GODDARD. Yes, sir; I am familiar with that group.

Senator NELSON. But I thought some of the rest of the audience and the record may not be. But this reads—and I will submit it for the record—"Dear Member, as you may know, the Pharmaceutical Manufacturers Association recently launched a major advertising program with the Reader's Digest." They mention that the response from the general public was indeed gratifying, "and over 1 million reprints of the ad were distributed to the public through various sources, among them the community pharmacy."

Then it goes on to suggest that the PMA has more copies available. They say:

> A copy of the February insert is enclosed, along with a prepaid postcard requesting 50 copies of the reprint. Present inventory precludes us from offering more. However, if you would like more than 50 copies of the June reprint at no cost, please indicate and we will forward them in the latter part of May.

Quite obviously this is part of a program of reaching the public by giving 50 to a pharmacist, for distribution to whomever he pleases—and I suppose particularly the general public.

(The letter referred to follows:)

PHARMACEUTICAL MANUFACTURERS ASSOCIATION,
Washington, D.C., January 26, 1968.

DEAR NARD MEMBER: As you may know, the Pharmaceutical Manufacturers Association recently launched a major advertising program with the Reader's Digest.

Our first supplement of "Medicines and Your Family's Health", which appeared in the November issue, was widely distributed to Congressmen, government administrators and related health groups. The response from the general public was indeed gratifying, and over one million reprints of the ad were distributed to the public through various sources, among them the community pharmacy.

Because pharmacists are directly and we hope favorably affected by this program, Willard Simmons, the Secretary of NARD has suggested that members of your association might be interested in having an opportunity to play a greater role in disseminating this health information to the public. We hope that you will agree with us that this successful public information effort can be a useful public relations medium between you and your customers.

A copy of the February insert[1] is enclosed along with a pre-paid post card requesting 50 copies of the reprint. Present inventory precludes us from offering more; however, if you would like more than 50 copies of the June reprint at no cost, please indicate and we will forward them in the latter part of May.

We certainly hope that this joint venture will continue to strengthen relationships between your profession and our industry. Any comments you have will be appreciated.

Sincerely,

C. JOSEPH STETLER.

Senator NELSON. Now you have commented that you were distressed by this type of advertising. Is there anything FDA intends to do about it?

Dr. GODDARD. There is nothing under our present regulations we can do about this type of advertising. Is that correct, Mr. Goodrich?

Mr. GOODRICH. So long as it is used by PMA. Now, if this ad were used by Parke, Davis, in accordance with the law it would be the responsibility of the manufacturer to include in all advertisements issued or caused to be issued, adequate information on side effects, contraindications, and effectiveness.

As long as this is a PMA ad, and not a Parke, Davis ad, the law would not apply to it.

There would still be an issue whether or not Parke, Davis caused this advertisement to be disseminated. We have no evidence that they did.

In the area of the oral contraceptives, where the message went to the public, we issued a statement of policy saying that where such drugs, prescription drugs, were advertised to the patient directly, that the promotional material would have to have adequate information for the patient on side effects, contraindications, at least, in terms that the laity could understand.

When we put our regulations out, we proceeded on the assumption that you hold, that the audience was the profession, and the regulations were oriented to get before the profession the knowledgeable understanding of this drug in terms professionals can understand, but which would not be particularly useful to the laity.

We have no regulations so far on advertising copy for prescription drugs that goes directly to the public.

You will recall that we did write to you in answer to your inquiry in connection with the first PMA Reader's Digest advertisement, stating where we were in this program, and what we could do and planned to do.

[1] Retained in committee files.

Senator NELSON. Do I understand you to be saying that under the law the FDA has the authority to supervise or control the advertising done by an individual company, but no authority over an association of which individual companies are members?

Mr. GOODRICH. The law says "manufacturer, packer, or distributor," and refers to an advertisement either issued by him or caused to be issued. I left open the issue, or the question, whether or not this could be proven to be an advertisement caused to be issued by Parke, Davis. I have no idea that it could or could not. I just have no opinion on that based in the facts I now have. But I would not rule out the possibility of taking some action if it could be proved that the company caused this advertisement to be issued by an association.

Senator NELSON. Well, now, as a lawyer, we are looking at a situation in which we have a nonprofit association with which the members voluntarily associate themselves. The association is controlled by the membership, and supported by the membership.

Under any reasonable concept of law, it seems to me that you can constructively impute to the members the actions of the voluntary association.

Mr. GOODRICH. I think you do. But do you go from there to the next step, that the manufacturer caused this advertisement to be disseminated? Now, that is what we would have to prove, in any event, sir.

Senator NELSON. The reason I used the legal language, "constructively impute," is that you may not be able to prove that in a specific instance a company actually said to its association, "Will you run this ad on our drug?"

Mr. GOODRICH. That kind of case would be easy for us.

Senator NELSON. Yes. But it seems to me it should be just as easy the other way, when in fact this is a member, and these members do directly control the association, And if they cannot throw a cloak around themselves and separate themselves from the creature they control, you simply could proceed on the grounds that you constructively impute it to them. Now, if they were not a member of the association, and were controlling the association, and ran a story on a drug made by a nonmember company, I would think then you would have to go to the specific case and prove the specific company had a specific agreement. But it does seem to me it is just automatic—certainly you control this company, we impute this to you, and you are in violation of FDA regulations. At least that is part of the law that ought to be explored very carefully.

Mr. GOODRICH. It is entirely possible that we could prove that this was caused to be disseminated by Parke, Davis.

Senator NELSON. I am not talking about that. Just the very fact that they are members, you impute it to them. That is the legal question that I think is important here.

Mr. GOODRICH. I am sure I would have great difficulties with the Department of Justice in doing that, but we will explore that.

Senator NELSON. I do not think you ought to have any trouble with a real lawyer.

Dr. GODDARD. You are not suggesting the Department of Justice does not have real lawyers.

Senator NELSON. I am suggesting that you probably would not have any trouble because they do have real lawyers.

Dr. GODDARD. Or that Mr. Goodrich is not a real lawyer. Most companies wish Mr. Goodrich were not.

Seriously, Senator, we will explore this. We are aware of the gradual creeping encroachment into public media of paid advertisement on prescription drugs in a variety of forms. And I think it is bad.

Senator NELSON. If the lawyers, with their great tendency to legalisms and legal conservatism, said you could not impute this to the Parke, Davis Co., which I think the court ought to take judicial notice of—but if they did, would you not be prepared to recommend that the law be amended so that the same authority applies to advertising of this kind as it does to advertising in medical journals, by individual companies?

Dr. GODDARD. If that is what it takes to stop this kind of practice; yes, sir.

Senator NELSON. Now, there is another part of this ad that troubles me—you quoted from it, and I will quote from it again: "The new drug was to prove effective against dozens of diseases."

The first implication is that it is just a drug indicated for wide use. But, all the scientific evidence we have is that it is a drug indicated for a very limited use—in typhoid fever and in diseases against which there is no other effective drug, and when the condition is very serious. But are there dozens of diseases in which this drug is indicated, really?

Dr. GODDARD. Dr. Ley—I would have to say that it is probable that there are dozens of conditions in which one could say this drug is indicated.

Now, the wording here is very carefully done, as you recognize. It says, "was proved." Now, that, in a historical sense, is true. It does not speak to the issue of what the indications are today, or that there has been a charged curtailment of the indications, and that even more curtailments are being considered, or that there are serious problems viewed with respect to the usage and overusage of this drug.

So the wording here is actually, in my opinion, factually correct. I think that if Dr. Ley and I sat down for a few minutes he and I could come up with a dozen indications for the use of this drug. Don't lose sight of the fact that one of the indications that is appropriate is for use in those conditions for which the organism has resisted other antibiotics, and these are serious conditions. And so there are literally dozens of those. Certain kidney infections, to give you one example.

It is that kind of clever wording that is in my opinion very misleading in this kind of advertisement. It leaves the impression this is still the case today. And technically that is correct. But it certainly does minimize the side effects part. We would not approve this kind of thing in an ad to a physician who knows what lies behind each word.

Senator NELSON. This does not say dozen. It says dozens—which means many dozens.

Dr. GODDARD. More than 1 dozen would be dozens, would it not, Senator—to quibble about grammar?

Senator NELSON. Well, if it is 2 dozen, they ought to say 2 dozen. I get the impression, when they say dozens that the——

Dr. GODDARD. I think it is misleading.

Senator NELSON. If I may say decades, I usually mean more than

two decades. I think the implication here is that there are a whole lot of diseases for which it is indicated.

Dr. GODDARD. That is the implication I draw from it, too, sir. And I think it is misleading, without question.

Senator NELSON. I understand your legal division is going to pursue this question further?

Dr. GODDARD. Yes, sir.

Mr. GORDON. I have one question about this.

The ad says, "Second in a series published as a public service by the Pharmaceutical Manufacturers Association."

Would you consider this a public service? Or would you say it is a public disservice to mislead?

Dr. GODDARD. To answer your second question, yes, I am a poor lawyer, and I have to rely on Mr. Goodrich here, as to what we would properly define as a public service.

Now, let me say, I just think this whole campaign in Reader's Digest—the first series of articles was full of errors. I think we detailed some of these to the committee. I think they were misleading, too.

Now, the drug industry has done things that it properly should receive credit for. I just do not think this is the way to get credit for them. Personal opinion.

Mr. GORDON. They misled in two out of two cases. Why do they have to resort to this type of activity?

Dr. GODDARD. This was apparently their decision, to help their image. That is the only conclusion I can draw.

Senator NELSON. I think in at least one respect, Doctor, the eight-page article on three drugs is a public service, because after all of the hearings we have held here, PMA uses only generic names in discussing the drugs.

Dr. GODDARD. Yes, sir. We noted that, too.

Senator NELSON. Which I was told is a very bad thing. But at least the PMA now is using just generic names in the three drugs they are mentioning.

Dr. GODDARD. Hopefully we can get that done in a compendium, Senator.

Senator NELSON. I hope so, too.

Go ahead, Doctor.

Dr. GODDARD. The exact number of patients who have suffered a serious or fatal blood disease as a result of the indiscriminate use of chloramphenicol is not known. Various estimates place the incidence rate of blood dyscarsias from chloramphenicol at 1 person in 10,000 to 1 person in 100,000 who receive the drug, general reactions.

Despite the risks associated with the use of chloramphenicol, if one may judge from the sales figures, use of the drug continues to be excessive. Where have the FDA, the manufacturers, and the medical profession failed? Is the general medical community unaware of, or unconcerned about, the risks associated with this drug? What must be done now? These are most difficult questions, and the answers do not come easily.

The "box warning" in the labeling is strongly worded and tells the physician quite bluntly the dangers of the drug, yet it has not accomplished its intended purpose.

What other steps might be taken? We have considered restricting the use of chloramphenicol to hospitals. However, aside from the legal problems involved, we have learned that more than half the chloramphenicol distributed in this country is purchased by, and presumably used in, hospitals.

Senator NELSON. How do you get a record of that kind?

Dr. GODDARD. The Goslin survey is one source of that information. Also we received from the company earlier this week detailed records showing that 59 percent of their drug was shipped to hospitals for their use. Now, that might be somewhat misleading. Fifty-nine percent would represent a maximum, Senator, because it includes hospitals which would dispense it on an outpatient basis.

A substantial amount is used.

I do have the Chloromycetin figures handed to me. These are from the firm. The estimated distribution of Chloromycetin to U.S. hospitals in 1967—this is by Parke, Davis—amounted to 18,700 kilograms, or 59 percent of the total kilograms distributed in the United States.

Senator NELSON. Some of that is, as you say, dispensed on an outpatient basis.

Dr. GODDARD. Primarily in the military and veterans' hospitals. Although it may include some of the university hospitals, too.

Senator NELSON. Is there any information or have any studies been made as to the differences among the hospitals in this respect. That is, we had testimony yesterday from one of the doctors that Johns Hopkins, many years ago, initiated the policy of requiring that the chief hematologist, I believe, countersign any prescription for chloramphenicol. Well, obviously in a hospital doing that, I suppose the usage would be generally quite specifically confined to indicated uses, though it might not be where you do not have a therapeutics committee or something.

Is there any information on the differences between hospitals?

Dr. GODDARD. Dr. Ley, do you have any comment on this?

Dr. LEY. We have no overall information which would answer your question, Senator. We have locally explored with four hospitals the proportion of hospital usage which is inpatient, and the portion which is outpatient.

This will vary considerably, and this is a very small sample, so I would be reluctant to predict any generalization which could be applied across the country. It would appear somewhere in the order of a fifth to a sixth of the usage may be in the outpatient clinic of the hospital itself.

We have no means, of course, of determining the amount of the drug which is used in the private physicians' offices of this country. That is the most difficult figure, and one that is almost impossible to obtain.

Senator NELSON. What I was getting at was—is there anything to demonstrate whether, say, teaching hospitals, large hospitals, use less of it for patients than smaller hospitals?

Dr. LEY. I have no information, sir.

Senator NELSON. Please continue.

Dr. GODDARD. In addition, restriction of the drug to hospital use

alone would pose an undue hardship on some patients for whom the drug is properly prescribed. There are fewer than 1,000 cases of typhoid fever in this country each year, but the major proportion occurs in rural areas which may not be served by hospitals and a few patients may require continued use of the drug after their hospital discharge. Some persons, therefore, would be deprived of appropriate treatment unless they undergo the inconvenience and expense of a hospital confinement.

Senator NELSON. Again, if the testimony of the experts before this committee is correct, that about 4 million people get the drug, and that 90 to 99 percent of that number should not get it, is the inconvenience to a relatively small number of people for whom it might be indicated outside the hospital, anywhere near as important as the exposure of over 3½ million people to a drug that may have lethal effects when prescribed for a condition that does not warrant it at all?

In other words, if you are weighing the equities, so to speak, isn't the inconvenience of a few people, however many that may be, much less important than the tragedies that we are having across the country? If you require that hospital admission be a prerequisite for administration of chloramphenicol 3½ million people are not going to go to the hospital. I doubt whether a doctor is going to send them there for acne, sore throats, head colds. And, then, the physician would see that this is a serious matter and therefore take another look at the literature, wouldn't he?

Dr. GOODARD. Senator, you are drawing an assumption here. First of all, let me point out and remind you that we believe at least 50 percent of it is administered in the hospital today. Now, that would indicate 2 million people receive the drug when hospitalized which is still excessive by any estimate—2 million people. You would admittedly get at part of the problem.

Now of course you are well aware of the fact that we can only restrict through labeling changes, and we do propose, in our labeling change, a sentence in the warning saying, "Because of the necessity of repeated blood studies during therapy, it is desirable that patients be hospitalized if possible."

Now, this is not what you are asking for, and I recognize that. But we have put the matter to our advisory group, and the problem has been before other advisory groups. Every time it answers this way.

Just because eminent physicians suggest it does not mean restriction solely to hospitals would solve the problem. They recognize much of the misuse in hospitals.

So I go back to what I said earlier and suggest that you also concomitantly examine the question of whether therapeutics committees can be brought into being in all the hospitals as a means of getting at the misuse in hospitals.

Now, beyond that, if you go more broadly, it certainly would require legislation. And I think it would raise a serious question, one that you and your colleagues would want to explore in some depth, in order to control the misuse of drug. I could suggest a system, yes. I could suggest one, that would, for example, limit the amount of the drug manufactured, and preposition it in warehouses at various points of the United States, so it will be quickly available to those who need it. Then it could only be obtained after filling out the proper

form. I could suggest that. But that, to me, raises for serious discussion —What is the proper role of a Federal agency? This would represent a marked change in the philosophy behind FDA in terms of its role with respect to the practice of medicine. And it is not one that I would suggest to you. It is one that you may wish to explore. But I am loath to suggest it at this point in time.

Senator NELSON. Well, I must say it is most frustrating.

Dr. GODDARD. It is.

Senator NELSON. I have not come up with an answer. I have just been asking questions.

Every expert that I have heard, and the material I have read, all say basically the same thing: it should only be used in a hospital, because if you are sick enough to have it, you ought to be in the hospital. Then Dr. Gilman goes on to say that it should be used in the hospital, and if there is an exception, that there should be a specific agreement between the doctor and the patient that he would see that patient every 48 hours, and that continuous blood studies should be made.

Now, this is the opinion of experts as I gather it from all over the country. Yet, their recommendations are being violated wholesale. Are we supposed to sit here as toothless souls—our Government or anybody else—who cannot protest the country? This is incredible to me.

Dr. GODDARD. I agree it is incredible, Senator. But how are you going to stop this practice from occurring? I am as baffled by it as you are, as to what steps can be taken.

I know of no other drug that has been given the prominence in terms of warnings to the medical profession that this drug has over the past 18 years. And yet the sales indicate it is being more widely used today than ever before.

I do not know how you can control it, other than taking steps through legislation, which I raised with you as one of the possibilities. Because after we are through talking about all the things we are going to do, there still will remain in your mind, I am sure, as it must in mine, a serious question as to whether these new steps will be any more effective, other than temporarily, in reducing the amount used. And then you ultimately have to come back and say "What is it that can be done that can control the misuse of this drug?" And I submit to you, sir, that it would require a legislative change, the nature of which has not been made in our society before with respect to this profession. And I am loath—it would have to be explored, I think, in greater depth with the physicians, with the hospital association, with the pharmaceutical manufacturers themselves, because it has rather profound implications.

Senator NELSON. You have no present authority to say that it should be confined to hospital use?

Dr. GODDARD. We could in the labeling, and that is as far as we could go. And we cannot enforce that.

Senator NELSON. This is a fine state of affairs, where tragedies are occurring all over this country, and we do not have any creative ideas for doing something about it.

We are not attempting to interfere with anybody's rights. There is

no right on the part of anybody in any profession to act contrary to all authority.

Now, how it has come about I suppose is a very complicated business—history, advertising, busy physicians, all kinds of things.

But the fact is that innocent people are dying from chloromycetin, and a whole lot more I suspect than is indicated in any statistics I have ever seen—to say nothing about those hidden thousands of cases who are just ill the rest of their lives, but do not die.

Now, I think that if a profession fails in its responsibility, somebody has to do something about it.

Dr. GODDARD. Sir, I believe we have some creative ideas that we are going to implement.

Now, I have already said that I am sure you will, after hearing these ideas, have reservations about how effective they can be. I have also suggested something to you this morning which has never been looked at before—that is the question of getting the Joint Commission on Accreditation into this. And they are a very powerful organization.

Now, perhaps through the combination of the things I am going to suggest to you, the suggestions I have already made, and the careful attention to this on a continuing basis, we can reverse a trend that is not only unfortunate, but unprecedented in the practice of medicine—and take the steps that will be needed to reduce the usage of this drug to a proper level.

Now, that is all I can suggest short of a significant legislative change.

Senator NELSON. I think after all these years there ought to be a significant change whether it is legislative or otherwise.

Now, you are going to receive a monthly report, I understand, of how many grams are being marketed.

Suppose 1 year from now there are still 4 million people getting it who should not. What do you say then? Do you say we still go on killing people, but we do not want to interfere with anybody's right to prescribe this drug? Do we require the inconvenience of a few people having to go to the hospital annually who otherwise would not go?

What do we do a year from now?

That will make 19 years.

Dr. GODDARD. Well, I would hope, Senator, that we would continue exploring these ideas with other segments of the medical community that are involved, and then reach a decision as to whether or not change was needed beyond what I can suggest based on our present legislative authorities. I cannot presume to speak for the medical profession of this country. I can only reflect the authorities that Congress has provided us, and take steps that we as an agency feel are enforceable—ones that will contribute hopefully to the solution of the problem. Beyond that, I have only suggested to you some additional steps that you might take. And I have viewed these hearings as a very healthy start at tackling this problem, Senator. And I share with you your concern that in spite of these steps I have mentioned we might very well not solve this problem in the next year.

Senator NELSON. One of the ideas that has been suggested here, which is worth exploring, it seems to me—I have no intention of interfering with the discretion of the medical profession. It is a great profession. But it would not be an interference, it seems to me, if we

had some legislation that authorized the FDA and the appropriate authorities in the field of medicine to come to specific agreements on a drug like this, or two or three or whatever number it may be, and be equipped with the authority to be really tough—just really tough.

Dr. GODDARD. Senator, you cannot do that without interfering with the practice of medicine. I will lay it on the table in front of you and say it cannot be done unless you are willing to interfere with the practice of medicine. When you say exercise discretion, you are then saying you have to control discretion—the selection of the drug to be prescribed. You have got to limit it.

Senator NELSON. Is it, in your judgment, an interference with the legitimate practice of medicine in a good teaching hospital to say to the doctor, "You cannot prescribe chloramphenicol for your patient without having the approval of representatives of the therapeutics committee, or having the order countersigned by the chief hematologist?" Of course that is an interference. You are saying to that fellow, that doctor, that you cannot do it without consultation because this is so serious a matter that you have to have it countersigned. Is that an interference with the practice of medicine?

Dr. GODDARD. Sir, that is a decision of that teaching hospital—the staff in its staff meeting agreed to it. That was self-regulation. It is quite a different thing than a Federal agency imposing its will upon the practitioners of medicine in their own offices. This is what would have to be done to get at this problem the way you suggest.

Senator NELSON. If you followed what Dr. Dameshek and some of the other experts said, all you are saying is that you are taking a very serious risk unless the drug is administered in the hospital. The next step after that ought to be that the Accreditation Committee move along the lines you suggest, and say that a hospital must have a therapeutic committee to be accredited. And the next step would be to persuade the therapeutics committee to follow this procedure, the countersigning, using their hematologist. This would not interfere with the valid practice of medicine, would it?

Dr. GODDARD. By your own description it is interference with the practice of medicine, and it is by mine. I am not saying what you suggest is wrong. I am simply pointing out that if you have the FDA do it, it is a basic philosophical change in what a Federal regulatory agency does vis-a-vis the practitioners.

Senator NELSON. Well, supposing the FDA and the medical profession and the Committee on Hospital Accreditation got together and said, "We will work out an agreement on a drug like this one and set up some rules, and ask the committee and the profession to enforce it themselves." I am not asking the Federal Government to do it. You would not be here, and these experts would not have appeared if the medical profession were policing itself. This is a ridiculous place to have to take up a professional matter. But it gets so bad that somebody has to do something. And if they do not do it, somebody else has to do it for them. That is the way it seems to me.

You cannot read what is happening to the victims of chloramphenicol around the country without being upset about that.

Dr. GODDARD. I agree.

Mr. GROSSMAN. Doctor—can we imply from what you say that the

Administration will not propose any legislation to go beyond what you have said this year?

Dr. GODDARD. That is correct.

Mr. GROSSMAN. Can I ask you one other thing.

What portion, do you feel, of the number of patients who get this drug should be in the hospital? You have talked here about typhoid fever, as well as people living in rural areas who might not be able to get into hospitals.

Now, wouldn't it be a fairly high proportion of these people who would be in hospitals, if we are talking about a very serious indication?

Dr. GODDARD. Yes, sir. But let us just take an example. Take a clinic, which characteristically sees patients on an out patient basis. They have good laboratory diagnostic facilities. They do sensitivity testing. They culture the urine, let us say, and recover an organism. They find a particular infection that the patient has is due to an organism that is sensitive to chloramphenicol and not sensitive to other broad spectrum antibiotics.

Now, a kidney infection is a very serious thing, and yet it is not necessarily one which requires the patient to be hospitalized. The urinary tract infection in general must be viewed as a serious infection, and yet in many instances these are treated on an outpatient basis.

Now, having said that, let me say that I would guess—and it is only a guess, based on what I have read, other experts' testimony, and my own limited knowledge of this—that perhaps 80 percent of the patients who require Chloromycetin would in fact be hospitalized during the acute phase of this illness. Now, that does not include follow up treatment that is often required.

Mr. GROSSMAN. But—this is another area where there are no statistics.

Dr. GODDARD. No statistics at all; no, sir.

Mr. GORDON. Dr. Goddard, do you have authority to take a drug off the market?

Dr. GODDARD. Yes, sir.

Mr. GORDON. You have done so in the past?

Dr. GODDARD. Yes, sir.

Mr. GORDON. Have you found that it has interfered with medical practice?

Dr. GODDARD. Of course. And I have said on a number of occasions that Congress gave us certain authorities which in and of themselves must be viewed as, in part, interfering with the practice of medicine. We make decisions on which drugs will enter the marketplace, and which drugs are to be taken out of the marketplace. And that was what Congress said we should do.

Mr. GORDON. All right. How about taking this drug off the market? Do you have the authority to do that?

Dr. GODDARD. Yes, sir. And we have discussed that on every occasion that this drug has been reviewed by eminent groups of scientists, who have advised us—either through the National Academy of Science or directly—and in every instance there is unanimous agreement, as far as I know, that the drug should not be taken out of the market.

Mr. GORDON. These people do not represent the public. The FDA represents the public.

Dr. GODDARD. Yes, sir.

Mr. GORDON. These are merely advisory committees.

Dr. GODDARD. Yes, sir.

Mr. GORDON. You have the authority to make the ultimate decision.

Dr. GODDARD. Yes, sir.

Mr. GORDON. Now, considering all these things we have been talking about, for weeks, and for years as a matter of fact, have you reached a decision that, on balance, it would do more harm than good if the drug were taken off the market completely?

Dr. GODDARD. Yes, sir. It is a preferred drug in Hemophilus influenzae meningitis—principally typhoid fever, and these other infections which are often life-threatening. The number of these cases in my opinion far exceeds the number of fatalities that occur because of the drug being misused.

Now, I am not minimizing the risk involved in misuse. I am simply saying that on balance, we have asked this question—this is the first question we have asked every advisory group, and they, every time, say that it should be left on the market.

Mr. GORDON. But they do not know the statistics, do they?

Dr. GODDARD. They have the same information we have, sir—the same that you have.

Mr. GROSSMAN. Which is not very good, is it?

Dr. GODDARD. No; not very good.

Mr. GORDON. If you have the authority to go all the way, to take a drug off the market, are you saying that you do not have the authority to go part way, to confine it to hospital use?

Dr. GODDARD. We could only try to confine it to hospital use by a change of labeling. I have read the new labeling we are going to discuss with the company, that portion of it which recommends the drug be used in the hospital. We have no way of enforcing this.

Senator NELSON. Is that going to appear on the new label?

Dr. GODDARD. Yes, sir.

Senator NELSON. How will that be worded?

Dr. GODDARD. I will read the warning in toto.

Warning, serious and fatal blood dyscraias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia and leukemia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antimicrobial effects. Chloramphenicol must not be used when other less potentially dangerous agents will be effective. It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza and infections of the throat, or as a prophylactic agent to prevent bacterial infections. (Last sentence underlined.)

Precautions. It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia or granulocytopenia, before they become irreversible. such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. Because of the necessity of repeated blood studies during therapy, it is desirable that patients be hospitalized if possible.

Senator NELSON. Read that last sentence again, please.

Dr. GODDARD. "Because of the necessity of repeated blood studies during therapy, it is desirable that patients be hospitalized if possible."

Mr. GROSSMAN. You would like to increase that 80 percent figure to 100 percent if possible?

Dr. GODDARD. Yes, sir. But we have to also say unless the other steps are taken, in terms of proper review of its usage in the hospitals, this is not going to necessarily change it.

Senator NELSON. I take it, then, because of that recommendation on the label, that it is your judgment and that of your consultants, that it is desirable to use chloromycetin only in the hospital, when possible. And that means using "possible" the way I understand it should be used in outpatient treatment only in exceptional cases.

Dr. GODDARD. Correct.

Now, it was my judgment, and Dr. Ley's judgment, after a discussion with our consultants, and after looking at the past history, and discussing it with our staff, that this was one additional step that we would take, plus the others I have yet to describe to you.

But I had to make that decision. I participated in the meeting of the advisory committee. I will tell you, sir, that our advisers did not vote unanimously on that point. Two of them said they felt, in spite of the very proper indications for outpatient use, that it should be labeled "for hospital use only." Four of them said, no, they felt such labeling was not proper. And so as is always the case, we had to make a decision, and ultimately I had to make one, and this represents our decision.

Now, we think that this, plus the other steps we are recommending will be helpful. Certainly we hope to exploit these steps along with the information developed from this public hearing. We hope to exploit these additional steps I am going to mention in such a way that it will help make a significant inroad into the excessive uses. I can only say that that is where we are today.

Senator NELSON. Then, if I understood you correctly, two of the six advisers were of the opinion it should be confined to hospital use only?

Dr. GODDARD. Yes. They also recognized the problem one has in defining a hospital. Does that include a nursing home? These kinds of things all get into it.

Now, here again, the decision has to be made on the basis of what would be effective. We cannot enforce either one of these, Senator. It comes down to how can you enforce this—not what we say on the label—because that is clearly not helping. You know, this drug has the toughest warning I think of any drug I am familiar with.

Senator NELSON. And it does no good.

Dr. GODDARD. It does no good. I cannot tell you that this new warning is going to do any good. I can tell you the new warning, plus the "Dear Doctor" letter we intend to send to every doctor and hospital administrator, plus the material we are going to provide the publishers of medical magazines and newspapers, plus the constant review on the monthly production data, and the rewarning of the profession when it indicates any upswing, plus the change in the reminder ad—these represent what we in our opinion feel we can do now within our present authority.

Mr. GORDON. Do you have the authority to prohibit all advertising and promotional activities with respect to this drug?

Dr. GODDARD. No, sir.

Mr. GORDON. You have no such authority?

Dr. GODDARD. No, sir.

Senator NELSON. The position I have been suggesting about requiring that administration be limited to hospitals only and the position you ultimately end up with are really very close together. Your position is that such a procedure is what ought to be followed but not required by law. The position of some of the experts who have testified is that this is what ought to be done, even if it does require enforcement by law. Is that the difference between the two?

Dr. GODDARD. Basically I would say the difference is—let me recast that in my words and see if we are in agreement.

Your experts have said even if the law has to be changed, it should be restricted to hospitals.

Senator NELSON. Some say that, yes.

Dr. GODDARD. Now, I submit to you that restriction to hospitals alone will not do the job. It has not so far. Approximately 2 million of the people a year receiving the drug are getting it in hospitals. Obviously additional steps have to be taken.

Senator NELSON. But you think it would be an improvement, or you do not think it should be recommended?

Dr. GODDARD. Labeling represents an improvement, by strongly suggesting only hospitalized patients should get it.

Now what I am trying to say is that in itself will not do the job. There are additional steps that have to be taken. I suggested you get the Joint Commission on Accreditation to testify as to the possibility of adding to their standards. I do not know what their reaction will be. I have not talked to Dr. Porterfield about this. I have talked to the Surgeon General of the Public Health Service as to what additional steps they might suggest, because they are dealing with problems of medical care. They have no suggestions.

Senator, believe me, we will consider carefully suggestions that would help diminish the excessive use of this drug. But, as you well know, we have authorities under which we operate quite properly. These authorities do not permit the policing of this situation in a way that would make effective reduction occur within a short period of time.

Senator NELSON. I am one of those that would be happy to give you more authority.

Go ahead, please.

Dr. GODDARD. I think, Senator, I have in effect summarized the rest of my statement—if I can just submit it for the record.

Senator NELSON. There have been so many interruptions during your presentation—we will print your statement in full at the conclusion of your testimony.

Mr. GORDON. Dr. Goddard, it seems incredible to me that the public, to such a large extent, is unprotected. What you really have told us here today, so far as I can see, is that the public has very little protection.

Dr. GODDARD. I do not believe that is so. I think the public in this country has a greater measure of protection than the public in most nations.

Mr. GORDON. That is not saying very much, however.

Dr. GODDARD. Well, I would like to ask you, Mr. Gordon, what it is you propose be done. I am at my wits' end as to what can be done within the authorities and the philosophy of what FDA is supposed to be doing.

Mr. GORDON. Well, for example, we discussed the possibility of re-restricting it to hospitals. We talked about the possibility of curtailing to a large extent, or abolishing, the promotional activities.

Dr. GODDARD. I have told you that in both instances we do not have the means to enforce those suggestions.

Mr. GORDON. I know now that you do not have the authority. But given this, it seems to me that we are not in very good shape.

Dr. GODDARD. What you are talking about basically is what protection do you have from your doctor—to put it in its baldest terms. Let us call a spade a spade. That is what you are talking about.

Now, I do not think you can legislate that. You are talking about one drug. You have to rely on the physician's judgment for every drug that he prescribes. And the physicians need good information. This committee is aware of the problem in that area. There needs to be greater self-regulation in the form of therapeutics committees, and a lot of these steps need to be taken.

But in the long run, I do not think you can regulate good practice of medicine.

Senator NELSON. I do not think anybody is suggesting that, really.

Dr. GODDARD. That is what it comes down to.

Senator NELSON. I think we are talking about an extra special case here in which—as you know—in a 15-year period, 35 to 40 million people in America have been givin a drug and have thus been exposed to a possibly lethal dose for a condition in which it is just not needed. And there is no disagreement at all about that. We should not be helpless in the face of that situation. And, certainly nobody could say it was an improper interference to say that there is a category of drugs which must be used only under certain circumstances.

I think that label ought to be a whole lot tougher. I think it ought to say "dangerous drug" at the top. I think it ought to say that medical evidence indicates that 90 to 99 percent of the people getting it should not be getting it, and great tragedies are occurring as a result. It should warn the doctor not to use it without making some careful investigations and studies. You ought to hit them in the teeth with it—hard. I do not see how we can expect to accomplish our goal with this new label. It contains a stronger warning, but physicians were not reading the last one.

Dr. GODDARD. Well, Senator, I am willing to consider your suggestions on rewording this. This is not the final copy yet. I do not think you have much faith in this either, even though it has been the strongest warning. These thoughts that you bring out are not unknown to the medical profession. There has never been a drug that has received the attention that chloramphenicol has in the form of editorials, news articles, tight language in the package circular, what is allowed in the ads and everything else.

Now, I do not see the difference between "dangerous drug," and saying "serious and fatal blood dyscrasia." The latter translates immediately to a physician that here is a drug to be reckoned with, or should.

But it apparently does not help. And I do not think it will change if you say "dangerous drug," I am sorry to say. But I am willing to consider that. Senator, you yourself said 18 years have gone by with this kind of information.

Senator NELSON. And that sure shocks me.

Dr. GODDARD. Yes, sir. And I say when you cut aside all the verbiage, it comes down to the fact that somebody has to make a decision. Are you going to have in this country a system that provides control, very tight control, on a drug or all drugs in a different fashion than we have ever had before. I am sorry—I am not trying to be obstreperous. I am simply trying to point out it gets down to that kind of fundamental issue.

Senator NELSON. I think it does.

Thank you very much. You have been a very gracious and pleasant witness.

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

STATEMENT OF DR. JAMES L. GODDARD, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Mr. Chairman, I appreciate the opportunity of appearing before your Committee today to discuss the Food and Drug Administration's action and intentions in regulating the interstate distribution on the antibiotic drug, chloramphenicol.

The Nation has watched with great interest the testimony unfolding before this Committee in the past weeks. The Committee's hearings have brought renewed attention to important questions that concern us all: Is this a drug too dangerous to remain on the market? Should its use be restricted in some way? Are the FDA, the medical profession, and the manufacturer of the drug taking all necessary steps to assure the safest possible use of the drug?

Before discussing these questions and alternatives, however, it may be useful to outline what has been done in the past. Chloramphenicol was first isolated in 1947 from a soil sample collected in Venezuela. It was found that liquid cultures of the organism, *Sterptomyces venezuelae*, possessed marked effectiveness against several Gram negative bacteria and also exhibited antirickettsial and antiviral activity. Shortly there after the chemical structural formula was determined and the antibiotic was prepared synthetically. And, as you know, it was later patented by Parke-Davis and Company.

In 1948, chloramphenicol was produced in amounts sufficient for clinical trials and general clinical use. It was found to be of value in the therapy of a variety of infections, including epidemic typhus in Bolivia and scrub typhus and typhoid fever in the Malay Peninsula. On January 12, 1949, the Parke-Davis New Drug Application for Chloromycetin, that company's brand of chloramphenicol, was allowed by FDA to become effective. In the summer of 1949, as the result of new legislation, Chloromycetin was classified as a "certifiable antibiotic," subject to the bacth certification provisions of the Food, Drug, and Cosmetic Act.

When chloramphenicol was first introduced in 1949, it was widely heralded as a "broad spectrum antibiotic" effective against an impressive range of microorganisms. It was also considered to be largely nontoxic. There was no indication at that time that the drug had any serious side effects.

Early in 1950, however, a few published reports drew attention to the possibility that chloramphenicol might cause serious and fatal blood dyscrasias. The 1951 edition of *New and Non-official Remedies* warned that "changes in the peripherial blood or blood forming organisms have been reported during the use of chloramphenicol." An editorial in *The Journal of American Medical Association*, June 28, 1952, referred to additional reports of blood disorders. It went on to say:

"A second and more serious type of reaction that has been encountered is production of a true aplastic anemia. In the experience of one group this anemia has occurred in patients who have previously received one or more courses of chloramphenicol without untoward effect. When the drug was subsequently administered, even in small doses, a severe blood abnormality has appeared. Even deaths have been reported."

In response to these reports, FDA conducted a nation-wide survey of case records in hospitals and clinics in an attempt to evaluate the magnitude of the problem and to determine whether a cause and effect relationship existed between the drug and the disease. This survey produced records of 410 cases of serious blood disorders, of which 177 were definitely known to have been associated with chloramphenicol. In 61 cases, chloramphenicol was the only drug administered. In half of these 177 cases, the blood disorders were fatal. They included aplastic anemia; hypoplastic anemia; thrombocytopenia; and granulocytopenia. In June 1952, the FDA discontinued certification of chloramphenicol, and in July 1952, the FDA referred the case histories obtained in the survey to the National Research Council (NRC). The NRC established a committee of outstanding hemotologists and internists, under the chairmanship of Dr. John Holmes Dingle, Professor of Preventive Medicine, Western Reserve University, to review and evaluate the chloramphenicol problem. On August 7, 1952, the Committee reported as follows:

"An *ad hoc* Conference was held on 6 August and reviewed all available data presented by the Food and Drug Administration and by Parke, Davis and Company.

"The consensus of the Conference was as follows:

"1. Certain cases of serious blood dyscrasias (aplastic anemia, thrombecytopenic purpura, granulocytopenia, and pancytopenia) have been associated with the administration of chloramphenicol.

"2. Although this complication has thus far been uncommon, it is sufficiently important to warrant a warning on the label of packages of the drug and in advertisements of the drug and the recommendation that chloramphenicol not be used indiscriminately or for minor infections.

"3. When prolonged or intermittent administration is required, adequate blood studies should be carried out.

"4. In view of the paucity of information at the present time the Conference hopes that further study of serious reactions to chloramphenicol and other drugs will be promoted. The records of the Veterans Administration and military forces could be of great value in providing some of the desired information."

The recommendations of the Committee were implemented and resumption of certification of the drug followed. All chloramphenicol was to be marketed with the following label warning: "Warning—Blood dyscrasias may be associated with intermittent or prolonged use. It is essential that adequate blood studies be made".

The following warning was to appear at the top of the package insert: *"Certain blood dyscrasias (aplastic anemia, thrombocytopenic purposa, granulocytopenia and pancytopenia) have been associated with the administration of Chloromycetin. It is essential that adequate blood studies be made when prolonged or intermittent administration of this drug is required. Chloromycetin should not be used indiscriminately or for minor infection".*

In announcing the reinstitution of certification for chloramphenicol, FDA said: "The administration has weighed the value of the drug against its capabilities for causing harm and has decided that it should continue to be available for careful use by the medical profession in those serious and sometimes fatal diseases in which its use is necessary".

FDA characterized its experience as "an impressive reminder that highly potent drugs must be treated with extreme care and should not be employed unless there is a clear-cut indication that they are needed".

The Kefauver Subcommittee on Anti-Trust and Monopoly subsequently reported that these warning measures were diluted by Parke-Davis instructions to its detail force, which the Subcommittee said presented the report of the National Research Council as a blanket clearance of the drug. Nonetheless, the use of the drug dropped off markedly after the new warning issued. This was a short-term reaction, however, and use of the antibiotic increased during the years that followed.

In 1955 Parke-Davis requested a deletion of part of the warning statement. The firm's letter pointed out that some patients with blood disorders attributable to Chloromycetin had received only a few capsules. The company regarded the warning, which referred to prolonged or intermittent therapy, as a legal liability in litigation.

We rejected this proposal, and while strengthening the warning was suggested, the decision was made to continue the warning as recommended by the scientific committee.

In December 1959, one of our physicians, who was also in private practice, was visited by Parke-Davis detail men who claimed that there was no more danger of blood dyscrasias with Chloromycetin than with any other antibiotic. The company was informed of this impropriety, and gave assurance that the statement was both unauthorized and contrary to company policy.

In April of 1960 the Council on Drugs of the American Medical Association made another report on blood dyscrasias associated with chloramphenicol. The report said that although the warning had been in use for a long time, physicians continued to use the drug indiscriminately for minor infections, including those associated with the common cold.

FDA asked the National Research Council in November 1960 to again consider the chloramphenicol problem in light of the new evidence accumulated since 1952. Specifically, FDA wished to obtain the Council's opinion as to whether chloramphenicol should be allowed to remain on the market; whether its use should be restricted to hospitals if it were to remain on the market and what label changes the Council would recommend if the drug was allowed to remain on the market.

The recommendations of the Council were received by FDA in January 1961. The Council concluded that, due to its therapeutic value, chloramphenicol should remain on the market; due to some of its proper indications for use, home treatment, as opposed to hospital treatment exclusively, was reasonable; due to its serious effects, further warnings and increased education of the medical profession were necessary.

In accordance with these recommendations the labeling of chloramphenicol was revised in February of 1961 to include a prominent "warning box" containing the following information:

"Warning—Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective. It must not be used in the treatment of trivial infections such as colds, influenza, or infections of the throat; or as a prophylactic agent to prevent bacterial infections. Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia."

Parke-Davis was required to mail the new prescribing information to all medical doctors and osteopaths in February 1961 with a statement that the prescribing information would accompany all oral and parenteral Chloromycetin products.

Between 1963, when our prescription drug advertising regulations were first adopted, and 1966, Parke-Davis advertised Chloromycetin by reminder ads, which carried no indications and no warnings. The regulations permitted this. In 1964, the Company decided to advertise the drug promotionally and met with our medical advertising group to consider how this should be done. Our physicians noted that the package insert had no "Indications" section, but instead described the broad range of antimicrobial activity of the drug. To correct this, an indications section was devised and other changes made to emphasize that the drug was only indicated for, and should be prescribed in accordance with, the important information in the "warning box." In 1966, the Company made the requested changes and discontinued the reminder ad campaign.

The labeling was reviewed again in 1966 by the Acting Deputy Director of the Bureau of Medicine and the "box warning" was changed to say that the drug must (instead of should) not be used in trivial infections or in any other conditions except as described in the box.

Despite these label revisions, editorials in the *Journal of the American Medical Association*, and warnings in other publications such as *The Medical Letter*, the use of chloramphenicol has increased and continues to increase. Most of this use,

we believe, is for medical conditions for which the drug is not indicated or for which it is expressly prohibited, such as acne, the common cold, simple infections and the like. We are disappointed by a current advertisement in the *Readers Digest* by the Pharmaceutical Manufacturers Association, which describes chloramphenicol as a prime member of a "class of drugs that fights 100 diseases" and characterizes it as a "broad spectrum" antibiotic effective against dozens of diseases, causing only occasional and sometimes serious side effects in some patients.

The exact number of patients who have suffered a serious or fatal blood disease as a result of the indiscriminate use of chloramphenicol is not known.

Various estimates place the incidence rate of blood dyscrasias from chloramphenicol at one (1) person in ten thousand (10,000) to one (1) person in one hundred thousand (100,000) who receive the drug.

Despite the risks associated with the use of chloramphenicol, if one may judge from the sales figures, use of the drug continues to be excessive. Where have the FDA, the manufacturer, and the medical profession failed? Is the general medical community unaware of, or unconcerned about, the risks associated with this drug? What must be done now? These are most difficult questions, and the answers do not come easily.

The "box warning" in the labeling is strongly worded and tells the physician quite bluntly the dangers of the drug, yet it has not accomplished its intended purpose.

What other steps might be taken? We have considered restricting the use of chloramphenicol to hospitals. However, aside from the legal problems involved, we have learned that more than half the chloramphenicol distributed in this country is purchased by, and presumably used in, hospitals.

In addition, restriction of the drug to hospital use alone would pose an undue hardship on some patients for whom the drug is properly prescribed. There are fewer than 1,000 cases of Typhoid Fever in this country each year, but the majority occur in rural areas which may not be served by hospitals and a few patients may require continual use of the drug after their hospital discharge. Some persons, therefore, would be deprived of appropriate treatment unless they undergo the inconvenience and expense of a hospital confinement.

Other measures have been suggested, such as requiring that every prescription for chloramphenicol be countersigned by a second physician or requiring permission by a board of physicians before the drug could be used. Such measures are not possible under current law, nor does it seem to me that such systems would be practical, desirable, or possible to enforce.

It has also been suggested that this drug, along with other "dangerous drugs," be restricted to use by physicians registered with the Government in much the same way that narcotics are handled. This is not possible under the present law, nor is it particularly desirable. Most drugs are potentially dangerous, even when properly used and certainly when misused. Where should the line be drawn? Establishing this group of drugs would, it seems to me, create more problems than it would solve.

It has also been suggested that detailed records, other than those kept by the pharmacist, be maintained for every patient in a hospital who receives this drug. The doctor would write his diagnosis and it would be kept in the hospital record. A copy of this record would be sent to the AMA, the PHS, or the FDA for review. Again, this is not possible under current law, nor is it practical for any such group to monitor prescribing practices to preclude misuse.

What then is the best way to approach this problem? How do we reach the physician with this most important prescribing information? These hearings, I believe, have created an atmosphere of interest throughout the country, and have made many physicians take notice of the grave risks involved in misuse of chloramphenicol.

We know additional action is necessary; we will not delay in taking this action. We plan to move with every means at our disposal to curb the misuse of chloramphenicol. We are taking, or soon will take, the following steps:

1. We are revising the chloramphenicol labeling so the indications for use are more restrictive and more clearly stated. We are revising the warnings to include the incidence of risk estimates of aplastic anemia developed by the California Medical Society. We are adding warnings against use of the drug in late pregnancy or in lactation. Leukemia also is to be listed as a possible side effect.

2. The FDA plans to send a "Dear Doctor" letter to every physician and hospital administrator throughout the country warning of the hazards of this drug and stating, in a positive manner, its indications for use. We will seek support at all levels of the medical profession, down to the county societies, to be sure the message gets through to all prescribers.

3. All "reminder ads" for the drug will be required to carry a brief summary of the dangers of the side effects associated with chloramphenicol; that is, every ad will be required to carry at least the "box warning."

In addition to these considerations, we have consulated with a special Ad Hoc Committee which met Monday, February 26, 1968 at the FDA Headquarters. This Committee was convened specifically to consider the chloramphenicol problem, and to advise the FDA on the action we proposed to take to improve the prescribing information for this drug and to disseminate this information throughout the medical community.

The Committee's opinion was that we should communicate directly with doctors and hospital administrators on new labeling for chloramphenicol. In addition, the Committee suggested contacting various professional publications—*Medical Tribune, Medical World News, AMA News,* and the journals of every State medical society—to ask their cooperation in publicizing the proper use of the drug and the hazards associated with its use. This will be done. The Committee will shortly give us further results of its considerations concerning pediatric dosages for the drug.

Mr. Chairman, we are most anxious to implement immediately all appropriate recommendations in order to take full advantage of the wide interest created by this Committee's hearings.

I thank you for your time and attention this morning. If there are questions, I would be happy to answer them.

(Whereupon, at 1 p.m. the subcommittee was adjourned, to reconvene subject to the call of the Chair.)

APPENDIX

Appendix I. Articles From Various Sources re Drug Chloromycetin (Chloramphenicol)

[From the New England Journal of Medicine, vol. 277, No. 19, Nov. 9, 1967, pp. 1035–1036]

Chloramphenicol-Induced Bone-Marrow Aplasia

Although chloramphenicol continues to be the leading single cause of drug-induced aplastic anemia, little progress has been made in elucidating the mechanism of its toxic effect. The reversible erythroid depression occurring concurrently with chloramphenicol therapy is a pharmacologic effect.[1] Although there is clearly a relation between this type of toxicity and dosage, there is none between dosage and reversibility. The occurrence of bone-marrow aplasia is only an occasional subject receiving chloramphenicol, coupled with the lack of a dose-effect relation, almost certainly indicates an individual susceptibility.

In sensitive bacteria chloramphenicol in small concentrations causes complete inhibition of protein synthesis. There is good evidence that this action is exerted through stereospecific binding of the drug to the 50–S ribosomal subunit, thereby inhibiting, in an as yet undefined manner, the formation of the peptide bond.[2] The drug does not seem to interfere with the function of messenger RNA (mRNA).[2] In mammalian cells in vitro on the other hand, concentrations many times the usual therapeutic levels are needed to inhibit protein synthesis significantly. Recently, Weisberger et al.[3] reported profound inhibition of mRNA-induced protein synthesis in a cell-free system from rabbit reticulocytes by small concentrations of chloramphenicol, reversed by increasing the concentration of messenger. They concluded that chloramphenicol inhibits protein synthesis in mammalian cells by interfereing with the binding of mRNA to ribosomes. However, other investigators are unable to corroborate these findings.[4] In similar systems about 20 per cent inhibition of amino acid incorporation into ribosomes can be demonstrated at therapeutic drug concentrations. This slight inhibition is unrelated to the concentration of messenger in the system. Furthermore, chloramphenicol does not bind to reticulocyte ribosomes, nor does it interfere with the ribosomal binding of mRNA.[4] The problem of whether hematologic toxicity from chloramphenicol is related to its effect on protein synthesis cannot be resolved at present. It is entirely possible that the reversible erythroid depression from the drug is related to its small inhibitory effect on protein synthesis as observed in vitro. The length of exposure may render this small effect significant in the overall metabolism of the erythroid cell.

Bone-marrow aplasia from chloramphenicol is more difficult to explain. Here some specific biochemical susceptibility is the most likely underlying factor. The demonstration that chloramphenicol inhibits the uptake of ^{14}C formate into nucleic acids of bone-marrow cells from patients who have recovered from chloramphenicol-induced aplastic anemia supports this hypothesis.[1] However, further studies in similar cases are needed to determine the significance of these findings.

Several observations in patients with chloramphenicol-induced aplastic anemia suggest that this drug exerts its action at the stem-cell level. Thus, the latent period between drug administration and the onset of anemia, the characteristic pancytopenia and the long duration of the aplasia after the drug has been discontinued are all compatible with an injury to a precursor pool common to all 3 cell lines. The persistence of aplasia long after discontinuation of the drug indicates either that chloramphenicol has a lethal effect on these cells or that, by affecting the genetic pattern of the stem ceil, it causes the

Note.—Numbered footnotes at end of article, p. 2654.

propagation of a defective short-lived cell line. Recovery from aplasia however, suggests the emergence of precursor cells with "new" mitotic competence. This may result from biochemical "recovery" of the injured cells through the development of alternate metabolic pathways or the emergenc of a genetically different line of stem cells. This genetically different line of stem cells may be "normal" or may differentiate into an autonomous leukemic cell population.

In the issue of the *Journal* Brauer and Dameshek record 3 examples of acute myeloblastic leukemia developing in patients who had aplastic anemia that followed chloramphenicol therapy.[5] As pointed out by the authors, aplastic anemia without known cause may be premonitory of acute leukemia; accordingly, any postulated relation between chloramphenicol and the leukemia in the 3 cases recorded must be regarded as conjectural. On the other hand, it is possible that acute leukemia would be seen much more frequently in patints with chloramphenicol-induced bone-marrow aplasia if they survived longer; most of these patients succumb to their disease within seven months from its onset. At present it is reasonable to consider any agent that is potentially myelotoxic as being also potentially leukemogenic. However, little can be said in this regard until more is known about the basic mechanisms by which chloramphenicol and other drugs injure the bone marrow.

REFERENCES

[1] Yunis, A. A., and Bloomberg, G. R. Chloramphenicol toxicity: clinical features and pathogenesis. *Progr. in Hematology* 4: 138–159, 1964.
[2] Das, H. K., Goldstein, A., and Kanner, L. C. Inhibition by chloramphenicol of growth of nascent protein chains in *Escherichia coli*. *Molecular Pharmacol.* 2: 158–170, 1966.
[3] Weisberger, A. S., Wolfe, S., and Armentrout, S. Inhibition of protein synthesis in mammalian cell-free system by chloramphenicol. *J. Exper. Med.* 120: 161–181, 1964.
[4] Zelkowitz, L., Tchou, H., Arimura, G. K., and Yunis, A. A. Chloramphenicol and protein synthels in mammalian cell-free system. *Clin. Research* 15: 67, 1967.
[5] See article, "Hypoplastic Anemia and Myeloblastic Leukemia Following Chloramphenicol Therapy," by Dr. Brauer and Dr. Dameshek, p. 2402, supra.

[From the American Journal of Disabled Children, vol. 114, October 1967, pp. 424–426]

CHLORAMPHENICOL OPTIC NEURITIS

APPARENT PROTECTIVE EFFECTS OF VERY HIGH DAILY DOSES OF PYRIDOXINE AND CYANOCOBALAMIN

(By Maj. Joseph G. Cocke, Jr., MC, USA, Fort Sam Houston, San Antonio, Tex.)

Over the last several years, there has been increasing recognition of an apparent deleterious effect of chloramphenicol on vision in the form of an optic neuritis. Recognition of this entity has not produced any uniform suggestion for treatment or prevention of the neuritis other than minimal total dosage or withdrawal of chloramphenicol once toxic eye signs are noted.

Experience with a previously reported [1] 12-year-old girl with cystic fibrosis who developed an episode of chloramphenicol optic neuritis (CON) following prolonged use of the drug has led to the suggestion that pyridoxine (B_6) or cyanocobalamin or both in very high daily doses may be of significant value in prevention of optic neuritis while the patient is receiving sustained chloramphenicol treatment.

REPORT OF A CASE

A 12-year-old girl with proved moderately severe cystic fibrosis (CF), developed an optic neuritis in January 1964 following total dosage of 135 gm chloramphenicol. From near total blindness associated with contricted visual fields, large central scotomata, papilledema, and retinal hemorrhages, her visual acuity improved to 20/50 for both eyes while receiving treatment. Also, visual fields widened except for small central scotomata, and fundus changes resolved save for minimal residual disc pallor. Therapy consisted of stopping chloramphenicol administration and administering large doses ascorbic acid, thiamine, pyridoxine,

---

NOTE.—Numbered footnotes at end of article, p. 2656.

and cyanocobalamin for six months. Following cessation of treatment, vitamin intake was limited to three daily multivitamin capsules which had been given regularly for years.

One multivitamin capsule contains 5,000μ vitamin A, 400μ vitamin D, 75 mg vitamin C, 2μg B_{12}, 2 mg B_6, 2 mg B_2, 3 mg riboflavin, 20 mg nicotinamide, and 5 mg calcium pantothenate. Measures for control of pulmonary infection, including antimcrobial agents other than chloramphenicol, were continued essentially as before the optic neuritis.

In April 1965, it was felt imperative to reutilize chloramphenicol (40 mg/kg/24 hr). Three daily multivitamins were continued but no additional vitamins were prescribed. Visual signs and symptoms were carefully monitored. After a total dose of 47 gm chloramphenicol, visual acuity deteriorated to 20/70 in each eye, temporal disc margins elevated, and visual fields contracted. With the exception of accentuated temporal disc pallor, visual examination results returned to pre-chloramphenicol treatment levels when administration of this drug was stopped, and vitamins B_6 (150 mg/24 hr) and B_{12} (150μg/24 hr) were added and continued regularly.

In September 1966, chloramphenicol therapy was restarted (80 mg/kg/24 hr dose reduced in mid-November 1966 to 40 mg/kg/24 hr), and dosage of vitamins B_6 and B_{12} was simultaneously increased to 200 mg/24 hr and 200μg/24 hr, respectively. The three daily multivitaminus and other treatment modalities were unchanged. Attempts to discontinue this drug therapy led only to decompensation unresponsive to any measure other than restarting of chloramphenicol.

As of July 14, 1967 the child has received a total dose of chloramphenicol in excess of 265 gm. Careful monitoring of visual acuity, fundus appearance, and visual fields have shown no deterioration. Interestingly, visual acuity has improved to 20/30 in each eye. Daily administration of chloramphenicol will continue until circumstances require its withdrawal.

COMMENT

Earliest description [2,3] of CON have implied an uncertain relationship between group B vitamins and chloramphenicol. In theory, the latter may either interfere directly with end effects of group B vitamins or cause vitamin B deficiency through destruction of intestinal bacteria necessary for synthesis or utilization of group B members. More recently, Wilson [4] has noted similarities between CON and visual disturbances reported in postwar studies of nutritionally deprived individuals.

The notion of nutritional deficiency, perhaps of group B vitamins, has been prevalent over the years. Consequently, vitamins have been used in treatment of CON in varying doses and under a wide range of therapeutic programs. Fifteen case reports [1-9] have involved use of vitamins, dosage largely unspecified, in treatment of CON. Twelve patients given vitamins showed a return to normal visual acuity or functional return of vision; three were left with significant residuals. Eighteen case reports [10-15] detail no treatment with vitamins. In these patients, ten improved or cleared spontaneously, and eight were left with significant visual impairments. A cause and effect relationship with improvement while receiving vitamins has not been established, but the method which most consistently has yielded the best results has combined both immediate withdrawal of chloramphenicol and the administration of vitamins.

Methods of prevention of CON have received relatively little attention to the present. Reliance has been placed on early detection of visual abnormalities. The utilization of group B vitamins in large doses as prophylaxis against CON has not previously been recorded. Observations that many patients had onset of CON while receiving multivitamin preparations have been interpreted by some [16] to minimize the value of vitamins in prevention of CON. Upon inquiry, however, the vitamin content of these preparations might best be categorized as small, randomly constituted, or unrecorded.

As early as 1950, Woolington et al [17] described routine administration of "massive" doses of vitamins B and C during therapy with chloramphenicol. In a five-year study of 632 patients so treated, no episode of apparent visual derangement was recorded, although visual changes were not specifically monitored.

That large amounts of group B vitamins could serve to protect against CON is largely inference derived from this study of Woolington and from the seemingly salutory effect of group B vitamins noted in treatment of this condition. Further support may be added from the observations of Huang et al[9] in four patients with CON in whom the administration of chloramphenicol was continued and treatment with vitamins alone instituted. Three patients so handled recovered excellent vision. A fourth child exhibited spontaneous improvement of CON while continuing chloramphenicol therapy. On relapse, vitamin administration was associated with partial improvement.

With these considerations, it was decided that the third course of chloramphenicol in this child would be arbitrarily accompanied by continuation of large does of vitamins B_6 and B_{12}. The conduct of this patient's three courses of chloramphenicol delineates somewhat of an experimental pattern, the main variable having been the use of vitamin B_6 and B_{12} on the third course with all other factors, such as the use of chloramphenicol, multivitamins, and auxiliary methods of treating CF, being basically unchanged.

The conclusion in this one instance would indicate that vitamin B_6 or B_{12} or both have in some unknown way permitted the safe administration of a total dose of chloramphenicol approximately 5½ times that which resulted in an optic neuritis on last previous administration. A broader conclusion than this from a single case report is tenuous at best. However, it would appear reasonable to administer very large doses of group B complex vitamins to any patient in whom a large total dose of chloramphenicol may be anticipated.

SUMMARY

A 12-year-old girl with cystic fibrosis (CF) experienced two consecutive episodes of chloramphenicol optic neuritis (CON) following total doses of 135 and 47 gm chloramphenicol, respectively. She has been spared a third occurrence, while continuing doses in excess of 200 gm chloramphenicol were given simultaneously with very large doses of vitamins B_6 and B_{12}. The suggestion is made that large doses of group B vitamins given concomitantly with large total doses of chloramphenicol may serve as a preventive measure against CON.

REFERENCES

[1] Cocke, J. G.; Brown, R. E.; and Geppert, L. J.: Optic Neuritis With Prolonged Use of Chloramphenicol, *J Pediat* 68 : 27–31, 1966.

[2] Gewin, H. M., and Friou, G. J.: Manifestations of Vitamin Deficiency During Aureomycin and Chloramphenicol Therapy of Endocarditis Due to *Staphylococcus aureus:* Report of a Case, *Yale J Biol Med* 23 : 332–338, 1951.

[3] Wallenstein, L., and Snyder, J.: Neurotoxic Reaction to Chloromycetin, *Ann Int Med* 36 : 1526–1528, 1952.

[4] Wilson, W.: Toxic Ambylopia Due to Chloramphenicol, *Scot Med J* 7 : 90–95, 1962.

[5] Cole, J. G.; Cole, H.; and Janoff, L.: A Toxic Ocular Manifestation of Chloramphenicol Therapy, *Amer J Ophthal* 44 : 18–20, 1957.

[6] Joy, R. J. T.; Scalettar, R.; and Sodee, D. B.: Optic and Peripheral Neuritis: Probable Effect of Prolonged Chloramphenicol Therapy, *JAMA* 173 : 1731–1734, 1960.

[7] Walker, G. F.: Blindness During Streptomycin and Chloramphenicol Therapy, *Brit J Ophthal* 45 : 555–559, 1961.

[8] Keith, C. G.: Optic Atrophy Induced by Chloramphenicol, *Brit J Ophthal* 48 : 567, 1964.

[9] Huang, N. N., et al.: Visual Disturbances in Cystic Fibrosis Following Chloramphenicol Administration, *J Pediat* 68 : 32, 1966.

[10] Lasky, M.; Pincus, M.; and Kotlan, N.: Bilateral Optic Neuritis Following Chloramphenicol Therapy, *JAMA* 151 : 1403–1404, 1953.

[11] Prevatt, A. L., and Hunt, J. S.: Chronic Systemic Meliodiosis: Review of Literature and Report of a Case With Note on Visual Disturbance Due to Chloramphenicol, *Amer J Med* 23 : 810–823, 1957.

[12] Denning, C. R.: Bruce, G. M.: and Spalter, H.).: Optic Neuritis in Chloramphenicol Treated Patients With Cystic Fibrosis, Seventy-Third Annual Meeting of the American Pediatric Society, Swampscott, Mass., May 3–4, 1963, abstract No. 93, p. 103.

[13] Lietman, P. S.; Di Sant'Agnese, P. A.; and Wong, V.: Optic Neuritis in Cystic Fibrosis of the Pancreas, *JAMA* 189 : 924–927, 1964.

[14] Steidl, E. M.; Néurite optique bilatérale causée par l'emploi thérapeutique prolongé du chloramphénicol, *Un Med Canada* 94 : 1061–1062, 1965.

[15] Chang, N.; Conrad, L. G.; and Gregg, R. H.: Optic Neuritis and Chloramphenicol, editorial, *Amer J Dis Child* 112 : 46–48, 1966.

[16] Chloramphenicol Blindness, *Brit Med J* 5449 : 1511, 1965.

[17] Woolington, S.S.; Adler, S.J.; and Bower, A.G.; "Five Year's Experience With Chloramphenicol," in *Antibiotics Annual 1956–57,* New York: Medical Encyclopedia, Inc., 1956, pp 365–375.

[From the Journal of the American Medical Association, Sept. 11, 1967, Vol. 201, No. 11, pp. 828–834]

BONE MARROW DEPRESSION INDUCED BY CHLORAMPHENICOL OR PHENYLBUTAZONE

LEUKEMIA AND OTHER SEQUELAE

(By Joseph F. Fraumeni, Jr., MD)

With two registries for adverse drug reactions, a follow-up survey was made of 151 cases reported of bone marrow depression following use of chloramphenicol (124 patients), phenylbutazone (24), or both drugs (3). Leukemia subsequently developed in three patients with bone marrow depression attributed to use of chloramphenicol, but only one had characteristics suggesting a cause-and-effect relationship between drug exposure and leukemia. A review of clinical and epidemiologic information provides inadequate evidence that either drug is leukemogenic. Among other sequelae in the survey were four cases of hemolytic anemia; these four cases included two with paroxysmal nocturnal hemoglobinuria. Several problems arise in evaluating a causal association between drug exposure and diseases such as leukemia.

The etiology of human leukemia is generally considered to be obscure. Epidemiologic studies, however, have demonstrated that sufficient doses of ionizing radiation can induce chronic myeloctic leukemia or acute leukemia.[1-4] Furthermore, clinical observation suggest strongly that these forms of leukemia are causally related to prolonged exposure to benzene.[5] Since ionizing radiation and benzene are bone marrow depressants, one may suspect leukemogenic potential in other agents that cause marrow hypoplasia. The possibility os consistent with observations that aplastic anemia occassionally precedes the diagnosis of chronic myelocytic leukemia and acute leukemia.[6] This "preleukemic" period, which may last many years, has been noted following exposure to radiation or benezene.[7]

A number of drugs with the capacity to depress bone marrow function have been suspected in the etiology of certain cases of leukemia, usually on the basis of case studies or uncontrolled surveys of leukemia patients. Among these drugs have been chloramphenicol,[8-10] sulfonamides,[11] aminopyrine,[12] and amphetamine sulfate.[13] Recently, interest has focused on phenylbutazone, for since 1960 a total of 29 cases of leukemia have been reported following its use.[14-27] Since there has been no information on the populations treated with this drug, it is unknown whether or not the leukemia cases were chance occurrences.

This paper presents the findings of a follow-up survey of cases previously reported to two drug-reaction registries because of bone marrow depression attributed to chloramphenicol or phenylbutazone, the drugs most commonly reported to cause aplastic anemia.[28] The study was undertaken to determine the frequency of leukemia following marrow depression and to evaluate evidence that either of the drugs may be leukemogenic.

MATERIALS AND METHODS

The patients with drug-induced bone marrow depression were ascertained from the Registry on Adverse Reactions of the American Medical Association (AMA) and the Adverse Reactions Branch of the Food and Drug Administration (FDA). Officials at each registry prepared a roster of physicians (total, 180) who had reported one or more cases (total, 234) of marrow depression attributed to phenylbutazone or chloramphenicol between 1954 and 1965. The marrow depression consisted of erythroid hypoplasia, leukopenia, thrombocytopenia, or pancytopenia, and was presumed to be exclusive or recognized leukemia, or other diseases or agents that might induce blood dyscrasias. Each physician was notified of the intended survey by a letter from registry officials, and was asked if we might contact him for follow-up information. The AMA and FDA then sent us a listing of 126 physicians who replied to the letter and were willing to participate in the survey, along with the number of cases reported by each physician. Because of confidentiality of the data, neither registry divulged any information on individual patients prior to the survey.

NOTE.—Numbered footnotes at end of article, p. 2666.

TABLE 1.—OUTCOME OF BLOOD DYSCRASIA ATTRIBUTED TO TOXIC EFFECTS OF CHLORAMPHENICOL OR PHENYLBUTAZONE; RESULTS OF FOLLOWUP SURVEY OF 154 PATIENTS

	Chloramphenicol			Phenylbutazone				
		Interval[1]			Interval[1]			
Outcome	Number cases[2]	Range[3]	Median	Number cases[2]	Range[3]	Median	Chloramphenicol and phenylbutazone	Total
Recovery	47 (37)	1 week–7 year.	1½ month	18 (72)	2 weeks–4 years.	1 month	2	67
Still under care	19 (15)	6 months–6 years.	4 years	4 (16)	1–5 years	4½ years		23
Death	50 (40)	1 day–3½ years.	1½ month	3 (12)	2 weeks–2 years.	10 months	1	54
Unknown	10 (8)							10
Total	126 (100)		9 months	25 (100)		1 year	3	154

[1] Interval=period between diagnosis of blood dyscrasia and outcome.
[2] Figures in parentheses are percentages.
[3] Range=shortest to longest interval.

Questionnaires for each reported case were then mailed to the 126 physicians. These forms were designed to elicit information on the outcome of the blood dyscrasia and on disorders which occurred subsequent to the onset of the dyscrasia. When leukemia was reported as one of these disorders, further data on the drug reaction and its course were requested from records of the registry and the reporting physician.

During the course of this study four of the responding physicians called our attention to a total of six patients who had *not* previously been registered at the AMA or FDA, but in whom leukemia developed following use of chloramphenicol or phenylbutazone. These patients were not included in the survey, but pertinent data submitted on these patients are summarized in a separate section below.

RESULTS OF THE SURVEY

Of 126 physicians sent questionnaires, 39 did not reply; ten returned forms which were not completed; and 77 sent completed questionnaires. Five physicians who did not complete the questionnaires said they were unable to recall cases previously reported; four had departed from the area or the original hospital; and one physician had died. In a few instances, a reply was received from an associate of the physician who originally reported the case to the registry. The 77 physicians who returned completed questionnaires (43% of the original roster of reporting physicians) provided followup data on 154 patients with bone marrow depression (66% of the total cases originally reported). Of these cases, 126 were attributed to chloramphenicol, 25 to phenylbutazone, and three to both drugs combined. The patients with toxic reactions to chloramphenicol consisted of 46 males, 77 females, and three with sex unrecorded; the median age at diagnosis was 38 years for males, and 19 years for females. The phenylbutazone reactions occurred in eight males and 17 females, with median ages of 51 and 48 years, respectively. Sixteen of the 77 physicians who returned questionnaires were from countries other than the United States.

Outcome of Blood Dyscrasia.—Table 1 summarizes the results of the marrow depression among the 154 cases in the survey. The median period of observation was nine months for the chloramphenicol group, and one year for the phenylbutazone series. For each outcome category there were no significant differences between the two drugs in the distribution of time intervals since diagnosis of the blood dyscarsia. Furthermore, there was a similar proportion of patients who were still being treated for toxic effects from each drug, at median intervals of 4 and 4½ years, respectively, following diagnosis. The chloramphenicol series, however, had a much higher proportion of deaths, while the phenylbutazone group had a greater frequency of recovery. These differences persist even if the patients with toxic reactions to chloramphenicol who were lost to follow-up (8%) are assumed to have recovered. Table 2 specifies the type of blood dyscrasia under treatment at the time of survey. Tables 3 and 4 show the reported causes of death.

TABLE 2.—NUMBER OF PATIENTS UNDER TREATMENT AT TIME OF SURVEY, ACCORDING TO SPECIFIC BLOOD DYSCRASIA

Blood Dyscrasia	Chloramphenicol	Phenylbutazone
Erythroid hypoplasia (E)	2	
Leukopenia (L)	4	1
Thrombocytopenia (T)	7	1
Pancytopenia	3	1
E and T	1	
L and T		1
Paroxysmal nocturnal hemoglobinuria (following pancytopenia)	2	
Total	19	4

TABLE 3.—NUMBER OF PATIENTS DYING WITH DRUG-ATTRIBUTED BLOOD DYSCRASIA, ACCORDING TO REPORTED CAUSE OF DEATH

Cause of death	Chloramphenicol	Phenylbutazone	Chloramphenicol and phenylbutazone
Hemorrhage	16		1
Infection	13		
Hemorrhage and infection	4		
Leukemia	5	[1] 1	
"Aplastic anemia"	2	2	
Other	[2] 2		
Unknown	8		
Total	50	3	1

[1] Myelofibrosis with myeloid metaplasia.
[2] One case had myocardial infarction; the other had pulmonary edema.

TABLE 4.—SITE OF HEMORRHAGE AND TYPE OF INFECTION AMONG PATIENTS DYING FROM CHLORAMPHENICOL-ATTRIBUTED BLOOD DYSCRASIA

	Number of cases
Anatomic site of hemorrhage:	
Cerebral	7
Gastrointestinal	7
Generalized	3
Unspecified	3
Total	20
Type of infection:	
Septicemia	11
Peritonitis	2
Pneumonia	1
Osteomyelitis with sepsis	1
Unspecified	2
Total	[1] 17

[1] In 11 patients who died the following organisms were found: E coli (4 cases), Pseudomonas (3), unspecified gram-negative organisms (2), Proteus (1), and Staphylococcus (1).

Leukemia.—Six cases of leukemia were reported in the follow-up of 154 cases and are summarized in Table 5. Myelofibrosis (case 6) was considered here as "leukemia" since it is usually grouped with chronic myelogenous leukemia as a myeloproliferative disorder. The blood dyscrasia preceding the diagnosis of leukemia was attributed to chloramphenicol in five patients, and to phenylbutazone in one. None of the patients had a prior history of radiation therapy. Four of the six patients were females, and the ages ranged from 2 to 71 years. Two of the cases were reported from outside the United States (cases 4 and 5).

Study of the records available on the individual cases revealed that in three of the six patients (cases 4 through 6), leukemia had been diagnosed *prior* to the date on which the original drug reaction was reported to the registry. Since submission of the report might have been influenced by the development of leukemia, these cases must be excluded from the series for any calculation of

outcome rates. Thus, among the remaining 151 patients who had drug-attributed marrow depression, three received a diagnosis of leukemia *after* submission of the initial registry report (cases 1 through 3).

Among these three cases (all from the chloramphenicol series), only one had characteristics which would suggest a causal relationship between drug intake and leukemia. In case 1, a complete hemogram performed five months after the start of intermittent chloramphenicol therapy was entirely normal. Eight months after therapy began, the diagnosis of aplastic anemia was made from bone marrow examination; serial blood counts showed persistence of this condition until 2½ years following the start of therapy when an abrupt conversion took place to acute myelogenous leukemia.

Patient 2 did not have a clearly defined sequence of drug ingestion—marrow hypoplasia—leukemia. The diagnosis of "aregenerative anemia" was made three months after therapy with chloramphenicol; however, granulocytic hyperplasia of the marrow was present throughout the course of the pancytopenia. The diagnosis of chronic myelogenous leukemia was not made until death, 3½ years after drug ingestion, but it seems possible that this patient was in an early phase of leukemia at the onset of the drug-attributed blood dyscrasia. In case 3, the "latent period" between start of chloramphenicol therapy and diagnosis of leukemia was relatively short (five months), and the reporting physician could not exclude the possibility that leukemia was actually present at the time of the initial leukopenia.

Other Sequelae.—The following diseases subsequently developed in nine patients who had recovered from hematotoxic effects of chloramphenicol: hepatitis in two; renal failure in two; and cirrhosis, systemic lupus erythematosus, lung cancer, hypernephroma, and Gaucher's disease in one each. In addition, two patients who were still under care for chloramphenicol-attributed marrow depression had a history of hemolytic anemia during treatment of the hypoplastic marrow with prednisone and testosterone. In one case the hemolysis was associated with a positive Coomb's test reaction and subsided without additional therapy; in the other case, the hemolysis was successfully treated by splenectomy. (These cases are distinct from the two patients with toxic effects from chloramphenicol, noted in Table 2, who were still receiving care for paroxysmal nocturnal hemoglobinuria.)

Of four patients who recovered from toxic reactions to phenylbutazone, cirrhosis, lupus erythematosus, aseptic necrosis of the femoral head, and gout developed in one each. Sequelae were also described in the two patients who recovered from hematotoxicity associated with the administration of both drugs; one patient had a transient granulocytic leukemoid reaction, and a disorder resembling Weber-Christian disease developed in the other. As with leukemia, it is possible that some of these diseases, although diagnosed subsequent to the blood dycrasia, were actually present at the time of drug administration.

TABLE 5.—LEUKEMIA REPORTED IN FOLLOW-UP SURVEY OF PATIENTS PREVIOUSLY REGISTERED FOR ADVERSE REACTION TO CHLORAMPHENICOL OR PHENYLBUTAZONE—SUMMARY OF CASES

	Sex	Age, years	Leukemia		Drug ingestion				Initial reaction	
			Type [1]	Latent period [2]	Drug [3]	Indication	Duration	Estimated dose, grams	Type	Latent period [4]
Case:										
1	F	67	AML	2½ years	C	Bladder and lung infection.	Intermittently—8 months	14	Pancytopenia (marrow-"aplastic anemia").	8 months.
2	M	57	CML	3½ years	C	(?)	5 days	8	Pancytopenia (marrow-"aregenerative anemia").	3 months.
3	F	2	ALL	5 months	C	Septicemia	3 days	5	Leukopenia (remitted after androgen therapy).	3 weeks.
4 [5]	M	14	ASCL	1 month	C	Tonsilitis	10 days	10	Leukopenia thrombocytopenia	1 week.
5 [5]	F	17	ASCL	2 months	C	do	10 days	10	Leukopenia, thrombocytopenia	1 week.
6 [5]	F	71	MF+MM	Several years	P	Arthritis	Intermittently—several years	[6] 0.4–0.6	Pancytopenia (marrow-"fibrosis").	Several years.

[1] CML=chronic myelogenous leukemia, AML=acute myelogenous leukemia, ALL=acute lymphocytic leukemia, ASCL=acute stem-cell leukemia, and MF+MM=myelofibrosis and myeloid metaplasia.
[2] Latent period=interval between start of drug therapy and diagnosis of leukemia.
[3] C=chloramphenicol, P=phenylbutazone.
[4] Latent period=interval between start of drug therapy and diagnosis of initial blood dyscrasia.
[5] Leukemia in cases 4 through 6 was mentioned on original report of adverse reaction to the registry and was excluded from survey for any calculation of leukemia frequencies.
[6] Daily.

CASE REPORTS OF LEUKEMIA FOLLOWING USE OF CHLORAMPHENICOL OR PHENYLBUTAZONE

During the course of this study reports were received of six additional cases of leukemia in the United States following bone marrow depression attributed to chloramphenicol or phenylbutazone. Toxic reaction to the drug, however, had not previously been registered at the AMA or FDA, so these cases are summarized separately in Table 6. Although lacking a reference population, the characteristics of these cases were generally more suggestive of a causal relation between drug intake and leukemia than the leukemia cases detected by the follow-up survey. All patients had myelocytic leukemia; in three it occurred subsequent to the use of chloramphenicol and in three others, following phenylbutazone therapy. All had evidence of bone marrow deficiency preceding the diagnosis of leukemia, which was termed "aleukemic" leukemia in four instances. There was no history of exposure to radiation thereapy. All patients were females, from 43 to 77 years of age. In the three patients treated with chloramphenicol, the infection antedated by many years the manifestation of hematological disorder. The estimated chloramphencol dose varied between 7 and 200 gm, with leukemia developing from 2 to 12 years after start of treatment. In three patients with leukemia following phenylbutazone treatment, the underlying rheumatic conditions were chronic and unlikely to be early manifestations of leukemia. The estimated doses of phenylbutazone exceeded 15 gm. and leukemia was diagnosed from 1 to 12 years after the start of treatment.

It is noteworthy that all previously reported cases of leukemia following the use of chloramphenicol or phenylbutazone occurred in countries other than the United States. Chloramphenicol has been implicated much less frequently than phenylbutazone in the etiology of leukemia. Mukherji [8] described a 63-year-old man in whom aplastic anemia developed following administration of 12 gm of chloramphenicol; the aplastic process persisted until seven months after drug exposure when a diagnosis was made of acute myelogenous leukemia. Lebon and Messerschmitt [9] reported the case of a 5-year-old boy who died of acute myelogenous leukemia following a one-year history of aplastic anemia, which may have been due to chloramphenicol therapy. In an epidemiologic study of leukemia in Israel, Davies and associates [10] noted that 20 of 150 leukemia patients received drugs a "short time" before the diagnosis of leukemia and in 11 cases the drug was chloramphenicol.

TABLE 6.—REPORTS RECEIVED OF LEUKEMIA FOLLOWING CHLORAMPHENICOL OR PHENYLBUTAZONE THERAPY—SUMMARY OF CASES NOT PREVIOUSLY REGISTERED FOR ADVERSE REACTION [1]

	Sex	Age, years	Leukemia		Drug ingestion				Initial reaction	
			Type	Latent period	Drug	Indication	Duration	Estimated dose, grams	Type	Latent period
Case:										
1	F	60	AML [2]	2 years	C	Frequent common colds	Intermittently—14 months	15	Leukopenia	23 months.
2	F	56	AML [2]	12–15 years (10 months after initial reaction)	C	Cystitis	Intermittently—12–15 years	200	Erythroid hypoplasia, leukopenia (marrow-maturation arrest of WBC)	12–15 years.
3	F	64	CML	9½ years	C	Sinusitis	1 week	7	Pancytopenia	1 month.
4	F	61	SML	12 years (7 months after initial reaction)	P	Rheumatoid arthritis	Intermittently—11–12 years	21	Leukopenia	11–12 years.
5	F	43	AML [2]	1 year	P	Bursitis	Intermittently—9 months	>15	Leukopenia (marrow-maturation arrest of WBC)	9 months.
6	F	77	AML [2]	3½ years	P	Rheumatoid arthritis	Intermittently—3 years	>50	Leukopenia	3 years.

[1] See table 5 footnote for explanation of symbols. In addition, SML=subacute myelogenous leukemia.

[2] Termed "aleukemic" leukemia at diagnosis.

TABLE 7.—REVIEW OF LITERATURE: LEUKEMIA FOLLOWING PHENYLBUTAZONE THERAPY

Author and year	Sex	Age, years	Leukemia		Phenylbutazone ingestion		
			Type [1]	Latent period [2]	Indication	Duration	Estimated dose, grams
Bean 1960	M	69	CML	16 months	Degenerative spondylitis (30 years)	3 weeks	10
	M	67	ALL	4 years	Spondylitis (many years)	Intermittently—4 years	>100
	M	70	?LL (subacute)	2 months	Sciatica (45 years)	5 months	24
	M	80	CML	1 year	Osteoarthritis and spondylitis (many years)	?	?
	M	66	LL or LSA	4 years	Arthritis of hips (9 years)	4 years	150
	M	63	CML	18 months	Osteoarthritis of knee (many years)	1 month	5
Cast, 1961	F	59	CML	19 months	Rheumatoid arthritis (10 years)	17 months	210
Garrett, 1961	F	64	?ALL	2 to 3 months	Arthritis of knees	1 to 2 months	12–18
Cadman and Limont, 1962	M	71	ASCL	11 weeks	Lumbago	6 days	4
Chalmers and McCarthy, 1964	F	52	Mono-ML (subacute)	3½ years	Rheumatoid arthritis (8 years)	Intermittently—3½ years	240
Thorpe, 1964	F	56	ASCL	1 month	Arthritis of ankle (acute)	17 days	5.1
Hart, 1964	M	58	AML	17 months	Back injury (35 years)	2 weeks	5.6
Woodliff and Dougan, 1964	M	78	AML	4 years	Arthritis (30 years)	Intermittently—4 years	[4] 0.3
	M	52	ALL	6½ years	Arthritis (6 years)	Intermittently—6 years	10
	M	80	AML	4 years	Arthritis (5 years)	4 years	>276
	F	80	AML	2½ years	Arthritis (5 years)	17 months	33
	F	58	AML	5 years	Arthritis (5 years)	Intermittently—5 years	8
Sen and Siddique, 1964	M	29	AML	4 months	Arthritis of knee	4 months	9
Chatterjea, 1964	M	46	AML	"Significant period"	?	Intermittently—"significant period".	?
Dougan and Woodliff, 1965	F	58	ALL	11 days	Arthritis	8 days	3.2
	M	60	CLL	3 years	Arthritis (3 years)	Intermittently—3 years	?
	M	59	ALL	8 years	Rheumatoid arthritis	Intermittently—8 years	50–100
Stewart, 1964	M	40	AL	4 weeks	Phlebitis	1 week	2–6
Perers and Sjöberg, 1965	M	40	AML	2 months	Phlebitis	5 days	[3] 1.0
	M	47	ALL	13 months	Cervical spondylosis	2 weeks	[3] 1.9
Golding et al, 1965	F	57	A Mono L	5 years	Rheumatoid arthritis (10 years)	5 years	430
Jensen and Roll	M	78	CML	15 months	Arthritis (4 years)	4 months	72
	M	67	AML	27 months	Rheumatoid arthritis (8 years)	Several months	27
	F	31	ALL	12 months	Rheumatoid (?) arthritis (19 months)	Intermittently—6 months	(?)

[1] See Table 5 for abbreviations. In addition, LSA=lymphosarcoma, A Mono L=acute monocytic leukimia, CLL=chronic lymphocytic leukemia.

[2] Latent period=interval between start of drug therapy and diagnosis of leukemia.

[3] Oxyphenbutazone.

[4] Daily.

Leukemia following phenylbutazone therapy has previously been reported in 29 cases as summarized in Table 7. Patients known to have received radiotherapy were not tabulated. As observed by Jensen and Roll [27] the diagnosis of leukemia was not well established in at least three patients (cases 3 and 5 of Bean [14] and that of Garrett [16]), and in certain other cases the brief "latent period" (time interval between phenylbutazone exposure and the diagnosis of leukemia) casts doubt on a causal relationship. Of the 26 patients with an apparently established diagnoisis of leukemia, 13 had time intervals of at least 18 months, the minimum latent period estimated for radiation-induced leukemia.[1] These patients consisted of seven men and six women, who ranged in age from 52 to 80 years, suffered from some form of chronic arthritis, and recived phenylbutazone from one month to eight years. One patient had chronic lymphocytic leukemia, but the remaining 12 had either chronic myelogenous leukemia or acute leukemia. Only one patient in this group (patient 1 of Woodliff and Dougan [21]) was noted to have bone marrow hypoplasia prior to the diagnosis of leukemia. It is of interest that two reports included retrospective leukemia surveys, in a search for prior exposure to phenylbutazone. At the leukemia registry of Western Australia, Dougan and Woodliff [24] found that five of 55 adult patients with acute leukemia had a history of phenylbutazone therapy, while only five of 417 patients with "chronic leukemia and allied disorders" had a similar history. Although no comparison group was given, Jensen and Roll [27] reported that among 50 patients admitted to a Danish hospital with actute leukemia, three were known to have received phenylbutazone at intervals of 12, 15, and 27 months prior to the diagnosis of leukemia.

COMMENT

This follow-up survey of patients registered with bone marrow depression showed that those with hematotoxic effects from chloramphenicol had a substantially less favorable outcome, with a greater mortality and lower recovery rate than those with phenydbutazone reactions. Deaths from chloramphenicol-induced marrow depression were attributed mainly to hemorrhage and infection. The hemorrhages were predominantly cerebral or gastrointestinal, and the infections were caused mostly by a variety of gram-negative organisms. Of additional interest in the chloramphenicol group was the occurrence of hemolytic anemia in four cases following the onset of bone marrow depression. Two of the patients were diagnosed as having paroxysmal nocturnal hemoglobinuria, recently recognized as a complication of aplastic anemia induced by drugs.[29] It is likely that some nonhematologic sequelae were actually present prior to onset of the blood dyscrasia, and may have contributed to the development of toxicity. Such disorders would include liver and kidney disease [30] and systemic lupus erythematosus.[31]

Wintrobe [32] has commented on certain features of registries on adverse drug reactions which would limit epidemiologic application of the data. Reports of adverse reactions come from different sources of varying reliability, represent only a small proportion of patients affected, provide no information on incidence of the reactions, and may not necessarily signify a causal relation to the drug which is implicated.[32] Use of these data for our follow-up survey of leukemia was further complicated by (1) the problem of clearly separating the drug exposure and adverse reaction from the outcome (leukemia); (2) the relative sparseness of the data (cases and person-years at risk), so that only very large increases in leukemia incidence could be detected; and (3) the possibility that physicians who did not respond observed different outcomes than those who did (the direction of this potential bias could not be assessed). Despite these limitations, recognized at the outset of the survey, we felt that some value should come from observations which could be made prospectively from the exceptional study group derived from the two registries. It is of interest that, whereas published case reports of leukemia following drug use have implicated phenylbutazone far more often than chloramphenicol, the latter drug was implicated in five of the six registered patients (Table 5), and three of the six unregistered patients (Table 6) in whom leukemia developed.

After excluding three cases in which the development of leukemia may have influenced reporting to the registry, in a total of 151 patients there were three cases of leukemia (2%). These cases were from the 124 patients in the chloramphenicol group, while leukemia did not occur among 24 patients in the phenylbutazone series or three patients registered with toxic effects following

use of both drugs. Although the frequency of leukemia among persons with chloramphenicol-attributed marrow depression appeared to exceed expectation—3/124 in our series as compared with the US age-adjusted leukemia mortality of 6/100,000/yr—an association observed between drug exposure and leukemia may have one or more of the following interpretations: (1) A causal relationship exists between drug exposure and the development of leukemia. (2) Patients undergoing drug therapy for disorders such as immunologic deficiency and collagen disease may be at high risk of leukemia. (3) The ailment being treated is a manifestation or a complication of leukemia in its early phase (eg, rheumatic complaint, fever, infection). (4) Another therapeutic modality is leukemogenic (eg, radiotherapy). (5) The sequence of drug intake and leukemia is a chance occurrence.

The possibility of a causal relationship between drug use and leukemia would be supported by the following case characteristics: relatively high dose of the administered drug; no evidence of leukemia at the time of drug use; and absence of diseases or other agents know or suspected to be leukemogenic. Furthermore, if the relationship is comparable to radiation-induced leukemia (1), the cytologic type should be chronic myelogenous or acute leukemia, and the interval between start of drug exposure and development of leukemia should exceed approximately 18 months. Among the three leukemia patients observed in the survey, only one had all the characteristics which would suggest a causal relationship between chloramphenicol exposure and leukemia. The significance of one case is, of course, unclear. Because of the small study group and relatively brief period of follow-up, the risk of leukemia would have to be very high for additional cases to have occurred. If exposure to marrow-depressing drugs does confer a later increased risk of leukemia, one might anticipate the risk to be greatest among persons in whom signs of marrow depression actually develop, as those in the present study. From a single case of leukemia following toxic effects from chloramphenicol, however, it is not possible to conclude that chloramphenicol is, or that phenylbutazone is not, leukemogenic. Since radiation-induced leukemia has a peak occurrence three to eight years after exposure, a more realistic opportunity for evaluating leukemia risk awaits a larger sample size and longer period of observation following the drug reaction.

Finally, an evaluation between drug exposure or toxic effects and leukemia should benefit from cytogenetic studies of individuals treated with drugs that affect bone marrow function. Chromosomal abnormalities of blood cells have been described in the following situations where marrow depression may predispose to leukemia: (1) persons exposed to marrow depressants which are definitely or probably leukemogenic-radiation [33] and benzene [34]; (2) children born with Fanconi's familial aplastic anemia, who appear to carry an excess risk of leukemia [35]; and (3) certain forms of refractory anemia which later progress to leukemia.[36, 37] Indeed, cytogentic aberrations have been observed in virtually all groups of individuals who are, or seem to be, at high risk of leukemia.[38] Demonstration of a consistent chromosomal abnormality in patients who receive a particular drug or in whom toxic effects develop would enhance the possibility that an observed sequence of drug exposure and leukemia may have a cause-and-effect relationship.

GENERIC AND TRADE NAMES OF DRUGS

Chloramphenicol—*Chloromycetin.*
Phenylbutazone—*Butazolidin, Butadion, Artrizin, Pyrabutol.*
Amphetamine sulfate—*Benzedrine, Linampheta, Amitrene, Amphedrine, Amphoid-S.*
Prednisone—*Deltasone, Deltra, Meticorten, Paracort, Cotone, Lisacort, Metasone.*
Aminopyrine—*Pyramidon, Kalmine.*
Oxyphenbutazone—*Tandearil.*

REFERENCES

[1] Brill, A.B.; Tomonaga, M.; and Heyssel, R.M.; Leukemia in Man Following Exposure to Ionizing Radiation, *Ann Intern Med* 56: 590–609 (April) 1962.
[2] Miller, R.W.: Radiation, Chromosomes and Viruses in the Etiology of Leukemia: Evidence From Epidemiologic Research, *New Eng J Med* 271: 30–36 (July 2) 1964.
[3] Court-Brown, W.M., and Doll, R.: Mortality From Cancer and Other Causes After Radiotherapy for Ankylosing Spondylitis, *Brit Med J* 2: 1327–1332 (Dec 4) 1965.
[4] Bizzozero, O.J., Jr.; Johnson, K.G.; and Ciocco, A.; Radiation-Related Leukemia in Hiroshima and Nagasaki, 1946–1964; I. Distribution, Incidence and Appearance Time, *New Eng J Med* 274: 1095–1101 (May 19) 1966.
[5] Vigliani, E.C., and Saita, G.; Benzene and Leukemia, *New Eng J Med* 271: 872–876 (Oct 22) 1964.

[6] DeGowin, R.L.: Preluekemic Phase of Acute and Chronic Myelocytic Leukemia, *Clin Med* 72: 1135–1143 (July) 1965.
[7] DeGowin, R.L.: Benzene Exposure and Aplastic Anemia Followed by Leukemia 15 Years Later, *JAMA* 185: 748–751 (Sept 7) 1963.
[8] Mukherji, P.S.: Acute Myeloblastic Leukemia Following Chloramphenicol Treatment, *Brit Med J* 1: 1286–1287 (June 1) 1957.
[9] Lebon, J., and Messerschmitt, J.: Myélose Aplasique d'Origine Médicamenteuse Myéloblastose aigue Terminal Réflexions Pathogéniques, *Le Sang* 26: 799–804 (No. 8) 1955.
[10] Davies, A.M., et al: Epidemiological Observations on Leukemia in Israel, *Arch Intern Med* 108: 86–90 (July) 1961.
[11] Leonard, B.J., and Wilkinson, J.F.: "The Acute Leukaemias," in Wilkinson, J.F. (ed.): *Modern Trends in Blood Diseases*, London: Butterworth & Co., 1955, pp 248–251.
[12] Scheuer-Karpin, R.: Myeloblastic Leuaemia After Analgesic Drugs (A Common Aetiology for Acute Leukaemia and Granulocytopenia), *Haematologica Polonica* 3: 33–45 (Fasc 1–2) 1959.
[13] Berry, J.N.: Acute Myeloblastic Leukemia in a Benzedrine Addict, *Southern Med J* 59: 1169–1170 (Oct) 1966.
[14] Bean, R.H.D.: Phenylbutazone and Leukaemia: A Possible Association, *Brit Med J* 2: 1552–1555 (Nov) 1960.
[15] Cast, I.P.: Phenylbutazone and Leukaemia, *Brit Med J* 2: 1569–1570 (Dec 9) 1961.
[16] Garrett, J.V.: Phenylbutazone and Leukaemia. *Brit Med J* 1: 53 (Jan 7) 1961.
[17] Cadman, E.F.B., and Limont, W.: Phenylbutazone and Leukaemia, *Brit Med J* 1: 798 (March 17) 1962.
[18] Chalmers, T.M., and McCarthy, D.D.: Phenylbutazone Therapy Associated With Leukaemia, *Brit Med J* 1: 747 (March 21) 1964.
[19] Thorpe, G.J.: Leukaemia and Phenylbutazone, *Brit Med J* 1: 1707 (June 27) 1964.
[20] Hart, G.D.: Acute Leukemia Following Phenylbutazone Therapy, *Canad Med Assoc J* 91: 449–450 (Aug. 29) 1964.
[21] Woodliff, H.J., and Dougan, L.: Acute Leukemia Associated With Phenylbutazone Treatment, *Brit Med J* 1: 744–746 (March 21) 1964.
[22] Sen, S., and Siddique, K.K.H.: Phenylbutazone and Leukaemia, *Bull Inst Postgrad Med Educ Res* 6: 23–24 (Jan) 1964.
[23] Chatterjea, J.B.: Leukaemia and Phenylbutazone, *Brit Med J* 2: 875 (Oct 3) 1964.
[24] Dougan, L., and Woodliff, H.J.: Acute Leukemia Associated With Phenylbutazone Treatment: A Review of the Literature and Report of a Further Case, *Med J Aust* 1: 217–219 (Feb 13) 1965.
[25] Perers, D., and Sjöberg, S.-G.: Akut Leukemia, Leukemoid Reaktion och Leukocytos efter Behandling med Oxifenylbutazon, *Sv Läkartidn* 63: 53–56 (Jan 5) 1966.
[26] Golding, J.R.; Hamilton, M.G.; and Moody, H.E.: Monocytic Leukaemia and Phenylbutazone, *Brit Med J* 1: 1673 (June 26) 1965.
[27] Jensen, M.K., and Roll, K.: Phenylbutazone and Leukaemia, *Acta Med Scand* 178: 505–513 (Oct) 1965.
[28] Huguley, C.M., Jr.: Hematological Reactions, *JAMA* 196: 408–410 (May 2) 1966.
[29] Quagliana, J. M.; Cartwright, G. E.; and Wintrobe, M. M.; Paroxysmal Nocturnal Hemoglobinuria Following Drug-Induced Aplastic Anemia, *Ann Intern Med* 61: 1045–1052 (Dec) 1964.
[30] Suhrland, L. G., and Weisberger, A. S.; Chloramphenicol Toxicity in Liver and Renal Diseases, *Arch Intern Med* 112: 747–754 (Nov) 1963.
[31] McDuffie, F. C.: Bone Marrow Depression After Drug Therapy in Patients With Systemic Lupus Erythematosus, *Ann Rheum Dis* 24: 289–291 (May) 1965.
[32] Wintrobe, M.M.: The Problems of Drug Toxicity in Man—A View From the Hematopoietic System, *Ann NY Acad Sci* 123: 316–325 (March 12) 1965.
[33] Bloom, A.D., et al: Cytogenetic Investigation of Survivors of the Atomic Bombings of Hiroshima and Nagasaki, *Lancet* 2: 672–674 (Sept 24) 1966.
[34] Tough, I.M., and Court-Brown, W.M.: Chromosome Aberrations and Exposure to Ambient Benzene, *Lancet* 1: 684 (March 27) 1965.
[35] Bloom, G.E., et al: Chromosome Abnormalities in Constitutional Aplastic Anemia, *New Eng J Med* 274: 8–14 (Jan 6) 1966.
[36] Freireich, E.J., et al: Refractory Anemia, Granulocytic Hyperplasia of Bone Marrow, and a Missing Chromosome in Marrow Cells: A New Clinical Syndrome? abstracted, *Clin Res* 12: 284 (April) 1964.
[37] Dameshek, W.: Sideroblastic Anemia: Is This a Malignancy? *Brit J Haemat* 11:52–58 (Jan) 1965.
[38] Fraumeni, J.F., Jr., and Miller, R.W.: Epidemiology of Human Leukemia: Recent Observations, *J Nat Cancer Inst* 38: 593–605 (April) 1967.

[From Blood, August 1967, Vol. 30, No. 2, pp. 251–254]

Editorial

RIDDLE: WHAT DO APLASTIC ANEMIA, PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) AND "HYPOPLASTIC" LEUKEMIA HAVE IN COMMON?

(By William Dameshek *)

In 1961, we reported 20 cases of severe aplastic anemia in which infusions of allogenic (homologous) bone marrow had been used as one of the therapeutic methods.[1] Seven of these patients made apparently complete recoveries; whether

*WILLIAM DAMESHEK, M.D.: *Attending Hematologist, The Mt. Sinai Hospital, and Professor of Medicine, The Mt. Sinai School of Medicine, New York, N.Y.*

[1] McFarland, W., Granville, N., Schwartz, R., Oliner, H., Misra, D. K., and Dameshek, W.: Therapy of hypoplastic anemia with bone marrow transplantation. Arch. Intern. Med. 108: 23, 1961.

coincidentally or in relationship to the marrow infusions is not clear. Since then, the use of allogeneic bone marrow infusions has been well-nigh discarded for the induction of transplantation, chiefly because of the difficulties involved with suppression of the rejection phenomenon, as well as for the possibility of development of the graft-vs.-host reaction. Of the recovered cases referred to above, three patients have subsequently (as of June 1967) developed the characeristics features of PNH. Originally it occurred to us that this unusually high incidence of PNH might have some obscure relationship to the infused allogenic marrow, but since PNH may follow aplastic anemia *without* the mediation of introduced marrow, this idea did not appear very likely.

During a recent trip to the Far East where aplastic anemia appears to be unduly prevalent (perhaps because the use of chloramphenicol is relatively uninhibited), it was evident that the incidence of PNH was also unduly high. Thus, in Manila, the Philippines, Dr. Allen Caviles of the Philippines General Hospital informed me that he had observed 71 cases of aplastic anemia in three years, 53 of which had been subject to follow-up; one of these had developed PNH. In the same period, nine cases of PNH had also been observed, five of them having been previously diagnosed as aplastic anemia. Dr. Tien-tse Hwang in Taipei, Taiwan, reported that he had observed 10–14 new cases of aplastic anemia annually, as well as seven cases of PNH at the two hospitals where he worked, one of them the large National Defense Hospital. Among the first 10 cases of hypoplastic anemia he had seen in 1966, one of them subsequently developed PNH. From these several observations, the factor of coincidence for the two apparently disparate conditions of aplastic anemia and PNH seems unlikely.

Dacie and Gilpin [2] were the first to broach the possiblity that PNH and aplastic anemia might be related. This was subsequently further emphasized by Dacie [3, 4] and particularly in Lewis and Dacie's recent paper. Of 46 cases of aplastic anemia, seven had a positive Ham test for PNH and two actually developed clinical evidence of the disease. Conversely, of 60 patients with PNH, 15 showed aplastic anemia sometime during their course. In two such cases of PNH we observed, the acid hemolysis tests became negative when aplastic anemia developed. In the cases presenting first as pancytopenia-hypoplasia, then later developing hemoglobinuria, it has been customary to stress PNH as the real or fundamental condition and the previously apparent hypoplasia as simply a pre-PNH manifestation.

Names are important chiefly from the symbolic standpoint; they project images! They might be described as "bullets" profoundly affecting our response to a given set of circumstances. Thus, the term "PNH" invokes the concept of a peculiar form of hemolytic anemia in which hemoglobinemia (and hemoglobinuria) develop nocturnally. This puts the disease into the category of the various hemolytic anemias and the hemoglobinurias, which are characterized (among other features) by shortening of the red cell survival time, an active bone marrow with blood reticulocytosis, hemoglobinemia, and bilirubinemia. It has been shown that the shortened red cell survival in PNH is due to an intrinsic defect of the red cell.[5, 6] Such defects are almost always of genetic origin. However, in PNH there is every indication that the disorder is an acquired one. How then can aplastic anemia and PNH be related?

Pancytopenia in PNH has been noted since the early writings on this disease. Thus Crosby,[7] pointing to the usual leukopenia and thrombocytopenia—i.e., pancytopenia—suggested that all the bone marrow cells were involved in the disease. It is the red cell defect, however, that gives this condition its distinctive quality. Surely, the various factors in plasma which could be implicated in the actual hemolysis of the red cells (complement, "properdin," etc.) are of little importance as compared with the red cell defect. Actually, PNH may be thought of as an acquired defect of the erythron occurring in a previously healthy individual. Once having developed, this defect is apparently self-perpetuating and ecologically

---

[2] Dacie, J. V., and Gilpin, A.: Refractory anemia: its incidence in three members of one family, with in one case a relationship to chronic haemolytic anemia with nocturnal haemoglobinuria. Arch. Dis. Child. 19: 155, 1944.

[3] Dacie, J. V.: Paroxysmal nocturnal hemoglobinuria. Proc. Roy. Soc. Med. 56: 587. 1963.

[4] Lewis, S. M., and Dacie, J. V.: The aplastic anemia—paroxysmal nocturnal haemoglobinuria syndrom. Brit. J. Haemat. 13: 236, 1967.

[5] Hellem, A. J., and Skaug, O. E.: Paroxysmal nocturnal hemoglobinuria. II. Permeability and phosphate turnover in the red blood cells. Scand. J. Clin. Lab. Invest. 7: 121, 1955.

[6] De Sandre, G., Ghiotto, G., and Mastella, G.: L'acetilcolinesterasi eritrocitaria. II. Rapporti con le malattie emolitiche. Acta Med. Patav. 16: 310, 1956.

[7] Crosby, W. H.: Paroxysmal nocturnal hemoglobinuria: Relation of clinical manifestations to underlying pathogenic mechanisms. Blood 8: 769, 1953.

advantageous. Indications of the defect are present, not only in the undue hemolysis in the presence of dilute acid,[8] but by a great reduction in red cell cholinesterase,[6] a striking sensitivity to complement and immune antibodies,[9, 10] a morphologic abnormality as seen by electron microscopy,[11] and by the presence of a shortened red cell survival time when the red cells of the patient are injected into a normal individual.[12] Thus, a certain proportion of the nucleated red cells of the bone marrow may be said to have developed an acquired, self-perpetuating abnormality which is sufficient to result in hemoglobinemia and/or hemoglobinuria. Stated in this way, PNH may be considered as a growth disturbance of the erythroblastic component of the marrow. Conceivably, it could be called "neoplastic," a new kind of growth.

Why should a previously healthy individual develop this defect involving at least a portion of his red cell series? Why should leukopenia and thrombocytopenia be so commonly present? This brings us squarely to the heart of the matter. The more than coincidental relationship of PNH to aplastic anemia and the fact that the latter disease has been commonly associated with exposure to various chemicals or ionizing radiation suggest the possibility that the same agent which results in total marrow destruction may result in injury but not total destruction of one or another component of the marrow. Thus, one may speculate that certain chemicals, which in large dosage may destroy all the elements of the marrow, may in smaller amounts result in "selective" destruction of one of the marrow components or perhaps only in the loss of a key enzyme of some cells. Such injured cells might retain the capacity to reproduce themselves despite this deletion, and in this manner the formation of a self-replicating clone of abnormal cells might be induced. PNH could thus be a form of neoplasia—of the red cell series—developing, at least in some cases, as the result of an insult to the marrow. Similar reasoning has been applied to the development of leukemia.

As cases of aplastic anemia are followed, whether these are chemically or radiologically induced, or in association with congenital defects (Fanconi syndrome, the Werner syndrome*), it becomes evident that a number of them eventually develop increasing groups of primitive leukocytes in the marrow—i.e., "acute" or primitive cell leukemia. It is conceivable that this type of leukemia is based upon the initial development of a small clone of primitive leukocytes with defective maturation; eventually such a clone may gain ecologic dominance. Thus it is evident that marrow hypoplasia may be followed in some cases by "hypoplastic" primitive cell leukemia. in others by the development of a new type of (defective) red cell growth—i.e., PNH. From this, one may infer that a sufficiently severe "insult" to the marrow—whether chemical, ionizing radiation, or viral—may result in a variable degree of injury with a variable degree of hypoplasia (hypoplastic anemia). In some cases, abnormal clones of either leukocytes or red cells could conceivably arise during the process of repair. If the preponderance of bizzarre cells were of the white cell type, "leukemia" would be diagnosed; if, on the other hand, the red cell injury were sufficiently marked as to result in hemoglobinuria, then the diagnosis of PNH would necessarily be made. Thus, at least some examples of the apparently different conditions of PNH, aplastic anemia, and "hypoplastic" leukemia might have a common denominator in the form of an "insult" to the marrow. As a correlative statement, what looks like "aplastic anemia" today might be either "acute leukemia" or PNH two years from now.

---

[8] Van den Bergh, A. A. H.: Ictere hemolytique avec crises hémoglobinuriques fragilité globulaire. Rev. Med. (Paris) 31 : 63, 1911.

[9] Ham, T. H., and Dingle, J. H.: Studies on destruction of red blood cells. II. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria; certain immunological aspects of the hemolytic mechanism with special reference to serum complement. J. Clin. Invest. 18 : 657, 1939.

[10] Rosse, W. F., and Dacie, J. V.: Immune lysis of normal human and PNH red blood cells. I. The sensitivity of PNH red blood cells to lysis by complement and specific antibody. J. Clin. Invest. 45 : 736, 1966.

[11] Cecchi, E., and Conestabile, E.: Paroxysmal nocturnal hemoglobinuria. Electron-microscopic study of red blood cells. Lancet 2 : 466, 1957.

[12] Dacie, J. V.: Diagnosis and mechanism of hemolysis in chronic hemolytic anemia with nocturnal hemoglobinuria. Blood 4 : 1183, 1949.

*With Dr. E. Perez-Santiago and Dr. Norman Maldonado, I have recently observed, at the Centro Medico of the University of Puerto Rico, a fascinating case of pancytopenia-hypoplastic anemia occurring in a young woman with the Werner syndrome (progeria). Subsequently, she developed increasing numbers of plasma cells in the bone marrow, and the previously diffuse hypergammaglobulinemia had begun a "monoclonal" spike. It was evident that she was now developing multiple myeloma.

It is conceivable that such a time lag might be essential to establish a sufficient mass of abnormal cells to result in clinical evidence of one or the other disease.

This attempt to put together in one pathogenetic package such apparently diverse abnormalities as aplastic anemia, PNH, and a form of leukemia is not meant to tear asunder the neat compartmentalization by which we, as physicians, tend to classify disease. Certainly, these "pigeonholes" have merit. On the other hand, in some circumstances they may impede at least conceptual progress. The usual tendency is to refer to the sequence of aplastic anemia-PNH as coincidental disorders, or perhaps as one condition "masquerading" for a time as another. It is conceivable that "lumping," as opposed to "splitting," might be better here. Thus, as in the myeloproliferative disorders and now perhaps in the field of aplastic anemia, PNH, and "hypoplastic" leukemia, a "vague" approach, as opposed to strict categorization, may have much in its favor. That a single "insult" to the marrow may be responsible for bringing about different kinds of abnormalities, sometimes occurring together, sometimes sequentially, deserves considerations, not only from the conceptual standpoint but from the experimental approach as well.

[From Clin-Alert, May 10, 1967]

CHLORAMPHENICOL

TOXICITY

For fifteen years the profession has been divided into those who fear the toxicity of chloramphenicol and rarely use the drug, and a large number who ignore the possibility of marrow aplasia and prescribe chloramphenicol freely. Chloramphenicol is prescribed much less frequently in Great Britain than in the United States. The British Committee on Safety of Drugs recommends that chloramphenicol not be used except for treating typhoid fever or H. influenza meningities, or, in the case of other infections, when no other antibiotic will suffice. If these recommendations are followed, the occasions for prescribing chloramphenicol would be few and far between. Leading Articles, British M.J. 1:649 (Mar. 18), 1967; Meade (London, Eng.), Ibid. 671.

[From New Drugs, 1967, ch. I, pp. 1–3]

ANTIBACTERIAL AGENTS

CHLORAMPHENICOL AND DERIVATIVES

Chloramphenicol (chloromycetin) is a broad spectrum antibiotic originally derived from *Streptomyces venezuelae*, but now produced synthetically. The drug is also available as the esters, chloramphenicol palmitate and chlroamphenicol sodium succinate. It was effective antimicrobial activity against many strains of gram-positive and gram-negative bacteria *Rickettsia*, and "viruses" of the psittacosis-lymphogranuloma group. However, because serious blood dyscrasias have occurred after therapy with chloramphenicol (see under Adverse Reactions), this drug should be used only for the treatment of typhoid fever, other salmonelloses, and infections that do not respond to less potentially dangerous agents. Chloramphenicol is highly effective in the treatment of typhoid fever, but is not so uniformly effective in other *Salmonella* infections. It also may be used in the treatment of infections of the meninges and of the urinary and respiratory tracts when the causative organism is susceptible to its action and other therapeutic agents are ineffective or are contraindicated. However, the physician should bear in mind the precautions to be exercised and the adverse reactions that may occur with chloramphenicol. As with other antibiotics that are effective systemically, there are few indications for its topical use.

ADVERSE REACTIONS

The most serious toxic effect associated with the use of chloramphenicol (chloromycetin) is *aplastic anemia with pancytopenia*. Data in the AMA Registry on Adverse Reactions indicate a disproportionately higher number of reports of aplastic anemia occurring in patients receiving chloramphenicol than in those receiving any other drug. About 75% of the blood dyscrasias associated

with chloramphenicol were report as cases of aplastic anemia with pancytopenia; other forms noted include erythroid hypoplasia without pnacytopenia, thrombocytopenia with no change in red or white blood cells, leukopenia, and agranulocytosis. Aplastic anemia has occured after the administration of small doses for short periods, as well as after prolonged therapy; the other forms of blood dyscrasias appear more likely to be associated with large doses or prolonged therapy and also are more likely to be reversible if the administration of chloramphenicol is discontinued.

Skin rash and gastrointestinal and neurologic reactions, including optic and peripheral neuritides, also have been reported. Sensitization may occur when the drug is applied topically. As with other antibiotics, an overgrowth of nonsusceptible organisms may occur when chloramphenicol is used.

In premature and newborn full-term infants, chloramphenicol has produced toxic reactions referred to as the "gray syndrome," which is characterized by abdominal distension, progressive pallid cyanosis, and peripheral vascular collapse; in a number of cases, death has resulted.

PRECAUTIONS

It is essential that adequate blood studies be made during treatment with this drug. However, although blood studies may reveal early peripheral blood changes such as leukopenia or granulocytopenia before they become irreversible, the studies cannot be relied upon to detect bone marrow depression prior to the development of aplastic anemia.

Because of the possibility that serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) may occur after both short-term and prolonged therapy with chloramphenicol [chloromycetin], the drug should be used only for serious infections caused by organisms that are susceptible to its antibacterial effect. Chloramphenicol should not be used when other less potentially dangerous agents will be effective; or in the treatment of trivial infections such as colds, influenza, or infections of the throat; or as a prophylactic agent to prevent bacterial infections of the respiratory tract.

The dosage recommendations for premature and newborn infants should not be exceeded: moreover, the levels of the drug in the blood should be carefully followed, since the concentration in premature infants and in those under two weeks of age differs from that in older infants. This difference is due to the immaturity of metabolic mechanisms for the disposition of chloramphenicol, as well as of many other drugs; thus, high blood concentrations result and tend to increase with succeeding doses.

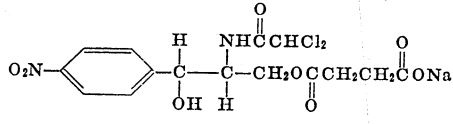
Since patients with impaired hepatic or renal function may retain an excessive amount of chloramphenicol because of decreased metabolism and excretion, the dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.

PHARMACOLOGY

Chloramphenicol [chloromycetin] is absorbed rapidly from the gastrointestinal tract and, after a single oral dose, the maximal blood concentration is reached within two hours. It appears to be well distributed, although not uniformly, in the body tissues. The drug passes readily into the cerebrospinal and pleural fluids, and appreciable quantities are found in the bile. It passes into the aqueous and vitreous humor of the eye and crosses the placental barrier. Chloramphenicol is rapidly conjugated by the liver to a monoglucuronide which has no antibacterial activity. It is excreted mainly in the urine. The rate of excretion is proportional to the blood level, and 5% to 10% of the total amount excreted is in the active form.

Chloramphenicol Sodium Succinate, U.S.P.

[Chloromycetin sodium succinate]



D-(—)-*threo*-2,2-dichloro-N[β-hydroxy-α(hydroxymethyl)-ρ-nitrophenethyl] acetamide, α-sodium succinate

ACTIONS AND USES

Chloramphenicol sodium succinate is similar to the parent compound in action, uses, and adverse reactions, and thus it has the same indications for use (see the Introductory Statement). However, because of its high aqueous solubility, it may be preferred for parenteral administration when oral therapy is not feasible, when it is important to achieve a high blood level quickly, or when higher blood concentrations are required than can be conveniently attained by oral administration. This ester is the preferred parenteral dosage form for pediatric use.

The sodium succinate derivative has no antibacterial activity in vitro; its effectiveness in vivo depends upon the liberation of the parent compound.

Concentrations of the drug in the cerebrospinal fluid average about one half of those in the serum; inflammation of the meninges does not appear to increase the rate of diffusion. After administration of chloramphenicol sodium succinate, the unchanged ester, free chloramphenicol, and metabolites of the latter appear in the urine.

ADVERSE REACTIONS

Chloramphenicol sodium succinate may produce the same adverse reactions as the parent compound (see the introductory statement on chloramphenicol). In particular, it should be borne in mind that the latter may cause aplastic anemia, thrombocytopenic purpura, and agranulocytosis, and that it has produced hypersensitivity and neurotoxic reactions.

A bitter taste, which occurs 15 to 20 seconds after injection and persists for 2 to 3 minutes, is experienced by patients receiving chloramphenicol sodium succinate intravenously.

Intramuscular injection of the sodium succinate ester is apparently less irritating than is injection of the base, although moderate local pain at the site of injection occurs in a substantial proportion of patients; a significant inflammatory reaction seems to occur only after repeated injections. Intravenous administration is also well tolerated.

PRECAUTIONS

Chloramphenicol sodium succinate should be used with the same precautions applicable to the parent compound. All patients receiving this form of the drug should have periodic hematologic studies and should be carefully observed for clinical manifestations of the blood dyscrasias that have been associated with the administration of chloramphenicol.

Dosage recommendations in premature or newborn infants should not be exceeded, and assay of blood concentration is advisable.

Chloramphenicol sodium succinate should not be used in trivial infections or in infections in which the causative organism has not been demonstrated to be susceptible to its effect.

DOSAGE AND PREPARATIONS

Routes of Administration.—Intramuscular, intravenous, subcutaneous.

Dosage.—Chloramphenicol sodium succinate is prepared for use by dissolving the powder in water for injection or other suitable aqueous diluents. A 10% solution is prepared for intravenous administration and the total dose is injected over a period of one minute or is added to a larger volume of fluid and infused slowly. A 25% to 40% solution is used for deep intramuscular injection, and a 10% solution is injected subcutaneously or added to fluids for subcutaneous clysis.

The dosage of chloramphenicol sodium succinate should be adjusted on the basis of the severity of the infection, response, and tolerance. If doses higher than the following are used for severe infections, they should be reduced after clinical improvement is noted.

The usual dose for *adults* and *children* is 50 mg. per kilogram (23 mg./lb.) of body weight given in divided doses every six or eight hours. *Premature infants* are given 25 mg./kg. (12 mg./lb.) daily in divided doses, usually at 12-hour intervals, either intramuscularly or intravenously. *Full-term newborn infants up to two weeks of age* are given 25 mg./kg. daily in divided doses every four to six hours by the intramuscular or intravenous route. Generally, in *infants over two weeks of age*, a daily dose of 50 mg./kg. is required to produce effective blood levels. However, even when using these general guides to infant dosage, chloram-

phenicol blood levels should be determined frequently for every premature and newborn infant, and an attempt should be made to maintain a blood level as near 10 to 20 μg./100 ml. of serum as possible. It is also advisable to make blood level determinations for any infant if the drug is given for more than four days.

Preparations.—Injection: Powder 250 mg., 1 gm.

Supplied by.—Parke, Davis & Company [Chloromycetin Sodium Succinate].

Year of introduction : 1959.
Evaluated for *N.N.D.* 1962. Revised : 1965.

[From Clin-Alert, Aug. 18, 1966]

CHLORAMPHENICOL

OPTIC TOXICITY

Blindness occurring in children with cystic fibrosis has been reported by several investigators, and it has been suggested that the ocular complications are due to severity of the disease or to its treatment (Clin-Alert No. 11, 1966). The authors studied 42 children with cystic fibrosis of whom 19 were found to have some degree of engorgement of the retinal vessels, and this was related to the severity of their lung disease and not to antibiotic therapy. Ocular damage was not observed in patients receiving very large amounts of tetracyclines, sulfonamides, erythromycin, and novobiocin. However, of 19 children who had been given chloramphenicol, one developed optic neuritis after receiving the drug for 69 weeks, and this caused permanent blindness. Chloramphenicol should probably not be given to children with cystic fibrosis for periods longer than one month because optic neuritis has occurred after only 3½ months of such treatment.—Keith et al. (London, Eng.), Arch. Dis. Child. 41 : 262 (June), 1966.

[From the American Journal of Disabled Children, July 1966, vol. 112, pp. 46–48]

OPTIC NEURITIS AND CHLORAMPHENICOL

(By Nora Chang, M.D., Conrad L. Giles, M.D., and Robert H. Gregg, M.D.,* Detroit)

Optic neuritis has been associated with chloramphenicol therapy in both adults and children.[1-9] It is our purpose to report two additional cases occurring in children with cystic fibrosis, who were treated with large doses of chloramphenicol over a prolonged period of time.

REPORT OF CASES

Case 1.—This 5-year-old white girl is one of apparently identical twins with moderately advanced cystic fibrosis. The diagnosis was established elsewhere on the basis of symptoms which began at the age of 2 months. The diagnosis was confirmed here at the age of 3 years on the basis of the clinical picture, the chest x-ray, and a sweat test (chloride greater than 100 mEq/liter).

Treatment included postural drainage, nighttime mist tent, pancreatic extract, vitamins, and sodium oxacillin at various times. At the age of 4½ years (July 1964), because of progression of her respiratory disease, she was given chloramphenicol in a dose of 750 mg/day (57 mg/kg). This dose was continued for a period of 6½ months, and the oxacillin was continued simultaneously. At this time the mother reported evidence of visual impairment and the chloramphenicol was discontinued and oxacillin continued.

Ocular examinations at that time revealed a vision of counting fingers only at two feet. Ophthalmoscopically she demonstrated dilated and tortuous veins with mild edema of the disc in each eye. The diagnosis of retinopathy of cystic fibrosis in association with optic neuritis, probably due to chloramphenicol, was made.

---

*Received for publication March 3, 1966. From the departments of pediatrics and ophthalmology, Wayne State University, and Children's Hospital of Michigan, Detroit. Reprint requests to 5224 St. Antoine St, Detroit 48202 (Dr. Gregg).

NOTE.—Numbered footnotes at end of article, p. 2676.

One month later, the vision had improved slightly to counting fingers at ten feet, and the retinopathy was less apparent, although definite pallor of each disc was noted. Examination two months after discontinuing the drug showed no change in vision, but less retinopathy and less pallor of the optic nerve head.

Four months later the vision rose to 20/200 in the left eye, but remained unchanged in the right eye. After five months, the disc still showed residual pallor although the vision had risen to 20/50 right eye, and 20/40 left eye.

Nearly six months after the initial evaluation, the vision was 20/40+ bilaterally, minimal optic nerve pallor was present, and no evidence of retinopathy was seen. No change was seen on subsequent examinations.

The respiratory symptoms have continued to progress in severity.

Case 2.—This 17-year-old white girl was said to be free of symptoms until the age of 9 years. A diagnosis of cystic fibrosis was made at the age of 13 in another hospital, was confirmed here (same basis as in case 1), and she has been followed here for most of the last four years. She has had advanced changes of cystic fibrosis with severe diffuse lung changes, marked clubbing, and exercise limitation throughout that time. In the past two years she has been intermittently febrile and cyanotic.

Initially, treatment consisted of pancreatic extract, vitamins, postural drainage, a nighttime mist tent and tetracycline.

There was some improvement on this regimen. She then moved from the city and when next seen in July 1963 at the age of 15, she was worse. Sodium oxacillin was begun (750 mg/day), but she did not improve, and after two months, chloramphenicol in a dose of 1.5 gm/day (49 mg/kg) was added. Some improvement followed and these medications were continued for the next 16 months. At this time she complained of photophobia, and chloramphenicol was discontinued and oxacillin continued. Her glasses had been changed by a local optometrist midway in this 16-month period.

She was referred to the ophthalmologist following the inability of her optometrist to improve vision above the level of 20/60. The patient had noted a slow decrease in central vision over the three months preceding her ophthalmologic evaluation.

Examination showed a marked reduction in vision to counting fingers at ten feet with a myopic correction in each eye. The remainder of her examination, except for a 12° central scotoma (to a 2 mm white test object at 1,000 mm), was normal. The condition of the retinal vessels and optic nerve head was physiologic.

When the patient was reexamined on March 1, 1965, the vision was 20/50— in the right eye and 20/40— in the left eye. Ophthalmoscopy was again normal.

Summary of reported cases

Case	Age, year	Sex	Basic disease	Dose, mg./kg.	Duration of Rx	Symptoms	Ocular findings	Outcome	Author
1	22	M	Bacterial endocarditis		2 months	Yellow; blurred vision	Decreased visual acuity; papillitis	Vision normal	Gewin et al.
2	24	F	Ulcerative colitis and abscess		5½ months	Blurring vision	Decreased visual acuity; bilateral scotomata; edema of nerve fibers; appearance of new vessel on nerve head.	Vision normal	Wallenstein. et al.
3	?	M	Bacterial endocarditis		1½ months	Cloudy vision; progressed to blindness.	Discs pale, blurred, edematous; numerous hemorrhages in various parts of fundi.	Poor vision recovery.	Lasky.
4	32	M	Chronic melioiodosis		21 months	2 episodes of visual complaints; blurred foggy vision; unable to read.	Decreased visual acuity; visual fields and fundi normal.	Vision normal	Prevatt et al.
5	44	M	Bacterial endocarditis		6½ months	Blurred vision, a feeling of "looking through a film."	Decreased vision; pericentral scotomata, constriction of visual fields bilaterally; edema of discs; dilated retinal veins.	Vision normal	Cole et al.
6	20	M	Melioidosis		Approximately 4 months.	Blurred vision; inability to focus.	Papilledema: constricted visual fields	Vision normal	Joy et al.
7	37	F	Pyelonephritis		Approximately 12 months intermittently.	Film in front of eyes.	Decreased visual acuity; scotomata bilaterally optic discs swollen, marked edema over maculae.	Vision normal	Wilson.
8	31	F	Polycystic kidney, pyuria		Approximately 10 months.	Failing vision	Decreased visual acuity; central scotomata bilaterally; myopic changes in retina and slight pallor of discs.	Vision slightly improved.	Wilson.
9	4	F	Cystic fibrosis		Approximately 15 months.	Peering at objects	Decreased vision; exotropia; optic atrophy bilaterally.	Poor vision recovery.	Keith.
10	2	M	Cystic fibrosis	27–53	24 months	Sat close to TV; had trouble feeding himself.		Vision normal	Leitman et al.
11	4	M	Cystic fibrosis	59	4½ months	Fell over toys; had trouble feeding himself.		Counts fingers at 2–3 feet.	Lietman et al.
12	5	M	Cystic fibrosis	40	8 months	Sat close to TV; held objects close; had difficulty finding toys.	Decreased visual acuity; bilateral central scotomata; blurred disc margins, and tortuous vessels.	Vision normal	Leitnam et al.
13	6	M	Cystic fibrosis	41	9 months	Sat close to TV; could not recognize brother at 10 feet.	Decreased visual acuity; bilateral central scotomata; edema of discs, engorged and tortuous veins.	Vision normal	Leitnam et al.
14	6	F	Cystic fibrosis	54	8 months	Held objects close	Decreased visual acuity; blurred and elevated disc margins; tortuous veins, clumping of macular pigment.	Remained on chloramphenicol; counts fingers at 6–7 ft.	Leitman et al.
15	6	M	Cystic fibrosis	45–60	3½ months	Held objects close, had difficulty seeing blackboard in school.	Disc blurred, hyperemic, and elevated; vessels tortuous; peripapillary capillary dilatation with hemorrhage.	Vision normal	Leitman et al.
16	5	F	Cystic fibrosis	57	6½ months	Did not read or watch TV	Decreased vision; retinopathy of cystic fibrosis and optic neuritis.	Vision improved	Present report.
17	17	F	Cystic fibrosis	49	16 months	"Light spot in front of eyes," difficulty in seeing.	Marked reduction in vision; central scotomata.	Vision normal	Present report.

In spite of repeated attempts to reexamine the patient, further follow-up was delayed until Aug. 23, 1965, when a vision of 20/20 was recorded in each eye and the disc and retina were normal.

COMMENT

It is presumed that the causative agent in these cases was chloramphenicol. All other therapeutic agents were continued after chloramphenicol was stopped. In the previously reported cases (now totaling 15), chloramphenicol was the only common drug.[1-9]

The retinopathy of cystic fibrosis of the pancreas, characterized by retinal hypervascularity or papilledema or both.[10] is not at all similar to the changes described here, and usually does not affect vision. These changes are thought to be related to the pulmonary status.

A summary of the clinical findings in our cases and those from the literature are given in the Table.

The mechanism of optic neuritis in this condition (or in any other) is not known.

SUMMARY

Two cases of optic neuritis associated long-term chloramphenicol therapy are reported.

GENERIC AND TRADE NAMES OF DRUGS

Chloramphenicol—*Chloromycetin.*
Sodium oxacillin—*Prostaphlin, Resistopen.*
Tetracycline—*Achromycin, Panmycin, Polycycline, Steclin, Tetracyn.*

REFERENCES

[1] Gewin, H.M., and Friou, G.J.: Manifestations of Vitamin Deficiency During Aureomycin and Chloramphenicol Therapy of Endocarditis Due to *Staphylococcus Aureus, Yale J Biol Med* 23: 332–338, 1951.
[2] Wallenstein, L., and Snyder, J.: Neurotoxic Reaction to Chloromycetin, *Ann Intern Med* 36: 1526–1528, 1952.
[3] Lasky, M.A.; Pincus, M.H.; and Katlan, N.R.: Bilateral Optic Neuritis Following Chloramphenicol Therapy, *JAMA* 151: 1403–1404, 1953.
[4] Prevatt, A.L., and Hunt, J.S.: Chronic Systemic Meliodosis: Review of Literature and Report of a Case, With Note on Visual Disturbance Due to Chloramphenicol, *Amer J Med* 23: 810–823, 1957.
[5] Cole, J.G.; Cole, H.G.; and Janoff, L.A.: A Toxic Ocular Manifestation of Chloramphenicol Therapy, *Amer J Ophthal* 44: 18–20, 1957.
[6] Joy, R.J.T.; Scalettar, R.; and Sodee, D.B.: Optic and Peripheral Neuritis: Probable Effect of Prolonged Chloramphenicol Therapy, *JAMA* 173: 1731–1734, 1960.
[7] Wilson, W.: Toxic Amblyopia Due to Chloramphenicol, *Scot Med J* 7: 90–95, 1962.
[8] Keith, C.G.: Optic Atrophy Induced by Chloramphenicol, *Brit J Ophthal* 48: 567–570, 1964.
[9] Lietman, P.S.; di Sant 'Agnese, P.A.; and Wong, V.: Optic Neuritis in Cystic Fibrosis of the Pancreas: Role of Chloramphenicol Therapy, *JAMA* 189: 924–927, 1964.
[10] Bruce, G. M.; Denning, C. R.; and Spalter, H. F.: Ocular Findings in Cystic Fibrosis of the Pancreas, *Arch Ophthal* 63: 391–401, 1960.

[From the Medical Journal of Australia, 1: 681–2, Apr. 16, 1966]

CHLORAMPHENICOL AND EYE DAMAGE

The more notorious side-effects of chloramphenicol, such as aplastic anæmia, are well enough known to need no comment, but it may not be generally recognized that prolonged administration of the drug can also seriously affect the sight. Two recent papers from the U.S.A. dealing with children whose serious degree of fibrocystic disease had necessitated their taking a prolonged course of the antibiotic, serve to highlight the problem, although there have been occasional reports of visual troubles assocated with chloramphenicol therapy since 1963.

The first report, by J. C. Cocke, R. E. Brown and L. J. Geppert, is from San Antonio, Texas,[1] and tells of a girl, aged nine years, who was given a total of 135 grammes of chloramphenicol over a four and a half month period for a resistant *Pseudomonas* infection. Three attempts were made to withdraw the drug, but on each occasion the child became febrile within 24 hours, and it had to be started again. Frequent physical, hæmatological and chemical tests revealed no signs of any adverse reaction to the drug until over a period of about three weeks she suddenly developed a marked loss of vision. On questioning, it appeared that the child had first noticed a gradual haziness of objects, then had difficulty with read-

[1] *J. Pediat.*, 1966, 68: 27 (January).

ing fine print, until finally even large print became obscure. One week before her admission to hospital she could distinguish the largest objects only as vague shadows. Apart from her defective vision, no abnormalities were detected on physical examination, and her chest symptoms were minimal. Her visual fields were found to be markedly constricted, and on both sides there were dense central scotomas. Her visual acuity was down to 5/400. On fundoscopic examination, the veins were seen to be moderately engorged and tortuous, and there were flame hæmorrhages radiating from the discs, which were slightly elevated.

Her chloramphenicol therapy was stopped at once, and she was treated with intramuscular injections of vitamin B^{12}, and oral doses of ascorbic acid, thiamine and multivitamin capsules (of six different types!) on a presumptive diagnosis of optic neuritis. Her vision slowly improved, although she needed streptomycin and colistin to control her chest symptoms, and after five months her vision had nearly returned to normal. Some residual signs of damage still remained, however.

In the other series, N. N. Huang, R. D. Harley, V. Promadhattavedi and A. Sproul from Philadelphia [2] tell of nine children with severe symptoms of fibrocystic chest involvement, whose ages ranged from six and a half to 14 years, and whose general condition varied from fair to poor (their condition required treatment with various other antibiotics and aerosol therapy, as well as the chloramphenicol), who were given courses that ranged from 81 to 252 days. The total doses given at the time the ocular symptoms became noticeable were from 81 to 283 grammes, and, as in the first case mentioned, frequent blood examinations had failed to demonstrate any abnormality.

The first complaint of the children was of impairment of vision. On being tested for visual ability they were all found to have a marked decrease in acuity, and bilateral central scotomas. Fundoscopic examination revealed disc blurring in six of the nine children, and three had retinal hæmorrhages. In addition, two of the children complained of numbness and cramps in their feet which caused them more discomfort than their visual disturbances. Subsequent developments varied, apparently quite haphazardly, and the confusion is such that no very definite conclusion can be derived from them. Two children died from the effects of their disease shortly after the eye signs were discovered, on having stopped taking chloramphenicol, the other having continued the therapy. No ocular improvement was noted in either of them before their deaths. Two others were given no vitamin or other treatment aimed specifically at the eye symptoms, which cleared up spontaneously in both cases, although one continued to take chloramphenicol. In the one who stopped treatment, vision improved in a matter of hours from the time of stopping the drug. Of the remaining five children, all of whom were given vitamins in varying combinations and quantities, one showed a quick improvement on stopping chloramphenicol, two showed improvement despite continuing with the drug, and two showed only slight improvement after first continuing with chloramphenicol, and then stopping it and taking corticosteroids instead.

The authors consider that the conditions they report represent forms of optic neuritis and retrobulbar neuritis, although they are at a loss to explain the mechanism of their causation by chloramphenicol. They do suggest, and this would seem very sensible, that those patients who for one reason or another require long-term courses of chloramphenicol therapy should, in addition to their usual hæmatological check-ups at regular intervals, have a frequent assessment of visual acuity, and that parents of patients should be advised to test their children's sight regularly with a small visual chart. In some instances, too, the development of numbness and cramps in the feet may be a forerunner of visual disturbance, and should also be watched for.

However, in explanation of some of the conflicting data mentioned above, there is evidence to suggest that some of the toxic effects of chloramphenicol may be related to a deficiency of vitamins of the B group, particularly riboflavine, and in a paper read at the recent annual meeting of the Australian Paediatric Association in Canberra on April 3, G. Morgan, G. Wise and D. O'Gorman Hughes, from the University of New South Wales, tell of four patients with chloramphenicol toxicity of differing varieties, one of whom developed amblyopia which was alleviated by the administration of B-group vitamins, despite his continuing with chloramphenicol.

None of which is to suggest that chloramphenicol is not a thoroughly efficient and often life-saving drug. But, as with such things as nuclear fission and motorcars, the greater the potential advantages, the greater the parallel dangers, not all of which can always be forecast.

[2] *J. Pediat.*, 1966, 68 : 32 (January).

[From Clin-Alert, Jan. 20, 1966]

CHLORAMPHENICOL

OPTIC TOXICITY

A. *Report From Texas:* Attention has been previously directed to apparent deleterious effects of chloramphenicol (Chloromycetin) on the eye (Clin-Alert No. 63, 1962; Clin-Alert No. 188, 1965). Nine cases of blindness due to optic atrophy presumably induced by the antibiotic are on record. The present authors report a case of probable chloramphenicol-induced optic neuritis in a 9-year-old child with cystic fibrosis of the pancreas. Treatment with a total of 135 Gm. chloramphenicol over an 18-week period resulted in loss of visual acuity secondary to bilateral optic neuritis. Vision gradually returned to near normal upon withdrawal of the antibiotic and the administration of high doses of vitamin B complex.—Cocke et al. (San Antonio, Texas), J. Pediat. 68:27 (Jan.), 1966.

B. *Report From Pennsylvania:* Visual disturbances were observed in 9 of 33 children with cystic fibrosis who received long-term (81 to 252 days) treatment with chloramphenicol. Daily doses ranged from 30 to 60 mg./Kg. The major clinical feature at onset of symptoms was marked bilateral reduction of visual acuity. Two patients had severe visual impairment and permanent residual effects with partial optic atrophy. Six children had varying degrees of blurring of optic discs, retinal hemorrhages or venous engorgement. Two other children had minimal fundoscopic changes. Visual field examination revealed bilateral central scotomas in all patients tested. Vitamin B complex therapy seemed to be of some benefit in overcoming the visual disturbances. The authors believe that the chloramphenicol-induced optic reaction probably represents a neurotoxic effect of the antibiotic rather than a complication of cystic fibrosis. "Frequent test of visual acuity in children receiving chloramphenicol must be carried out by the parents and/or physician in order to detect early signs of visual impairment."—Huang et al. (Philadelphia, Pa.), J. Pediat. 68:32 (Jan.), 1966.

[From the Journal of Pediatrics, January 1966, pp. 27–31]

OPTIC NEURITIS WITH PROLONGED USE OF CHLORAMPHENICOL

CASE REPORT AND RELATIONSHIP TO FUNDUS CHANGES IN CYSTIC FIBROSIS

Treatment over 4½ month period with 135 Gm. of chloramphenicol resulted in loss of visual acuity to 5/400 secondary to optic neuritis in a 9-year-old girl with cystic fibrosis of the pancreas. Partial return of vision occurred after cessation of therapy and administration of large doses of B-complex vitamins. The suggestion is made that visual and fundal changes in cystic fibrosis may be directly and all but entirely related to prolonged use of chloramphenicol in the control of pulmonary complications in cystic fibrosis.

(By Joseph G. Cocke, Jr., Captain, MC, USA.* Richard E. Brown, Captain, USAF (MC), and Leo J. Geppert, Colonel, MC, USA, San Antonio, Texas)
(From the Pediatric Service, Department of Medicine, and the Ophthalmology Service, Department of Surgery, Brooke General Hosptial, Brooke Army Medical Center, Fort Sam Houston, Texas)

The hematopoietic toxicity of chloramphenicol is well known. Certain less frequent manifestations of toxicity have also been noted, such as anaphylaxis, psychiatric, disturbances,[1, 2] and skin and mucous membrane involvement.[3] Most particularly, there has been increasing recognition to the apparent deleterious effects of chloramphenicol on the optic nerve and fundus in the form of an optic neuritis.[4–14]

Concurrently, visual and fundal changes in cystic fibrosis[15] of the pancreas, not unlike optic neuritis, have been described. Originally these changes were

*Address, Pediatric Service, U.S. Army Hospital, Fort Ord, Calif.

NOTE.—Numbered footnotes at end of article, p. 2681.

related to the severity of the pulmonary disease. More recently, vision alterations have been reported related to prolonged use of chloramphenicol.

Recent experience with optic neuritis in a child with cystic fibrosis has led to this case report, and subsequent suggestion for refinement of concepts relating to visual and fundal changes in cystic fibrosis.

CASE REPORT

C. L. was a 9-year-old Caucasian girl with proved cystic fibrosis and moderately extensive pulmonary disease. With no previous experience with extensive antibiotic therapy, she began a course of treatment with chloramphenicol in late August, 1963, which continued until the middle of January, 1964. The total dose given over the 4½ month period was 135 Gm.; the daily dose was 1 Gm. The organism, *Pseudomonas aeruginosa*, was sensitive to chloramphenicol. Three attempts were made to withdraw the drug. On each occasion the child became febrile within 24 hours. Treatment with alternate drugs was unsuccessful, and symptoms cleared only after restarting chloramphenicol. Physical, hematologic, and chemical examinations at weekly or biweekly intervals showed no sign of adverse change. In October, 1963, her vision was 20/40 in both eyes. Her basic disease remained stable under treatment.

Other than chloramphenicol, the patient was taking 400 mg. of glyceryl guaiacolate, pancreatic supplement tablets with each meal, and one standard multivitamin capsule daily, In addition, positive pressure inhalation therapy followed by postural drainage was done on a regular basis.

On Jan. 17, 1964, the child was admitted to the hospital following discovery of a severe loss of vision that had been concealed for 3 or 4 weeks. On retrospective questioning, the onset was noted to have been gradual, starting with haziness of objects. Within a week or so, fine, then large, print became blurred. One week prior to admission she could see no more than shadowy outlines of even the largest objects. Her teacher could date a deterioration of handwriting and reading ability to the approximate time of onset of visual symptoms.

Physical examination on admission showed a normal temperature, pulse, and respiration rate. She was 127 centimeters (50 inches) tall and weighed 23 kilograms (50.5 pounds). Pulmonary findings were minimal with no evidence of superimposed acute infection. There was no cyanosis or clubbing of the fingers. Positive neurologic finding were limited entirely to the optic nerve with no evidence of clouded sensorium nor other cranial or peripheral nerve involvement. Fundoscopic examination revealed choked nerve heads bilaterally with elevation of one to two diopters of the disc. Veins were moderately engorged and tortuous. There were flame hemorrhages radiating from the disc. Visual fields showed peripheral constriction with dense central scotomas (Fig. 1). Visual acuity was 5/400.

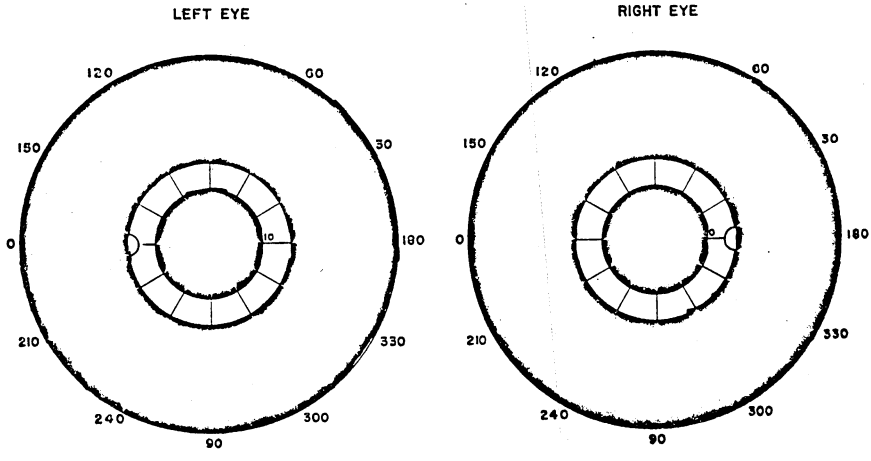


Fig. 1. Visual fields Jan. 22, 1964. Vision 5/400 in both eyes.

Laboratory data

Admission urinalysis was normal, hematocrit was 40 percent and the hemoglobin level was 12 Gm. per 100 ml.; total white count was 12, 100 c.mm. with 82 percent neutrophils, 16 per cent lymphocytes, and 12 percent eosinophils. None of these values changed notably throughout hospitalization. A lumbar puncture showed a pressure of 180 mm. at rest. No cells were present in the spinal fluid; protein was 11 mg. per 100 ml.; sugar, 62 mg. per 100 ml.; there was no increase in globulin. Serum total protein was 7.3 Gm. per 100 ml. with 5.0 Gm. per cent albumin and 0.80 Gm. gamma globulin. Determinations of serum sodium, potassium, chloride, CO_2, calcium, and phosphorus were normal on two separate occasions. Throat and sputum cultures repeatedly grew *Pseudomonas aeruginosa.*

With a working diagnosis of optic neuritis from chloramphenicol, therapy consisted primarily in stopping the drug and administering 1,000 μg of B_{12} intramuscularly and 150 mg. of both thiamine and ascorbic acid orally daily, coupled with 6 standard multivitamin capsules a day. The pulmonary problem was handled with a continuation of the intermitten positive pressure inhalation and postural drainage program. In addition, streptomycin and colistin were required toward the end of the hospital course to combat recrudescence of pneumonitis.

Visual acuity was noted to improve slowly. By the seventeenth hospital day, vision was 20/400 in both eyes. On the twenty-seventh hospital day it was 20/100 bilaterally, and remained thus until discharge. Very little improvement in visual fields was noted during hospitalization. The fundus showed slow resolution of the swelling of the nerve head with a decrease in the extent of the hemorrhages and exudates and an improvement in the retinal edema. On the thirty-ninth hospital day, the patient was discharged with treatment of three multivitamin capsules and 50 μg of B_{12} orally daily. She was followed through July, 1964; visual acuity improved to 20/50 in the right eye and 20/60 in the left eye. The fundus showed resolution of all acute changes and minimal postneuritic optic atrophy. Visual fields (Fig. 2) demonstrated small bilateral central scotomas and no change in the peripheral constriction.

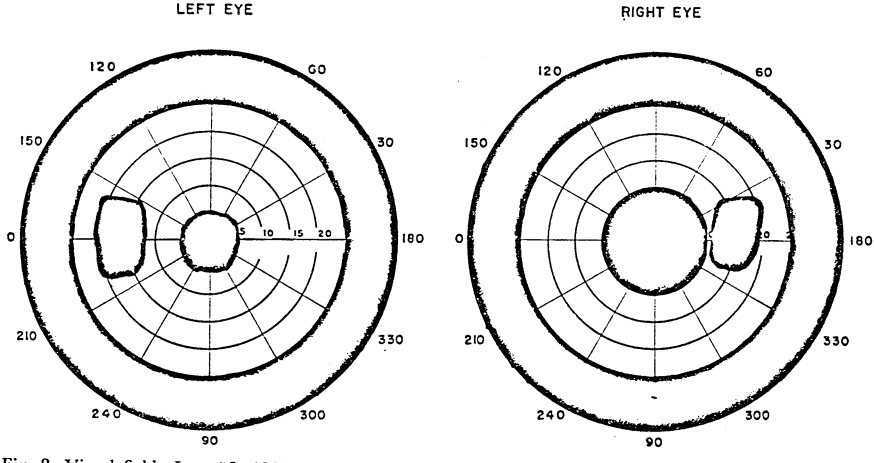


Fig. 2. Visual fields June 25, 1964. Vision 20/50 left eye; 20/60 right eye.

DISCUSSION

There are 15 fairly detailed case reports and two abstracts[4-14] of visual changes related to prolonged use of chloramphenicol in the English literature. Initial visual symptoms have been, primarily, haziness and blurring of vision and halos about objects. After a variable length of time, loss of visual acuity occurs.

Acute fundus changes have been described as papilledema, venous engorgement with occasional flame hemorrhages, and exudates. Visual fields show moderate

peripheral constriction with central scotomas of varying sizes. Related peripheral nerve symptoms of burning, tingling, or numbness of extremities have been reported in several cases.[5, 7, 9, 11]

Pathologic changes have recently been reported in 2 children with cystic fibrosis.[14] Both cases showed loss of the ganglion cell layer of the retina and a degree of demyelinization of the optic nerve fibers centrally to the chiasm.

A definite cause and effect relationship has not been established between prolonged use of chloramphenicol and deleterious effects on vision. However, circumstantial evidence leads to this conclusion in the individual cases.

The prognosis for the eventual return of visual acuity in any given case would appear to be good. Peripheral field changes usually show slight to moderate improvement.

The rationale for treatment of these visual disturbances with high doses of B–complex vitamins after cessation of chloramphenicol therapy lies in the suggestions previously made that the neurotoxicity is related to an interference with the B–complex group either directly at the cellular level,[9] or indirectly through sterilization of the gut.[11]

Bruce and associates[15] attribute visual changes to cystic fibrosis per se, speculating as to the relationship with severe pulmonary changes. Lietman and colleagues[14] propose two separate ocular lesions in cystic fibrosis: One, as described by Bruce, presumably with no effect on visual acuity; and the other, an optic neuritis with visual impairment, but without specific objective signs on funduscopic examination.

A more unified concept as to the etiology of the visual and ocular pathology may be derived by reinterpretation of the results of these observers. On close comparison all cases, ours included, have a strikingly similar funduscopic picture, consisting in almost every instance of the one lesion that best explains acute loss of acuity and relates to chloramphenicol as the underlying common denominator, namely, papilledema as a manifestation of optic neuritis. Macular changes are not necessary to explain the visual loss associated with optic neuritis. Previously the relative absence of macular abnormalities had been responsible for the division of ocular lesions in cystic fibrosis into the two categories noted above. The visual changes in cystic fibrosis may perhaps be considered as directly, and all but entirely, related to the prolonged use of chloramphenicol.

By elimination of the consideration that fundus changes may be due to cystic fibrosis per se, and by assuming that optic neuritis does occur with recognizable fundus changes, as this unified concept suggests, sight-conserving measures may be made more practical. Any child receiving long-term chloramphenicol therapy, who is found to have papilledema, venous engorgement, hemorrhages, exudates, and/or visual impairment, might reasonably and prudently be considered for drug elimination or dosage reduction. Further, the potential protective role of B–complex vitamins in long-term therapy with chloramphenicol seems deserving of study.

Chloramphenicol remains one of the most useful drugs for the treatment of pulmonary complications of cystic fibrosis. Recognition of yet another flaw in the two-edged sword that is chloramphenicol is essential lest we be guilty of adding more weight to the burden of those already heavily taxed.

SUMMARY

A case of probable chloramphenicol optic neuritis in a 9-year-old female with cystic fibrosis of the pancreas is presented. Treatment with 135 Gm. of chloramphenicol over a 4½ month period resulted in a loss of visual acuity secondary to bilateral optic neuritis. Gradual return of vision to near normal occurred after withdrawal of chloramphenicol and treatment with high doses of B–complex vitamins. It is suggested that in cystic fibrosis, visual changes may be directly, and all but entirely, related to the prolonged use of chloramphenicol.

REFERENCES

1 Hill, C. F. L., Armstrong, J. V., McDonald, C. K., and Anott, E. N.: Treatment of typhoid fever with chloramphenicol, Lancet 2 : 802, 1950.

2 Phadke. M. V., Joshi, V. S., and Naik, S. G.: Toxicity of chloramphenicol in children, J. Indian M. A. 37 : 26, 1961.

[3] Tomaszewski, T.: Side-effects of chloramphenicol and aureomycin, with special reference to old lesions, Brit. M. J. 1: 388, 1951.
[4] Gewin, H. M., and Friou, G. J.: Manifestations of vitamin deficiency during aureomycin and chloramphenicol therapy of endocarditis due to *Staphylococcus aureus:* Report of a case, Yale J. Biol. & Med. 23: 332, 1951.
[5] Wallenstein, L., and Snyder, J.: Neurotoxic reaction to chloromycetin, Ann. Int. Med. 36: 1526, 1952.
[6] Laskey, M., Pincus, M., and Kotlan, N.: Bilateral optic neuritis following chloramphenicol therapy, J.A.M.A. 151: 1403, 1953.
[7] Cole, J. G., Cole, H., and Janoff, L.: A toxic ocular manifestation of chloramphenicol therapy, Am. J. Ophth. 44: 18, 1957.
[8] Prevott, A. L., and Hunt, J. S.: Chronic systemic melioidosis: Review of literature and report of a case, with note on visual disturbance due to chloramphenicol, Am. J. Med. 23: 810, 1957.
[9] Joy, R. J. T., Scalettar, R., and Sodee, D. B.: Optic and peripheral neuritis: Probable effect of prolonged chloramphenicol therapy, J.A.M.A. 173: 1731, 1960.
[10] Walker, G. F.: Blindness during streptomycin and chloramphenicol therapy, Brit. J. Ophth. 45: 555, 1961.
[11] Wilson, W.: Toxic ambylopia due to chloramphenicol, Scot, M. J. 7: 90, 1962.
[12] Denning, C. R., Bruce, G. M., and Spalter, H. F.: Optic neuritis in chloramphenicol treated patients with cystic fibrosis, Abst. No. 93, p. 103, Amer. Pediat. Soc., Seventy-third Ann. Meet., Swampscott, Mass., May 3–4, 1963.
[13] Huang, N. N., Promadhat, J., and Sproul, A.: Longterm therapy with chloramphenicol and optic neuritis in patients with cystic fibrosis, Abst. No. 162, p. 79, Third Interscience Conference on Antimocrobial Agents and Chemotherapy, 1963.
[14] Lietman, P. S., di Sant'Agnese, P. A., and Wong, V.: Optic neuritis in cystic fibrosis of the pancreas, J.A.M.A. 189: 924, 1964.
[15] Bruce, G. M., Denning, C. R., and Spalter, H. F.: Ocular findings in cystic fibrosis of the pancreas, Arch. Ophth. 63: 391, 1960.

[From J. Chron. Dis. 1964, vol. 17, pp. 899–914]

Fatal Aplastic Anemia

An Epidemiological Study of Its Relationship to the Drug Chloramphenicol

(By Kathryn M. Smick, M.D.,* Philip K. Condit, M.D.,† Rebecca L. Proctor, M.D.,‡ and Vernon Sutcher, M.A.§)

(The Division of Preventive Medical Services, California State Department of Public Health)

(Received 20 November 1963)

The purpose of this study was: (1) to determine the frequency of exposure to chloramphenicol, and also of exposure to other drugs and agents, in persons who died from aplastic anemia in the period January 1957 through June 1961 in California; (2) to determine the manner in which chloramphenicol was used both before and after the onset of aplastic anemia; and (3) to estimate the risk of fatal aplastic anemia in California among persons receiving chloramphenicol.

Causative Factors in Aplastic Anemia

A number of specific agents have long been known to cause aplastic anemia. Prominent among them are benzene from occupational exposure and gold and organic arsenical compounds used in medical treatment. Although exposure to benzene, gold and arsenical compounds has decreased, aplastic anemia has continued to occur. Consequently attention has focused on the role of other potentially toxic agents. These include ionizing radiation, non-medicinal chemicals, and drugs used in the practice of medicine.

The antibiotic chloramphenicol is the drug most commonly suspected in recent years of an etiological role in aplastic anemia. Incrimination of the drug as a toxic bone marrow depressant has been well documented since chloramphenicol

---

*Formerly Public Health Medical Officer, Bureau of Communicable Diseases, California State Department of Public Health. Now at the Contra Costa County Health Department, Martinez, California.
†Bureau Chief, California State Department of Public Health.
‡Public Health Medical Officer, California State Department of Public Health.
§Associate Public Health Statistician, Bureau of Communicable Diseases, California State Department of Public Health.

became commercially available in 1949.[1-5] In addition, since 1953, the Study Group on Blood Dyscrasias of the Council on Drugs of the American Medical Association has maintained a Blood Dyscrasia Registry and has published semi-annual compilations of voluntarily reported blood dyscrasias associated with drugs and chemical agents. During this period, chloramphenicol was the drug most often associated with pancytopenia. The three nation-wide surveys of the United States Food and Drug Administration between 1952 and 1957 also indicated that chloramphenicol had been used with greater frequency than any other drug in persons who subsequently developed aplastic anemia.[6-8]

In the early years of chloramphenicol use, the evidence of its toxicity was derived entirely from clinical case reports and from the frequency of its association with blood dyscrasias. In recent years, laboratory and clinical studies have contributed a variety of findings supporting the earlier indications of chloramphenicol toxicity for bone marrow.[9-14]

Animal experimentation to detect chloramphenicol toxicity has not been particularly rewarding. However, recent work suggests that chronic bone marrow toxicity can be produced in monkeys by feeding them with chloramphenicol.[15]

The physiological and biochemical mechanisms involved in toxic bone marrow suppression are not known. Also unknown is the relationship of mid reversible changes to the severe changes of aplastic anemia. *In vitro* studies with human bone marrow cultures hold promise of elucidating the nature of chloramphenicol's effect on bone marrow function. Already such studies have shown, by measuring Fe^{59} uptake and incorporation, that chloramphenicol causes a marked decrease in iron uptake by red blood cells thus directly interfering with heme synthesis.[16]

VITAL STATISTICS

Available morbidity data on aplastic anemia are derived from a variety of sources and are not necessarily representative of the occurrence of this disease in the general population. Representative statistical data concerning the occurrence and distribution of aplastic anemia are available only for fatal cases in which the cause of death was recorded as aplastic anemia on the death certificate. Table 1 indicates the numbers and rates of deaths from aplastic anemia in the United States, California and Canada. Approximately 60–80 persons die each year in California from aplastic anemia while about ten times as many die in the United States—that is, about five deaths from aplastic anemia per million population. Table 2 shows that in 1960 the risk of dying from aplastic anemia in California varied from about one person per million at ages 25–34 years to 27 persons per million at ages 65 years and over, with the years of childhood and youth involving greater risk than the years between ages 25–54 year.

---

[1] Development and purpose of registry on blood dyscrasias, *J. Amer. med. Ass.* 170, 1925, 1959.

[2] Dameshek, W.: Chloramphenicol—a new warning (Editorial), *J. Amer. med. Ass.* 174, 1853, 1960.

[3] Blood dyscrasias associated with chloramphenicol (chloromycetin) therapy, *J. Amer. med. Ass.* 172, 2044, 1960.

[4] Registry on Blood Dyscrasias: Report to Council, *J. Amer. med. Ass.* 179, 888, 1962.

[5] Ersley, A. J. and Winthrobe, M. M.: Detection and prevention of drug-induced blood dyscrasias, *J. Amer. med. Ass.* 181, 114, 1962.

[6] Lewis, C. N., Putnam, L. E., Henricks, F. D., Kerland, I. and Welch, H.: Chloramphenicol (chloromycetin) in relation to blood dyscrasias with observations on other drugs, *Antibiot. & Chemother.* 2, 601, 1952.

[7] Welch, H., Lewis, C. N. and Kerland, I.: Blood dyscrasias, a nationwide survey, *Antibiot. & Chemother.* 4, 609, 1954.

[8] Welch, H., Lewis, C. N., Weinstein, H. I. and Boeckman, B. B.: Severe reactions to antibiotics, *Antibiot. Med. clin. Ther.* 4, 800, 1957.

[9] Krakoff, I. H., Karnofsky, D. A. and Burchenal, J. H.: Effects of large doses of chloramphenicol on human subjects, *New Engl. J. Med.* 253, 7, 1955.

[10] Rubin, D., Weisberger, A. S. and Clar, D. R.: Early detection of drug-induced erythropoietic depression; *J. lab. clin. Med.* 56, 453, 1960.

[11] Rosenbach, L. M., Caviles, A. P. and Mitus, W. J.: Chloramphenicol toxicity: reversible vacuolization of erythroid cell, *New Engl. J. Med.* 263, 724, 1960.

[12] McCurdy, P. R.: Chloramphenicol bone marrow toxicity, *J. Amer. med. Ass.* 176, 588, 1961.

[13] Saidi, P., Wallerstein, R. O. and Aggeler, P. M.: Effects of chloramphenicol on erythropoiesis, *J. lab. clin. Med.* 57, 247, 1961.

[14] Gussoff, B. D., Lee, S. L., and Lichtman, H. C.: Erythropoietic changes during therapy with chloramphenicol, *Arch. intern. Med.* 109, 104, 1962.

[15] Hrenoff, A. K. and Anderson, H. H.: Chronic toxicity of chloramphenicol to bone marrow of macaques, *Med. Exp.* 4, 183, 1961.

[16] Vas, R., Bain, B. and Lowenstein, L.: Effect of chloramphenicol in human bone-marrow cultures, *Blood* 20, 424, 1962.

TABLE 1.—DEATHS FROM APLASTIC ANEMIA, CALIFORNIA, 1949-61, UNITED STATES, 1949-60 AND CANADA, 1950-60

Year	California		United States		Canada	
	Number	Rate	Number	Rate	Number	Rate
1949	63	5.9	638	4.3	(1)	(1)
1950	64	6.0	610	4.0	73	5.3
1951	61	5.5	671	4.4	73	5.2
1952	54	4.6	828	5.3	73	5.1
1953	70	5.8	774	4.9	66	4.5
1954	50	4.0	681	4.2	64	4.2
1955	53	4.1	633	3.9	55	3.5
1956	53	3.9	656	3.9	69	4.3
1957	59	4.2	669	3.9	64	3.9
1958	59	4.0	843	4.9	87	5.1
1959	61	4.0	[2] 921	5.2	91	5.2
1960	81	5.2	[3] 971	5.4	75	4.2
1961	86	5.2	(1)	(1)	(1)	(1)

[1] Not available.
[2] Includes Alaska.
[3] Includes Alaska and Hawaii.

Note: Rates are per 1,000,000 population.

Sources: National Office of Vital Statistics; Dominion of Canada, Bureau of Statistics; and State of California, Department of Public Health.

TABLE 2.—APLASTIC ANEMIA DEATH RATES BY AGE AND SEX, CALIFORNIA, 1960

	Total	Age groups						
		<15	15–24	25–34	35–44	45–54	55–64	>64
California population	15,717,000	4,764,000	2,080,000	2,130,000	2,278,000	1,793,000	1,296,000	1,376,000
All deaths	[1] 135,334	11,201	2,221	2,932	6,383	12,965	20,949	78,643
Aplastic anemia deaths	81	14	9	3	6	3	9	37
Male	36	4	5	1	2	0	4	20
Female	45	10	4	2	4	3	5	17
	Death rates per 1,000,000 population							
All deaths	8,610.7	2,351.2	1,067.8	1,376.5	2,802.0	7,230.8	16,164.4	57,153.3
Aplastic anemia deaths	5.2	2.9	4.3	1.4	2.6	1.7	6.9	26.9

[1] Includes 40 cases age not stated.

Source: State of California, Department of Public Health.

CORRELATION BETWEEN DEATHS AND SALES

If chloramphenicol is responsible for a substantial proportion of aplastic anemia deaths and the pattern of prescriptions is more or less constant over time then fluctuations in the number of deaths might be expected to correlate with fluctuations in the volume of sales of chloramphenicol. In connection with the present study, an effort was made to determine if there was a statistical association in time between the volume of chloramphenicol sales and the number of deaths from aplastic anemia. The mortality and sales data for California, the United States and Canada were charted on a population ratio basis as shown in Figs. 1–3.[17] Sales reached a peak in 1951, dropped off precipitously during the early 1950's and then increased again during the late 1950's. A time lag occurs between sales by the manufacturer and deaths from aplastic anemia because of the normal lapse of time until the drug is actually taken and aplastic anemia develops. To test the hypothesis that sales of chloramphenicol and deaths from aplastic anemia are associated, Kendall partial rank correlation coefficients (tau) were computed with the effect of population held constant.

[17] Manufacturer's sales data provided by Parke, Davis & Co.

Deaths were compared with sales in the same year, sales in the previous year and sales two years previously. Since precise significance levels for partial tau are not available, approximate significance values were obtained by using the tables for first-order tau. For California and the United States, all correlation coefficients were significant at <0.05. The relationship is strongest between deaths and sales of chloramphenicol two years previously for California and between deaths and sales in the previous year for the United States. The Canadian data show no relationship between sales and deaths. (It has been suggested that some of the drug sold in Canada may be re-sold to other countries. If true, this would mitigate any relationship to aplastic anemia deaths in the Canadian population). These partial correlations for the United States and California are consistent with the hypothesis that there is a casual relationship between chloramphenicol and aplastic anemia. The death certificate study here reported represents a further investigation of this hypothesis.

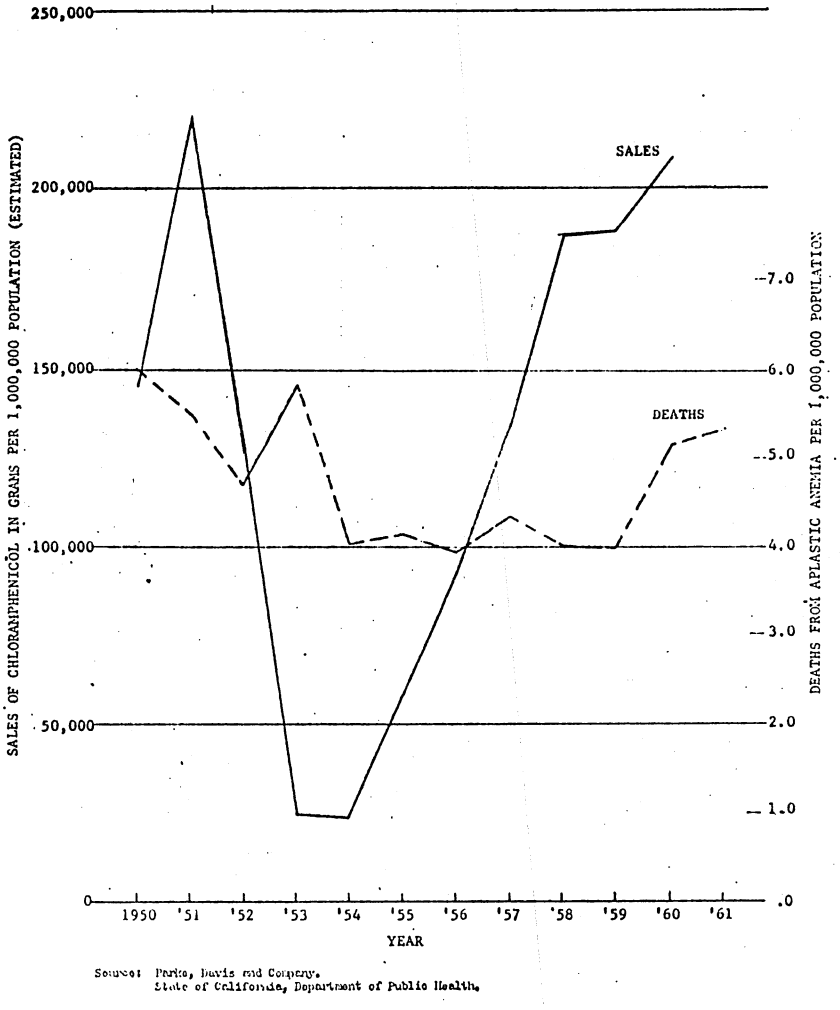


FIG. 1. Death rates for aplastic anemia and sales rates for chloramphenicol, California, 1950–1961.

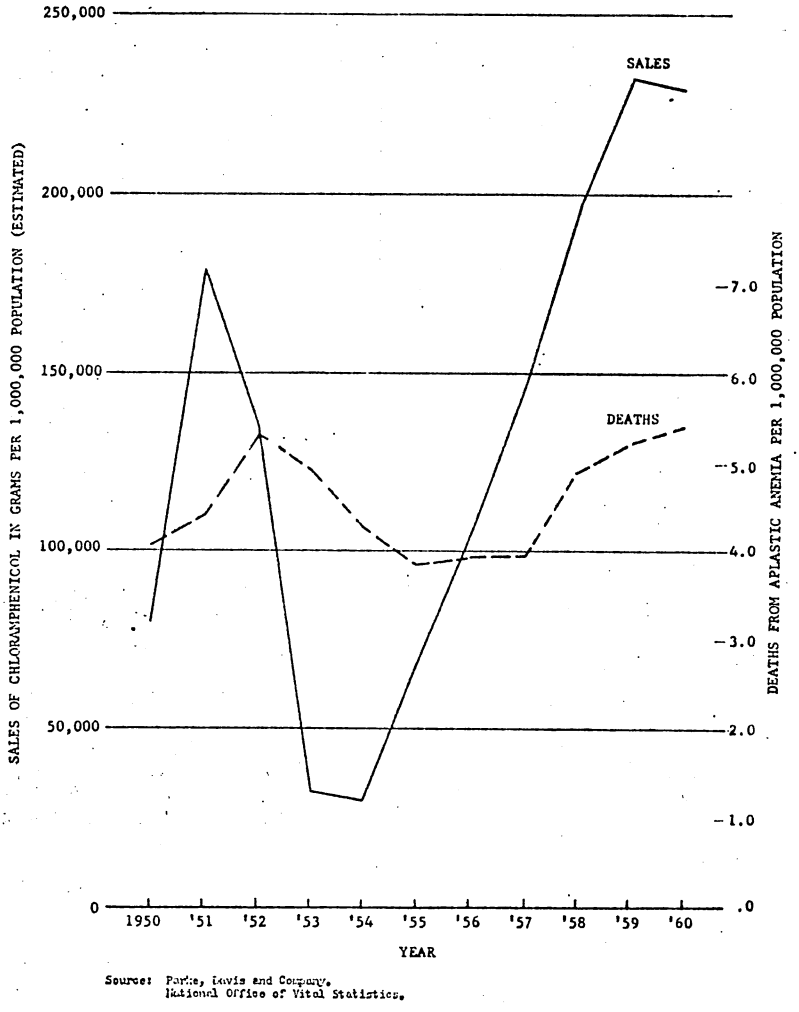


FIG. 2. Death rates for aplastic anemia and sales rates for chloramphenicol, United States, 1950–1960.

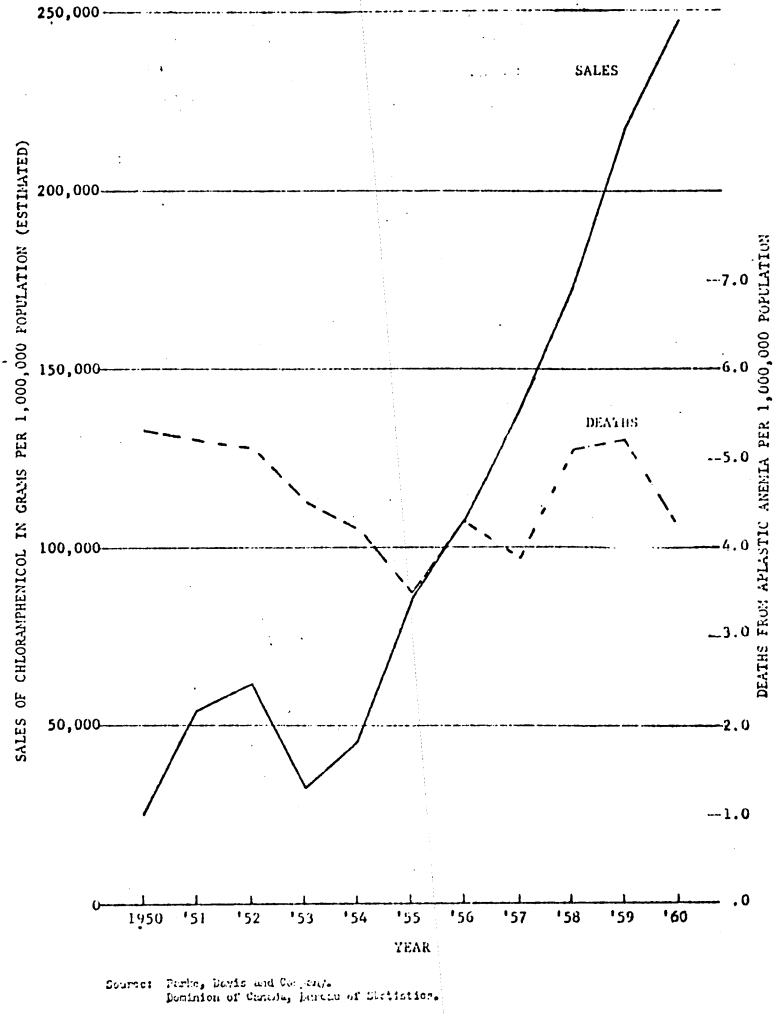


FIG. 3. Death rates for aplastic anemia and sales rates for chloramphenicol, Canada, 1950–1960.

METHODS OF STUDY

The study *population* consisted essentially of all reported deaths with aplastic anemia or pancytopenia recorded as the underlying cause (International Statistical Classification No. 292.4) in the study period January 1957–June 1961. Before drawing the study *sample*, the study population was adjusted by excluding 34 deaths which did not occur in hospitals; by excluding 6 deaths in which pancytopenia was obviously secondary to a condition other than primary aplastic anemia; and by adding 17 deaths actually due to aplastic anemia but incorrectly coded to some other classification. Deaths which did not occur in hospitals were excluded from the study primarily because laboratory evidence would not be available to confirm the diagnosis of aplastic anemia. Hence, the number in the study population (283) differs from the number of officially reported aplastic anemia deaths (306) for the 4½-year period. The study sample was randomly selected and consisted of one-third of all hospital aplastic anemia deaths in the 3½ years. January 1957 through June 1960, and all of the hospital aplastic anemia deaths in the second half of 1960 and the first half of 1961. Initially 149 deaths were included. Eleven deaths (nine leukemias and two myleomas) were then excluded leaving a final study sample of 138 deaths.

Hospital records were the sole source of study information in analyzing deaths from aplastic anemia. The following information was extracted from the hospital records: (1) date of clinical onset of blood dyscrasia defined as appearance of persistent or progressive symptoms of bleeding, weakness or infection or of laboratory findings suggestive of aplastic anemia; (2) laboratory findings with emphasis on blood and bone marrow; (3) autopsy findings; (4) other diseases past and present; (5) family history; (6) exposures to drugs, chemical agents, and ionizing radiation; and (7) various characteristics of the usage of chloramphenicol.

The medical information recorded on death certificates is subject to inaccuracies. The significance of the results in a study like the present one depends on accuracy of diagnosis in the study sample from the viewpoint of hematological disease. The medical record data were reviewed by the study staff to evaluate the diagnosis, particularly to separate those cases with medical record evidence supporting a diagnosis of aplastic anemia, from those cases with satisfactory evidence of a diagnosis of another blood dyscrasia, and from those cases lacking sufficient evidence for any definitive hematological diagnosis. These categories were designated as 'aplastic anemia,' 'other blood dyscrasias' and 'undiagnosed,' respectively. The criteria for designating a study death as aplastic anemia were: (1) bone marrow findings consistent with aplastic anemia; (2) pancytopenia of peripheral blood; and (3) absence of conditions of which aplastic anemia (pancytopenia) might be only symptomatic.

RESULTS

The criteria used resulted in dividing the 138 deaths into three categories: (i) 86 of these met the study criteria for 'aplastic anemia'; (ii) 25 had 'other blood dyscrasias'; and (iii) 27 were 'undiagnosed'. In all study deaths in all three categories there was evidence of a severe blood disorder. The 86 cases classified as 'aplastic anemia' showed pancytopenia and bone marrow findings consistent with aplastic anemia. In the second category—'other blood dyscrasias'—there was pancytopenia in only 9 cases while bone marrow findings supported a diagnosis other than aplastic anemia in more than half. Myeloproliferative and myelofibrotic disorders predominated. The quantity and quality of the diagnostic medical evidence in the first two categories were good. However, in the second category—'other blood dyscrasias'—the medical evidence did not lead the physician who certified the cause of death to the diagnosis which the study team considered a logical consequence of available data.

Age-sex ratio

The age-sex composition of the study sample varied remarkably with the three diagnostic categories. The 'aplastic anemia' category had an equal number of males and females and a high proportion (30 per cent) of deaths in persons under

15 years of age. The 'other blood dyscrasias' category was two-thirds male with no persons under 35 years. The 'undiagnosed' category was characterized chiefly by persons of advanced age.

Family history

Occurrence of a family history of blood dyscrasias in the study sample was of interest because of recent knowledge of drug-induced blood disorders related to a genetic deficiency of an enzyme in the red blood cells. Most hospital records contained no reference to blood dyscrasias in the family. Only nine indicated familial occurrence of such a blood disorder. Because of the few recorded familial cases and the variety and vagueness of the disorders described in other members of the families, it is impossible to relate family history findings to the study sample.

Related diseases

Certain disease conditions may have been related to the development of blood dyscrasias in the study sample. Viral diseases are thought to be capable of precipitating aplastic anemia in the weeks immediately following the acute episode. Collagen diseases may involve bone marrow as part of a systematic process. Impairment of liver or kidney function may interfere with detoxification and excetion of drugs or chemicals. These conditions occurred in the study sample, their frequencies varying with the diagnostic category. Prior to onset of symptoms of blood dyscrasias, viral infections as well as other infections occurred predominantly in the 'aplastic anemia' category. Nineteen out of a total of 24 persons with viral infections and 21 out of a total of 28 with other infections were in the 'aplastic anemia' category. Five of a total of six persons with collagen disease were in the 'aplastic anemia' category. Thirteen persons with renal disorders and a large number of persons with miscellaneous medical conditions were distributed throughout the three categories.

Viral infections less than one month before the onset of the blood dyscrasias were recorded for 10 persons, all in the 'aplastic anemia' category. All were children under 15 years of age except one person aged 21 years. Four had had rubeola, two of whom also had had frequent upper respiratory infections; the other six had had respiratory infections. Four, including the two with rubeola, had been treated with chloramphenicol, three with other antimicrobials but no record of chloramphenicol, and one with another drug not known to be toxic to blood. Blood counts before the onset of blood dyscrasias were available for only two of the ten persons. In one the blood was described as normal 5 days before the onset of bleeding. In the other there were peripheral blood changes consistent with viral infection. The above observations permit no conclusions as to the influence of viral disease on the subsequent development of aplastic anemia since many of these cases might have received chloramphenicol for the viral infection.

Exposure to toxic agents

Exposure was defined as contact with a drug or chemical agent by ingestion, injection, inhalation, or skin or mucous membrane contact in the 6 months preceding clinical onset of blood dyscrasia. It also included therapeutic application of ionizing radiation and, in the case of radioactive isotopes, diagnostic or therapeutic application at any time during the person's life. Data on diagnostic X-rays were omitted, not because they were considered insignificant but because the medical records did not provide this information.

The exposure data for the study sample of 138 deaths are summarized in Table 3. Eighty-eight persons were reported to have had exposure to a total of 118 different drugs plus a number of incompletely identified drugs, other chemical agents and radiation. Forty-six persons—one-third of the study sample—were exposed to agents known to be toxic to blood. Chloramphenicol accounted for the exposures of 30 persons, while 11 other agents accounted for exposures of the remaining 16. These 12 agents (listed on p. 908) are commonly or potentially toxic for blood cells and are designated as agents known to be toxic for blood in the remainder of this paper.

TABLE 3.—NUMBERS AND PERCENTAGES OF STUDY SAMPLE BY DIAGNOSTIC CATEGORY AND EXPOSURE TO DRUGS AND OTHER AGENTS

Exposure	Total	Diagnostic category		
		Aplastic anemia	Other blood dyscrasias	Undiagnosed
Total	138 (100.0)	86 (100.0)	25 (100.0)	27 (100.0)
Agents toxic to blood	46 (33.3)	32 (37.2)	5 (20.0)	9 (33.3)
Chloramphenicol	30 (65.2)	25 (29.1)	1 (4.0)	4 (14.8)
Other	16 (34.8)	7 (8.1)	4 (16.0)	5 (18.5)
Agents not known to be toxic to blood	25 (18.1)	17 (19.8)	4 (16.0)	4 (14.8)
Drugs not specified and chemical agents	17 (12.3)	13 (15.1)	2 (8.0)	2 (7.4)
No exposure	14 (10.1)	11 (12.8)	2 (8.0)	1 (3.7)
No information	36 (26.1)	13 (15.1)	12 (48.0)	11 (40.7)

Note: If a death is classified in more than one type of exposure, it is assigned to the one above.
Figures in parentheses are percentages.

4-Amino-pteroylglutamic acid
Chlorpromazine
Colchicine
Diphenylhydantoin
Gold preparations
Phenylbutazone
Chloramphenicol
Prochlorperazine
Quinacrine
Sulfonamides
Thiotepa
Ionizing radiation

Most cases had been exposed to more than one agent. However, seven drugs, at least three chemical agents and ionizing radiation constituted the single recorded exposure in a total of 18 study deaths.

Agents	*Death*	*Agents*	*Death*
Chloramphenicol	3	"Reducing pills"	1
Ionizing radiation	3	Penicillin	1
Meprobamate	2	Toluene	1
Phenylbutazone	1	Toxaphen insecticide spray	1
Digitoxin	1	Insecticide sprays with unknown ingredients	3
Protamin zinc insulin	1		

The exposure to digitoxin occurred in an elderly man who had anemia with renal disease and uremia, not aplastic anemia. It was not certain that the penicillin exposure actually antedated the onset of aplastic anemia. The toluene exposure was considered a likely but not certain event. The hospital records of many of the cases with a single recorded exposure offered no assurances that careful exposure histories had been taken.

Although the bone marrow depressant effects of ionizing radiation are well-known, most hospital records of study deaths contained no reference to radiation exposure. Seven persons were stated to have had such exposure, of whom six were women past middle age. Three of these had received pelvic X-ray therapy for non-malignant menopausal conditions 12–20 years before the onset of aplastic anemia. One had received 90 μC of radioactive iodine for diagnostic study 5–8 months before the onset of aplastic anemia and had also received chloramphenicol, meprobamate and other drugs. One had had 6000 μC of radioactive phosphorus for polycythemia vera 5 years before anemia. The sixth person had X-ray treatment for carcinoma 5 years before the onset of a myeloproliferative disorder. The record of the remaining person, an elderly man, indicated only that extensive diagnostic X-ray and isotope studies had been done. It is difficult to assess the significance of these exposures to radiation. They were not of such magnitude nor did the time relationship to the blood dyscrasias suggest that they were causal. On the other hand, knowledge of the long-term effects of such exposures is meagre and the possibility of causal relationship cannot be disregarded.

About 15 percent of the study sample (20 cases) had reported exposure to chemical agents other than drugs. Half of these exposures were to insecticides and

half to a variety of other chemical agents. Medical record information was often inadequate to identify the chemicals in the products to which exposure occurred. In four cases, the only recorded exposure was to insecticides.

The drugs associated with three or more deaths each are described graphically in Fig. 4 according to whether they were given alone, with other agents known to be toxic, or with other agents not known to be toxic to blood.

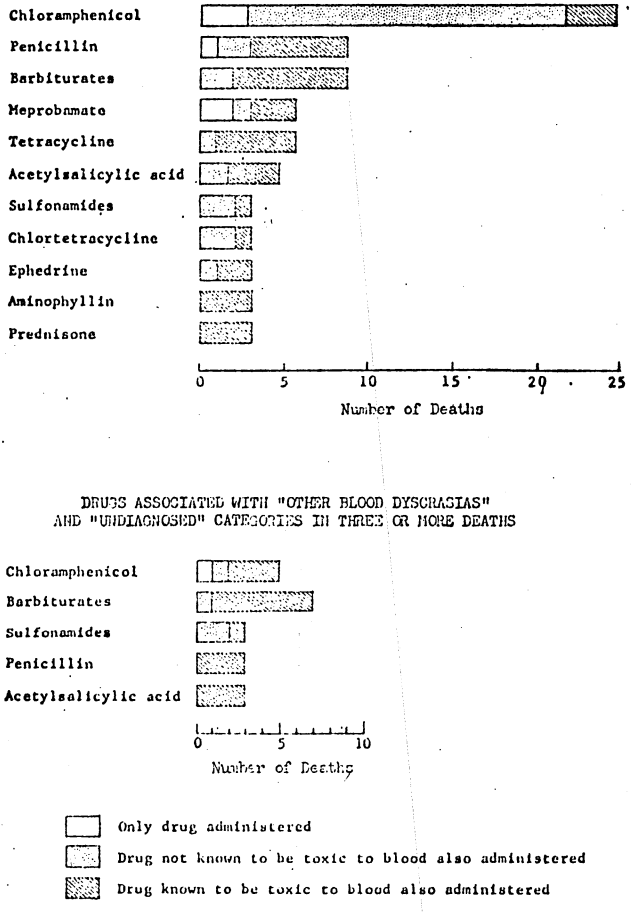


FIG. 4. Drugs associated with 'aplastic anemia' category in three or more deaths.

Exposure to chloramphenicol

Antimicrobial drugs were given to 42 persons most of who were in the 'aplastic anemia' study category. More persons (30) received chloramphenicol than received all other antimicrobial drugs combined (28). Half the persons who received chloramphenical had also received another antimicrobial drug, for the most part not known to be toxic to bone marrow.

Of the 30 chloramphenicol exposures, 25 occurred in the 'aplastic anemia' category. Their age distribution is shown in Table 4.

TABLE 4.—NUMBER AND PERCENTAGE OF STUDY DEATHS IN "APLASTIC ANEMIA" CATEGORY EXPOSED TO CHLORAMPHENICOL,[1] BY AGE GROUP

Age group, years	Aplastic anemia deaths	Exposure to chloramphenicol		
		Number	Percent of total deaths	Percent of exposure
All ages	86	25	29.1	100.0
<15	26	10	38.5	40.0
15–44	25	8	32.0	32.0
45–64	16	4	25.0	16.0
>64	19	3	15.8	12.0

[1] Within 6 months of clinical onset of aplastic anemia.

The following is a résumé of case history information for the 30 persons in the study sample reported to have received chloramphenicol.

"Ten individuals under age 15 years, two boys and eight girls, and all in the category 'aplastic anemia', received chloramphenicol. Nine had taken the drug for upper respiratory conditions (including the complications of otitis media, allergies, rubeola, and tonsillitis) and one for furuncles. Most of the children had taken the drug of three or more episodes of illness, and also received other antibiotics. The total dosage for all courses of treatment was estimated to be 1–15 g. The time interval between the last ingestion of chloramphenicol and the clinical onset of aplastic anemia was as follows: not stated in two; 2–3½ months in four, and in four others, previously treated with chloramphenicol, the symptoms of aplastic anemia occurred while taking the drug.

"Six individuals, aged 15–34 years, three males and three females, all in the 'aplastic anemia' category, received chloramphenicol. They were treated for urethritis (two), pharyngitis, a cold, pneumonia, and acne. Four had a single course of the drug with estimated dosage of 1–10 g; aplastic anemia followed in 1 week, 2 months, 3 months and 4 months. One had two courses with a total dosage of approximately 45 g, followed in one month by aplastic anemia. The remaining person had more than 50 g in small daily doses over a 5-month period terminating with onset of aplastic anemia.

"Three women, aged 35–54 years, had chloramphenicol. One, treated with several short courses of the drug for furuncles, had a diagnosis of anemia 6 months before treatment. The relationship of this anemia to the furuncles and to the manifestations of aplastic anemia 6 months after the furuncles is not clear. Two had chloramphenicol in the hospital following minor surgery 1 month and 6 months before onset of aplastic anemia.

"Six individuals, aged 55–74, two men and four women, were treated with chloramphenicol. Three had only one course of the drug in a period of 5–10 days followed in 1½, 2 and 3 months by aplastic anemia. The conditions treated were upper respiratory infection, virus pneumonia, and chest cold. Three persons had intermittent treatment over periods of 6–9 months with dosages estimated at 25–100 g. The conditions treated were chronic purulent bronchitis unresponsive to other drugs, chronic urinary tract infection in a person who had reacted adversely to other drugs, and chronic finger nail infection.

"Five individuals, aged 75 years and over, four men and one woman, received chloramphenicol for chronic respiratory symptoms, pneumonia, and urinary tract infections. In three cases dosage and dates were not stated. One man received a total of about 28 g over a 21-month period and had evidence of aplastic anemia 2 months after last treatment. Another received 22 g in two courses within a 2-week period and developed symptoms of aplastic anemia 2 months later."

The 30 study deaths with chloramphenicol exposure differed epidemiologically from the 108 study deaths without record of chloramphenicol.

1. The chloramphenicol-exposed group was younger than the remainder of the study sample. The average age for the 30 chloramphenicol-exposed deaths was 35.6 years and for the 108 not so exposed, 52.2 years.

2. The average time between clinical onset of blood dyscrasia and death was shorter among those exposed to chloramphenicol than among those not so exposed—an average of 3.1 months for those with chloramphenicol compared to 7.3 months for those without chloramphenicol.

3. There was a concentration of cases with clinical onset in the months of April and May among persons exposed to chloramphenicol (Fig. 5). This peak af-

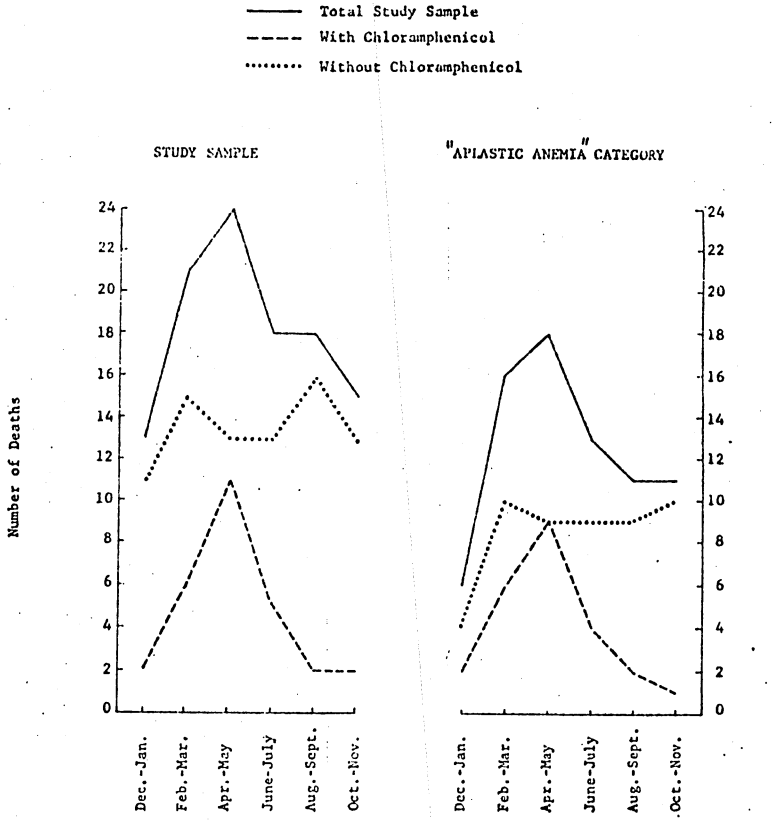


FIG. 5. Study sample and 'aplastic anemia' category with and without chloramphenicol by month of onset.

fected all ages but was more pronounced in the young. There was no such concentration by month of onset at any particular time of year among persons not exposed to chloramphenicol.

The above three findings suggest that cases of aplastic anemia associated with chloramphenicol constitute a rather distinct entity.

Characteristics of use of chloramphenicol

Before onset of blood dyscrasia.—The salient features of chloramphenicol usage among the group studied can be summarized as follows: The drug had been used for a variety of conditions ranging from acne to life-threatening staphylococcal pneumonia. It was most commonly employed for non-hospitalized patients, without prior bacteriological studies or drug sensitivity tests, and without blood studies. The only two persons reported to have had bacteriological identification of the causative organisms (*Staphylococcus*) also had sensitivity tests indicating sensitivity to other antimicrobial drugs as well as to chloramphenicol. As far as could be ascertained from hospital records only two of the 30 persons who received chloramphenicol had blood counts during treatment with the drug.

Of the 30 persons who received chloramphenicol during the six months before the onset of the blood dyscrasia, 12 received two or more courses. Another 12 received only one course of 10 days or less. The remaining six received chloramphenicol as follows: one continuously for 5–6 months, one intermittently for 6 months, one intermittently for 7–9 months, one intermittently for 8 months, one a "long course" and one an unknown amount of unknown duration.

After onset of blood dyscrasia.—The manner in which chloramphenicol was used in the study sample *after* onset of blood dyscrasia was also observed. In view of widespread medical information on the toxicity of chloramphenicol for bone marrow, it is of interest that 24 of the 138 study cases received treatment with chloramphenicol after the onset and diagnosis of blood dyscrasia. Twenty of these cases were in the "aplastic anemia" category, two in the "other blood dyscrasias" category, and two in the "undiagnosed" category. Recurrent life-threatening infections are a major problem in the treatment of aplastic anemia. The severity of the chloramphenicol-treated infections in the study sample is suggested by the fact that eight persons were infected by *Staphylococcus* and seven by *Pseudomonas*. It is clear that the medical basis for treatment of infections following onset of blood dyscrasias differed strikingly from that of infections preceding blood dyscrasias.

Eighteen of the 24 persons had bacteriological identification of the causative microorganism, and also had antibiotic sensitivity tests. In 10 the organism was sensitive to chloramphenicol and to one or more of the other commonly used antibiotics; in three the test results were not in the medical records. In no case was it stated that chloramphenicol was the only drug to which the organism was sensitive.

Half of the 24 patients treated with chloramphenicol during the course of their blood dyscraisia did not receive the drug until the last two weeks of life, several not until the last day of life. In some cases the risk of chloramphenicol to already severely depressed bone marrow was recognized by the physician and was considered to be less hazardous than treatment of the infection with a possibly less effective antibiotic. In those 12 cases treated with the drug only in the last two weeks of life, the prognoisis was grave in all cases. Those persons received it for only one day in 8 cases, for 2–3 days in 3 cases, and for 7 days in one case. Among the persons who received chloramphenicol earlier than 2 weeks before death two persons received three courses, in one case totalling 7 days and in the other 25 days. The person treated most extensively with chloramphenicol after onset of blood dyscrasia received four courses, two of 10 days each, one of 20 days and one of 4 weeks, beginning 22 months before his death. Since all of the study cases terminated fatally regardless of the nature of treatment, it is impossible to assess the effect of chloramphenicol on the course of the blood dyscrasia.

Only 3 of the 24 persons who received chloramphenicol after onset of a blood dyscrasia had also received it in the 6 months preceding onset of the blood dyscrasia. On additional two persons received it about 8 and 12 months before onset of blood dyscrasias.

Estimate of risk of chloramphenicol-associated fatal aplastic anemia

The number of deaths from aplastic anemia associated with chloramphenicol between 1957 and 1960 was estimated in the following way. The number of study cases in the first 3½ years was multiplied by three since a 1-in-3 random sample of all reported deaths were reviewed. Estimated aplastic anemia deaths for this period were 40, corrected for rounding in the sample. Since a 100 per cent sample of deaths was studied in the last half of 1960, the estimated number 4, is actually the sample value for that period. Thus, it is estimated that a total of at least 44 aplastic anemia deaths with recorded exposure to chloramphenicol occurred in the 4-year period 1957–1960. On the basis of sales data provided by the manufacturer and on the assumption that 4 g. of chloramphenicol was an average course of treatment, the number of persons in California receiving chloramphenicol in the study years was also estimated. The ratio of the estimated number of persons with aplastic anemia who had received chloramphencol to the number of persons receiving the drug in California indicates the risk of fatal aplastic anemia among persons treated with chloramphenicol to be 1:60,000. This estimate of risk is believed to be conservative for two reasons.

(1) The number of deaths from aplastic anemia associated with chloramphenicol is probably underestimated due to (a) exclusion of out of hospital deaths from the study; and (b) incompleteness of hospital records on prior drug administration.

(2) The number of persons in the general population receiving the drug is probably overestimated since (a) available sales figures are not restricted to chloramphenicol prescribed by physicians but also include drug use by veterinarians; and (b) the 4 g dosage used in these calculations is lower than the 10 g estimate generally believed to be the actual dosage administered.

COMMENTS

This study was carried out at the request of the California State Legislature because of concern with potential hazards to the public health from chloramphenicol and other antibiotic drugs. Prior to this study the evidence of an association between chloramphenicol and aplastic anemia consisted of clinical case reports, the Food and Drug Administration surveys, the American Medical Association's Blood Dyscrasia Registry, and pathological findings of suppression of bone marrow function by chloramphenicol. Concomitant with this study a statistical investigation was carried out; a significant statistical correlation was found between the volume of chloramphenicol sales and the number of reported aplastic anemia deaths. This study, based on a random sample of reported aplastic anemia deaths, showed a more frequent association with chloramphenicol than with any other drug or agent with a risk of aplastic anemia of at least 1:60,000 persons treated. No single piece of evidence establishes a definitive link between chloramphenicol and aplastic anemia. However, all findings point in the same direction and, combined, strongly suggest that chloramphenicol is causally related to aplastic anemia.

The study data reveal that during the time period covered by the study, in many instances chloramphenicol was used injudiciously for conditions in which another medication would have been equally effective. Chloramphenicol was rarely used according to the criteria recommended by the American Medical Association's Council on Drugs, the American Academy of Pediatrics, the Food and Drug Administration and many eminent medical authorities.

Since periodic blood counts can not be relied on to detect signs of bone marrow toxicity before irreversible aplastic anemia develops, then judicious use of the drug must be depended on to minimize the toxic effects. Judicious use prohibits it for prophylaxis, for trivial conditions, and for infections in which a less dangerous drug may be equally effective.

SUMMARY

A study of reported aplastic anemia deaths in California indicates that there were at least 30 cases with exposure to chloramphenicol among 138 deaths comprising a random sample of deaths attributed to aplastic anemia during 1957–1961. Exposure to chloramphenicol occurred with greater frequency than exposure to any other single agent. It is conservatively estimated that the risk of fatal aplastic anemia in persons receiving chloramphenicol is 1:60,000; probably the risk is much greater. Examination of the indications for use of chloramphenicol and the controls on its use, as reported in the hospital records of the persons who subsequently died of aplastic anemia, suggests that chloramphenicol was used often for minor conditions where its potential advantage over other means of treatment was dubious.

Acknowledgments.—Valuable assistance was provided by Lester Breslow, M.D., and William H. Clark, M.D., as consultants in epidemiology; William R. Gaffey, Ph.D., and Florence Morrison, M.A., as statistical consultants; and Ruth C. Steinkamp, M.D., as consultant in hematology.

[From Prescribers' Journal, 4:2, 1964, pp. 2–5]

CHLORAMPHENICOL

(By Maxwell M. Wintrobe, M.D., College of Medicine, University of Utah, Salt Lake City)

The Registry on Blood Dyscrasias of the American Medical Association began to collect reports of blood dyscrasias associated with consumption of drugs and exposure to various other potentially toxic agents in 1955. By June, 1963, a total of 1,484 reports had been received, chiefly from physicians in the United States. In addition, 550 reports had been gleaned from medical journals published outside the United States, thus providing a total of 2,034 reports. The total number of drugs and chemical substances mentioned in these reports was 463.

In considering the above data it must be recognized that (1) they probably represent only a small fraction of the blood dyscrasias which have occurred in association with exposure to various drugs and chemical substances. Reporting has been voluntary and has not depended even on a systemic or organized cam-

paign to encourage physicians to report to the Registry; and (2) not all instances of blood dyscrasia associated with the taking of some drug or other chemical agent necessarily represent true cause and effect relationships. In some instances the association may have been purely coincidental.

It is noteworthy, nevertheless, that of the above-mentioned 2,034 reports, 407 were associated with consumption of chloramphenicol. In 171 instances this was said to be the only drug to which the patient had been exposed. In an additional 33 cases, another drug had been taken which was not considered to be potentially harmful and in 133 cases the potential toxicity of the drugs taken in addition to chloramphenicol was uncertain. Only in 70 instances was the associated drug thought to be potentially toxic.

It can hardly be denied that data such as these make chloramphenicol suspect as a possible cause of blood dyscrasia. It is especially significant that of the 171 instances in which only chloramphenicol had been taken, the blood dyscrasia observed was aplastic anaemia, with pancytopenia, in 128; in an additional 18 cases there was erythroid hypoplasia without pancytopenia. Only in 7 cases was thrombocytopenia, without change in red or white cells noted, and only in 16 instances was leucopenia or agranulocytosis observed. This disproportionate incidence of aplastic anaemia is probably very significant.

Were these occurrences only a matter of coincidence, one would have expected that the number of cases in the various categories of reported dyscrasias associated with exposure to a single agent would have been similar to the incidence of various dyscrasias in the whole series. The data for the whole series of more than 2,000 reports are—

	Percent
Aplastic anaemia with pancytopenia	31.4
Thrombocytopenia	15.5
Leucopenia or agranulocytosis	38.1
Erythroid hypoplasia without pancytopenia	4.1
Haemolytic anaemia	5.8
Megaloblastic anaemia	2.5
Miscellaneous	2.6
Total	100.0

In contrast to these figures, it is to be noted that of the blood dyscrasias associated with chloramphenicol 74.9 per cent were reported as cases of aplastic anaemia with pancytopenia.

Aplastic anaemia is the most serious of the blood dyscrasias associated with drug therapy: the mortality rate is in excess of 50 per cent and, even when recovery does take place, it is only after months or years of serious illness.

Unfortunately, there are no adequate data by which one could estimate the likelihood of development of aplastic anaemia in association with exposure to chloramphenicol. However, even if the reports received represent only a very small fraction of the cases of aplastic anaemia which occur, in view of the wide use of this antibiotic the incidence must be assumed to be low. The mode of action of the drug in producing irreversible bone marrow injury also is unknown. A number of studies indicate that the administration of chloramphenicol in such doses that serum concentrations reach high levels is associated with (1) evidence of reduced utilization of iron for haemoglobin synthesis, as indicated by increase in serum iron and increased saturation of the iron-binding globulin; and (2) interference with the production or maturation of thhe erythroid cells, as indicated by vacuolation of erythroblasts, a progressive increase in the myeloid : erythroid ratio in the bone marrow, and reticulocytopenia. There is also some evidence that (3) modest reduction in the number of platelets; and (4) vacuolization of marrow granulocyte precursors and leucopenia may take place.

These changes, observed in human subjects, have been reversible. It remains to be determined whether the same or a different mechanism, perhaps one depending on a subtle congenital abnormality in the metabolic handling of chloramphenicol, is involved in the development of severe and irreversible aplastic anaemia. It is interesting that in a number of reported cases, bone narrow damage was observed after the second or third exposure to chloramphenicol, rather than following the first. No clear association with the amount of drug consumed has been observed. Paradoxically, in many instances of aplastic anaemia, the use of the drug could not have been justified on the basis of the recognized primary indications for the administration of chloramphenicol.

The lessons to be learned

The observations concerning chloramphenicol described above do not justify prohibition of the use of this valuable antibiotic. However, certain limitations are indicated. Similar limitations apply to therapeutics in general.

1. Many modern therapeutic agents are potentially very valuable—but they are also potentially harmful.
2. The indiscriminate use of a potentially toxic therapeutic agent in the absence of a clearcut indication is not justified.
3. A shotgun should not be used when a rifle would be better. An exact diagnosis permits the use of a specific agent instead of a "wide spectrum" therapeutic agent which the physician hopes will bring down the target he cannot see.
4. A cannon should not be used to kill a mouse. The risks involved in the use of a therapeutic agent should be weighed against the seriousness of the disease to be treated and the possibility of treating the condition with another agent which is less potentially toxic should be considered.
5. The physician must at all times be alert to the possible occurrence of an adverse reaction.
6. Specifically, with reference to chloramphenicol, it would seem wise to restrict the daily oral dose to approximately 30 mg. per kg. body weight and to limit the course of therapy to 14 days. It has been suggested, but not proved that, when higher doses must be used, or therapy must be prolonged or repeated, serum iron and iron-binding capacity and reticulocyte counts may be found to give warning of impending trouble.

[From the Journal of the American Medical Association, May 11, 1964, vol. 188, No. 6, pp. 531–532]

Drug-Induced Blood Dycrasias

I. Aplastic Anemia

(By Allan J. Erslev, M.D. Philadelphia*)

Aplastic anemia is a frequent manifestation of drug toxicity, and is characterized by pancytopenia and a fatty hypoplastic bone marrow.[1-3] It seems best to restrict the term aplastic anemia to conditions in which the red marrow has been largely replaced by fatty tissue, although normal or even hypercellular foci occasionally may be present.

A drug or chemical is believed to play an etiological role in about one half the cases reported. Chloramphenicol appears to be by far the most important offender,[4] but published case reports and those sent to the Registry on Blood Dyscrasias of the American Medical Association attest to the potential bone marrow toxicity of mephenytoin (Mesantoin), sulfonamides, phenylbutazone (Butazolidin), some insecticides and solvents, and many other compounds (Table). However, it is difficult to separate drug-induced from idiopathic cases, and unfortunately there is no test which provides proof of an etiological relationship. Therefore, conclusions must be drawn on the basis of personal judgment and statistics, particularly since everyone in our industrialized society is exposed to potentially toxic chemicals.

The characteristic signs and symptoms of severe pancytopenia are weakness and pallor, hemorrhage and ecchymoses, and a decreased resistance to infections. The demonstration of a pancytopenia in the absence of adenopathy, splenomegaly, bone tenderness, or evidence of an underlying disease strongly indicates a diagnosis of aplastic anemia. The crucial piece of evidence is the demonstration of a hypocellular fatty bone marrow. Bone marrow aspirations should be made

---

*Dr. Erslev is Cardeza Research Professor of Medicine, Jefferson Medical College.

[1] Huguley, C. M., Jr.: "Drug-Induced Blood Dyscracias," in *DM Disease-a-Month*, Chicago: Yearbook Medical Publishers, Inc., October, 1963.

[2] Scott, J. L.; Cartwright, G. E.; and Wintrobe, M. M.: Acquired Aplastic Anemia: Analysis of Thirty-Nine Cases and Review of Pertinent Literature, *Medicine (Balt)* 38: 119 (May) 1959.

[3] Harris, J. W.: *Red Cell: Production, Metabolism, Destruction, Normal and Abnormal*, Cambridge, Mass.: Harvard University Press, 1963.

[4] McCurdy, P. R.: Chloramphenicol Bone Marrow Toxicity, *JAMA* 176: 588 (May 20) 1961.

from several sites and these examinations should preferably be supplemented by a bone marrow biopsy.

The most important therapeutic measure is to suspect all drugs or chemicals in the patient's environment and, if possible, discontinue the exposure. Since recovery, whether spontaneous or in response to the removal of an etiological agent, is very slow, the goal of therapy is to prevent death from complications during the period of waiting. Transfusion should be given sparingly to maintain a hemoglobin level that is sufficient for reasonable activity. The prophylactic use of antibiotics is inadvisable, but the patient should be instructed to report promptly any symptoms or signs of infection. If infection develops, it should be treated quickly, vigorously, and persistently. Transfusion of fresh blood from donors with high leukocyte counts (chronic myeloid leukemia or myelofibrosis) has been claimed to be beneficial in severe infections.[5] Likewise, fresh blood from donors with high platelet counts (polycythemia vera) may be helpful in counteracting severe hemorrhagic episodes.[6] Testosterone[7] in pharmacological doses, prednisone, and splenectomy occasionally have appeared to induce permanent remissions.

DRUGS ASSOCIATED WITH APLASTIC ANEMIA

	All reports	Sole agent[1]
Total reports of aplastic anemia in Registry (through December 1963): 674.		
Chloramphenicol (Chloromycetin)	299	157
Sulfonamides (antibacterial):[2]		
Sulfamethoxypyridazine (Kynex Midicel)	12	3
Sulfisoxazole (Gantrisin)	28	3
Other	118	18
Sulfonamide derivatives (nonantibacterial):[2]		
Acetazolamide (Diamox)	10	3
Chlorothiazide (Diuril)	12	1
Chlorpropamide (Diabinese)	4	2
Tolbutamide (Orinase)	11	6
Analgesics: Phenylbutazone (Butazolidin)	34	16
Anticonvulsants:		
Mephenytoin (Mesantoin)	22	7
Trimethadione (Tridione)	5	2
Benzene	10	8
Other organic solvents	48	18
Insecticides:		
Benzene hexachloride (Lindane)	13	7
Chlorophenothane (DDT)	19	3
Chlordane	12	4
Gold	10	8

[1] Reports in which patient received listed drug either alone or with other presumably innocent drugs.
[2] Risk of aplastic anemia from most sulfonamide derivatives is slight, but as a group they are frequently associated with development of aplastic anemia.

Since the mortality rate, even in well-treated cases of aplastic anemia, is about 50%, the most appropriate approach is prevention. Aplastic anemia is obviously a rare complication and in a serious illness the usefulness of a potentially toxic drug may far outweigh its possible harm. However, the mere awareness that certain drugs are prone to produce aplastic anemia should lead to caution in their use and to the institution of hematological safeguards; although the pathogenesis is still unknown, it appears that in some cases the reaction is reversible before the self-perpetuating, almost irreversible aplastic phase sets in. Therefore, patients who require treatment with these drugs should have a white blood cell count and differential, an estimation of platelets, a reticulocyte count, and a hemoglobin determination at the onset of treatment and at reasonable intervals thereafter. The results of these tetsts should give warning of early bone marrow injury and, if heeded, may result in a decrease in the incidence of fatal drug-induced aplastic anemia.

[5] Freireich, E. J., et al.: Transfusion of Granulocytes From Donors With Chronic Myelocytic Leukemia to Leukopenic Recipients, abstracted, *J Clin Invest* 41: 1359 (June) 1962.
[6] Freireich, E. J., et al.: Response to Repeated Platelet Transfusion From Same Donor, *Ann Intern Med* 59: 277 (Sept.) 1963.
[7] Shahidi, N. T., and Diamond, L. K.: Testosterone-Induced Remission in Aplastic Anemia of Both Acquired and Congenital Types. Further Observations in 24 Cases, *New Eng J Med* 264: 953 (May 11) 1961.

GENERIC AND TRADE NAMES OF DRUGS

Chloramphenicol—*Chloromycetin.*
Phenylbutazone—*Butazolidin.*
Testosterone—*Androlin, Andronaq, Andrusol, Malestrone, Mertestate, Neo-Hombreol F, Oreton, Testrandrone, Testosteroid, Testrone, Testryl.*
Prednisone—*Paracortol, Sterane, Sterolone.*
Sulfamethoxyridazine—*Kynex, Midicel.*
Sulfisoxazole—*Gantrisin.*
Acetazolamide—*Diamox.*
Chlorothiazid—*Diuril.*
Chlorpropamide—*Diabinese.*
Tolbutamide—*Orinase.*
Trimethadione—*Tridione.*

[From Archives of Internal Medicine, November 1963, vol. 112, pp. 747–754]

CHLORAMPHENICOL TOXICITY IN LIVER AND RENAL DISEASE

(By Leif G. Suhrland, M.D., and Austin S. Weisberger, M.D., Cleveland*)

Erythropoietic depression can be detected in patients receiving chloramphenicol before any noticeable decrease occurs in peripheral blood values. Previous studies,[1,2] have shown that an increase in serum iron content and an increased saturation of iron-binding globulin precedes the fall in hematocrit by an appreciable interval in patients exhibiting toxic effects. These changes have been correlated with prolonged plasma clearance (T/2) of radioactive iron (Fe^{59}), delayed appearance of Fe^{59} in circulating erythrocytes, and decreased marrow uptake of Fe^{59} as detected by external scanning. Utilizing these techniques it has been shown that erythropoietic depression due to chloramphenicol is more frequent than in general realized. Early detection permits discontinuation of the drug before irreversible damage to the hematopoietic system occurs.

The mechanism by which chloramphenicol produces erythropoietic depression is unknown. There is evidence that the nitrobenzene moiety may be important since replacement of the nitro group by a methylmercapto, a methylsulfonyl, or a sulfamoyl group results in increased erythropoietic toxicity.[2-4] Other factors such as the amount and duration of therapy may be factors in producing toaxicity. Kunin, Glazko, and Finland[5] have shown that the half life of chloramphenicol metabolites is increased in severe renal disease and in some patients with hepatic cirrhosis. The possible relationship of these observations to hematologic toxicity was not, however, investigated.

The present study was undertaken to determine whether decreased excretion or impaired conjugation might be factors in producing erythropoietic depression. Accordingly, the incidence of erythropoietic depression was determined in patients with either renal or hepatic insufficiently and correlated with alterations in serum concentration of chloramphenicol metabolites. It was found that there was a marked increase in the incidence of erythropoietic depression in both liver and renal insufficiency and that there was a significant increase in serum concentration of free or active chloramphenicol in all patients developing hematologic toxicity.

MATERIALS AND METHODS

Sixteen patients with hepatic insufficiency due to Laennec's cirrhosis of the liver were studied. The diagnosis was established by clinical findings and confirmed by laboratory evidence of impaired liver function. The ages ranged from 30 to 64 years with a mean age of 42 years. There were six white males, one Negro male, six Negro females, and three white females. Of these 16 patients, two had ascites, three had jaundice, four had both ascites and jaundice, and seven patients had neither ascites nor jaundice.

Nineteen patients with chronic renal insufficiency were also chosen for study. All had hyposthenuria and blood urea nitrogen values of over 22 mg% but less than 70 mg%. All of the patients had chronic pyelonephritis associated with other

---

*Received for publication April 12, 1963; accepted May 10. Presented in part at 44th annual session of the American College of Physicians, April, 1963. Assistant Professor of Medicine (Dr. Suhrland); Professor of Medicine (Dr. Weisberger). From the departments of medicine of Highland View Hospital and the University Hospitals of Cleveland, and from the School of Medicine, Western Reserve University. Supported by USPHS grant He 03952–05.

NOTE.—Numbered footnotes at end of article, p. 2706.

diseases such as diabetes, hypertensive cardiovascular disease, obpstructive uropathy, or renal calculi, but none had any detectable liver disease. There were six white males, seven Negro males, four white females, and two Negro females in the group with ages ranging from 36 to 88 and a mean age of 56.

Sixteen patients without renal or hepatic insufficiency were selected to match as nearly as possible the two previous groups insofar as age and sex distribution and degree of anemia. Four patients had hemiplegia, two patients had amputation of the lower extremity secondary to arteriosclerosis obliterans, two patients had osteomyelitis, four had paraplegia due to trauma, two had quadriplegia secondary to compression fracture of cervical vertbra, two patients had brain tumors.

Chloramphenicol was administered orally in divided doses of 0.5 gm four times daily for a period of one month unless evidence of erythropoietic toxicity as previously defined was detected.[2] Before administering the drug, two initial blood samples were obtained on separate days for peripheral blood and iron studies. Thereafter, samples were drawn once weekly during the study period with patients in a fasting state between hours of 8 AM and 9 AM. Routine blood cell counts were performed at weekly intervals. Serum iron, iron-binding globulin (IBG) saturation, and plasma clearance of Fe^{59} (T/2) and its appearance in the erythrocyte were determined by methods previously described.[2,3] External scintillation counting was performed over the liver, spleen, and sacrum after Fe^{59} administration.

Bone marrow examinations were performed on all patients exhibiting toxic effects as determined by ferrokinetic data and on the majority of the patients included in the nontoxic group.

Assay for chloramphenicol and its metabolic products.—Free chloramphenicol and its chief metabolites were measured in the serum and urine of 45 of the 51 patients included in this report by the following modifications of the methods of Glazko et al [6] and Levine and Fischbach.[7]

Arylamine was determined by diazotization of 1.0 ml of an acid filtrate of serum (prepared by addition of three volumes of 4% trichloroacetic acid to one volume of serum) with 2.0 ml of 0.5% N HCl and 0.5 ml of 0.1% sodium nitrite. After five minutes, 0.5 ml of 0.5% ammonium sulfamate was added and allowed to stand for three minutes and coupled with 0.5 ml of 0.1% naphthylethylenediamine hydrochloride. After incubation at 37 C for three hours, the purple color change was read at 555 mμ and compared with standards (100 mg/liter chloramphenicol, treated as for serum) after correction for undiazotized blanks prepared by substituting water for sodium nitrite.

Total nitro compounds were determined by the above procedure after reduction of 1 ml acid filtrate with 1 ml titanous chloride (0.25% in 0.5 N HCl) for two minutes, followed by precipitation of the titanium by 0.5 ml of 1.4 N NaOH. Correction was made for the preformed arylamine measured above. This fraction consists chiefly of free chloramphenicol plus that conjugated as the glucuronide.

Extractable chloramphenicol, hereafter referred to as the "free" form and representing the microbiologically active form of the drug, was measured by applying the above procedure for total nitro compounds to an extract made by diluting 1 ml serum with 2 ml phosphate buffer (0.2 MpH 6.0), treating twice with 10 ml chloroform-ethyl acetate (3:1), backwashing the extracts with 10 ml of the same buffer, evaporation of the extracts on a water bath, and resolution in 1 ml 1% trichloroacetic acid.

Urine was assayed in the same manner as serum after a 20-fold dilution.

Criteria for erythropoietic depression.—Patients were classified as exhibiting either definite erythropoietic depression (toxic) or no significant depression (nontoxic) on the basis of ferrokinetic studies as well as on the basis of changes in the peripheral blood. A significant rise in serum iron, increase in iron-building globulin (IBG) saturation, prolongation of plasma clearance of Fe^{59}, delayed appearance of Fe^{59} in erythrocytes, and decreased marrow uptake of Fe^{59} were considered evidence of erythropoietic depression. The criteria for considering the changes in these parameters significant of toxicity were essentially the same as those described in a previous publication.[2] The ferrokinetic changes were correlated with a decrease in reticulocyte count and a subsequent fall in hemoglobin and hematocrit values. The appearance of vaculoated erythroblasts in the marrow was considered further evidence for toxicity but was not relied upon as the sole criterion.

RESULTS

Employing the criteria previously outlined, erythropoietic depression was demonstrated in eight of 16 patients (50%) with hepatic insufficiency and six of 19 patients (32%) with renal insufficiency (Table 1). No erythropoietic depression or toxicity was demonstrable in 16 patients without hepatic or renal insufficiency. In the patients with liver disease erythropoietic depression occurred in seven of nine patients (78%) with either ascites or jaundice and in all four patients with both ascites and jaundice (Table 2).

TABLE 1.—INCIDENCE OF ERYTHROPOIETIC DEPRESSION

Condition	Number	Number toxic	Percent toxic
No liver or renal disease	16	0	0
Renal disease	19	6	32
Liver disease	16	8	50

TABLE 2.—ERYTHROPOIETIC DEPRESSION IN LIVER DISEASE

Signs	Number	Number toxic
Ascites	2	1
Jaundice	3	2
Ascites and jaundice	4	4
No ascites or jaundice	7	1
Total	16	8

The duration of treatment of the patients showing toxic effects varied from 10 days to 28 days. In the majority of the patients chloramphenicol was discontinued after the second week of therapy with a mean time of 18 days for all patients showing toxic effects. Only one patient in this group received chloraphenicol for the full 28 days.

The changes in serum iron and per cent saturation of IBG are summarized in Table 3. The initial value represents the average of two determinations obtained on separate days. In both toxic groups there was a significant rise in serum iron accompanied by a marked increase in per cent saturation of IBG. This increase in per cent saturation of IBG in the toxic groups represented an absolute change of 64% over initial values. In the nontoxic groups with liver or renal disease slight increases in serum iron and per cent saturation of IBG were observed, but the mean changes in per cent saturation of IBG were less than 15% over initial values. Ferrokinetic studies with Fe^{59} demonstrated a prolonged plasma clearance time (T/2) and a delay in the appearance of the Fe^{59} in RBC in both toxic groups (Fig 1 and 2). After six days maximum amounts of radioactivity

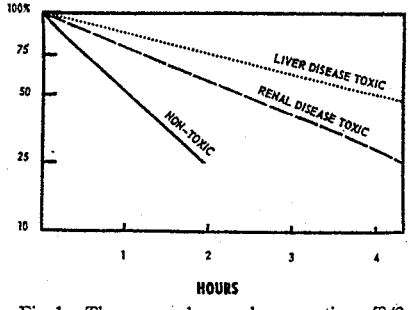


Fig 1.—The mean plasma clearance time, T/2. T/2 for nontoxic patients was 65 minutes; for renal disease with toxicity, 140 minutes, and for liver disease with toxicity over 240 minutes.

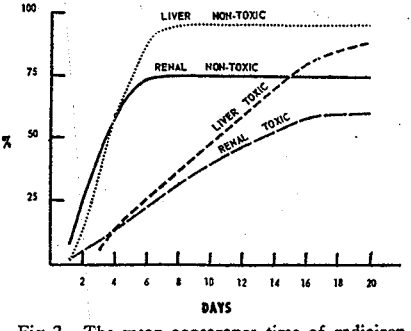


Fig 2.—The mean appearance time of radioiron in circulating RBC. Both the liver and renal nontoxic groups have normal appearance times with maximal amounts of Fe^{59} present after six-seven days. The delayed appearance of radioiron in the toxic groups is shown with maximal amounts of Fe^{59} not reached for 16-18 days.

appeared in the red cells in the nontoxic groups, but in the toxic groups maximum radioactivity did not appear until after 16 days.

TABLE 3.—SERUM IRON AND PERCENT SATURATION OF IBG [1]

	Number	Mean serum Fe (μg percent)		Mean IBG saturation, percent	
		Initial	Maximum	Initial	Maximum
Liver disease:					
Toxic group	8	78±45	286±74	27±13	91± 8
Nontoxic group	8	77±43	127±32	25±11	39±10
Renal disease:					
Toxic group	6	47±26	240±68	20±14	84±16
Nontoxic group	13	51±21	89±35	18± 9	30±11
No liver or renal disease: Nontoxic	16	97±45	131±54	30±13	39±19

[1] Iron-binding globulin.

Changes in peripheral blood values of the toxic and nontoxic groups are shown in Table 4. The toxic group in patients with liver disease had a mean fall in hematocrit of 8%, and the toxic group with renal disease showed a mean decrease of 5%. The hematocrit values of patients comprising the nontoxic groups did not change significantly. The reticulocyte counts of all groups decreased under treatment, but the magnitude of the fall in both toxic groups was greater than in the patients without erythropoietic depression. It should be noted that the mean control reticulocyte counts of patients with liver and renal disease were more than twice the value in patients without liver or renal disease.

TABLE 4.—PERIPHERAL BLOOD CHANGES IN CHLORAMPHENICOL TOXICITY

	Hematocrits		Reticulocyte counts	
	Control value	Lowest on drug	Control value	Lowest on drug
Liver disease:				
Toxic	35±5.8	27±5.7	1.7±0.4	0.4±0.2
Nontoxic	41±3.3	40±5.4	1.7±0.4	0.9±0.3
Renal disease:				
Toxic	38±6.8	33±8.6	2.1±0.3	0.6±0.2
Nontoxic	33±4.7	31±5.2	1.6±0.3	1.0±0.2
No liver or renal disease	43±4.0	41±3.8	0.8±0.3	0.9±0.3

The blood levels of "free" chloramphenicol, total nitro compounds, and arylamines were measured in all but one patient in each of the hepatic and renal insufficiency groups and in 12 of the 16 patients without renal or liver disease. The serum levels of "free" chloramphenicol are summarized in Table 5. In the groups of patients without renal or liver disease and showing no erythropoietic depression, serum "free" chloramphenicol ranged from 0 to 3.4μg/ml with a mean of 1.2μg/ml. In the patients with liver or renal disease but no erythropoietic depression, serum "free" chloramphenicol ranged from 2.0μg to 12.0μg/ml with a mean of 3.9μg/ml. In five patients with renal disease and erythropoietic depression, serum "free" chloramphenicol ranged from 15.0μg to 25.0μg/ml with a mean of 20.3μg/ml. Serum "free" chloramphenicol concentration in the eight patients with liver disease and toxicity were 8.0μg to 30.0μg/ml with a mean of 19.0μg/ml. Standard deviations are shown, and the differences in serum "free" chloramphenicol values between the groups without erythropoietic depression and the liver and renal disease groups showing erythropoietic toxicity are statistically significant with a P value of less than 0.005. No correlation could be drawn between hematologic toxicity and serum levels of total nitro compounds or arylamine (Fig 3, *a* and *b*).

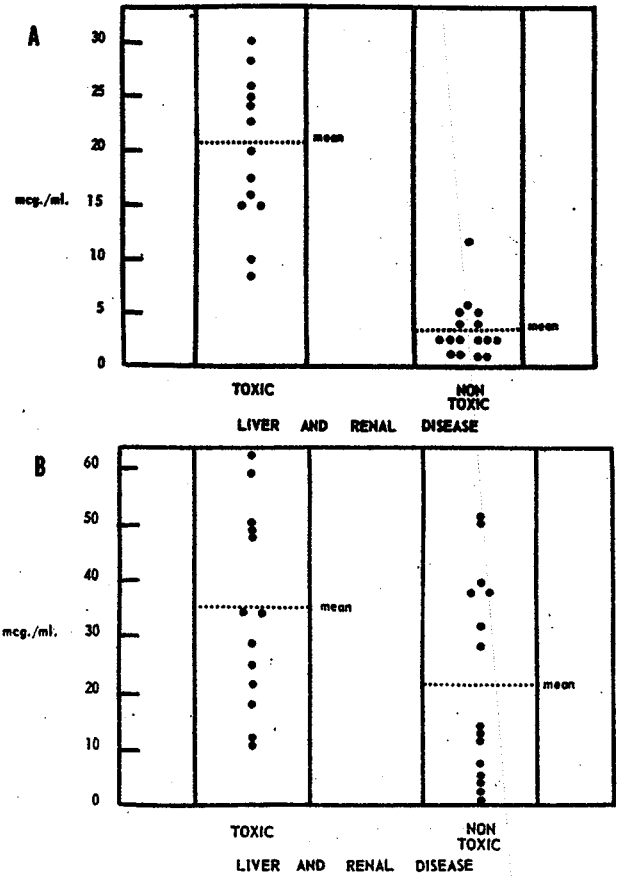


Fig 3.—*A*, Maximum serum levels of free chloramphenicol. Distribution of serum free chloramphenicol levels in liver and renal disease. Only one patient in the nontoxic group has a serum level of over 5μg/ml. *B*, Maximum serum levels of total nitro compounds. Lack of correlation between total nitro compounds and toxicity. The slightly higher mean value in the toxic group is due to elevated levels of free chloramphenicol.

TABLE 5.—SERUM LEVELS OF "FREE" CHLORAMPHENICOL

Patients	Range, serum level μg/Ml	Mean, μ/Ml	SD
No liver or renal disease: Nontoxic	0–3.4	1.2	±0.7
Renal and liver disease: Nontoxic	2.0–12.0	3.9	±2.4
Renal disease: Toxic	15.0–25.0	20.3	±4.8
Liver disease: Toxic	8.0–30.0	19.0	±7.7

Between nontoxic and toxic groups $P<0.005$.

The correlation between the rise in serum level of "free" chlorampenicol and the rise in serum iron in one patient with liver disease is shown in Fig. 4. Chloramphenicol in a daily dose of 2.0 gm was administered for 14 days and produced a continual rise in serum "free' chloramphenicol to 30.4μg/ml. Paralleling this increase in "free" chloramphenicol the serum iron rose from 38μg% to a high of 332μg%. During this period the hematocrit did not change appreciably and fell to significant levels only after the drug had been discontinued. Also after cessation of chloramphenicol administration, the serum iron propmptly returned to pretreatment levels. The reticulocyte count, not shown, fell to a low of 0.2% on day 15 but rose to 7.0% six days after chloramphenicol was discontinued.

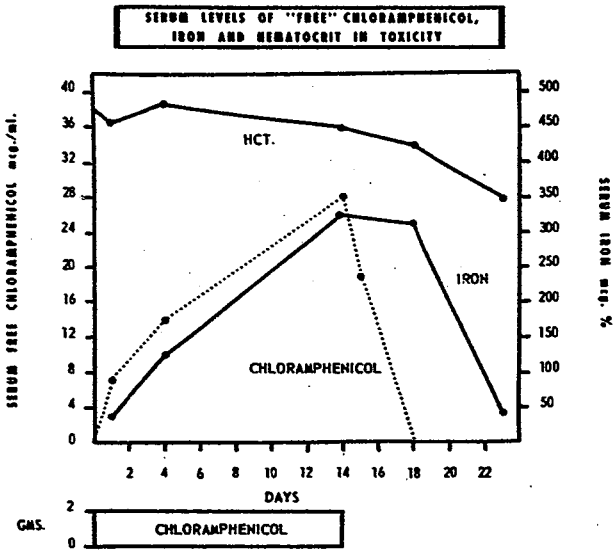


Fig 4.—In a patient with liver disease and toxicity, the relationship between increase in serum iron and free chloramphenicol is demonstrated. The hematocrit did not change significantly until one week after the drug had been discontinued.

COMMENT

The data demonstrate that an increased incidence of erythropoietic depression due to chloramphenicol occurs in patients with hepatic or renal insufficiency. In patients with liver disease the toxicity appears to be correlated with the degree of hepatic damage. Thus, a much higher frequency of toxicity was observed in patients with either jaundice or ascites than in those without these complications. Furthermore, erythropoietic depression occurred in all patients with both jaundice and ascites. No direct correlation was observed between the degree of nitrogen retention and incidence of erythropoietic depression. It should be noted that administration of chloramphenicol was discontinued as soon as a significant rise in serum iron level was observed and before any evidence of erythropoietic depression could be detected in the peripheral blood. Accordingly, one might anticipate a greater degree of toxicity in these patients if administration of chloramphenicol had been continued for a longer period of time. In addition, the amount of drug administered per patient represents a comparatively low dosage schedule. If larger amounts of chloramphenicol had been used, a much higher incidence of toxicity could have been anticipated.

Drug hypersensitivity did not seem to be a factor since previous exposure to the drug had no relationship to the development of toxicity. Furthermore, three patients who had recovered from erythropoietic depression were treated with small daily doses of 250 mg for 28 days. There was no evidence of toxicity in this group.

It is apparent that the toxicity of the free drug and its metabolic products differ. Thus, there was a lack of correlation between arylamine, the monoglucuronide metabolites, and erythropoietic depression. In every instance erythropoietic depression was correlated with a high free chloramphenicol serum level. This suggests that those who developed toxic effects were either unable to conjugate at a normal rate or unable to excrete the free form of the drug.

McCurdy has obtained similar results on the correlation between bone marrow depression and elevated levels of free chloramphenicol in serum or plasma.[8] In this report toxicity was defined by reticulocytopenia and abnormal vacuolated blast cells in the bone marrow. The elevated mean plasma level of free chloramphenicol found six-eight hours after a dose of the drug was quite similar to our mean values in spite of different dosage schedules and routes of administration. The metabolites were not measured. It should be emphasized that the blood samples in the present report were drawn 10–12 hours following the last dose of

the drug with the patients in a fasting state. This tended to minimize fluctuation in serum iron due to diurnal variation and changes in chloramphenicol blood levels due to difference in rate of absorption from the gastrointestinal tract.

The reason for the correlation of erythropoietic depression with high free chloramphenicol levels is not known. Studies on the mechanism of chloramphenicol toxicity in vitro have, in general, revealed no effect on immature erythrocytes or bone marrow function unless levels far exceed those found in the blood when therapeutic doses of the drug are employed.[9,10] The amount of chloramphenicol required to produce in vitro depression far exceeds the levels observed in this study. Although protein synthesis by bacterial ribosomes in cell-free systems is readily inhibited by chloramphenicol, mammalian ribosomes are not affected by remarkably high concentrations of chloramphenicol.[11,12] This biological difference makes it possible to use chloramphenicol advantageously in the treatment of bacterial infections. However, chloramphenicol probably does have some effect on hemoglobin synthesis since the drug blocks the reticulocyte response in patients with pernicious anemia receiving cyanocobalamin (vitamin B_{12}) and also prevents the reticulocyte response to iron in patients with iron deficiency anemia.[13] Since patients with liver disease and renal disease are known to have a shortened erythrocyte life-span and an inadequate marrow compensatory activity, chloramphenicol might be expected to induce anemia with greater frequency in these patients. However, bone marrow function as reflected by peripheral blood values did not appear to be a factor in the development of toxic effects.

The manner in which chloramphenicol affects hemoglobin synthesis in immature cells is not known. Preliminary experiments indicate that chloramphenicol may interfere with the deposition of messenger ribonucleoprotein on the ribosomes of mammalian reticulocytes.[14] Whether these observations are related to the profound changes that occur in iron metabolism is still speculative. Nevertheless, the serum iron is a sensitive index of early toxic effects and often begins to rise three-four days after beginning treatment. Similarly when the drug is stopped, the serum iron promptly returns to pretreatment levels. These changes in serum iron and per cent saturation of IBG are consistent and may represent a specific biochemical lesion produced by the drug. The majority of the patients who did not develop toxic effects did show slight elevation in serum iron during treatment, but these were not sufficient to be interpreted as being significant of toxicity. In addition, other bone marrow depressants such as radiation, alkylating agents, and antimetabolites do not produce a consistent elevation of serum iron and per cent saturation of IBG.

The relationship of erythropoietic depression to aplastic or hypoplastic states associated with chloramphenicol remains unknown. However, it is reasonable to assume that the erythropoietic depression observed in this study represents a reversible stage in the development of aplastic anemia that is usually irreversible. Therefore, in severe renal or liver disease chloramphenicol should be used with caution and followed carefully with frequent serum iron and reticulocyte counts. If possible, determination of free chloramphenicol in the serum would be an additional safeguard. In liver disease the presence of both ascites and jaundice or other evidence of severe parenchymal damage constitutes a contraindication to the use of this drug.

SUMMARY

In 16 patients with liver disease treated with chloramphenicol eight developed erythropoietic depression. In this group with liver disease, the frequency of toxic effects was markedly increased in the presence of both ascites and jaundice. In 19 patients with moderately severe renal disease six showed signs of toxic effects. A group of 16 patients without renal or liver disease showed no evidence of bone marrow toxic effects.

An elevated level of serum free chloramphenicol was found in all instances of erythropoietic depression. There was no correlation between the metaoblic products of chloramphenicol and toxicity. Drug hypersensitivity did not appear to a factor in the development of erythropoietic depression.

Mrs. Janet Bullinger provided technical assistance, and Dr. Robert Greenway aided in serum iron and chloramphenicol determination.

Leif G. Suhrland, M.D., Highland View Hospital, 3901 Ireland Dr., Cleveland 22, Ohio.

REFERENCES

[1] Rubin, D.; Weisberger, A. S.; Botti, R. E.; and Storaasli, J. P.: Changes in Iron Metabolism in Early Chloramphenicol Toxicity, J Clin Invest 37: 1286, 1958.
[2] Rubin, D.; Weisberger, A. S.; and Clark, D. R.: Early Detection of Drug Induced Erythropoietic Depression, J Lab Clin Med 56: 453, 1960.
[3] Suhrland, L. G., and Weisberger, A. S.: Hematologic Toxicity of a Chloramphenicol Analogue, Amer J Med Sci 244: 54, 1962.
[4] Jiji, R. M.; Gangarosa, E. J.; and de la Macorra, F.: Chloramphenicol and Its Sulfamoyl Analogue, Arch Intern Med 111: 70, 1963.
[5] Kunin, C.; Glazko, A. J.; and Finland, M.: Persistence of Antibiotics in Blood of Patients With Acute Renal Failure: II. Chloramphenicol and Its Metabolic Products in the Blood of Patients With Severe Renal Disease or Hepatic Cirrhosis, J Clin Invest 38: 1498, 1959.
[6] Glazko, A. J.; Wolf, L. M.; and Dill, W. A.: Biochemical Studies on Chloramphenicol: I. Colorimetric Methods for the Determination of Chloramphenicol and Related Nitro Compounds, Arch Biochem 23: 411, 1949.
[7] Levine, J., and Fischbach, H.: The Chemical Determination of Chloramphenicol in Biological Materials, Antibiot Chemother (NY) 1: 59, 1951.
[8] McCurdy, P.: Plasma Concentration of Chloramphenicol and Bone Marrow Suppression, Blood 21: 363, 1963.
[9] Yunis, A. A., and Harrington, W. J.: Patterns of Inhibition by Chloramphenicol of Nucleic Acid Synthesis in Human Bone Marrow and Leukemic Cells, J Lab Clin Med 56: 831, 1960.
[10] Borsook, H.; Fischer, E. H.; and Keighley, G.: Factors Affecting Protein Synthesis in Vitro in Rabbit Reticulocytes, J Biol Chem 229: 1059, 1957.
[11] Allen, E. H., and Schweet, R. S.: Synthesis of Hemoglobin in a Cell-Free System: I. Properties of the Complete System, J Biol Chem 237: 760, 1962.
[12] Von Ehrenstein, G., and Lipmann, F.: Experiments on Hemoglobin Biosynthesis, Proc Nat Acad Sci 47: 941, 1961.
[13] Saidi, P.; Wallerstein, R. O.; and Aggeler, P. M.: Effect of Chloramphenicol on Erythropoiesis, J Lab Clin Med 57: 247, 1961.
[14] Weisberger, A. S., and Wolf, S.: Unpublished observations.

[From the Journal of the American Medical Association, July 27, 1963, vol. 185, No. 4, pp. 273–279]

THE USE AND ABUSE OF THE BROAD SPECTRUM ANTIBIOTIC

(By Edwin M. Ory, M.D., and Ellard M. Yow, M.D., Houston)

(From the Department of Medicine, Baylor University College of Medicine, and the Ben Taub Infectious Disease Research Laboratory, Jefferson Hospital)

The term "broad spectrum antibiotics" was originally used to designate antibiotics that were effective against both gram-positive and gram-negative bacteria, in contrast to penicillin, which is effective chiefly against gram-positive organisms, and streptomycin, which is active primarily against gram-negative bacteria. The broad spectrum antibiotics have an antimicrobial spectrum which includes some gram-positive and some gram-negative organisms, as well as certain rickettsiae, larger viruses, protozoa, and pleuropneumonia-like organisms. Although the antimicrobial spectra of other antibiotics vary in their breadth of coverage, this article will be limited to a discussion of the tetracyclines and chloramphenicol.

The Tetracyclines

There are four basic tetracyline homologues. The first two were prepared entirely by fermentation methods. Chlortetracycline hydrochloride was isolated from *Streptomyces aureofaciens* by Duggar [1] in 1948 and oxytetracycline, produced by *S rimosus*, was introduced in 1950. Tetracycline was prepared by catalytic hydrogenation of the chlorine radical and introduced for clinical use in 1953. Demethylchlortetracycline, produced by a mutant of Duggar's original strain, was described in 1957 [2] and was introduced for clinical use in 1959.[3-6] Many other homologues of the tetracyclines have been produced and some are under investigation.[7] However, none of these is available yet for clincial use.

Various additives and combinations have been developed and marketed. It is claimed that they increase absorption, reduce gastrointestinal irritation, prevent overgrowth of *Candida* (*Monilia*) and other fungi, and are synergistically active against bacteria. In general, such effects are either minor or negligible and have been exaggerated in the promotion of the various preparations.[8] Fixed combinations of tetracyclines with other antibiotics rarely offer a therapeutic advantage, for the second antibiotic in such combinations is usually present in smaller

---

NOTE.—Numbered footnotes at end of article, p. 2714.

than therapeutically effective quantities and there are no known specific indications for fixed combinations of antibiotics. In addition, the incidence of side effects and the expense to the patient is sometimes increased when mixtures are used.

In general, all of the tetracyclines have the same antibacterial spectrum when each tetracycline is tested against individual strains of organisms. In most instances, when an organism is resistant to one tetracycline it will be resistant to the other homologues.[9]

Pharmacology

The tetracyclines are incompletely absorbed from the gastrointestinal tract[8] and large amounts can be recovered from the stools after oral administration.[10] This property may contribute to the changes in fecal flora and anal irritation. Absorption is probably increased and higher blood levels are attained if the antibiotic is taken during the fasting state. On the other hand, some patients have less gastric irritation if the drug is taken after a meal.

The tetracyclines are inactivated by the formation of chelates when they combine with metallic ions, chiefly calcium and magnesium, in the gastrointestinal tract. Because of this property, various preparations, including combinations with citric acid, a phosphate complex, sodium hexaphosphate, and glucosaminic hydrochloride, have been developed. However, no significant therapeutic superiority has been demonstrated by the use of these combinations. Aluminum hydroxide markedly reduces absorption.[8, 11-13]

The tetracyclines are absorbed by the stomach, duodenum, and ileum, but very little is absorbed by the colon. The distribution of the tetracyclines in body tissues and fluids varies slightly with each homologue.[11, 12] The drugs are present in the milk of lactating women and pass through the placenta into the fetus; they also appear in the salvia, cornea, sclera, iris, and vitreous humor. Levels are lower in spinal fluid than in blood. The highest spinal fluid levels are obtained with tetracycline, the lowest with chlortetracycline, and intermediate levels occur with oxytetracycline. The concentrations of chlortetracycline in the bile are 8 to 16 times higher than those in the blood. Demethylchlortetracycline is also concentrated in the liver and bile.[13] The drugs have an affinity for fast-growing tissues, liver, tumors, and areas of new bone formation. This property has recently been utilized in the development of a test for gastric carcinoma.[14] Prolonged administration of the tetracyclines may produce a yellowish discoloration of the teeth.[15] Tetracycline has been found to diffuse into ischemic tissues in measurable amounts.[4 16 17]

The tetracyclines are bound to plasma protein in varying amounts. However, the binding is reversible and may be one of the most important factors responsible for the differences in renal clearance rate among the various tetracyclines.

The principal mechanism of excretion is by the kidneys, probably by simple glomerular filtration. Kunin and associates[18] have studied the excretion rates of the various homologues under various conditions of pH, urine flow, and renal function. They have shown that the half-life of tetracycline plasma levels is prolonged and is increased in the presence of oliguria and renal failure. The half-life may increase from a normal value of 8 hours up to 108 hours in patients with renal failure. Chlortetracycline is an exception; since it is rapidly inactivated in alkaline solutions at body temperature, its half-life is not significantly increased in the presence of renal failure.[4]

Adequate blood levels are obtained when tetracycline, oxytetracycline, and chlortetracycline are administered in doses of 250 to 500 mg four times daily. Demethylchlortetracycline produces somewhat higher and more prolonged blood levels because of its slower renal excretion and greater stability. Therefore, adequate blood levels are obtained when 150 mg is given 4 times daily.[3]

ANTIMICROBIAL SPECTRUM

The tetracyclines inhibit a broad range of microbial agents, including both gram-positive and gram-negative bacteria. *Mycobacterium tuberculosis*, rickettsial the psittacosis-lymphogranuloma venereum group of large viruses, and the agent of primary atypical pneumonia (Eaton agent).[19] The latter is now known to be a pleuropneumonia-like organism. The most sensitive organisms in the gram-positive group include the pneumococcus, *Streptococcus viridans*, some strains of staphylococci, and most strains of group A beta hemolytic streptococci.[20]

Sensitive gram-negative organisms include most strains of *Escherichia coli*, the meningococcus, gonococcus, *Hemophilus influenzae*, and *Pasteurella*, *Brucella*, and *Shigella* strains, *Aerobacter* and *Proteus* species vary considerably in their sensitivity to the tetracyclines. Some strains of *Pseudomonas aeruginosa* and *Bacteroides* have been found to be sensitive to the tetracyclines.

The tetracyclines are generally considered to be bacteriostatic agents; they suppress the multiplication of organisms and depend on the host defense mechanisms to eradicate the remaining organisms. When the host defenses are good, excellent therapeutic results will be obtained in certain infections, such as uncomplicated pneumococcal pneumonia, tularemia,[21] and certain gram-negative bacillary urinary tract infections. On the other hand, superior results are obtained when a bactericidal agent such as penicillin is used in eradicating group A beta hemolytic streptococci from the pharynx; penicillin is also more effective in pneumococcal meningitis in which phagocytosis may be less efficient than in the lung and in which the cerebrospinal fluid concentrations are obtained more consistently with penecillin than with the tetracyclines.

Certain organisms develop resistance to tetracyclines more readily than others. Some gram-negative bacilli, such as *E coli* and *Aerobacter* and *Proteus* organisms. readily become resistant. Staphylococci also develops resistance to this group of drugs.[22] Pneumococci have not been observed to develop resistance. In one study, in which 218 strains of group A beta hemolytic staphylococci were tested, 42 strains (or 20%) were found to be resistant to tetracycline and demethylchlortetracycline.[23] It is difficult to tell whether resistance develops by means of mutation and selection in those organisms that were previously sensitive, or whether superimposed infections with organisms of established resistance occur after the strains have been eradicated. Probably both mechanisms occur under certain circumstances.

Adverse effects and toxicity

The tetracyclines are relatively safe antibiotics when given in moderate dosage and when the course of therapy is not prolonged. Even when therapy has been given over a long period of time, such as in chronic bronchitis, the adverse effects have been few if the patient was otherwise in good general health.

The most frequent untoward effects have been nausea, vomiting, and diarrhea. These effects can be minimized if the lowest effective dose is given after meals. The symptoms usually subside when the drug is discontinued.

Superimposed infection with other resistant organisms, particularly with *Staph aureus* and strains of *Pseudomonas*, *Proteus*, and other gram-negative organisms, has been the most serious hazard to patients receiving prolonged or large doses of the tetracyclines. This is particularly true in patients who are hospitalized with chronic debilitating illnesses, such as chronic pulmonary disease and neoplastic disease, in patients who are being treated with corticosteroids, or in those who are receiving radiation or antitumor therapy. This complication, however, is not limited to tetracycline therapy. These patients may develop superimposed infections regardless of therapy, and it is difficult to assess the role of tetracycline drugs in producing such effects.

Drug fever and rashes have been observed infrequently. Local application is more likely to be associated with dermatitis, but this form of therapy is rarely indicated. Photosensitivity, manifested by marked sunburn after exposure to direct sunlight, has developed during therapy with demethylchlotetracycline. This reaction apparently occurs more frequently and is more severe in southern areas where the sunlight is more intense.

Blood dyscrasias have been observed in patients who have received tetracycline therapy, but causal relationship has not yet been definitely established. Patients who develop agranulocytosis and pancytopenia while receiving tetracyclines have recovered without discontinuation of the therapy.

Other less well-known adverse effects have been described and are of interest, although they are rarely of clinical importance. Each of the earlier homologues has produced morphologic and functional changes in the liver during prolonged intravenous therapy, a negative nitrogen balance, and increased riboflavin excretion into the urine.[12]

THERAPEUTIC INDICATIONS AND CLINICAL USE

The effectiveness of the tetracyclines in the treatment of a large group of infections has been well established. The tetracyclines have been in use longer than

any other antibiotics except penicillin and streptomycin, and they have proved to be unusually safe, well-tolerated, and effective, as well as convenient to use orally. Reactions are usually not serious and are very rarely fatal.

As newer antibiotics have been introduced they have supplemented the tetracyclines and have filled in the therapeutic gaps when used against organisms usually resistant to them, eg. *Proteus Pseudomonas*, and other resistant strains of coliform organisms.

The chief disadvantage of tetracycline therapy is the expense as compared to that of penicillin and sulfonamides. In addition, certain organisms either develop resistance or are replaced by resistant strains after prolonged or repeated courses of tetracycline therapy.

In the following clinical situations, the tetracycline drugs are considered as first or equal choices:

Respiratory infections.—(a) Pneumonitis due to Eaton Agent (primary atypical pneumonia), psittacosis, *II influenzae*, or pneumocci (in patients allergic to penicillin or when oral therapy is necessary); (b) chronic bronchitis due to mixed organisms, especially *II influenzae* and pneumococci;[24] (c) infections due to some strains of *Klebsiella* (combined with streptomycin or kanamycin); and (d) acute bronchitis of undetermined etiology.

Urinary tract infections.—Infections due to sensitive coliform organisms, especially when they are acute and not acquired in the hospital (often combined with streptomycin, kanamycin or the colistine [colistin sulfate and colistimethate sodium]).

Other gram-negative infections.—(a) Infections due to sensitive strains of *E coli, Aerobacter, Proteus*, and coliform organisms (frequently combined with streptomycin, kanamycin, or the colistins if bacteremia is present); (b) brucellosis (either alone or combined with streptomycin); (c) tularemia (either alone or combined with streptomycin); (d) *Bacteroides* (usually alone or combined with another antibiotic if sensitivity studies indicate that another antibiotic would be effective); and (e) *Shigella.*

Rickettsial diseases.—(a) Rocky mountain spotted fever and (b) typhus fever.

Vital diseases and miscellaneous.—(a) Psittacosis, (b) lymphopathia venerum, (c) trachoma, and (d) granuloma inguinale.

Clostridial infections.—(a) Tetanus and (b) *Clostridium perfringens* (gas gangrene).

Protozoal diseases.—Amebiasis.

In general documented evidence reveals little difference in therapeutic effectiveness between the four main tetracycline homologues. There may be an occasional strain that exhibits a differential sensitivity pattern favoring one homologue over another, but these differences are quantitative rather than qualitative. If a given patient fails to respond to one tetracycline homologue, there is rarely any advantage in changing to another homologue.

PREPARATIONS

The four homologues are marketed under a variety of brand names, each containing a specific salt or additive, with the claim that there is optimal absorption. It has been emphasized that there is little, if any, advantage of one salt or additive over the other. On the other hand, those homologues that contain calcium and dicalcium salts actually depress absorption.[6, 25] Therefore, calcium compounds are no longer incorporated in commercial preparations of the tetracyclines. When prolonged treatment is to be given, their combination with antifungal agents such as nystatin and amphotericin B may delay or decrease the overgrowth of *Candida* organisms about the anus and in the vagina.

Oral preparations of tetracycline, oxytetracycline, and chlortetracycline are available in capsule and tablet form in 50, 100, and 250 mg sizes. They also are supplied in liquid form for administration as drops and by the teaspoonful. Capsules of demethylchlortetracycline contain 150 mg. Liquid preparations of this homologue also are available. The tetracyclines are prepared for topical application as ophthalmic and otic solutions and ointments and as troches and surgical powders.

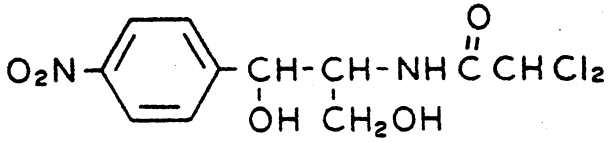
If a patient is unable to take tetracycline orally, intravenous administration by continuous drip should be initiated. The usual dose for adults is 500 mg every 8 to 12 hours, occasionally, larger doses are indicated. There are several preparations available for intramuscular injection. However, intramuscular administra-

tion is extremely painful and is seldom tolerated by the patient for very long periods.[26, 27] Combining such preparations with a local anesthetic lessens the immediate pain, but persistent tenderness prevents prolonged administration by this route. If individual doses do not exceed 100 mg the drug is tolerated much better, but the levels achieved are lower than those that can be obtained when the drug is given orally or intravenously.

Preparations containing vitamins, acetylsalicylic acid (aspirin), acetophenetidin (phenacetin), caffeine, or antihistamines contain only 125 mg of tetracycline and have no advantage over the antibiotic alone.

Chloramphenicol

Chloramphenicol was isolated in 1947 from culture filtrates of *Streptomyces venezuelae*. The chemical formula was soon identified and the antibiotic was successfully synthesized. The formula is presented below:



The aromatic ring structure appears to be essential for biologic activity. The isomers of chloramphenicol are inactive. A wide variety of alterations in the molecule have been made, but most of these changes have resulted in loss of antibiotic potency, and none of the resulting formulations have been superior to the parent drug.

Chloramphenicol is generally considered to be a bacteriostatic agent, although, by varying the concentration, a bactericidal effect can be demonstrated against some strains of microorganisms. Chloramphenicol acts on sensitive bacteria by inhibiting protein synthesis. Considerable information is available as to the precise enzyme systems involved. These vary with different organisms.[28] In the light of the known toxicity of chloramphenicol, it is interesting that its effect on the host cells differs from its effect on bacterial cells.

Chloramphenicol has a broad antimicrobial spectrum and is active against many strains of gram-positive and gram-negative bacteria, the rickettsiae, and a few strains of viruses. There is, however, considerable variation in the sensitivity of different strains of organisms within the same species. Ths variability is most frequently encountered among the gram-negative bacilli. Although Fisher[29] and Hodgman[30] stated that staphylococci maintain their in vitro sensitivity to chloramphenicol despite its extensive use in hospitals, other investigators have noted chloramphenicol-resistant strains of staphylococci in increasing numbers.[31]

Antibiotic synergism and antagonism have been extensively studied in vitro and in experimental animals; however, these phenomena are difficult to assess clinically and there is little documentation of such a clinical phenomenon.

Pharmacology

Crystalline chloramphenicol is absorbed unchanged as the metabolically active form of the drug. It is almost completely absorbed from the gastrointestinal tract. Therapeutic levels appear in the blood within 30 min after ingestion, reach their peak in 2 hours, and disappear within 12 to 22 hours.[32,33] The height and duration of the blood levels are generally proportional to the dose. Circulating chloramphenicol is rapidly conjugated by the liver to a monoglucuronide which has no biological activity and is highly water soluble. A small amount of chloramphenicol is converted, probably also in the liver, to a biologically inactive aminodial hydrolysis product.[30, 32, 33]

Assays for chloramphenicol are carried out by two methods: (a) the microbial assay method, which uses a turbimetric procedure against *Shigella sonnei* and measures active chloramphenicol only and (b) the chemical assay method which determines total aromatic nitro compounds, including both active chloramphenicol and the inactive metabolites. Comparative determinations by the two methods indicate that most of the chloramphenicol in the blood is in the active form. Sixty per cent of the active chloramphenicol in the blood is reversibly bound to the plasma albumin.

Seventy to ninety per cent of an administered dose is recovered in the urine within 24 hous. The rate of excretion is proportional to the blood level.[30,32,35] Five to ten per cent of the total urinary excretion is active chloramphenicol. The remainder consists of inactive aromatic nitro compounds, the glucuronide comprising the major portion. The active chloramphenicol is excreted by glomerular filtration. The filtration rates are low, indicating that the protein-bound portion does not pass the glomerular membrane. The glucuronide is excreted by the renal tubules. The clearance rate of the inactive fraction is 3 to 5 times that of creatinine. Less than 3% of the total does is excreted in the bile, primarily as the monoglucuronide, and less than 1% of the total does appears in the stool.

Kunin, Glazko, and Finland[36] studied serum levels in anuric patients. They reported that the serum half-life of active chloramphenicol was not significantly prolonged in anuric patients; however, the half-life of the metabolic products of chloramphenicol was markedly extended in patients with severe renal disease but no toxic effects were observed. The same investigators found that the serum half-life of active chloramphenicol was prolonged in patients with cirrhosis of the liver. This appears to be due to a slower rate of glucuronide conjugation in these patients.[37]

Distribution

After chloramphenicol has been absorbed, it rapidly diffuses throughout most of the body fluids. The chief factor which limits diffusion throughout the various body fluids appears to be due to protein binding. Thus, the spinal fluid concentration is only 30% to 50% of that in the blood stream. Chloramphenicol appears to diffuse into joint and pleural spaces in somewhat higher concentrations. It penetrates the aqueous and vitreous humor of the eye and crosses the placental barrier. The concentration in the newborn infant's blood is 30% to 80% of that in the maternal blood.[38]

THERAPEUTIC INDICATIONS AND CLINICAL USE

Although chloramphenicol is a broad spectrum antibiotic whose effectiveness has been established in a variety of infections due to gram-positive and gram-negative organisms, its toxic effects may be extremely serious and it should not be used when penicillin, the tetracyclines, or erythromycin are effective. This fact reduces the specific indications for the use of this drug to severe salmonella infections, especially typhoid fever. Formerly, chloramphenicol was considered the drug of choice in the treatment of *H influenza* meningitis. A recent comparative study of a large group of patients indicated a mortality rate of 24.5% with oxytetracycline, 8.4% with tetracycline, and 12.5% with chloramphenicol therapy.[39]

Chloramphenicol is highly effective and specific in the treatment of typhoid fever. Bacteremia ceases within a few hours after the first dose. During the next 2 days the patient begins to feel better, although the temperature remains elevated. During the third and fourth day there is dramatic improvement with fall in temperature and disappearance of symptoms. The dose for adults is 2 to 3 gm of chloramphenicol per day administered at 6- or 8-hour intervals. If treatment is discontinued as soon as the patient becomes afebrile, relapse will often occur. This can be prevented in the majority of cases by continuing chloramphenicol for at least 12 days after the afebrile state has been reached.

The effectiveness of chloramphenical is less dramatic in other salmonella infections and is usually ineffective in eradicating the carrier state.

The development of the newer semisynthetic penicillins may reduce the need for chloramphenicol in the treatment of staphylococcic infections. Probably there are some urinary tract infections in which chloramphenicol is the drug of choice when the organism is resistant to the tetracyclines, erythromycin, and other antibiotics, or to some of the newer antibiotics, such as the colistins, but such instances are uncommon.

There is no justification for employing chloramphenicol prophylactically in surgical patients or in those with salmonella infections or respiratory infections due to virsuses.

Chloramphenicol (as well as most antibiotics) has been used far more extensively than the above indications justify, despite repeated warnings in the literature. Several authors have emphasized that fatal reactions have occurred in

patients who received chloramphenicol for minor respiratory infections or some other infection for which the indication for chloramphenicol was questionable or absent.

Toxicity

The most common and serious toxic effect associated with chloramphenicol therapy is the development of aplastic anemia. This may occur after the administration of small doses for short periods or may appear only after prolonged therapy. Aplastic anemia is the most important complication of chloramphenicol therapy; it occurs more commonly in association with this antibiotic than with any other drug.[40-42] If the aplastic anemia is detected early, and the antibiotic is discontinued, the bone marrow may recover, but often the disease ends fatally.

Other forms of bone marrow depression may occur with chloramphenicol therapy, such as leukopenia, granulocytopenia, and thrombocytopenia. These are more likely to be associated with large doses or prolonged therapy and are more likely to be reversible if the drug is discontinued. Consequently, all patients requiring chloramphenicol therapy should have frequent blood counts, at least twice weekly in the early weeks of therapy and once weekly later. However, it should be emphasized that, although frequent blood counts can be relied upon to detect early changes in the peripheral blood, pancytopenia of the bone marrow may occur without warning.

Recent reports suggest that many patients receiving chloramphenicol therapy have demonstrated hematopoietic changes which may be unrecognized but reversible. Some patients exhibited a marked delay in uptake of radioactive iron by the red blood cells and others have developed anemia. The earliest demonstrable toxic effects on the hematopoietic system are an increase in plasma iron and in the saturation of iron-binding globulin, reflecting a decrease in the iron uptake of the erythroid tissue.[43-46]

Morphologic changes resulting from chloramphenicol therapy have been described by several investigators.[16, 30 43-47] A depression in the reticulocyte count below 0.5% occurs in the peripheral blood of most patients during the toxic phase, and bone marrow aspirations reveal striking vacuolation in young erythroid cells.[46] These changes are usually reversible and disappear within a few days after the drug is discontinued. In fact, rapid bone marrow recovery is usually accompanied by evidence of hyperplasia (reticulocytosis and sometimes thrombocytosis and leukocytosis). Such a rebound phenomenon is not observed in those patients in whom the bone marrow depression is not reversible. Chloramphenicol seems to act at the proerythroblast level, at which maximum vacuolation is seen, rather than at the stem-cell level. Patients with anemia in whom the marrow is active appear to be particularly sensitive to the marrow-depressing effect of chloramphenicol. Increasing the dosage of chloramphenicol above 40 mg/kg of body weight appears to induce hematopoietic depression.

When chloramphenicol is administered in higher concentrations than those ordinarily used, it depresses leukocyte respiration and inhibits the synthesis of nucleic acid by normal and leukemic bone marrow cells. The exact mechanism of bone marrow suppression remains unexplained. There has been one case of acute myeloblastic leukemia reported after chloramphenicol therapy.[18]

Premature and newborn infants are particularly susceptible to the toxic effects of chloramphenicol and there have been several reports of deaths of newborn infants due to chloramphenicol therapy.[30, 49-51] In most cases, the drug was given within 48 hours after birth and the majority of infants affected were premature by birth weight. They developed a symptom complex called the "gray syndrome." Almost all of them received doses larger than 100 mg/kg of body weight daily. The symptoms appeared after 3 or 4 days of treatment. The first evidence of toxicity was vomiting or regurgitation of feedings, followed by refusal to suck and abdominal distention. Respiratory distress, flaccidity, and an ashen gray color then developed. Deaths occurred in the seriously affected babies 24 to 48 hours after the onset of the first symptoms. In the others the symptoms usually disappeared within 24 to 36 hours after the drug was discontinued. Blood concentrations, which were reported in a few infants, showed progressive accumulation of total nitro compounds to unusually high levels. However, autopsy studies did not reveal the cause of death and no characteristics changes were found.

Further studies, including the reproduction of the "gray syndrome" in animals, have elucidated the pathogenesis of this entity. In the newborn infant the

immature liver is deficient in conjugation mechanisms and there is a decrease in the renal tubular secretion of the chloramphenicol glucuronid. This results in abnormally progressive accumulations of chloramphenicol and some of its degradation metabolites. The toxic effect in the newborn infant has been directly related to the high level of active chloramphenicol that accumulates in the blood stream after repeated doses. Thus, the "gray syndrome" in newborn infants may be prevented by reducing the size of the dose to no more than 25 mg/kg per day in premature infants or infants under 2 weeks of age.[52-54]

Other toxic reactions resulting from chloramphenicol therapy include nausea and, occasionally, diarrhea. The gastrointestinal symptoms are mild and the drug is usually well tolerated. Secondary infections, due to the presence of yeasts, may also occur.

Allergic reactions are rare. Angioneurotic edema, vesicular and maculopapular eruptions, and fever have been observed. In addition, acute necrosis of the liver has occurred after chloramphenicol therapy and peripheral neuritis associated with optic neuritis has been reported during the prolonged administration of relatively large doses.[55]

PREPARATIONS AND DOSAGE

Chloramphenicol can be given orally, intramuscularly, subcutaneously, intravenously, and rectally. It is available in 50, 100, and 250 mg capsules for oral administration. This preparation contains crystalline chloramphenicol; effective blood levels are usually obtained within one-half hour after ingestion. However, in patients who are severely ill, particularly in those with signs of peripheral circulatory collapse, absorption is often delayed and intravenous therapy should be utilized.

A liquid preparation of chloramphenicol, available as the palmitate ester, is designed for use in young children.[30, 56] This preparation is palatable in contrast to the extremely bitter taste of the crystalline form. Therapeutic levels are not attained until 2 or 3 hours after administration because the ester must be hydrolyzed before absorption occurs. Since as much as 50% of the dose is lost in the stool, the amount given must be higher than when the drug is administered in the crystalline form.[53] Each 4 cc contains 125 mg of chloramphenicol and the recommended dose is 100 to 200 mg/kg of body weight per day, given at 6- or 8-hour intervals.

A preparation containing chloramphenicol and dihydrostreptomycin is marketed. There are no specific indications for this preparation.

Two preparations are available for intramuscular administration, a microcrystalline powder and a suspension. The latter is prepared by adding physiologic saline or sterile water. Effective blood levels may not be obtained for 2 to 3 hours after intramuscular administration. Peak blood levels will be lower but will last longer than with the same dose of an oral preparation.

Chloramphenicol sodium succinate is a highly water-soluble ester and hence is more readily absorbed than the microcrystalline form. It is available in sterile vials containing crystalline powder equivalent to 1 gm of chloramphenicol which may be dissolved in sterile water, normal saline, or glucose solutions. This preparation is suitable for intramuscular, subcutaneous, or intravenous use. Therapeutic blood levels are obtained within one-half hour after intramuscular administration. Peak blood levels occur in 1½ to 2 hours and therapeutic levels persist for 6 to 8 hours. This is the preferable preparation for parenteral use.

Several preparations are available for topical administration, including a cream, an ointment, drops for ophthalmic use, and drops for otic use. However, there is little indication for the use of these formulations.

The dose of chloramphenicol in adults is 2 to 3 gm daily.

Baylor University College of Medicine, Texas Medical Center, Houston (Dr. Yow).

GENERIC AND TRADE NAMES OF DRUGS

Chloramphenicol—*Chloromycetin.*
Chlortetracycline hydrochloride—*Aureomycin Hydrochloride.*
Oxytetracycline—*Terramycin.*
Demethylchlortetracycline hydrochloride—*Declomycin Hydrochloride.*
Tetracycline—*Achromycin, Panmycin, Polycycline, Tetracyn.*
Kanamycin sulfate—*Kantrex.*
Nystatin—*Mycostatin.*
Amphotericin B—*Fungizone.*
Erythromycin—*Erythromycin, Ilotycin.*
Dihydrostreptomycin sulfate—*Dihydrostreptomycin Sulfate.*

REFERENCES

[1] Duggar, B. M., et al: Aureomycin: Product of Continuing Search for New Antibiotic, *Ann NY Acad Sci* 51: 177–181 (Nov) 1948.
[2] McCormick, J. R. D., et al: New Family of Antibiotics: Demethyltetracyclines, *J Amer Chem Soc* 79: 4561–4563 (Aug. 20) 1957.
[3] Kunin, C. M., and Finland, M.: Demethylchlortetracycline: New Tetracycline Antibiotic that Yields Greater and More Sustained Antibacterial Activity, *New Eng J Med* 259: 999–1005 (Nov 20) 1958.
[4] Kunin, C. M.; Dornbush, A. C.; and Finland, M.: Distribution and Excretion of Four Tetracycline Analogues in Normal Young Men, *J Clin Invest* 38: 1950–1963 (Nov) 1959.
[5] Shapiro, J. L., and Phillips, F. M.: Demethylchloretetracycline in Clinical Practice, *JAMA* 176: 596–602 (May 20) 1961.
[6] Sweeney, W. M.; Dornbush, A. C.; and Hardy, S. M.: Demethylchlortetracycline and Tetracycline Compared, *Amer J Med Sci* 243: 296–308 (March) 1962.
[7] Dimmling, T.: Experimental and Clinical Investigation with Pyrrolidinomethyl Tetracycline, *Antibiot Ann* 7: 350–357, 1959–1960.
[8] Sweeney, W. M., et al: Absorption of Tetracycline in Human Beings as Affected by Certain Excipients, *Antibiot Med* 4: 642–656 (Sept. 10) 1957.
[9] Wood, W. S., et al: Tetracycline Therapy; Clinical and Laboratory Observations on 184 Patients with Tetracycline, *Arch Intern Med* 59: 351–363 (Sept.) 1954.
[10] Sweeney, W. M.; Dornbush, A. C.; and Hardy, S. M.: Antibiotic Activity in Urine and Feces After Oral and Intravenous Administration of Demethylchlortetracycline, *New Eng J Med* 263: 620–624 (Sept. 20) 1960.
[11] Kunin, C. M., and Finland, M.: Clinical Pharmacology of Tetracycline Antibiotics, *Clin Pharmacol Ther* 2: 51–69 (Jan.–Feb.) 1961.
[12] Kunin, C. M.: The Tetracyclines, *Pediat Clin Amer* 8: 1001–1012 (Nov.) 1961.
[13] Kunin, C. M.; Jones, W. F.; and Finland, M.: Enhancement of Tetracycline Blood Levels *New Eng J Med* 259: 147–156 (July 24) 1958.
[14] Berk, J. E., and Kantor, S. M.: Demethylchlortetracycline-Induced Fluorescence of Giastric Sediment. *JAMA* 179: 997–1000 (March 31) 1962.
[15] Annotations. Tissue Localization of Tetracycline. *Brit Med J*, 1: 1401 (May 19) 1962.
[16] Du Buy, H. G., and Showacle, J. L.: Selective Localization of Tetracycline in Mitochondria of Living Cells, *Science* 133: 196–197 (Jan.) 1961.
[17] Finland, M.: Medical Progress; Emergence of Antibiotic-Resistant Bacteria, *New Eng J Med* 253: 909–922 (Nov. 24) 1955.
[18] Kunin, C. M., et al: Persistence of Antibiotics in Blood of Patients with Acute Renal Failure. I. Tetracycline and Chlortetracycline, *J Clin Invest* 38: 1487–1497 (Sept.) 1959.
[19] Kingston, J. R., et al: Eaton Agent Pneumonia, *JAMA* 176: 118–123 (April 15) 1961.
[20] Houser, H. B., et al: Effect of Aureomycin Treatment of Streptococcal Sore Throat on Streptococcal Carrier State, Immunologic Response of Host, and Incidence of Acute Rheumatic Fever, *Pediatrics* 12: 593–606 (Dec.) 1953.
[21] Overholt, E. L., et al: Analysis of Forty-Two Cases of Laboratory-Acquired Tularemia: Treatment with Broad Spectrum Antibiotics, *Amer J Med* 30: 785–806 (May) 1961.
[22] Knight, V., et al: Studies on Staphylococci from Hospital Patients. II. Effect of Antimicrobial Therapy and Hospitalization on Carrier Rates, *Ann NY Acad Sci* 65: 206–221 (Aug. 31) 1956.
[23] Kuharic, H. A.; Roberts, C. E., Jr.; and Kirby, W. M. M.: Tetracycline Resistance of Group A Beta Hemolytic Streptococci, *JAMA* 174: 1779–1782 (Dec. 3) 1960.
[24] Normal, P. S., et al: Long-Term Tetracycline Treatment of Chronic Bronchitis, *JAMA* 179: 833–840 (March 17) 1962.
[25] Boger, W. P., and Gavin, J. J.: Evaluation of Tetracycline Preparation, *New Eng J Med* 261: 827–832 (Oct. 22) 1959.
[26] Kent, B.; Yow, E. M.; and Townsend, E.: Concentration of Tetracycline in Serum Following Parenteral Administration, *J Lab Clin Med* 47: 203–209 (Feb.) 1956.
[27] McKechnie, J., and Yow, E. M.: Comparison of Patient Tolerance of Procaine Penicillin, Tetracycline, and Oxytetracycline when Administered Instramuscularly, *Antibiot Med* 7: 765–770 (Dec.) 1960.
[28] Wissman, C. L., et al: Mode of Action of Chloramphenicol. I. Action of Chloramphenicol on Assimilation of Ammonia and on Synthesis of Proteins and Nucleic Acids in *Escherichia Coli*, *J Bact* 67: 662–673 (June) 1954.
[29] Fisher, M. W.: Susceptibility of Staphylococci to Chloramphenicol: Survey of Experimental and Clinical Experiences, *Arch Intern Med* 105: 413–423 (March) 1960.
[30] Hodgman, J. E.: Chloramphenicol, *Pediat Clin* 8: 1027–1042 (Nov.) 1961.
[31] Koch, M. L.: Increased Incidence in Pathogenic Chloramphenicol-Resistant Staphylococci Accompanying Increased Use of Drug in Hospital Practice, *Antibiot Med* 3: 458–460 (Dec.) 1956.
[32] Glasko, A. J., et al: Biochemical Studies on Chloramphenicol (Chloromycetin). II. Tissue Distribution and Excretion Studies. *J Pharmacol Exp Ther* 96: 445–459 (Aug.) 1949.
[33] Kelly, R. S.; Hunt, A. D.; and Tashman, S. G.: Studies on Absorption and Distribution of Chloramphenicol, *Pediatrics* 8: 362–367 (Sept.) 1951.
[34] Krakoff, I. H.; Karnofsky, D. A.; and Burchenal, J. H.: Effects of Large Doses of Chloramphenicol on Human Subjects, *New Eng J Med* 253: 7–10 (July 7) 1955.

NOTE.—Additional references available from the author on request.

[From the Journal of the American Medical Association, July 27, 1963]

USE AND MISUSE OF ANTIBIOTICS

Effective chemotherapy for combating infectious diseases has become a possibility only during the past 15 years, and the list of complex, highly potent drugs is continually changing and increasing. The dramatic consequences of this

breakthrough in pharmacological, microbiological, and clinical science are reflected in sharply declining death rates the world over. Unfortunately, however, the plethora of new drugs and combinations of drugs may be a mixed blessing to physicians who attempt to thread their way through a maze of conflicting claims concerning such complex matters as sensitivity spectra, blood levels, potency, and safety.

Many of the new antimicrobials are clearly outstanding contributions to the art of chemotherapy and are, as such, real triumphs of pharmacological research. Others are molecular modifications of established compounds and are introduced with claims that some desired feature—such as greater potency, more rapid absorption, more sustained blood levels, reduced bacterial resistance, or fewer side effects—has been added to the more familiar properties. Since all such claims need to be viewed skeptically until they have been confirmed by impartial investigators and extended experience, compounds of this type often make only a numerical rather than a qualitative contribution to the list of available drugs, and thus add only confusion.

Other formulations offered by the pharmaceutical industry tend to make careful clinicians definitely uneasy. These include the fixed-ratio mixtures of two or more antimicrobial agents, which are said to be designed to reduce the chances of superinfection, patient sensitization, or bacterial resistance, and the formulations containing additives that are claimed to enhance absorption, delay excretion, or otherwise affect blood levels or potency. Clearly violating the principles of rational therapy are the complex combinations of antipyretics, antihistaminics, or vitamins, with minimal amounts of the antibiotic. Since the host of ingenious topical preparations—lozenges, aerosols, and ointments—appear to sensitize as often as they relieve, their value also is open to serious question. Obviously, the opportunities for misuse or even frank abuse of antimicrobial chemotherapy are rife for the unwary, and unquestionably some physicians have been guilty of misusing these agents.

With this Therapeutic Number the Council begins its sponsorship of a series of authoritative communications which should help to bring the physician up to date on individual aspects of antibiotic therapy and increase his sense of security in prescribing these agents. Ory and Yow (p 273) write about the tetracyclines and chloramphenicol, and Hewitt (p 264) differentiates the burgeoning group of penicillins from one another.

Ory and Yow stress the fact that the tetracyclines are similar in their antibacterial spectra and should always be administered singly rather than as mixtures which increase both the cost and hazard for the patient. These authors also discredit many promotional myths, such as claims for additives designed to increase absorption, reduce gastrointestinal irritation, prevent overgrowth of Candida, and so on, and wisely point out once again the frequently forgotten distinction between the primarily bacteriostatic and the primarily bacteriocidal drugs. Referring to the grim record of chloramphenicol as a cause of serious and fatal blood dyscarsias, they remind us that it should not be used when other antibiotics are effective, a fact which limits its specific indications to the treatment of severe salmonelloses, particularly typhoid fever.

The choice and administration of one of the many available penicillins is an art in itself, and Hewitt's refresher course is timely indeed. Although the newer ones may help to mitigate the problems of penicillinase resistance, they do not supplant the older penicillins which, as Hewitt reminds us, continue to the drugs of choice in many clinical situations. At the same time he advocates oral administration whenever possible, and suggests doing away with the needlessly sensitizing topical and aerosol preparations altogether.

Subsequent contributions to this series will present definitive information and considered opinion on other aspects of antibiotic therapy. Perhaps it will become possible in the future to match organism, patient, and antimicrobial drug precisely; if so, all patients may one day reap the benefits of a fairly exact and predictable science. But, then and now, before prescribing any drug the physician may well reflect on Hewitt's wise admonition:

"With further contributions now being made by the molecular manipulation of all agents, the physician must more than ever make a clear decision on whether antibiotic therapy for an individual patient is necessary at all."

[From Clin-Alert, Apr. 30, 1963, No. 108]

CHLOROMYCETIN

The Hematology Committee of the British Association of Clinical Pathologists reviewed 40 cases of Chloromycetin (chloramphenicol)-induced blood dyscrasias, 35 of which were hitherto unreported. Thirty-one patients died. Onset of toxic symptoms varied widely (immediately after the drug was given to one year after cessation of therapy). Dosage analysis revealed that while a high dose and repeated courses seem more likely to cause trouble, single courses of less than 10 Gm. Chloromycetin can cause fatal aplasia. Use of Chloromycetin is justified only in treatment of life-endangering infections when no other effective antibiotic is available * * * example, typhoid fever. There is every indication, however, that Chloromycetin has been used indiscriminately in a wide variety of mild infections and that extravagant doses have been given.—Sharp (Secretary), British M.J. 1 : 735, 1963.

[From the British Medical Journal, No. 5332, pp. 735–737, Mar. 16, 1963]

CHLORAMPHENICOL-INDUCED BLOOD DYSCRASIAS: ANALYSIS OF 40 CASES

(By A. A. Sharp, M.D.)

Presented on behalf of the Haematology Committee* of the Association of Clinical Pathologists

Ten years have elapsed since the first reports were published to inform the medical profession that chloramphenicol could act as a bone-marrow poison and that the resulting aplasia could be irreversible and lead to the death of the patient (*British Medical Journal*, 1952).

Since then reports of the toxic effects of chloramphenicol have continued to appear, but the drug has remained in use as a popular and useful antibiotic. The *British Medical Journal* (1961) was again provoked to give warning of the dangers of this drug, but deaths attributable to chloramphenicol have continued to be reported. The latest report of the Study Group of Blood Dyscrasias of the American Medical Association (January, 1962) recorded 73 cases of pancytopenia, 4 with thrombocytopenia, 4 with leucopenia, and 17 with anaemia which were caused by this drug.

The Haematology Committee of the Association of Clinical Pathologists decided to ask members of its association how many cases of chloramphenicol-induced blood dyscrasias they had encountered and to report such cases to the secretary of this Committee. To date, reports of 35 hitherto unpublished and five published cases of suspected chloramphenicol blood dyscrasias have been received. This is admittedly a random sample of such cases, and while there are obviously still an unspecified number of unpublished cases it was thought worth while to report an analysis of the clinical and laboratory data supplied with these case reports.

ANALYSIS OF CLINICAL DATA

Time.—These 40 cases occurred in the period 1953–62.

Severity.—Thirty-one of the 40 patients have died. In 27 death was attributed directly to chloramphenicol therapy.

Age and sex.—There is no obvious specific age or sex incidence.

Interval between therapy and diagnosis of marrow damage.—The commonest interval was 1–3 months after the cessation of therapy; in two cases the blood dyscrasias developed immediately after the drug had been given, in two cases at approximately 9 months, and in one case 1 year after cessation of therapy.

Dose.—In 18 patients the total dose of chloramphenicol was 10 g. or more, and in four it exceeded 50 g., one receiving 250 g. In eight patients, however, the total dose was less than 10 g., and in one infant the amount given did not exceed 2 g. Six received intermittent or continuous courses or unspecified amounts over one year, and 12 had more than one course of the drug. In 14 cases details of therapy were insufficient to assess the total dosage of the drug the patient had received.

---

*Dr. E. K. Blackburn (chairman), Dr. M. G. Nelson, Dr. F. G. J. Hayhoe, Dr. J. Humble, Dr. D. Robertson-Smith, Dr. G. H. Tovey, and Dr. A. A. Sharp (secretary).

Blood picture.—In 21 cases the peripheral blood showed a severe pancytopenia (anaemia, leucopenia, and thrombocytopenia). Twelve cases showed selective aplasia with either leucopenia or thrombocytopenia. No case showed selective red-cell aplasia. In seven cases specific data relating to the peripheral blood picture were not given.

Clinical presentation.—The commonest presenting symptom was spontaneous bleeding—for example, epistaxis, purpura, menorrhagia. In one case jaundice was the earliest sign of complication.

Prognosis.—The details of the marrow changes were available in only 25 reports. All 12 patients with aplastic marrows died. In eight the marrow was classified as hypoplastic, but they too died. The marrow derived from five of the nine patients who recovered was hypoplastic. Therefore recovery may take place if the marrow is not completely aplastic. Complete marrow aplasia would appear to carry a hopeless prognosis.

DISCUSSION

Chloramphenicol is an efficient antibiotic, but its use is justified only in the treatment of life-endangering infections when no other effective antibiotic is available—for example, typhoid fever.

Yet this series has shown that fatalities apparently due to chloramphenicol therapy have occurred in numbers sufficient to cause concern. Further, it would seem that this drug has been used indiscriminately in the treatment of a wide variety of mild infections and that extravagant doses of the drug have been administered.

Hutchison and Pinkerton (1962) have suggested that the incidence of blood dyscrasias due to chloramphenicol might be 1 in 80,000 patients treated, in which case it might be argued that this risk justifies the use of this antibiotic in even trivial infections. However, these authors based their imputation on the number of deaths reported to the Registrar-General, and incidence based on the Registrar-General's report can be misleading; it is likely that more cases do exist than are officially recorded.

Dameshek (1960) has stated that in the majority of fatal cases the patient would not have died if he had not received this drug. There would appear to be no justification for using chloramphenicol to treat nonspecific pyrexial illnesses or nasopharyngeal infections in childhood, or recurrent bronchitis, asthma, chronic or post-prostatectomy urinary infection, recurrent boils, or superficial skin infections unless it has been shown by careful bacteriological sensitivity tests that the offending organism is sensitive to no other antibiotic.

This present series shows that, while a high dose and repeated courses appear to be more likely to cause trouble, single courses of less than 10 g. can cause fatal aplasia.

The wide distribution of the time of onset of symptoms attributable to the toxic effect of the drug suggests that two possible mechanisms exist: (1) a hypersensitivity reaction—immediately dangerous but probably reversible; this is often accompanied by immediate systemic symptoms; (2) a slow direct poisoning of marrow "stem" cells due to the accumulation and retention of the drug or its breakdown products in the blood or tissues and so to the delayed effect. The variation of the toxic dose suggests that an individual idiosyncrasy to this drug may exist.

A retrospective survey such as that presented here can never be satisfactory, as significant data are not collected and not all cases are reported. Thus no statistical analysis of dose, time relationships, or incidence rates can be calculated. Only by insisting that chloramphenicol and other drug-induced dyscrasias are notified to some responsible authority as they occur can the case be made whether the popularity or efficiency of this drug as an antibiotic outweighs its established toxic effect.

The purpose of this paper has been to stress once more the dangers of using this antibiotic and to appeal for the compulsory notification of this and other drug-induced blood dyscrasias to a responsible central body in order that a true assessment of the relative risks can be made. This appeal is especially pertinent to the present concern of the medical profession and lay public regarding the dangers of modern drug therapy.

In the meantime this Committee would be grateful if any doctor encountering a case where it is suspected that chloramphenicol might have produced damage to the bone-marrow would send the relevant data to the secretary of this Committee.

The Committee expresses its thanks to the Council of the Association of Clinical Pathologists for their encouragement and permission to publish these data; to the Chairman of Council, Professor D. F. Cappell, for his criticism and advice; and to all those members of the Association who took the trouble to supply the Committee with case reports. It also wishes to thank Dr. M. M. Wintrobe, Chairman of the Study Group of Blood Dyscrasias of the American Medical Association, for his advice and encouragement.

[From the Journal of the American Medical Association, July 14, 1962, vol. 181, No. 2, pp. 114–119]

Detection and Prevention of Drug-Induced Blood Dyscrasias

(By Allan J. Erslev, M.D., Philadelphia, and Maxwell M. Wintrobe, M.D., Salt Lake City*)

The reluctance of most physicians to report cases of suspected drug-induced blood dyscrasias is due to the difficulty in establishing a definite casual relationship between drug and disease; the evidence for this in most cases is inadequate. Unfortunately, this reluctance may lead to a delay in the recognition of toxic effects of new drugs. For example, cases of suspected chloramphenicol-induced aplastic anemia were observed sporadically soon after the drug was released in 1949, but so few case reports appeared that its potential toxicity was not apparent until 3 years later. By that time 12 individual groups had accumulated 37 cases of chloramphenicol-induced aplastic anemia, enough to warrant publication of a firm, but belated, warning.

In order to prevent similar delays, the Council on Drugs of the American Medical Association established a Study Group on Blood Dyscrasias to act as a clearinghouse for all suspected cases caused by drugs and chemicals.[1] Report forms were distributed, and physicians were urged to report immediately all cases of blood disease in which a drug or chemical might have been of etiological significance. Cooperation has been excellent. Since the institution of this program in 1955, a total of 1,195 cases of blood dyscrasia have been reported in this country alone. The reported cases are tabulated, and a summary is distributed semiannually to all cooperating physicians, to heads of various departments of medical schools, and to medical libraries, medical societies, hospitals, and drug companies.[2]

Because of the great number of cases and the variety of drugs involved and because of the fact that, in such a summary, well-founded as well as less plausible suspicions may be tabulated together, it is obviously difficult to accept these case reports as scientific proof of the toxicity of a drug. However, when used in conjunction with published reports on the effects of drugs on blood cells and with knowledge of the approximate annual consumption of specific drugs, these tabulations have provided much useful information. They have kept the medical profession aware of the potential toxicity of new as well as of older drugs in common use and have led to specific warnings of the toxicity of the phenothiazines[3,4] and chloramphenicol.[5] In addition, it is contemplated that the Study Group will from time to time publish an analysis of all the cases in the Registry in the hope that this will result in a better understanding of the heterogeneous group which has been designated as drug-induced blood dyacrasias.[6] Only through

---

Brit. med. J., 1952. 2, 136.
——— (1961). 1, 1019.
Dameshek, W. (1960). *J. Amer. med. Ass.*, 174, 1853.
Hutchinson, H. E., and Pinkerton, P. H. (1962), *Scot. med. J.*, 7, 96.

*Associate Professor in Medicine, Cardeza Foundation, Jefferson Medical College (Dr. Erslev); and Professor of Medicine, University of Utah, College of Medicine (Dr. Wintrobe).

[1] Development and Purpose of Registry of Blood Dyscrasias, *JAMA* 170: 1925–1926 (Aug. 15) 1959.

[2] Registry on Blood Dyscrasias: Report to Council, *JAMA* 179: 888–890 (March 17) 1962.

[3] Blood Dyscrasias Associated with Chlorpromazine Therapy, *JAMA* 160: 287 (Jan. 28) 1956.

[4] Blood Dyscrasias Associated with Promazine Hydrochloride Therapy, *JAMA* 165: 685–686 (Oct. 12) 1957.

[5] Blood Dyscrasias Associated with Chloramphenicol (Chloromycetin) Therapy, *JAMA* 172: 2044–2045 (April 30) 1960.

[6] Huguley, C. M.; Erslev, A. J.; and Bergsagel, D. E.: Drug-Related Blood Dyscrasias, *JAMA* 177: 23–26 (July 8) 1961.

a better understanding of the pathophysiology of these iatrogenic disorders will it be possible to detect them earlier and, perhaps, to prevent them altogether.

PATHOGENESIS

The drug-induced blood dyscrasias may appear as leukopenias, thrombocytopenias, anemias, or pancytopenias or, in some cases, as defects in clotting factors. As a corollary, the Study Group urges that all cases in which drugs cause adverse effects on the clotting mechanism be reported; however, these disorders are outside the scope of the present discussion.

The pathogenesis of drug-induced cytopenias often is believed to involve an immune mechanism. It is envisioned that certain drugs in a few hypersensitive individuals will render the blood cells antigenic and that these antigens will elicit a destructive antibody response. Such a sequence of events has been demonstrated convincingly in cases of thrombocytopenia caused by allylisopropylurea (Sedormid)[7] or quinidine[8] and in cases of hemolytic anemia caused by stibophen (Fuadin)[9] or quinidine.[10] If strict immunologic criteria are used, these appear to be the only cases in which we can be certain of a pathogenetic antigen-antibody mechanism. Moeschlin and Wagner[11] have described leukocyte agglutinins in aminopyrine-induced agranulocytosis, and leukocyte agglutinins or platelet agglutinins have been found in many other cases of cytopenias suspected of having been caused by drugs.[12,13] These agglutinins, however, are active against normal cells; thus, their action is not, as in the first cases mentioned, only against cells "coated" with the particular drug in question. It is important to realize that the presence of an agglutinating substance does not necessarily indicate that an immune mechanism is operating, since many unrelated chemicals and proteins are capable of coating and clumping blood cells.[14]

In those cases in which an immunologic pathogenesis has been established or strongly suspected, the blood dyscrasia has always been characterized by peripheral cellular destruction and a bone marrow which shows compensatory hyperplasia. In blood dyscrasias characterized by bone marrow suppression or bone marrow hypoplasia, the evidence that they are caused by an immune mechanism with circulating antibodies has not been convincing. In short, although some cases of drug-induced blood dyscrasias have been induced by an antigen-antibody mechanism, the great majority cannot be explained adequately in this manner. The pathogenesis in these cases is obscure, but it may be related to a deficiency in the metabolic handling of certain drugs. This deficiency may be qualitative and depend on the genetic deletion of certain enzymes, or it may represent merely a quantitative individual difference in susceptibility to specific drug actions.

A genetic deficiency of the enzyme glucose-6-phosphate dehydrogenase has explained the sporadic occurrence of hemolytic anemia after the ingestion of primaquine and other oxidant drugs.[15] It has been shown that glucose-6-phosphate dehydrogenase is necessary for the generation of reduced triphosphopyridine nucleotide (TPN) which, in turn, replenishes the red blood cell stores of reduced glutathione which is vital for prevention of the hemolysis by oxidizing compounds. A deficiency may result in the oxidation of the sulfhydryl groups of the globin chains and cell membranes, in turn, producing denatured hemoglobin, Heinz bodies, and red blood cell lysis.[16] A deficiency in the red blood cell content of glucose-6-phosphate dehydrogenase and in the regeneration of reduced glutathione can be recognized easily with appropriate laboratory tests and should be looked

---

[7] Ackroyd, J. F.: Role of Sedormid in Immunologic Reactions that Results in Platelet Lysis in Sedormid Purpura, *Clin Sci* 13 : 409–423 (Aug.) 1954.

[8] Schen, R. J., and Rabinovitz, M.: Thrombocytopenic Purpura Due to Quinidine, *Brit Med J* 2 : 1502–1505 (Dec. 20) 1958.

[9] Harris, J. W.: Studies of Mechanism of Drug-Induced Hemolytic Anemia, *J Lab Clin Med* 47 : 760–775 (May) 1956.

[10] Freedman, A. L.; Barr, P. S.; and Brody, E. A.: Hemolytic Anemia Due to Quinidine: Observations on Its Mechanism, *Amer J Med* 20 : 806–816 (May) 1956.

[11] Moeschlin, S., and Wagner, K.: Agranulocytosis Due to Occurrence of Leukocyte-Agglutinins, *Acta Haemat* 8 : 29–41 (July-Aug.) 1952.

[12] Tullis, J. L.: Role of Leukocyte and Platelet Antibody Tests in Management of Diverse Clinical Disorders, *Ann Intern Med* 54 : 1165–1180 (June) 1961.

[13] Zuker, M. B., et al.: Thrombocytopenia with Circulating Platelet Agglutinin, Platelet Lysin and Clot Retraction Inhibitor, *Blood* 14 : 148–161 (Feb.) 1959.

[14] Jandl, J. H.: Agglutination and Sequestration of Immature Red Cells, *J Lab Clin Med* 55 : 663–681 (May) 1960.

[15] Beutler, E.: Drug-Induced Hemolytic Anemia, in *Metabolic Basis of Inherited Disease*, edited by J. B. Stanbury; J. B. Wyngaarden; and D. S. Fredrickson, New York City: McGraw-Hill Book Company, 1960, pp. 1031–1067.

[16] Jacob, H. S., and Jandl, J. H.: Effects of Sulfhydryl Inhibition on Red Blood Cells. I. Mechanism of Hemolysis, *J Clin Invest* 41 : 779–792 (April) 1962. II. Role of Thiols in Oxidant Drug Action, *J Clin Invest* 40 : 445–475 (March) 1961.

for carefully in all cases of hemolytic anemia, whether exposure to drugs has occurred or not. A hypersensitive person may respond to minimal concentrations of a chemical; for example, children have developed hemolytic anemia after exposure to aniline laundry marks[17] or to naphthalene in moth-protected clothing.[18] Drugs marked by an asterisk in the table have been associated with the production of oxidative hemolytic anemia.[15]

Other biochemical abnormalities of blood cells, which render them hypersensitive to specific drugs and chemicals, will undoubtedly be found. Since these abnormalities would be primarily genetic, it is important to obtain a complete family history and to inquire about consanguinity, which often may be the first clue to a genetic mechanism.[19] Because of this interest, the report form distributed by the Study Group on Blood Dyscrasias contains a space for checking the presence or absence of consanguinity.

A quantitative difference in the response to a drug may also be of pathogenetic importance in the development of many blood dyscrasias. In a number of drugs, the difference between therapeutic and toxic levels is quite small, and severe cellular suppression or destruction may be caused by a minor metabolic deviation from the normal. In order to relate the development of a blood dyscrasia to this mechanism, excessive doses of a drug given to normal individuals should cause the same type of toxic reaction which is observed when regular doses are given to hypersensitive individuals.

Results of recent studies strongly suggest that chloramphenicol-induced bone marrow suppression represents an accentuated normal response to the drug. Toxicity studies in animals, with the possible exception of monkeys,[20] have failed to reveal that chloramphenicol has marrow-suppressive properties. However, studies in man have shown that large doses given for prolonged periods of time will cause bone marrow suppression and maturation arrest. Krakoff and co-workers[21] and Ozer and co-workers[22] gave large doses of chloramphenicol to 5 people, and all 5 developed pancytopenia and bone marrow suppression. In addition, studies by Saidi and co-workers[23] and by Rubin and co-workers[24] have shown that mild reversible bone marrow suppression is a common complication of chloramphenicol therapy. Results of in vitro studies of normal bone marrow have shown also that chloramphenicol in high concentrations inhibits desoxyribose nucleic acid (DNA)[25] and heme synthesis[26] in a manner which could explain the lack of cellular proliferation and the impairment of iron utilization observed in vivo. The metabolic handling of chloramphenicol has been studied in a few patients after they had recovered from chloramphenicol-induced pancytopenia, and, in these patients, the drug was found to be detoxified and excreted in a perfectly normal manner.[27] Consequently, it appears that the pancytopenia which occassionally is found in patients treated with chloramphenicol may represent an exaggerated response to the suppressive action of chloramphenicol on bone marrow. A few cases have been reported in which the action of chloramphenicol on the blood cells has been suggestive of an antigen-antibody reaction,[6] but, in the great majority of cases, there is no evidence that this is caused by an immunologic mechanism or by a genetic abnormality in the handling of or in the response of this drug.

---

[17] Graubarth, J., et al.: Dye Poisoning in Nursery: Review of 17 Cases, *JAMA* 128: 1155–1157 (Aug. 18) 1945.

[18] Dawson, J. P.; Thayer, W. W.; and Desforges, J. F.: Acute Hemolytic Anemia in Newborn Infant due to Naphthalene Poisoning: Report of 2 Cases, with Investigations into Mechanism of Disease, *Blood* 13: 1113–1125 (Dec.) 1958.

[19] Motulsky, A. G.: Drug Reactions, Enzymes and Biochemical Genetics, *JAMA* 165: 835–837 (Oct. 19) 1957.

[20] Hrenoff, A. K., and Anderson, H. H.: Chronic Toxicity of Chloramphenicol to Bone Marrow of Macaques, *Med Exp* 4: 183–190, 1961.

[21] Krakoff, I. H.; Karnofsky, D. A.; and Burchenal, J. H.: Effects of Large Doses of Chloramphenicol on Human Subjects, *New Engl J Med* 253: 7–10 (July 7) 1955.

[22] Ozer, F. L.; Truax, W. E.; and Levine, W. C.: Erythroid Hypoplasia Associated with Chloramphenicol Therapy, *Blood* 16: 997–1001 (July) 1960.

[23] Saidi, P.; Wallerstein, R. O.; and Aggeler, P. M.: Effects of Chloramphenicol on Erythropoiesis, *J Lab Clin Med* 57: 247–256 (Feb.) 1961.

[24] Rubin, D., et al.: Changes in Iron Metabolism in Early Chloramphenicol Toxicity, *J Clin Invest* 37: 1286–1292 (Sept.) 1958.

[25] Yunis, A. A., and Harrington, W. J.: Patterns of Inhibition by Chloramphenicol of Nucleic Acid Synthesis in Human Bone Marrow and Leukemic Cells, *J Lab Clin Med* 56: 831–838 (Dec.) 1960.

[26] Ersley, A. J., and Lossifides, I. A.: In Vitro Action of Chloramphenicol and Chloramphenicol-Analogues on Metabolism of Human Immature Red Blood Cells, to be published.

[27] Glazko, A. J.: Personal communication.

ETIOLOGY

A total of 411 drugs have been mentioned as possible etiological agents in the 1,195 cases of blood dyscrasia reported in this country since 1955. Of these cases, 488 have been associated with the administration of a single drug and 707 with the administration of combinations of drugs. It is particularly difficult to pinpoint the responsible agent when a number of drugs have been administered, and it is hard to prove a specific cause-effect relationship even when a single drug has been given. Studies of the cases of agranulocytosis [28] and hypoplastic anemia [29] have suggested that about 40% are of idiopathic origin; that is, they could not be associated with a specific cause. Furthermore, civilized man is exposed to so many chemicals at work and at home (food additives, detergents, solvents, and "smog") that it is impossible to assert that the single drug he received was the only significant chemical exposure. Consequently, not all of the 109 drugs listed as having been given alone were necessarily of etiological importance.

After a thorough analysis of these cases, as well as a critical review of the pertinent literature, the Study Group has compiled a list of 54 drugs believed to be potentially toxic to the blood cells (see table). This list does not state the degree of toxicity of the individual drugs but merely states that these drugs have been associated with the development of blood dyscrasias under circumstances which have convinced the members of the Study Group that a cause-effect relationship exists. In addition to being a useful compilation of potentially toxic drugs, this list may be used to evaluate cases in which multiple drugs have been administered. These cases can be divided into 2 categories: In the first category are those cases in which one of the drugs administered is known to be potentially toxic and, presumably, is responsible for the detrimental effects. In the second category are those cases in which 2 or more drugs were administered, none of which are known to be toxic. In these latter cases, a greater degree of suspicion of the potential toxicity of the unknown drugs is justifiable.

DRUGS OR CHEMICALS SHOWN BY DIRECT OR CIRCUMSTANTIAL EVIDENCE TO BE ASSOCIATED WITH BLOOD DYSCRASIAS

Acetanilid [30]	Pamaquin [30]
Acetazolamide	Phenindione
Acctophenetidin [30]	Phenylbutazone
Allylisopropylacetylurea	Phenylhydrazine [30]
Aminopyrine	Primaquine [30]
Aminosalicylic Acid [30]	Primidone
Arsphenamine	Probenecid [30]
Benzene	Promazine
Carbutamide	Pyrimethamine
Chloramphenicol	Quinacrine
Chlordane	Quinidine
Chlorothiazide	Quinine
Chlorpromazine	Ristocetin
Chlorpropamide	Stibophen
Colchicine	Streptomycin
Diphenylhydantoin Sodium	Sulfacetamide [30]
Dipyrone	Sulfadiazine
Gamma Benzene Hexachloride	Sulfamethoxypyridazine [30]
Gold Salts	Sulfanilamide [30]
Imipramine	Sulfisoxazole
Lead	Sulfoxone [30]
Mepazine	Thiazolsulfone [30]
Meprobamate	Thiobarbital
Methimazole	Thiouracils
Methylphenylethyl Hydantoin	Tolbutamide
Naphthalene [30]	Trimethadione
Nitrofurantoin [30]	Trinitrotoluene

[28] McGovern, F. H.: Granulocytopenia Following Ingestion of Causalin *JAMA* 115: 1359 (Oct. 19) 1940.

[29] Scott, J. L.; Cartwright, G. E.; and Wintrobe, M. M.: Acquired Aplastic Anemia: Analysis of 39 Cases and Review of Pertinent Literature, *Medicine* 38: 119–172 (May) 1959.

[30] These drugs have been associated with the induction of hemolytic anemia principally in patients with glucose-6-phosphate dehydrogenase-deficient cells.

An analysis of the 411 drugs mentioned as possible etiological agents revealed that a relatively small number of chemicals were associated with the great majority of cases. The 14 most important agents are tabulated in Figures 1, 2, and 3 and are divided into 3 groups; i.e., those drugs or chemicals used alone, those used in association with other drugs or chemicals not known to be toxic, or those used in association with drugs or chemicals known to be potentially toxic.

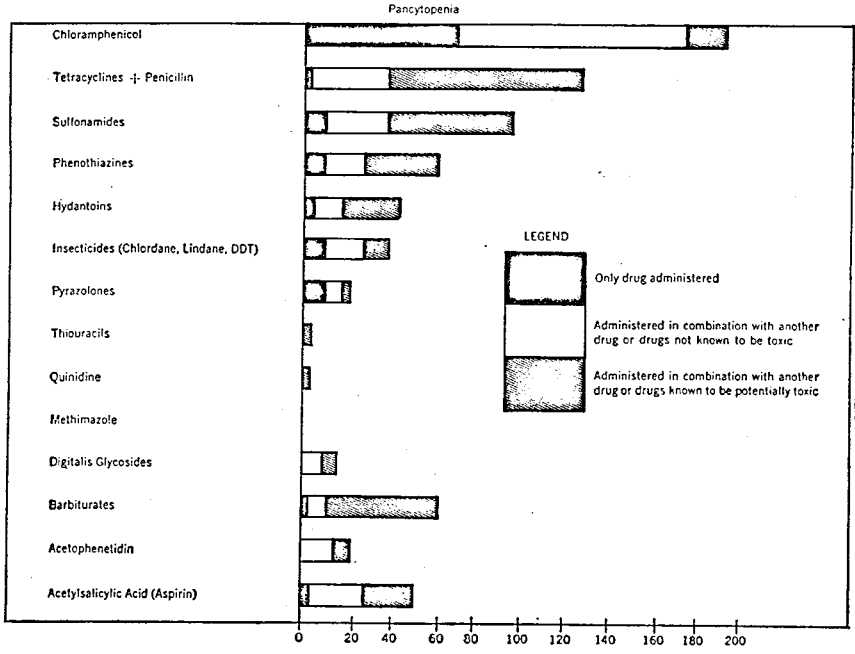


Fig. 1.—Drugs commonly associated with development of pancytopenia.

Figure 1 emphasizes the dominant role of chloramphenicol in the etiology of drug-induced pancytopenias. Not only had chloramphenicol been administered to 200 patients who subsequently developed pancytopenia, but, in one-third of these, it was the only drug given. The tetracyclines and penicillin were associated also with a large number of cases but in only 3 instances were they administered alone. Other commonly used drugs, such as, acetylsalicylic acid (Aspirin), acetophenetidin (Phenacetin), and barbiturates, were found to be associated with a considerable number of cases of pancytopenia but very rarely were they the only drug given. These findings suggest a chance association rather than an etiological relationship; this is supported by the fact that the relative frequency with which these commonly used drugs were associated with pancytopenia, leukopenia, and thrombocytopenia is about the same as the relative frequency with which these diseases occur.

The following drugs all have been associated with a significant number of cases of pancytopenia: sulfonamide such as sulfisoxazole (Gantrisin), diuretics such as acetazolamide (Diamox), hypoglycemic agents such as chlorpropamide (Diabinese), phenothiazines such as chlorpromazine (Thorazine) and promazine (Sparine), hydantoins such as diphenylhydantoin (Dilantin) and methylphenylethyl hydantoin (Mesantoin), and pyrazolones such as aminopyrine (Amidopyrine), dipyrone, and phenylbutazone (Butazolidin). However, in order to gain a valid impression of the potential toxicity of these drugs, it is necessary to know the extent of their annual consumption by humans. Unfortunately, such data are not readily available, and one must rely on estimates.

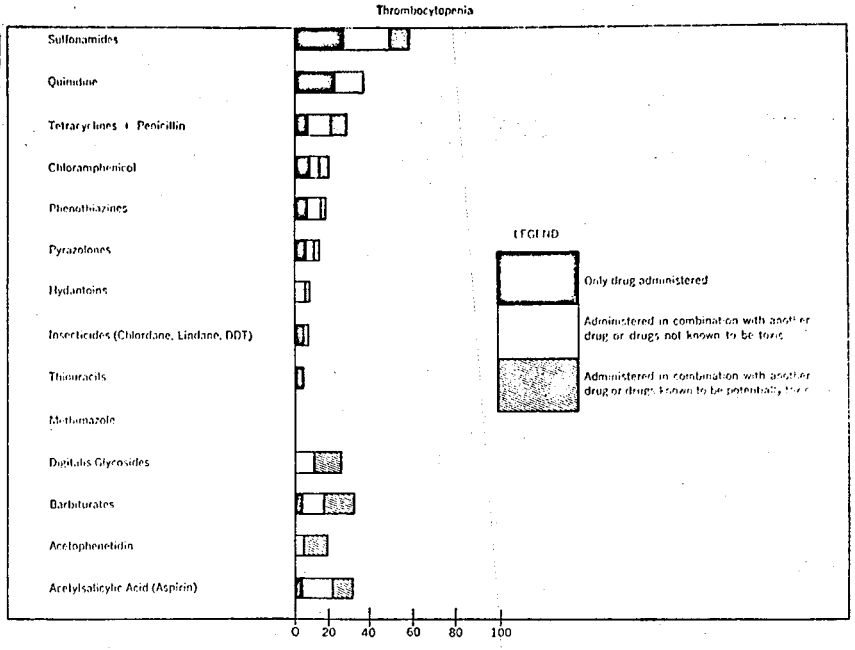


Fig. 2.—Drugs commonly associated with development of thrombocytopenia.

Figure 2 shows that the sulfonamides and quinidine, when given alone or with other drugs not known to be toxic, are associated with the development of a number of cases of thrombocytopenia, thus establishing a convincing cause-effect relationship.

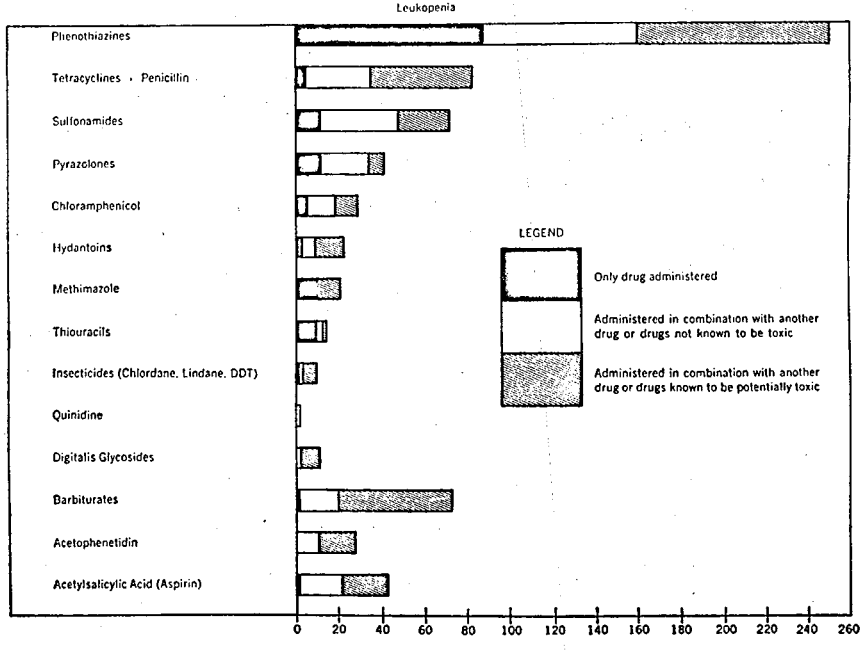


Fig. 3.—Drugs commonly associated with development of leukopenia.

Figure 3 shows that the phenothiazines such as chlorpromazine, promazine, trifluoperazine (Stelazine), prochlorperazine (Compazine), and perphenazine (Trilafon) are quantitatively the most important offenders in the production of leukopenia and agranulocytosis. It is probable that the pyrazolones such as aminopyrine, dipyrone, and phenylbutazone or the antithyroid agents such as propylthiouracil or methimazole (Tapazole) are more toxic since they still are associated with a significant number of cases of leukopenia, despite their relatively infrequent use. The etiological role of the tetracyclines, penicillin, sulfonamides, and chloramphenicol is difficult to assess, since these drugs are used frequently in treating infections associated with unrecognized leukopenia.

DETECTION AND PREVENTION

When treating patients with cytopenias, it is always important to consider the possibility that a drug or a chemical may have played an etiological role in their development. A thorough occupational and personal history will reveal a significant degree of exposure to a toxic agent in about 50% of patients with thrombocytopenia, leukopenia, and pancytopenia. This information will lead to the only rational therapy known—discontinuing further exposure to the suspected agent. It is gratifying to see this simple remedy result in rapid improvement. However, the absence of a prompt response does not rule out cause-effect relationship, since the blood dyscrasia may have reached a slowly reversible or a completely irreversible stage.

In an attempt to establish a definite etiological relationship, appropriate in vitro tests for agglutimins, hemolysins, clot retraction inhibitors, or cellular enzymes (glucose-6-phosphate dehydrogenase) should be carried out. Unfortunately, a useful in vitro test for drug action on bone marrow has not yet been developed. In vivo tests based upon the readministration of a small amount of the suspected drug should be reserved only for those cases in which the suspected agent is considered to be of extraordinary value in the future management of the patient. When this valuable, but somewhat dangerous, test is used, it is important to realize that a negative response to a small test dose will only rule out an antigen-antibody mechanism and not the possibility of the more common biochemical hypersensitivity. In order to test biochemical sensitivity, the suspected drug has to be readministered for a prolonged period of time. However, such a therapeutic trial is rarely justified unless conditions for thorough hematological supervision are available.

It has been shown that early detection of some blood dyscrasias will lead to prevention of serious hematological complications. Peripheral cellular destruction can be stopped promptly if the offending drug is discontinued, and bone marrow suppression may be reversed completely if it is detected early enough. The most important requisite for early detection is the realization that the administration of drugs always entails a risk and that for some drugs this risk may be quite substantial. Administration of these drugs should always be preceded by appropriate blood counts; i.e., white blood cell count, determination of hematocrit levels and hemoglobin concentration, platelet count, and reticulocyte count. Because of the short "lifespan" of the reticulocytes, this count is the most sensitive index to a change in the rate of red blood cell production. Recently, it has been shown that serum iron will increase if suppression of the erythroid marrow prevents normal iron utilization, and this increase may be an early and sensitive index of bone marrow suppression.[31] Thus, these hematological values should be determined at reasonable intervals; i.e., weekly for drugs like chloramphenicol and the pyrazolones which involve greater risk and less frequently for drugs like the antithyroid compounds, quinidine, the hydantoins, and the phenothiazines, which often are administered for prolonged periods. A change in any one of these values should immediately lead to further hematological study and to temporary or permament discontinuation of the suspected drug.

SUMMARY

Since 1955, the Study Group on Blood Dyscrasias of the AMA Council on Drugs has received reports on 1,195 cases of blood diseases suspected of having been caused by drugs. A review of these reports reveals that such commonly used drugs

[31] Rubin, D.; Weisberger, A. S.; and Clar, D. R.: Early Defection of Drug Induced Erythropoietic Depression, *J Lab Clin Med* 56 : 453–462 (Sept.) 1960.

as acetylsalicylic acid and penicillin are associated with all varieties of blood diseases but that this association is coincidental and is rarely present if the drugs are given alone. On the other hand, some drugs are predominantly associated with specific blood diseases and often have been found to be the only drugs given to patients who subsequently develop a blood disease. Chloramphenicol is the drug most often associated with pancytopenia; the sulfonamides are most often associated with thrombocytopenia; and the phenothiazines are most often associated with leukopenia. A simple awareness of the potential toxicity of drugs will lead to appropriate examinations and to the establishment of safeguards for the detection and possible prevention of drug-induced blood dyscrasias.

1025 Walnut St., Philadelphia (Dr. Erslev).

[From the Journal of the American Medical Association, Mar. 17, 1962, vol. 179, No. 11, pp. 888–890]

REGISTRY ON BLOOD DYSCRASIAS

REPORT TO THE COUNCIL*

In 1952, the Council on Drugs became concerned with the probelm of hematotoxicosis from the ever-increasing number of therapeutic agents. The Council's former Committee on Research recommended that a Registry on Blood Dyscrasias be formed; and after a 2-year pilot study, the Registry was permanently established. Reports are tabulated for each 6-month period, and the summary tabulation is distributed to medical schools, hospitals, medical societies, and collaborating physicians.

With expansion, the need for a résumé of the tabulated information has become apparent. The reports received by the Registry for the period January 1 to June 30, 1961, were used for this purpose. The information must be considered raw data, since reports are received from many sources and no follow-up is possible.

The résumé is intended to provide concise information regarding common associations between drugs and blood dyscrasias, to acquaint physicians with the existence of the Registry, and to encourage them to report cases of blood dyscrasia in which drugs or other chemicals may be the suspected cause.

RÉSUMÉ OF REPORTS RECEIVED BY REGISTRY ON BLOOD DYSCRASIAS JANUARY 1 TO JUNE 30, 1961

In the period from January 1 to June 30, 1961, 138 new cases of blood diseases suspected of having been caused by drugs or chemicals were reported to the Study Group on Blood Dyscrasias of the American Medical Association. These included cases which were published in the American medical journals during the same period. Forty-eight cases noted in foreign medical journals are reviewed separately.

These findings increase the total number of cases reported since 1955 to 1,504 and the total number of drugs and chemicals reported to be associated with the development of blood dyscrasias to 411. Because of the large number of drugs involved, it has become increasingly difficult to evaluate the data and establish firm etiological relationships between specific drugs and specific blood disorders. However, certain previously unsuspected hematological side effects of drugs may be recognized much earlier if data are gathered from all over the country. Therefore, the Study Group on Blood Dyscrasia feels that it is important to continue to act as a clearinghouse for all suspected instances of hematological side effects which may arise from the use of drugs.

In order to transform the accumulated data into useful information, the Study Group has recommended that a brief analysis of the reported material be prepared. A copy of the complete tabulation is available upon request from the Council on Drugs.

An analysis of the new cases added to the tabulation during the first 6 months of 1961 does not justify any sweeping conclusions or condemnations. The drugs appearing in the tabulation are those which are known to have produced toxic

*The Council has authorized publication of the above report.

reactions and which continue to cause trouble when used or are those drugs which are widely used.

A total of 163 different drugs and chemicals were associated with the 138 cases reported to the Registry during the period in review.

A.—Ninety-eight drugs were associated with one case each. Of these, only imipramine hydrochloride (Tofrānil) requires special mention. This drug was introduced, in 1959, for the treatment of depression. Since that time, it has been reported as a possible causative agent in 9 cases of leukopenia, 2 of which were fatal. However, only one additional case has been reported in the first 6 months of 1961.

B.—Thirty-one drugs were associated with 2 cases each. The potentially toxic effect of quinidine (Asarum, Conchinine, Conquinine, Pitayine, Quindate) on platelets is empahisized by the fact that 2 patients developed thrombocytopenia after the administration of quinidine, the only drug used.

C.—Twelve drugs were associatetd with 3 cases each. Dexamethasone (Decadron, Deronil, Gammacorten), a synthetic analagoue of hydrocortisone, was reported to be associated with 2 cases of pacytopenia and 1 case of leukopenia. This drug is mentioned because it had not previously been associated with the development of blood dyscrasias. However, in all 3 cases, other drugs known to be potentially toxic were administered concurrently; thus, it seems dubious that dexamethasone was the offending agent.

D.—Eight drugs were associated with 4 cases each. A definite cause-effect relationship could not be established in any of these cases because of the variety of blood disorders induced and the many other drugs used concomitantly.

E. Fourteen drugs were associated with 5 or more cases each:

Acetophenetidin (Phenacetin)—8 cases
Acetylsalicylic Acid (Aspirin)—15 cases
Chloramphenicol (Chloromycetin)—56 cases
Chlorothiazide (Diuril)—7 cases
Chlorpromazine (Thorazine)—11 cases
Diphenhydramine (Benadryl)—6 cases
Diphenylhydantoin Sodium (Dilantin Sodium)—5 cases
Meprobamate (Equanil, Meprospan, Meprotabs, Miltown)—7 cases
Novobiocin (Albamycin, Cathomycin)—5 cases
Penicillins—17 cases
Phenobarbital (Luminal)—10 cases
Promazine (Sparine)—5 cases
Sulfisoxazole (Gantrisin)—6 cases
Tetracycline (Achromycin, Panmycin, Polycycline, Tetracyn)—18 cases

As in previous tabulations, the drug associated with the highest number of blood dyscrasias in this period is chloramphenicol. It was the only drug administered *in 23 of the 56 new cases* reported to be associated with the use of chloramphenicol; in 28 of the remaining 33 cases, it had been employed in conjunction with drugs not known to cause blood dyscrasias. These results support the contention that chloramphenicol has a definitely toxic action on the bone marrow; therefore, it is mandatory for the physician to be aware of the potential toxicity of this otherwise valuable antibiotic.

The drugs associated with the next highest number of blood dyscrasies are the tetracyclines and penicillins. In none of the reported cases was one of these antibiotics used as the only drug; in most of the cases they were used in conjunction with drugs known to have toxic potentialities. It is quite possible that the penicillins and tetracyclines have been listed frequently because they have been used in the treatment of early symptoms of illnesses which were later recognized as blood diseases.

Acetylsalicylic acid was reported to have been given to 15 patients who developed blood dyscrasias. This is probably a gross underestimate, since acetylsalicylic acid in some form is used so extensively that it is fair to assume that the great majority of all patients with blood dyscrasias have been exposed to this drug. However, it has been used so long and with such impunity that it seems unlikely that this drug has hidden hematoxic properties. The same may be true in the case of phenobarbital, a widely used sedative.

The remaining drugs, with the possible exception of novobiocin, are all recognized as having potentially hematotoxic side effects; they should be used only with full awareness of this potential danger. As a guide, the members of the Study Group have listed a number of drugs which, in their opinion, have been

shown to have definite hematotoxic side effects. The list does not state the degree of toxicity of the individual drugs; but it indicates that certain drugs have been associated with the development of blood dyscrasias in a manner which has convinced the Study Group that a specific cause-effect relationship exists (Table).

DRUGS OR CHEMICALS SHOWN BY DIRECT OR CIRCUMSTANTIAL EVIDENCE TO BE ASSOCIATED WITH BLOOD DYSCRASIAS

Drug	(1) Hemolytic anemia	(2) Pancytopenia	(3) Thrombocytopenia	(4) Leukopenia	(5) Anemia
Acetanilid	X				
Acetazolamide			X		
Acetophenetidin	X				
Allylisopropylacetylurea			X		
Aminopyrine	X			X	
Arsphenamine		X	X	X	X
Benzene		X	X	X	X
Carbutamide		X	X	X	X
Chloramphenicol		X	X	X	X
Chlordane		X	X	X	X
Chlorothiazide			X	X	
Chlorpromazine				X	
Chlorpropamide		X	X	X	X
Colchicine		X	X	X	X
Diphenylhydantoin sodium					X
Dipyrone				X	
Gamma benzene hexachloride		X	X	X	X
Gold salts		X	X	X	X
Imipramine				X	
Lead					X
Mepazine				X	
Meprobamate		X	X	X	X
Methimazole				X	
Methyl-phenyl-ethyl-hydantoin		X	X	X	X
Naphthalene	X				
Nitrofurantoin	X				
Pamaquin	X				
Para-aminosalicylic acid	X				
Phenindione				X	
Phenylbutazone		X	X	X	X
Phenylhydrazine	X				
Primiaquine	X				
Primidone					X
Probenecid	X				
Promazine				X	
Pyrimethamine			X	X	X
Quinacrine		X	X	X	X
Quinidine	X		X		
Quinine			X		
Ristocetin			X		
Stibophen	X				
Streptomycin		X	X	X	X
Sulfacetamide	X				
Sulfadiazine				X	
Sulfamethoxypyridazine	X	X	X	X	X
Sulfanilamide	X			X	
Sulfisoxazole			X	X	
Sulfoxone	X				
Thiazolsulfone	X				
Thiobarbital				X	
Thiouracils				X	
Tolbutamide		X	X	X	X
Trimethadione		X	X	X	X
Trinitrotoluene		X	X	X	X

In the foreign medical journals, 48 cases incriminating 34 different drugs were reported during the first 6 months of 1961:

Twenty drugs were associated with 1 case each.
Seven drugs were associated with 2 cases each.
Two drugs were associated with 3 cases each.
Two drugs were associated with 4 cases each.

With the exception of benzene (Benzol, Cyclohexatriene), no definite cause-effect relationship could be established between these 31 drugs and chemicals and the associated blood dyscrasias. The fact that benzene was reported to be the only

possible offending agent in 3 cases of pancytopenia reemphasizes this drug's known marrow-suppressive properties.[1]

Three drugs were associated with 5 or more cases:

Acetophenetidin (Phenacetin)—5 cases.

Aminopyrine—8 cases.

Sulfonyldianiline (Dapsone, Avlosulfon)—8 cases.

Sulfonyldianiline was reported to have been the only drug given to 8 patients who subsequently developed anemia.[2] This drug has previously been associated with the development of one case of pancytopenia and 2 cases of anemia. Its chemical name is 4,4-diaminodiphenylsulfone, and it is used for the treatment of leprosy and dermatitis herpetiformis. Since it is so rarely used, the large number of cases in the tabulation must be viewed with some concern. Sulfonyldianiline should be used only with full awareness of its potentially toxic effect.

Aminopyrine, an old drug of well-known toxicity, continues to be responsible for many cases of granulocytopenia. Acetophenetidin was found to be associated with a number of cases, both here and abroad; this is not surprising in view of its wide employment as an analgesic.

This analysis did not unearth any new, commonly used toxic drugs. However, it did reemphasize the fact that many drugs are potentially toxic, and that there is always a calculated risk in administering drugs to patients. In order that the medical profession may be served in the most efficient manner, the Study Group urges every physician to report to the AMA Council on Drugs immediately if he should suspect that a blood disease may have been caused by a drug or chemical. A smoothly functioning reporting system will aid the Study Group in the early detection of any hematotoxic properties in new drugs and will enable it to alert the medical profession to such potential dangers. Report forms may be obtained from the Council on Drugs, American Medical Association, 535 N. Dearborn St., Chicago 10.

[From the Journal of the American Medical Association, July 8, 1961, vol. 177, No. 1, pp. 23–26]

Drug-Related Blood Dyscrasias

(By Charles M. Hugulay, Jr., M.D., Atlanta, Ga.; Allan J. Erslev, M.D., Philadelphia, Pa.; and Daniel E. Bergsagel, M.D., Houston, Tex.*)

Side effects of drugs constitute a continuing problem which has 2 aspects: (1) the known risk of occasional idiosyncrasy from an established drug and (2) the as yet undetermined potentiality of a newly introduced drug to produce serious side effects in an occasional patient. Among the most serious side effects of drugs is the development of a blood dyscrasia: agranulocytosis, aplastic anemia, hemolytic anemia or thrombocytopenia.

The Study Group on Blood Dyscrasias of the AMA Council on Drugs is charged with the task of investigating possible relationships of drugs to blood dyscrasias. Although the medical profession is aware of the possibility that blood dyscrasias may be produced by newly introduced drugs, the lack of a means for reporting such instances has sometimes led to long delays in the accumulation of a sufficient number of cases to arouse a suspicion concerning the drug. To provide a more rapid means of collecting information, a Registry of Blood Dyscrasias has been established, and physicians are encouraged to report to this Registry all cases of drug-induced blood dyscrasias. A simple report form has been devised and all drugs known to have been administered during the past 6 months preceding the onset of the blood dyscrasia are listed. In addition to the reports submitted, a search of the world literature is now made so that cases gathered from this source are also incorporated in a semi-annual tabulation. This tabulation is available upon request.

---

[1] McLean, J. A.: Blood Dyscrasia After Contact with Petrol Containing Benzol, *Med J Aust* (no. 2) 47: 845 (Nov. 26) 1960.

[2] Gentele, H.; Lagerholm, B.; and Lodin, A.: Macrocytic Anemia Associated with Dermatitis Herpetiformis and 4,4-Diaminodiphenylsulfone Treatment, *Acta Dermatovener (Stockh)* 40: 334, 1960.

*Associate Professor of Medicine, Emory University School of Medicine (Dr. Huguley); Associate Professor of Medicine, Jefferson Medical College (Dr. Erslev); Associate Hematologist, Department of Medicine; University of Texas, M. D. Anderson Hospital and Tumor Institute (Dr. Bergsagel).

A registry, established to study blood dyscrasias that might be related to drugs, received 448 reports of such cases during the year 1960. There were 97 cases of pancytopenia. Among the 31 cases in which a single drug was implicated, 5 drugs were associated with more than 1 case: chloramphenicol, methyl-phenyl-ethyl-hydantoin, phenylbutazone, and the 2 insecticides, gamma benzene hexachloride and chlordane. There were 44 cases of thrombocytopenia, and among the 16 cases in which a single drug was implicated the one most frequently involved was quinidine (5 cases). Among 93 cases of leukopenia there were 8 in which chlorpromazine was the only drug implicated. It is evident that certain drugs must be used only if the physician is alert, and alerts his patient, to the fever, sore throat, weakness, pallor, or bleeding that may be the first sign of developing blood dyscrasia.

Such a system has many inadequacies, but it does make available more cases for study than the review of the literature alone. Thus, the Registry has served to emphasize the continued high association of chloramphenicol administration in patients who develop aplastic anemia, the potentiality of chlorpromazine and promazine to produce agranulocytosis, and the production of thrombocytopenia by ristocetin (Spontin). Attention has been called to such findings by a series of statements published in the Journal.[1-4]

A total of 1,318 cases of blood dyscrasias possibly related to drugs were reported to the Registry as of Dec. 31, 1960. In many instances, multiple drugs had been given. However, even when only one drug had been administered prior to diagnosis, a causal relationship might not have existed. This is particularly true of drugs which are used very commonly. Nevertheless, when reports indicate a frequent association of a particular drug with blood dyscrasias, caution is warranted.

REPORTS TO THE REGISTRY OF BLOOD DYSCRASIAS

During the year 1960, the Registry received 448 reports of blood dyscrasias. There were 97 cases of pancytopenia. Of the 31 cases in which exposure to only one agent was reported, five drugs were associated with more than one case: chloramphenicol (Chloromycetin), methyl-phenyl-ethyl-hydantoin (Mesantoin), phenylbutazone (Butazolidin), and the insecticides, gamma benzene hexachloride and chlordane (see Table 1). Chloramphenicol was reported as the only drug given to 19 patients and had been given in association with other drugs in 34 other patients, a total of 53 of the entire 97 cases of pancytopenia.

TABLE 1.—REPORTED INCIDENCE OF PANCYTOPENIA ASSOCIATED WITH DRUG ADMINISTRATION (1960)

Drug	Only drug	With other drugs	Total
Total cases			97
Chloramphenicol (Chloromycetin)	19	34	53
Methyl-phenyl-ethyl-hydantoin (Mesantoin)	2	3	5
Phenylbutazone (Butazolidin)	3	3	6
Gamma Benzene hexachloride (insecticide)	2	1	3
Chlordane (insecticide)	2	3	5

Thrombocytopenia was reported in 44 cases. Here again only five drugs were reported in more than one case as the only drug administered. The drugs are listed in Table 2.

[1] Blood Dyscrasias Associated with Chlorpromazine Therapy, *JAMA* 160:287 (Jan. 28) 1956.
[2] Blood Dyscrasias Associated with Promazine Hydrochloride Therapy, *JAMA* 165:685–686 (Oct. 12) 1957.
[3] Development and Purpose of Registry of Blood Dyscrasias, *JAMA* 170:1925–1926 (Aug. 15) 1959.
[4] Blood Dyscrasias Associated with Chloramphenicol (Chloromycetin) Therapy, *JAMA* 172:2044–2045 (April 30) 1960.

TABLE 2.—REPORTED INCIDENCE OF THROMBOCYTOPENIA ASSOCIATED WITH DRUG ADMINISTRATION (1960)

Drug	Only drug	With other drugs	Total
Total cases			44
Chloramphenicol (Chloromycetin)	3	3	6
Quinidine	5	3	8
Sulfamethoxypyridazine (Kynex, Midicel)	3	0	3
Chlorothiazide (Diuril)	3	1	4
Hydrochlorothiazide (HydroDiuril)	2	0	2

Leukopenia was reported 93 times. Only 4 drugs appeared more than once as the only drug administered prior to onset. These drugs are listed in Table 3.

TABLE 3.—REPORTED INCIDENCE OF LEUKOPENIA ASSOCIATED WITH DRUG ADMINISTRATION (1960)

Drug	Only drug	With other drugs	Total
Total cases			93
Chlorpromazine (Thorazine)	8	13	21
Imipramine (Tofranil)	2	6	8
Methimazole (Tapazole)	2	1	3
Phenylbutazone (Butazolidin)	4	3	7

Of the entire 448 cases, chloramphenicol had been given alone to 24 patients and together with other drugs to 46 patients, a total of 70 patients. Phenylbutazone was the only drug administered to 8 patients and was received by a total of 17 patients. Both of these drugs were associated with cases of each type of blood dyscrasia under discussion here. As a rule, other drugs tended to be related to only one type of dyscrasia; for example, of the 22 patients who developed a dyscrasia after receiving chlorpromazine, 21 had leukopenia, and all 8 cases associated with quinidine administration were thrombocytopenia.

Members of the Study Group have compiled a list of cases with hypoplastic anemia and agranulocytosis seen in their respective institutions during 1959 and 1960. In each case an opinion was rendered as to whether the dyscrasia probably was or probably was not caused by a specific drug. In this 2-year period, 74 cases of hypoplastic anemia were seen at these 8 institutions and, of these, 33 were thought to be unrelated to drugs. Thirty-three were associated with the administration of chloramphenicol and 8 with other drugs. The idiopathic cases were about equally divided by age and sex, whereas among the cases associated with chloramphenicol administration there were 28 females and only 5 males. Twenty-seven of these 33 patients were in the 1 to 10-year-old age group. This predilection of hypoplastic anemia associated with chloramphenicol for young girls has been noted previously.[5] Thirty-three of the total 74 patients were already dead, and only 9 had recovered during the short period of follow-up.

The production of a blood dyscrasia by a drug is not usually the result of the pharmacological properties of the drug but more often is the consequence of an idiosyncrasy in the patient which produces a sensitivity to the drug. In some types of drug-related blood dyscrasias, the pathogenetic mechanism is understood and can be demonstrated by laboratory methods. In other types, the mechanism is wholly unknown.

Drug-induced hemolytic anemia is a classic example of the type of blood dyscrasia in which the pathogenetic mechanism has been demonstrated. In the red blood cells of the susceptible person there is a deficiency of an enzyme, glucose-6-phosphate dehydrogenase (G-6-PD), which is important in the metabolism of glucose. A side effect of the action of the enzyme is the maintenance of a supply of reduced glutathione (GSH). Deficiency of this enzyme in erythrocytes is a newly recognized heritable disorder and can be demonstrated by incuba-

[5] Welch, H.; Lewis, C. N.; and Kerlan, L.: Blood Dyscrasias: Nationwide Survey, *Antibiot Chemother* 4: 607–623 (June) 1954.

tion with acetylphenylhydrazine, which results in a fall in the erythrocyte content of GSH. The depletion of GSH is somehow related to the susceptibility of the erythrocyte to destruction. It is possible by testing for G–6–P dehydrogenase activity or for glutathione instability in the erythrocytes to determine the susceptibility of a given person to drug-induced hemolytic anemia. Among the drugs which can produce acute hemolytic anemia in susceptible persons are the 8-aminoquinoline antimalarials, such as primaquine, certain sulfonamides, acetanilid, acetophenetidin, nitrofurantoin (Furadantin), and many others. Favism is associated with the same or a closely related heritable deficiency. The subject has been reviewed by Beutler.[6]

Hemolytic anemia can also be produced through an immune mechanism in which antibodies are formed against a combination of the drug and the erythrocyte and may lead to agglutination of and damage to the erythrocyte only in the presence of the drug. Such a mechanism has been demonstrated in hemolytic anemias produced by stibophen (Fuadin)[7] and quinidine.[8] This is very rare.

Thrombocytopenia has been produced through a similar immune mechanism by drugs such as allylisopropylacetylurea (Sedormid),[9] quinidine, and quinine. This mechanism, however, has not been demonstrable in all cases of thrombocytopenia attributed to drugs.

In some cases of agranulocytosis due to drugs, an immunologic mechanism has been demonstrated, for example, in agranulocytosis produced by aminopyrine.[10] In other cases such a mechanism could not be shown. Aminopyrine and dinitrophenol, the drugs first shown to produce agranulocytosis, are now seldom the cause of granulocytopenia because they are seldom used. The antithyroid drugs, propylthiouracil, methylthiouracil, and methimazole (Tapazole) and the phenothiozine derivatives, notably promazine (Sparine) and chlorpromazine (Thorazine) are the more common causes of agranulocytosis today.

Aplastic anemia remains the most difficult problem among drug-induced blood dyscrasias because it has such a serious prognosis and because it takes so long to recognize the casual relationship to a drug. The mechanism of production is unknown. Only a very small proportion of the patients who receive a drug capable of producing aplastic anemia will be sensitive to it. Pancytopenia may appear only after prolonged administration or repeated courses of the drug. Most patients with aplastic anemia have received several drugs. Furthermore, aplastic anemia may occur in patients who have had no known exposure to drugs or toxic chemicals. These factors may be responsible for the late recognition of the relationship of a drug to aplastic anemia. Nevertheless, some drugs have been so often associated with aplastic anemia as to leave no doubt that they can produce it. In recent years the most common agent associated with aplastic anemia has been chloramphenicol (chloromycetin).

Because chloramphenicol is associated with such a large proportion of the cases of pancytopenia reported in recent years, it is appropriate to consider in more detail the hemopoietic effects of this drug. Chloramphenicol has been observed to cause a general inhibition of protein synthesis by bacteria[11] and has been shown to block the synthesis of many enzymes.[12] Two types of hematological toxicity have been observed: (1) a temporary erythroid hypoplasia, associated with anemia and occasionally with thrombocytopenia and leukopenia, and (2) a severe, often fatal, pencytopenia.

---

[6] Beutler, E.: Drug-Induced Hemolytic Anemia, in *Metabolic Basis of Inherited Disease*, edited by J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson, New York: McGraw-Hill Book Company, 1960, pp. 1031–1067.

[7] Harris, J. W.: Studies on Mechanism of Drug-Induced Hemolytic Anemia, *J Lab Clin Med* 47: 760–775 (May) 1956.

[8] Freedman, A. L.; Barr, P. S.; and Brody, E. A.: Hemolytic Anemia Due to Quinidine: Observations on Its Mechanism, *Amer J Med* 20: 806–816 (May) 1956.

[9] Ackroyd, J. F.: Role of Sedormid in Immunologic Reaction that Results in Platelet Lysis in Sedormid Purpura, *Clin Sci* 13: 409–423 (Aug.) 1954.

[10] Moeschlin, S., and Wagner, K.: Agranulocytosis Due to Occurrence of Leukocyte-Agglutinins, *Acta Haemat* 8: 29–41 (July-Aug.) 1952.

[11] Gale, E. F., and Folkes, J. P.: Assimilation of Amino Acids by Bacteria: 15. Actions of Antibiotics on Nucleic Acid and Protein Synthesis in Staphylococcus Aureus, *Biochem J* 53: 493–498 (Feb.) 1953.

[12] Brock, T. D.: Chloramphenicol, *Bact Rev* 25: 32–48 (March) 1961.

The temporary erythroid hypoplasia has been observed mainly in patients given large doses of chloramphenical, 4 to 12 gm. daily for 10 to 35 days.[13–16] A retriculocytopenia,[13, 15–17] a rise in serum iron, a reduced rate of clearance of plasma Fe-59, and blockade of the uptake of Fe-59 by erythrocytes[14] have been the first changes noted. These changes are followed by anemia. Some patients have developed thrombocytopenia[13, 15] and some have had leukopenia.[15, 16] Marrow studies have revealed erythroid hypoplasia[15] with abnormal vacuolization of the cytoplasm of erythroblasts[16, 17] and sometimes of cells of the myeloid series.[13] When chloramphenicol is discontinued, all of these abnormalities are reversed. Reticulocytosis develops within 5 to 7 days, with peaks as high as 17.6%,[16] and the hemoglobin level returns to normal. Following recovery from erythroid hypoplasia, one of the above patients was given 2 gm. of chloramphenicol per day for 7 days without recurrence of toxicity, but when the dose was raised to 12 gm. per day the anemia reappeared.[13] Patients with infection or anemia seem to be more susceptible to this effect of chloramphenicol than are normal people.[17] The administration of chloramphenicol to patients with pernicious anemia blocks the reticulocyte response to vitamin B_{12} and, in patients with iron deficiency anemia, it blocks the response to intramuscular administration of iron.[17] Reticulocytosis occurs in these patients several days after chloramphenicol is discontinued.

The other hematologic response to chloramphenicol is a severe pancytopenia. All of the marrow cell types are affected, and the marrow is hypoplastic. The process is progressive over a long period of time, and recovery, if it occurs, is slow. This complication has been observed in patients treated with conventional doses, and appears to be more common in children, especially young girls.[5] Test doses of chloramphenicol have seldom been given to patients who have recovered from pancytopenia. One unpublished case has been reported; the patient received a second course of chloramphenicol following recovery from marrow toxicity thought to be due to previous chloramphenicol administration.[18] This patient, a 15-month-old male infant, received 125 mg. of chloramphenicol every 6 hours for 8 doses before the initial dyscrasia was reported. The total leukocyte count fell from 9,800 per cubic millimeter on the day therapy was started to 3,800 on the second day, 1,900 on the fourth day and then gradually returned to normal. This dose of chloramphenicol is tolerated without demonstrable blood changes by the vast majority of patients who receive it and, thus, this reaction is suggestive of a drug idiosyncrasy. The mechanism by which chloramphenicol produces aplastic anemia appears to be different from that which leads to the acute changes in erythropoiesis. The difference may be only quantitative, however.

SUMMARY

It is incumbent upon the physician to maintain a lively awarness of the risk of blood dyscrasia associated with the use of certain drugs and to use such drugs only when the potential benefits of administration considerably outweigh the relatively small risk of developing a blood dyscrasia. When it is necessary to use such drugs, it is important that appropriate hematological studies be made at intervals and that the patient be warned to report immediately the development of fever, sore throat, weakness and pallor, or a bleeding tendency. Conversely, it is also important that the physician be aware that in the event of development of infection or easy bruising in a patient who has been taking such drugs, blood cell counts must be made immediately. If agranulocytosis, thrombocytopenia, or pancytopenia is present, further administration of the drug must be stopped. Needless to say, this is the most important therapeutic measure.

---

[13] Krakoff, I. H.; Karnofsky, D. A.; and Burchenal, J. H.: Effects of Large Doses of Chloramphenicol on Human Subjects, *New Engl J Med* 253: 7–10 (July 7) 1955.

[14] Rubin, D.; Weisberger, A. S.; Botti, R. E.; and Storaasli, J. P.: Changes in Iron Metabolism in Early Chloramphenicol Toxicity, *J Clin Invest* 37: 1286–1292 (Sept.) 1958.

[15] Ozer, F. L.; Truax, W. E.; and Levin, W. C.: Erythroid Hypoplasia Associated with Chloramphenicol Therapy, *Blood* 16: 997–1001 (July) 1960.

[16] Rosenbach, L. M.; Caviles, A. P.; and Mitus, W. J.: Chloramphenicol Toxicity: Reversible Vacuolization of Erythroid Cells, *New Engl J Med* 263: 724–728 (Oct. 13) 1960.

[17] Saidi, P.; Wallerstein, R. O.; and Aggeler, P. M.: Effect of Chloramphenicol on Erythropoiesis, *J Lab Clin Med* 57: 247–256 (Feb.) 1961.

[18] Unpublished Report.

[From the Journal of the American Medical Association, May 20, 1961, vol. 176, No. 7, pp. 588–593]

CHLORAMPHENICOL BONE MARROW TOXICITY

(By Paul R. McCurdy, M.D., Washington, D.C.*)

The capacity of chloramphenicol to suppress bone marrow activity has recently been reemphasized.[1] Although the incidence of irreversible or slowly reversible blood dyscrasia caused by chloramphenicol is not great, the serious nature of these effects is sufficient reason to restrict its use to situations in which an equally effective and less toxic antibiotic is not available. The purpose of this report is to present studies in 15 patients in whom early toxicity was recognized by morphologic studies available to the clinician, and the drug was discontinued before irreversible damage occurred.

Recent studies [2, 3, 3a] have suggested that the occurrence of marrow toxicity due to chloramphenicol is more frequent than is indicated by sporadic reports of aplastic anemia which continue to appear in the literature. Using sensitive radioiron techniques, Rubin et al. found evidence for suppression of red blood cell production in 5 of 15 patients tested.[2] Saidi and associates reported morphologic changes in the primitive red cells of the marrow in each of 10 patients who received 40–85 mg/kg. of chloramphenicol per day, whereas 12 subjects who received 11–45 mg/kg. per day had no such changes.[3, 3a] When Krakoff et al. gave 6 or more grams of chloramphenicol daily to 4 patients with carcinoma, toxic depression of the hemoglobin and reticulocyte count was found in each.[4] The latter 2 reports suggest that the occurrence of toxicity is partially dose-dependent, an effect which previously has not been emphasized.

Eleven patients were seen in consultation because of anemia or bleeding during chloramphenicol therapy. Four others were being treated with chloramphenicol without the physician in charge being aware of the subtle hematologic changes that were under way. Depression of erythropoiesis, manifested in a drop in reticulocyte count, was the first and most frequent warning of trouble; it was followed in order by suppression of thrombopoiesis and leukopoiesis. The reversible stage is unpredictable and sometimes quite short. In each of these cases the bone marrow recovered after chloramphenicol administration was stopped. Chloramphenicol should not be given for trivial infections. When it must be used, serial reticulocyte counts should be done, and a sudden or severe drop calls for study of the bone marrow.

MATERIAL AND METHODS

Intensive hematologic investigations on 15 instances of bone marrow depression believed to have been produced by chloramphenicol form the clinical material for this report. Eleven patients (cases 1–9, 14, and 15) were seen in consultation because of an anemia or because of bleeding and thrombocytopenia. Four patients (cases 10–13) were being treated with chloramphenicol, but the physicians in charge were not aware of the subtle hematologic changes which were under way. In 12 of the 15 patients bone marrow punctures and cell studies were done during the period of toxicity. The slides of all these were available for retrospective interpretation of morphologic changes. In two instances the marrow was examined early during recovery, and in the final case the marrow was not examined. In 4 patients, serial bone marrow aspirates were examined before, during, and after recovery from the suppressive effects of chloramphenicol.

REPORT OF CASES

Case 1.—A 64-year-old Negro male was admitted to the hospital because of mental deterioration and heart disease and was treated for pneumonia with 2 gm. (28 mg/kg.) chloramphenicol daily for 24 days. The hematocrit reading fell from 40 vol.% prior to therapy to 21 vol.%. Reticulocyte count was 0.4%, platelet

*From the Department of Medicine, Georgetown University School of Medicine and Georgetown Medical Division, D.C. General Hospital. Assistant Professor of Medicine, Georgetown University School of Medicine and Medical Officer, D.C. General Hospital.

NOTE.—Numbered footnotes at end of article, p. 2742.

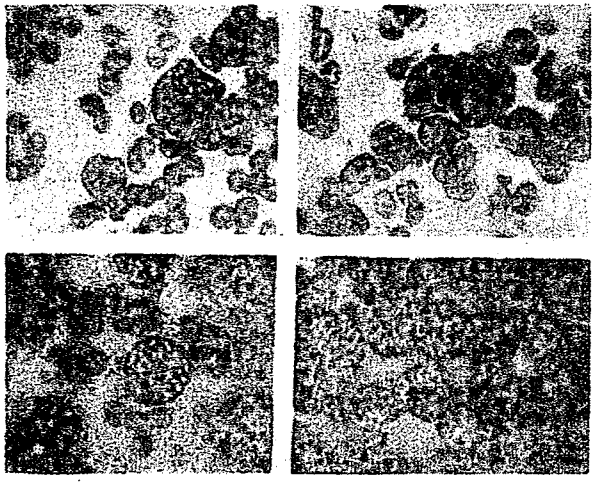


Fig. 1.—Vacuolization of primitive red cell precursors of marrow in chloramphenicol toxicity. *a*, Case 1; *b*, Case 7; *c*, Case 9; *d*, Case 13.

count was 27,000, and white blood cell count was 5,200. Bone marrow was normally cellular, but red blood cell elements were reduced and early forms contained vacuoles (Fig. 1*a*). White blood cells were normal on the peripheral blood smear. The patient had also received meprobamate, choline theophyllinate, tetracycline, and bis-hydroxycoumarin, but all had been discontinued 2 or 3 weeks prior to the discovery of marrow toxicity. He was given 600 ml. of sedimented red blood cells, and chloramphenicol was discontinued, but he died of heart disease prior to complete marrow recovery. At postmortem examination, 5 days after administration of the last drug, there was still a definite reduction of erythroid cells in the marrow. Other marrow elements were normal. There was minimal early liver cirrhosis.

Case 2.—A 50-year-old Negro female was admitted because of pneumonitis. She received 2 gm. (42 mg/kg.) of chloramphenical daily for 17 days and again for 27 days after a 6-day rest. At the end of the second course, the hematocrit was 23 vol.%, reticulocyte count 0.0% and white blood cell count 10,375. Platelets were adequate on the peripheral blood smear. The bone marrow was cellular, but there was a reduction in the red blood cell elements. The rubriblasts and prorubricytes were vacuolated. The drug was stopped and 600 ml. of sedimented red cells were administered. The hematocrit reading rose to 31 vol.%, where it stabilized. Twelve days later, the reticulocyte count was 2.3%. Although she had received promethazine hydrochloride in addition to streptomycin during the first course of chloramphenicol, no medicaments except milk of magnesia and cascara were given during the second course, when marrow suppression became evident. One month later, after apparently complete recovery from marrow hypoplasia, she died of her pulmonary infection. At postmortem examination, the liver was found to contain minimal fatty infiltration. The bone marrow was hyperplastic in all hematopoietic elements.

Case. 3.—A 55-year-old Negro male was admitted because of coma and convulsions. He had a short, acute psychosis, compatible with dilirium tremens. He was given 2 gm. (37 mg/kg.) of chloramphenicol prophylactically for 22 days. At the end of this time he had hematemesis. The hematocrit level had fallen from 45 to 26 vol. % and the platelet count was 30,000. Reticulosytes were 0.1% and the white blood cell count, 3,600. The marrow was hypocelluar and the primitive rubriblasts contained vacuoles. He was given 2,000 ml. of whole blood and chloramphenicol therapy was discontinued. Four days later the hematocrit reading was 35 vol.%, reticulocytes 1.8%, white blood cells, 7,375, and platelets were 47,000. After 2 weeks the hematocrit was 44 vol.%, reticulocytes 1.5%, white