COMPANY	PRODUCT	NO. ISSUES		NO. PAGES
CIBA				
	1. Doriden	11		18
	2. Ismelin	7		21
	3. Regitine	6		6
	4. Ritalin	10		23
	5. Ser-Ap-Es	6		19
			Total...	87
Dome				
	1. Aminet	3	Total...	3
duPont				
	1. Symmetrel	4	Total...	7
Eaton Laboratories				
	1. Furadantin	7	Total...	7
Endo Laboratories				
	1. Percodan	3		3
	2. Valpin	2		2
			Total...	5
Flint Laboratories				
	1. Choloxin	2	Total...	6
Geigy				
	1. Butazolidin	10		20
	2. Hygroton	9		21
	3. Pertofrane	8		16
	4. Preludin	7		14
	5. Tofranil	12		23
			Total...	94
Glenwood				
	1. Patoba	12	Total...	12
Hoechst				
	1. Lasix	9	Total...	36
Ives Laboratories				
	1. Isordil	2	Total...	2

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COMPANY	PRODUCT	NO. ISSUES		NO. PAGES
Key Pharmacal				
	1. Nitroglyn	9	Total...	9
Lakeside Laboratories				
	1. Cantil	6	Total...	6
Lederle Laboratories				
	1. Aristocort	6		12
	2. Artane	6		12
	3. Declomycin	6		12
	4. Diamox	4		4
	5. Hydromox	7		14
	6. Pathibamate	10		20
			Total...	74
Lilly, Eli, & Co.				
	1. Aventyl	10		28
	2. Dymelor	12		39
	3. Darvon	12		24
			Total...	91
McNeil				
	1. Butiserpine	11		11
	2. Butisol	11		22
			Total...	33
Massengill Company				
	1. Oberdrin-LA	9	Total...	9
Mead-Johnson				
	1. K-Lyte	4		8
	2. Mucomyst	5		20
	3. Peri-Colace	11		11
	4. Quibron	3		6
	5. Vasodilan	12		48
			Total...	93

AMERICAN FAMILY PHYSICIAN
1966

COMPANY	DRUG	NO. ISSUES	NO. PAGES
Abbott			
	1. Compocillin	5	10
	2. Erythrocin-Sulfas	7	18
	3. Surbex-T	1	1
		Total...	29
Armour			
	1. Chymar	1	2
	2. Chymoral	2	4
	3. Pentritol	3	6
		Total...	12
Cole			
	1. Indo-Niacin	3	Total... 6
Endo			
	1. Hycomine	2	4
	2. Valpin	12	12
		Total...	16
Fesler			
	1. Trichotine	5	Total... 5
Geigy			
	1. Butazolidine-Alka	6	6
	2. Persantin	7	10
	3. Pertofrane	2	14
	4. Preludin	4	8
		Total...	38
Hankskraft			
	1. Zymenol	5	Total... 5
Lederle			
	1. Peretinic	6	Total... 6
Massengill			
	1. Obedrin-LA	6	Total... 6

COMPANY	DRUG	NO. ISSUES	NO. PAGES
McNeil			
	1. Butigel-Zyme	4	4
	2. Butiserzapide	11	20
	3. Butiserpine	5	5
	4. Parafen-Forte	12	12
	5. Tylenol	9	19
		Total...	60
Mead-Johnson			
	1. Trind	8	8
	2. Vasodilan	4	32
		Total...	40
Neisler			
	1. Rynatan/Rynatuss	3	6
	2. Dainite-KL	5	5
		Total...	11
Ortho			
	1. Delfen	3	3
	2. Ortho-Novum	10	22
		Total...	25
Parke-Davis			
	1. Benadryl	7	7
	2. Benylin	7	7
	3. Cosanyl	3	3
	4. Carbrital	12	12
	5. Initia	5	5
	6. Myadec	7	7
	7. Thera-Camber	11	11
		Total...	52
Pfizer			
	1. Bonine	2	4
	2. Daricon	3	3
	3. Diabinese	3	11
		Total...	18
Roche			
	1. Librium	8	8
	2. Valium	5	5
		Total...	13

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APPENDIXES

HEARING DATES*

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

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, FEBRUARY 19, 1969

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

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

Present: Senators Nelson, McIntyre, and Dole.

Also present: Senator Byrd of Virginia.

Chester H. Smith, staff director and general counsel; Benjamin Gordon, staff economist; Jay Cutler, acting minority counsel; and Elaine C. Dye, clerical assistant.

Senator NELSON. The committee is pleased to welcome this morning the Senator from Virginia, Senator Harry Byrd, who will at this time introduce one of his distinguished constituents as the first witness this morning.

Senator Byrd.

STATEMENT OF HON. HARRY F. BYRD, JR., A U.S. SENATOR FROM THE STATE OF VIRGINIA

Senator BYRD. Thank you, Mr. Chairman, Senator McIntyre. I appreciate the committee giving me the opportunity to present this morning to the committee, a splendid, outstanding citizen of Virginia, Dr. William J. Hagood, Jr., from Clover in Halifax County.

For the benefit of my New Hampshire friends I might say that Halifax County is near the border of North Carolina. It is one of the larger counties of our State, and Dr. Hagood, along with his cousin, Dr. Warren Hagood, his uncle, Dr. James D. Hagood, practice medicine and operate a medical clinic in Halifax County.

These are Virginians, all three, who have the confidence of the people of their area. Dr. William J. Hagood, Jr., who will speak this morning, is well known throughout the State. He is public spirited. He takes a keen interest in the problems of the people of our State.

I might say that his partner, and his uncle, Dr. James D. Hagood, is the senior member of the Virginia Senate. He is the president pro tempore of the Virginia Senate. He is chairman of the senate finance committee. He has been elected to the Virginia Senate more times than Carl Hayden was elected to the U.S. Senate, and he is equally as beloved in our State, and in the Virginia Senate, as was Senator Hayden in the U.S. Senate.

So it is a privilege and a pleasure to present to this distinguished committee a very fine Virginian, and one in whom the people of Virginia have great confidence, Dr. William J. Hagood, Jr.

Senator NELSON. Thank you, Senator Byrd.

Dr. Hagood comes from a part of your State where my wife has so many relatives, it is almost a mathematical certainty that one of them was a patient of the Hagood Clinic.

Senator BYRD. I might say, Mr. Chairman, that we in Virginia are very proud of the fact that Mrs. Nelson is a native of Wise County in our State.

Senator NELSON. Thank you, Senator Byrd.

First let me mention that Senator Tom McIntyre is a new member of the Senate Small Business Committee, and a new member of the Monopoly Subcommittee, and, as chairman, I am pleased to have him join us this morning in these hearings.

This morning the Senate Small Business Committee's Monopoly Subcommittee resumes its hearings on problems in the drug industry.

Our first witness was to be Dr. Philip R. Lee, Assistant Secretary for Health and Scientific Affairs with the Department of Health, Education, and Welfare. I should have said the "former" Assistant Secretary because Dr. Lee's resignation became effective just this past Monday. Dr. Lee has resigned from his post with HEW to accept the position of chancellor at the University of California Medical Center in San Francisco and he was asked to report to the university immediately.

We are, of course, disappointed that he is unable to be with us in person. However, Dr. Lee has submitted his statement for the record and it will be printed in the record in full. This statement has been distributed to the press.

(The statement of Dr. Lee follows:)

STATEMENT BY PHILIP R. LEE, M.D., ASSISTANT SECRETARY FOR HEALTH AND SCIENTIFIC AFFAIRS, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Mr. Chairman, last September 25th, I had the honor of appearing before the Subcommittee to report on some of the interim findings and recommendations of the Task Force on Prescription Drugs. At that time, we had not reached our findings on the principal charge to the Task Force—to determine whether it is both necessary and feasible to include prescription drugs as a benefit in the Medicare program.

We have now completed our studies and the answer to both questions is an unequivocal yes.

To reach this conclusion, the Task Force needed and obtained detailed information about the manufacture, distribution, promotion, prescribing, and use of prescription drugs in this country and abroad. We have made this information widely available in a series of five interim reports and four background papers, entitled "The Drug Users," "The Drug Makers and The Drug Distributors," "The Drug Prescribers," and "Current American and Foreign Programs." A fifth background paper, "Approaches to Drug Insurance Design," and a final summary report are in press and will be released very shortly. Mr. Chairman, I am pleased to submit these reports for the Subcommittee's records.

These reports say a great deal about the use of prescription drugs in our society. Most central to our mission, however, was their use by the elderly. We found that our 20 million citizens age 65 and older spend nearly three times as much each year for prescription drugs as the average for all Americans. We found that a significant number of these drugs are used over long periods of time in the treatment of serious chronic conditions. At the same time, we found that for many of the elderly, their incomes, assets, protection through health insur-

ance, and the relief they obtain through income tax deductions are simply inadequate.

These and other findings point directly to the need for a Medicare drug insurance program, and we have spelled out in great detail the alternatives for the development of such a program. The recommendations of the Task Force related to the Medicare program are now under study in the Departmnt, and I expect that the Secretary will reach a decision on this within the next few weeks. He has not yet had the opportunity to review many of the other recommendations of the Task Force.

In reaching our conclusions, Mr. Chairman, the members of the Task Force were not unaware of the sensitive social and economic issues that are involved in the marketing of prescription drugs. We were aware of the significant price differences between brand name drugs and their generic name counterparts, and of questions that have been raised about their relative efficacy. We also had to consider the profusion of available drugs, including large numbers of combination products and so-called "me-too" drugs, and whether Federal funds should be used to support the market for these and other non-essential drugs. In other words, we had to decide whether the scope of benefits in a Medicare drug program could be restricted without reducing the quality of health care and without depriving physicians of access to valuable therapeutic agents.

Although these and other aspects of the Task Force investigations were all related to the question of including prescription drugs as a Medicare benefit, many of them have much wider significance. One of them that is of particular concern to me, has to do with the explosive growth of drug research, development, promotion, and marketing, and the profound effect this has had upon the use of drugs, and indeed, upon the entire practice of medicine.

In our lifetime, the pharmaceutical industry has become an increasingly complex research and development enterprise. Beginning with research at the turn of the century related to epinephrine and other sympathomimetic drugs, we can trace a continuing series of developments, including vitamins, insulin, the sulfonamides, analgesics, antibiotics, steroids, antimalarials, tranquilizers, antihistamines, and the growing battery of modern chemotherapeutic agents and biologicals. Drug development, production, and sales in the last thirty years have raised the drug industry in the United States from a $300 million to a $5 billion-a-year operation.

The striking growth in the availability of increasingly potent and dramatically effective drugs has done much to increase the effectiveness of the physician in lengthening life and alleviating suffering. At the same time, it has made the pharmaceutical industry, the makers and sellers of drugs, among the most influential members of what has been called "the health team." Its influence has been brought about not only as a result of epochal advances in biology, pharmacology, chemistry, and medicine, but also because of profoundly significant changes in the scope and methodology of drug promotion.

Much has been said in these hearings and elsewhere about the use of advertising and promotion to create a market for new drugs and maintain markets for older ones. The Task Force has expressed similar concerns. Substantially less interest has been aroused, however, by the efforts of industry to mold the attitudes of medical students, medical faculty members, professional organizations, and those who are responsible for large-scale purchase of or reimbursement for prescription drugs, including both public and private agencies.

This problem was highlighted by the recent decisions on the part of students at two medical schools, Western Reserve and Harvard, to return drug industry gifts. These actions clearly reflected the concern of these students about the involvement of the drug industry in programs of medical education and information, because the drug industry is engaed here not only in educating but in selling.

It is through his early medical training that the physician-to-be forms attitudes about the use of drugs, their relative merits, and the function of drug manufacturers as sources of reliable information. In many medical schools it is not unusual for representatives of drug firms to take part actively in physician training as lecturers, consultants, and simply as sources of information. The medical student, under these circumstances, naturally associates drugs with their suppliers as well as with their chemical and clinical properties. And here, Mr. Chairman, is the point at which the strategy of names begins to take on great importance. For it is during his training that the student begins to associate useful medicinal drugs with their trade names as well as, and often in place of, their generic names.

It is also important to note the extent to which those who are responsible for the teaching of pharmacology and pharmacy are supported by the pharmaceutical industry. All indications are that the major drug houses provide financial support to departments of pharmacology, schools of pharmacy, and individual scientists engaged in teaching and research that is very considerable indeed. Through grants, contracts, fellowships, guest lectureships, and unrestricted support, many in academic medicine have developed very close ties to the drug makers for necessary support which amounts to millions of dollars each year. That this academic-industrial relationship has been productive, there is no doubt. But there can also be no doubt that the medical profession, our medical students, and the public have the right to an honest and open accounting of this relationship.

In the case of the American Medical Association, for example, it would appear that more than half of its total revenue is derived from the pharmaceutical advertising carried in various AMA publications.

The effect of the very substantial involvement of the pharmaceutical industry in the practice of medicine, Mr. Chairman, finds its ultimate expression in the drugs prescribed by physicians.

Last year, over a billion prescriptions were filled in the United States at a retail cost of over three billion dollars. Each of these prescriptions represented a tacit assurance by the physician that the patient was receiving the most appropriate drug that could be prescribed—the most appropriate in terms both of performance and cost. Yet I wonder how many physicians were really prepared to give that assurance.

The problem is not a simple one for the physician or his patient. There are now more than 7,000 prescription drugs available in this country. This therapeutic arsenal includes some 1,200 generally available drugs and 6,000 combinations, most of them marketed in a number of different dosage forms.

In the past twenty years there have been 715 new single chemical entities marketed. Duplicate single products have numbered 1,407; compounded products 3,840; and new dosage forms 1,820. Thus a total of 7,782 new products and new dosage forms have been marketed in the last two decades alone.

How does the physician respond to this profusion of new products? Of the 1.1 billion prescriptions written last year, 67 percent were written for 200 drugs and 85 percent for 500 drugs. Among the 200 most frequently prescribed drugs are 119 single chemical entities and 81 combination products. The development and use of fixed drug combinations, as we have noted in our reports, has become increasingly popular within the past twenty years, but the widespread reliance on their use has generated sharp criticism. The Council on Drugs of the American Medical Association has long held the prescribing of such fixed drug mixtures to be irrational, and you will recall that near the outset of your own hearings, a noted authority on infectious diseases said:

"A careful review of fixed branded combinations on the market, including combinations of penicillin and sulfonamides, penicillin and streptomycin, tetracycline and antifungal agents, and tetracycline and novobiocin, does not substantiate the claims that the combination is superior to one of the agents used separately. The combinations are expensive, deny the physician flexibility in dosage, are primarily promotional devices, and have the inherent problem that the patient undergoes the risk of serious adverse reactions to two or more drugs rather than a single defined agent. The physician cannot determine which component is causing trouble if a bad reaction is encountered. I personally believe that we would do much better without these preparations."[1]

The National Academy of Sciences National Research Council has completed a careful evaluation of the 2,824 drugs marketed between 1938 and 1962, the year in which the Food, Drug and Cosmetic Act was amended to require that drugs marketed be both safe and effective. The NAS–NRC has taken a similar position with respect to a number of the fixed drug combinations. The actions by the Academy and the Food and Drug Administration are sure to rouse the ire of industry, but more importantly they should make many of the physicians who have been prescribing drugs now described as ineffective question their own observations with respect to these drugs.

One of the consequences of the introduction of safe and effective drugs is better health and well-being for many people. Another consequence is drug-induced

[1] Kunin, Calvin M.: Statement in U.S. Senate, Subcommittee on Monopoly, Select Committee on Small Business, "Competitive Problems in the Drug Industry," U.S. Government Printing Office, Washington, D.C., 1967.

disease, or what Moser [2] has called diseases of medical progress. His recent book includes 27 chapters describing a host of problems from discoloration of the teeth, to drug dependance and death. A search of the medical literature during a recent four-year period revealed 178 citations on the untoward effects of iron; in less than three years, 63 articles on the effect of tetracyclines on teeth; and in a four and one-half year period, 112 articles on the adverse effects of LSD.

Attention is now being directed to many of these problems. In one recent study, of 830 patients with chronic illness admitted to the medical wards of a hospital for treatment and rehabilitation, approximately 35 percent reported at least one adverse reaction to drugs administered during their hospital stay. This incidence of adverse drug reactions is considerably higher than the 5–20 percent reported in earlier studies of hospitalized patients.[3] It should also be noted that 80 percent of the reactions observed were moderate or serious.

Studies of adverse drug reactions on an outpatient or ambulatory basis are, of course, far more difficult. In recent years several computer based systems have been developed that will permit study of this problem as well as the prescribing habits of physicians. At the University of Southern California a study of prescribing patterns has identified four types of inappropriate prescribing: (1) inappropriate drug quantities by single prescription; (2) inappropriate amounts of individual drugs in patients' possession that result from multiple prescriptions; (3) inappropriate concurrent prescriptions; and (4) inappropriate drugs for specific disease entity.[4] One example of the kind of problem uncovered in this study was the patient who received over 100 prescriptions for trannquilizers and hypnotics over a nine-month period. She received the prescriptions from her regular clinic and from a hospital emergency room. Neither facility has access to the other's medical records. At the end of the nine months, the patient had over 1,100 fifty-milligram capsules of chlorpromazine, 2,000 ten-milligram tablets of trifluoperazine, and 650 two hundred-milligram capsules of amobarbital theoretically in her possession. The potentials for abuse in such a situation are obvious.

Another kind of problem more subtle and more difficult to assess has recently been discussed in an excellent editorial in the *New England Journal of Medicine*.[5] This is the duress imposed by the attitudes of the medical profession and society. The physician knows he will be more severely criticized if he fails to treat a curable condition than if he overtreats a dozen that require little or no treatment. As the editorial stated.

"Actions speak stronger than words, but strong words scold inaction. Treatment, moreover, is gratifying to both doctor and patient in proportion to its specificity, incisiveness and magnitude. Under conditions when choice is possible, operation is preferred to pills, pills to diet, diet to nothing at all. The patients' desires, the doctors' peace of mind, the opinion of the medical profession, and the societal attitudes press for vigorous treatment. Is it therefore any surprise that the physician who has to choose between over- and under-treatment almost invariably opts for the former?"

The editorial concluded: "Basic to good treatment are the physician's integrity and education. The shape of the therapeutic structure erected on these two foundations is determined by the interaction between individual and circumstances. It is a complex process which pharmaceutical advertising influences but usually does not dominate, and constraints placed on this factor alone will improve therapeutics but little. A better appreciation of the principles of medical therapy is required by society at large, and the necessary educational process must involve everyone—those who give, those who receive, those who intermediate, and the many who choose to write about what's wrong with medicine. When one man treats another, the exchange involves not only a whole patient, but also a total physician."

Mr. Chairman, I have tried to describe and diagnose, if you will, a malady that affects physician, patient, and the public generally. If the diagnosis is accurate a prescription is in order.

One of the basic ingredients of this prescription must be education. In pharmacology, the major problem is that the subject is taught early in the medical cur-

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[2] Moser, R. H.: *Diseases of Medical Progress*, Springfield, Illinois, Charles C. Thomas. 1964, p. 543.

[3] Borda, I. T., Sloan, D., and Jack, H.: "Assessment of Adverse Reactions Within a Drug Surveillance Program," JAMA 205:644–647, August 26, 1968.

[4] Maronde, Robert, M.D., Professor of Medicine and Pharmacology School of Medicine, University of Southern California: Personal Communication.

[5] Editorial: "Treatment by the Whole Individual," New England Journal of Medicine 280:271–272, January 30, 1969.

riculum as a basic science when it really is a clinical science as well. As a result, the clinical uses of drugs do not receive the attention they deserve.

The situation was very well stated by the President of the American Medical Association in a recent address:

"Certainly there needs to be a recognition by all elements concerned with medical education that pharmacological principles should not and cannot be limited to a single or conservative series of courses given fairly early in the curriculum of the modern medical student, which almost universally now includes 4 years of medical school and 4 more years of internship and residency.

"The goal of pharmacologic teaching is not a theoretical one. It is not limited to action at the molecular level. It must in part be practical and it should include information concerning safe and effective use of drugs. A key principle is that all drugs are potentially toxic. The student as well as the practicing physician must remain continually aware of the possibility that any drug may do harm as well as good. Such continual awareness comes only from repeated exposure to pharmacologic education."

And he stated: "It is my belief, which I share with many other people who are concerned with this problem, that ideally students should be educated in pharmacology in such a way that as physicians they will have the basic tools for continued learning about new drugs and new developments in therapeutics that will appear during their years of active practice. Furthermore, they should be educated so that during the years of practice they will be oriented to the continuing education of pharmacologic experts in medical schools and not to the advertising of pharmaceutical manufacturers." [6]

In its background paper, "The Drug Prescribers," the Task Force reported on steps taken at a number of medical schools to bridge the gap between pharmacology as a basic and clinical science.

At Harvard University, for example, students are offered an elective seminar on advanced pharmacology in the fourth year which employs a case history approach to drug therapy in which emphasis is placed on problems of drug interaction and adverse drug reactions. I understand that twice as many students apply for admission to this course as can be accepted.

At Columbia University and the University of Florida, clinical pharmacology is now being taught in the third and fourth years in addition to the basic science course.

A number of other schools have begun or are planning to offer similar courses. The Task Force has recommended that a course in clinical pharmacology be included as part of the regular medical curriculum in all schools and that Federal support be provided where the need is apparent.

Perhaps even more important than the urgent need to improve the educational opportunities in our schools of the health professions is the need to improve educational programs and sources of drug information for interns, residents, and practicing physicians, for unless the physician is prepared to go on learning for as long as he practices medicine, there is little hope that he will be able to deal effectively with the obstacles to rational prescribing.

Information on prescription drugs reaches the physician from many sources: medical journals; journals of prescribing such as *The Medical Letter* and *Pharmacology for Physicians;* drug compendia; formularies; textbooks; industry advertising; drug samples; detail men; and postgraduate education.

Surprisingly few of these sources, however, provide the objective, current, and comparative data that the physician needs in order to make sound therapeutic judgments. You may recall, Mr. Chairman, that when I last appeared before the Subcommittee, I spoke of the need to support the efforts of State and local medical societies, in cooperation with medical schools and other health institutions, to provide regularly scheduled postgraduate seminars of current developments in drug therapy. I also discussed the Task Force recommendations about establishments of a comprehensive drug compendium and support for a journal of prescribing.

These are recommendations which I felt should be of tremendous interest to the medical profession, and so on November 7, 1968 I sent a letter to all of the Nation's 306,000 physicians describing our recommendations to provide better drug information and asking for their comments. I am pleased to submit a copy of my letter for the record.

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[6] Wilbur, Dwight L.: "Pharmacology and the Practicing Physician," Proceedings of the Western Pharmacology Society 10:5–11 (1968).

During the first several weeks, through December 4, we received 3,307 replies. Of these 2,554 contained comments and 753 were simply requests for copies of the Task Force reports. Since that time we have received several hundred more replies which we have not fully tabulated, but the nature and direction of the response did not appear to differ from the early replies.

Of those with comments, 1,709 or 66.9 percent were favorable to the recommendations overall, 529 or 20 percent were clearly negative, and 316 or 12.4 percent could not be judged either favorable or unfavorable.

On the specific issues discussed in the letter, the responding physicians indicated as follows:

1,621 physicians commented on our proposal for a comprehensive drug compendium. Of these, 1,246 or 77 percent were in favor and 375 or 23 percent were opposed.

1,419 replied to the recommendation for a journal of prescribing. 858 of them or 60 percent were favorable and 561 or 40 percent were opposed.

1,138 commented on the expansion of undergraduate training in clinical pharmacology. 751 or 66 percent were in favor and 387 or 34 percent were opposed.

1,070 physicians discussed our proposed support for continuing education courses in drug therapy. 789 or 74 percent were in favor and 281 or 26 percent were opposed.

What do these replies mean? First, they indicate the serious thought that many physicians have given to the problems involved in obtaining objective and reliable prescribing information. Beyond that, any judgments must be tempered with caution. This was not a survey in any statistical sense and it is therefore impossible to say that it does or does not represent the thinking of the entire medical community. But these replies clearly do show that a significantly large number of physicians are finding it difficult to live with the traditional ways of obtaining drug information.

Much more can be done, Mr. Chairman. For example, medical centers could establish drug information centers, staffed on around-the-clock basis very much like the existing poison control centers, to provide rapid access and complete information on the use of drugs as well as on the handling of adverse reactions. The National Library of Medicine is now developing through the Lister Hill Biomedical Communications Center, a plan for a communications network that would put such information at the physician's fingertips. The potential of this program, not only as a source of up-to-date drug information, but as a mechanism for continuing education, must not be overlooked.

In order to assess the impact of various kinds of information, programs of drug utilization review should be undertaken. These should help to identify thoughtless or harmful prescribing and to promote more rational therapeutic decisions. The Department of Health, Education, and Welfare, which already has a substantial stake in this problem, has not supported nearly enough research in the past, and to help remedy the situation I have established an Interdepartmental Committee on Drug Utilization Review. This committee will review and coordinate the Department's research efforts in this area.

Education is important but it is not enough. Another basic essential is forceful but reasonable Federal drug regulation. Some in the medical profession, including those in academic medicine, have tended to disparage the Food and Drug Administration, and in the past, some of this may have been justified. Even today, despite the dramatic gains of the past few years, more remains to be done. Experience, some of it tragic, has made it very clear that the Food and Drug Administration needs to be strengthened in the public interest and for the benefit of the medical profession and the pharmaceutical industry.

Critics of the FDA, friend and foe alike, agree that it needs a broadened scientific capability, that its scientific base is considerably less than that of the pharmaceutical industry it is charged to regulate. To meet this need, the Task Force has recommended establishment of a drug research center within the FDA which would provide additional opportunities within the agency for the kinds of drug research which underlie its regulatory mission. The Task Force has suggested in its Fifth Interim Report a number of examples of research that could be undertaken by such a center.

Education of the physician and the regulation of industry are but two elements; the third is a far better understanding on the part of society of the principles and problems of medical therapy. I believe that one of the most effective means of achieving better public understanding has been Congressional hearings such as these. They have generated wide public interest and they

have provided a means of determining the extent to which those of us in public service are discharging our responsibilities with wisdom, integrity, and energy. I believe that Congress needs to be provided with greater staff resources and funds for special studies in order to fulfill its obligation to society. Legislation and appropriations are but two key Congressional functions. Oversight of the Executive Branch is of equal importance.

Another essential for better public understanding is better public information. These hearings and the reports of the Task Force on Prescription Drugs have aroused considerable concern about the use and cost of prescription drugs, thanks to the efforts of but a few dedicated journalists. But these are matters which vitally affect all Americans and they deserve much broader public discussion.

It is important for those outside of the medical profession to look inside, at us. But it is equally important that we in the profession critically appraise our own activities and our own responsibilities. We should demand, for example, to know how much support our medical societies obtain from sources outside of the profession, particularly how much comes from the drug industry.

We should be interested in knowing where the support for publication of drug studies comes from. Certainly every study done under a Federal grant is identified as such. Should we want to know less about funding of such studies by private sources?

In conclusion, Mr. Chairman, I would like to state my conviction that the problems facing the medical profession in the use of prescription drugs must be solved by doctors themselves. We can benefit greatly from the attention that has been drawn to the problems of drugs in our society. But I doubt that any solution that comes from outside of the profession, or that lacks the understanding and support of physicians can produce the changes that are urgently needed in medical education, prescribing practices, and the protection of the American people.

But there is growing evidence that physicians—and medical students—are deeply concerned, and I expect that this concern will be evidenced in support of measures both public and private to help assure that the medical profession—not the makers and sellers of drugs—will retain its critical responsibilities in this area.

Thank you, Mr. Chairman.

Senator NELSON. I would like, at this time, to pay tribute to Dr. Lee. During his tenure of office with HEW he proved to be a very able and dedicated public servant. He will be sorely missed. We have had many occasions to call upon his services and he never failed to respond promptly and to cooperate fully. He has been present at a good many of our hearings, and his good counsel has added immeasurably to the study we are conducting. Our thanks and best wishes go with him as he undertakes his new duties.

Today's witness will be Dr. W. J. Hagood of the Little Retreat Clinic in nearby Virginia. Dr. Hagood is in private practice and is one of several physicians who requested an opportunity to appear before the subcommittee. The Pharmaceutical Manufacturers Association also asked us to extend an invitation to Dr. Hagood and we are happy to do so.

We have a biographical sketch of Dr. Hagood which will be printed in the record prior to Dr. Hagood's statement.

(The biographical sketch of Dr. Hagood follows:)

BIOGRAPHICAL DATA

Name: William Joseph Hagood, Jr.
Born: Victoria, Virginia, January 6, 1918
Education:
Harlan High School, Harlan, Kentucky
Eastern State Teachers College, Richmond, Kentucky (Bachelor of Science)
Medical College of Virginia, Richmond, Virginia (MD) 1943

Fraternity: Phi Chi (Medical)
Internship: Medical College of Virginia
Private Practice:
Associated with Dr. James D. Hagood and Dr. Warren C. Hagood in General Practice at the Little Retreat Clinic, Clover, Virginia
Medical Activities:
Member, Medical Society of Virginia, 1946–
Member, American Medical Association, 1946–
Member, American Academy of General Practice, 1949–
President, Halifax County Medical Society, 1949
Member, State Board of Medical Examiners, 1949–1954
Chief of Staff, Halifax Community Hospital, 1956
President, Virginia Academy of General Practice, 1961–1962
Special Consultant in General Practice to Medical College of Va., 1962–
Member, Medical Education Advisory Committee of State Council of Higher Education, 1962
Alternate Delegate, American Academy of General Practice, 1962–1964
Delegate, American Academy of General Practice, 1963–1965
Member, Radiation Advisory Board, Virginia, 1965
Member, Advisory Committee on Regional Medical Programs, Va., 1966–
Vice-Speaker, Congress of Delegates, American Academy of General Practice, 1965–1967
Speaker, Congress of Delegates, American Academy of General Practice, 1967–
Civic Activities:
Member, Lions Club
President, Lions Club
Zone Chairman, Lions International
County Chairman, United Fund, Halifax County, Virginia
Member, Parent's Advisory Committee, Bridgewater College, Bridgewater, Virginia, 1966–1968
Member, Executive Board of the Piedmont Area Council, Boy Scouts of America, 1967–
Military Activities:
Army of United States, Dec. 1943—March 1946
Battalion Surgeon, 84th Infantry
Campaigns: Rhineland, Ardennes, Central Europe
Decorations and Citations: Purple Heart, European African Middle Eastern Service Medal, Meritorious Service Unit Plaque, Bronze Star Medal, Combat Medical Badge, Rank, Captain.
Hobbies: Raising roses, Writing, Public Speaking
Religious Activities:
Denomination, Southern Baptist
Member, Clover Baptist Church
Deacon, Clover Baptist Church
Sunday School Teacher, 1950–
Vice Moderator Dan River Baptist Association 1952
Moderator Dan River Baptist Association, 1953–1954, 1956–1959
Member, Virginia Baptist General Board, 1957–1962
Member, Executive Committee, Virginia Baptist General Board 1957–1963
Chairman, Committee on New Baptist Building, Virginia Baptist Board, 1958–1962
Vice-President, Baptist General Association of Virginia, 1962–1963
President, Baptist General Association of Virginia, 1964–1965
Member, Committee on Boards, Southern Baptist Convention, 1963, 1968
Member, Faculty Christian Focus Week:
Bluefield College, Virginia, 1961
Campbell College, Buies Creek, N. C., 1962
Chowan College, Murfreesboro, N. C., 1964–1966
Averette College, Danville, Va., 1967–1968
Married: Aileen Brillhart, Troutville, Virginia
Children:
Dianne 23, R.N., married Jon A. Lucy and living in Gloucester Point, Va.
Nancy 21, Senior, Bridgewater College, Bridgewater, Virginia
Jean 15, 9th Grade
Mark 12, 7th Grade

Senator NELSON. Doctor, you may proceed to present your statement in any fashion you see fit, either reading it or if at any time you wish to extemporize on any aspect of your statement, you are certainly free to do so. Your statement will be printed in full in the record as well as whatever extemporaneous remarks you make.

I trust you have no objection that if a question occurs to us from time to time during the course of your statement, we ask it.

Dr. HAGOOD. No, sir.

Senator NELSON. Thank you, Dr. Hagood. We appreciate your taking time from your busy practice to make your contribution toward these hearings we have been conducting for almost 2 years now.

STATEMENT OF DR. WILLIAM J. HAGOOD, JR., PRIVATE PHYSICIAN, LITTLE RETREAT CLINIC, CLOVER, VA.

Dr. HAGOOD. Thank you, Senator Nelson and Senator McIntyre. I appreciate very much the opportunity of you letting me appear before your subcommittee, and also I wish to thank you again for letting me change the date because of a conflict in schedule.

I would like the record to state that I am appearing as a private citizen. This statement I make this morning is my own. I do not represent any organization. I do not own any stock in any drug company. In fact I am not beholden to any drug company in any manner at all.

I am William J. Hagood, Jr., M.D., of Clover, Va. I am a general practitioner, and while there are some people who would like to believe that the GP has no business in the airy goings-on of political Washington, I think to the contrary we have something very important to contribute. I am grateful to you for letting me come, and I earnestly hope my being here will be helpful.

I said I live in Clover. You can get there from here by going south 100 miles to Richmond, the site of the Medical College of Virginia. That is where I got my academic medical education the same years a certain nurse trained there who later married the distinguished chairman of this committee. From Richmond you turn south and west on Route 360 for another 100 miles; there you'll find Clover, a tobacco farming community, near Danville, in south-central Virginia. In Clover my uncle, Dr. J. D. Hagood, started the Little Retreat Clinic that has served that farming community for over four decades. I've been in practice there 23 years and now operate the clinic with my cousin, Dr. Warren C. Hagood, who has been there 15 years.

We are, as I guess the foregoing suggests, small operators, if you compare us with some of the larger institutions that have presented their testimony here previously. We are professionals who continually strive to give the public in our area the best in medical care using as aids to accomplish this these two things—continuing education and the best of physical facilities.

Our clinic is completely equipped for the type of service Warren and I wish to offer the public, and that is comprehensive and continuing medical care. We have modern X-ray equipment that we use carefully and regularly. We have a laboratory sufficient and adequate for our needs. My associate and I daily stake our reputations on the results handed us by our laboratory technician. She does blood counts, throat and urine cultures, cholesterol and uric acid levels, et cetera. Warren and I have over 150 diabetics in our practice and this techni-

cian tells us what any given one's blood sugar level is 20 minutes after she takes the specimen. We have four identical and completely equipped examining rooms, with the best diagnostic aids available, down to the point of having pushbutton adjustable examining tables. A room has been set aside and especially equipped to test vision, hearing, and to do electrocardiograms. Another room is equipped with a hospital bed, oxygen, ultrasonic and diathermy equipment. Warren and I have some convictions that are evidenced by printed signs and lack of printed signs, that is, we have conspicuously posted "No Smoking" and there is a conspicuous absence of "Colored only" and "White only" signs. In all modesty, I doubt that many patients in large cities have more modern or comfortable or more effective medical care facilities than ours. You, Mr. Chairman, or anyone is welcome to inspect our clinic at any hour where Warren and I give daily a 24-hour service to our patients.

We have no medical specialists staffing our clinic. But we have, and we use, every necessary specialty in medicine available to us. In surrounding cities we can call upon urologists, orthopedists, psychiatrists, dermatologists when needed. We have surgeons, internists, obstetricians, gynecologists and a pediatrician at our community hospital just 17 miles away. And we use them. We have built up over the years, a good relationship with these people. Of course, our primary reason for doing this is about 15 percent of our patient's problems require services we are not trained to supply. A second, important reason for our regular contact with them is that they teach us. They show us how we can better diagnose conditions we might otherwise miss or misidentify. They educate us to handle what we can handle and equally important, they help us to recognize situations we cannot adequately meet. A third reason is we teach them about our medical way of life. These three reasons mold both groups of physicians into a useful team whereby Warren and I can deliver comprehensive and continuing medical care.

Essentially, then, what we have in Clover is a group practice without walls. We look isolated. We are not. As a matter of fact, we are very much in touch. Back in the days when artificial kidneys were experimental curiosities the life of one of our patients was threatened by a mounting potassium level in his bloodstream. Smith Kline & French made a service item, an exchange resin, that would attack and reverse this lethal trend in our patient. Four hours and twenty minutes after a phone call to Smith Kline & French in Philadelphia this drug was delivered to the front door of the Halifax Community Hospital, South Boston, Va. The patient recovered thanks to the drug. The cost to the patient, nothing.

This was a service item Smith Kline & French made available to the medical profession gratis. They didn't even ask for a report on the results of their drug.

Unfortunately some of the witnesses who have testified before your committee have left the impression drug companies have doctors as prisoners. In my experience, it is the companies who are captives of the doctors. The drug companies do what doctors want them to do; and that is, doctors want good drugs, successful firms have produced them, and those pharmaceutical houses have been justly recognized for their performance by the repeated prescribing of their reliable drugs. To be sure, there have been drugs manufactured and marketed by reputable drug houses that were not what they had been represented

as being. Laws have been passed by the most reliable governmental deliberative body in the world, the Congress of the United States, and some of those laws were not what they had been represented as being. Fortunately, drug houses and Congress, each in its own time, have removed no good drugs and no good laws from the people. And I need not remind you of the time record or the batting average. My point is, both institutions are good but not perfect, and both need constant attention in order to get the desired results.

Let me tell you what enters into my consideration in choosing a drug for my patient.

To do so, I must again illustrate how unrealistic it is to pretend it is drug companies alone that make up my mind for me.

Senator NELSON. May I interrupt for a second, Doctor.

Dr. HAGOOD. Yes.

Senator NELSON. I don't think we have had any testimony that I can recall before the committee that asserted that drug companies alone make up the minds of all doctors in prescribing the drugs. But the testimony has been that it is a variable situation in which some doctors rely much too heavily upon the advertising and the promotion of the companies. It has not been that we have had witnesses saying all doctors rely upon the drug companies to make up their minds.

Dr. HAGOOD. It was my feeling that this was alluded to, as I read through some of the proceedings of this. For instance. On page 570 of the Nelson hearings there is a statement there by Dr. Cluff; on May 15, 1967, there was a statement by Dr. Holloman; Dr. Carstenson on May 17, 1967, made the statement that led me to make this statement. Dr. Modell in June 1967 and Dr. Magee on page 492 of the Nelson hearings, and these were the statements from which I drew this.[1]

Senator NELSON. Did any of those witnesses in their statements, state that drug companies are the only influence on doctors, for all doctors on all drugs that they prescribed.

Dr. HAGOOD. To my knowledge they did not say that drug companies alone do this.

Senator NELSON. That was the reason I was raising this. You see, so many of the medical publications, throwaways supported exclusively by drug advertising, other publications supported heavily by drug advertising, would take excerpts from statements and then draw a broad conclusion from them which caused doctors to believe that witnesses before the committee, distinguished witnesses, were saying that all doctors are simply victims of the propaganda of the drug companies and all doctors rely solely upon drug company promotion and advertising for their prescribing practices. I am not aware of any testimony to that effect.

Please go ahead.

Dr. HAGOOD. I am, I suspect, no more an avid reader than most GP's; that is to say I read, regularly and rather fully, two or three national medical journals. In addition, I am active in my local and State medical societies. I am a member of the AMA. I belong to the American Academy of General Practice. A look at any one of the dozens of programs of AAGP in promoting postgraduate education shows the

[1] See hearings, "Competitive Problems in the Drug Industry"; testimony of: Dr. Cluff, pt. 2, pp. 559–580; Dr. Holloman, pt. 1, pp. 4–54; Dr. Carstenson, pt. 1, pp. 228–237; Dr. Modell, pt. 1, pp. 283–305; Dr. Magee, pt. 2, pp. 486–499.

extent of information offered me from that source. Indeed, membership in that association requires each member to complete every 3 years 150 hours of approved postgraduate education. The fact that over 31,000 general practitioners are part of AAGP shows we GP's are indeed interested in, and are obtaining, the professionally organized and administered postgraduate education some of your witnesses have in effect suggested does not go on.

I am not operating in a vacuum, you see. In addition to all the more formal types of communication I've just touched upon I have the valuable, indeed, invaluable guidance of my fellow physicians. Everyone in the profession is informed speedily when a new pharmaceutical becomes available, thanks in a large measure to efforts of drug companies who produce them. We all agree, certainly, not all new drugs are destined to become essentials of medicine. Personally, I would rarely want to have the distinction of being the first physician to use any new drug the day it reached the pharmacy; nor do I want to be the last. In deciding whether, and when, to try a new drug, I find it most helpful to have the advice of my professional friends.

There are, of course, publications aimed at providing early guidance on the new drugs. The Medical Letter is a well-known source. I am proud today I am a charter subscriber to that letter, and I still retain volume I, No. 1, in my office, near my desk and close at hand. I think of the letter as a source of useful opinion, and that is saying a great deal. But, at the same time, Mr. Chairman, it is no Bible, and its authors do not, I am sure, want anyone to think it is one. Many doctors consider the Medical Letter to be entirely too negative, if not nihilistic, and I think it does have a certain pontifical, academic ring about it. I am afraid doctors who spend their entire day seeing patients tend to be a little annoyed at what appears to be ivory tower pronouncements from on high.

Senator NELSON. Could you tell me in what way—I am not a reader of the Medical Letter, of course—in what way it is negative or nihilistic.

Dr. HAGOOD. Their conclusions are rather tersely drawn, and they are very forthright in saying that this is good, this is not good, and in doing this there is this feeling out in the practicing profession, there we use drugs and we know, to begin with, there is a large element of the placebo effect, for one instance. We also know that there are differences in patient reactions to drugs. In fact, in my own practice I know that there are families, if you please, in which I can use certain drugs and that there are other families that I cannot use these drugs, and this is one of the reasons for this. Someone in one of those families has had a reaction to a drug, and this becomes known in the family. So when the same condition comes up in another member of this family, and maybe this is a first drug of choice and I would like to prescribe this, and if I mention this drug, why they immediately say, "No, sir, Doctor, I am just not going to take this because this made my aunt so sick we thought she was going to die," or she had a rash or something of that sort. As a result, why, we use another drug or fortunately we have other drugs that we can use.

Nevertheless, as you read the Medical Letter you find that this thing is somewhat cut and dried.

As I said, I read this letter, I take this into my consideration, but again I have to make my own decisions based upon the situation as it arises daily in my office.

Senator NELSON. Thank you.

Dr. HAGOOD. May I proceed?

Senator NELSON. Yes, sir.

Dr. HAGOOD. I suspect they are not entirely unique in this regard; I imagine practical politicians feel the same way toward those proud theoreticians of political science who make profound analyses of politics but who have never actually taken the risk of running for office.

What I am saying, gentlemen, is there is a whole ranges of sources of information, impressions, and advice operating side by side with commercial sources. To pretend the doctor has only drug companies' opinions to look at is to ignore reality. The fact is we have a great many communication channels, all of them of value, and none of them unleavened by others. So long as drug therapy is heavily subject to professional judgment rather than solely to hard science, this multichannel approach will be the best one overall. The last thing we need now and in the future is a monolithic concept of therapy, which says this drug, in this patient, in this dosage, is the alpha and the omega of therapy. That approach, I am positive, has no basis in either medicine or science.

Senator NELSON. May I interrupt for a moment?

Dr. HAGOOD. Yes, sir.

Senator NELSON. I don't think anybody before this committee has suggested one monolithic approach. Do you know of any?

Dr. HAGOOD. No; I do not and I certainly hope its does not arise.

Senator NELSON. Thank you.

Dr. HAGOOD. This leads me—may I proceed?

Senator NELSON. Yes, sir.

Dr. HAGOOD. This leads me to comment on the concept of a single drug compendium, that has been discussed before this Subcommittee. We have, of course, the Physicians' Desk Reference, and I must say that book, as good as it is, is becoming a bit large for my desk. It is not perfect, but I find it outrageous it is condemned because it is "just advertising" as some have said. Of course, the material in it is paid for by drug companies. But what of that? Currently, meaning 1969, isn't every syllable in it written in conformance with labeling requirements of the Food and Drug Administration? Where can you show me evidence entries violate FDA-approved descriptions of drugs? Surely, if any do, FDA has ample power to correct the matter. But on what basis is the PDR to be brushed aside?

Gentlemen, I am not here to glorify that book, or any other. But I will tell you this; the current edition of PDR has an estimated circulation of 450,000. That is 318,500 more than the combined estimated circulation of this country's three official compendia of standards; U.S. Pharmacopeia, National Formulary, and Homeopathic Pharmacopeia of the United States. That book, the PDR, is one doctors use more than any other. Take that one away, and you will have removed a working reference. Is it inadequate? Fix it. Is it incomplete? Expand it. But look at it. It now contains entries on nearly 2,600 drugs. It is now 1,415 pages long, 2 inches thick, and weighs 3 pounds, 9½ ounces. Yes, I weighed the 23d edition on my baby scales when it was delivered

to my office January 19. Fortunately, the PDR won't triple its weight this year, as does a newborn its first year of life, but the book will add three-quarters of a pound during the year as the four quarterly supplements are glued in. The prospect of one immense book that fully describes all drugs in PDR plus several thousands of others is not attractive to me in the least. Such a book may be an interest to somebody; but not to me. I am a practicing physician, not a librarian. I need to know a great deal about less than a hundred drugs, not 2,000, as there are now in PDR, and certainly not the 6,000 of 7,000 that would be found in an encyclopedia of the sort being described.

Unless you make your compendium more valuable and practical than the PDR, your compendium will be replaced by a private tome that does this. So you are asking for competition now. Maybe your compendium will force the PDR to become even better. I say this because in the day-to-day active medical practice the doctor wants correct, practical information that is concisely stated. And please—no fine print because one can't underline passages that need emphasis without blotting out print. You may force the physician to keep a copy of your compendium in his office, but you will never force him to use it unless it fits his needs better than other available sources. The sine qua non your new book must offer, practicability in practice. My final note on the compendium is—I don't know what you will have published, but you must leave the ultimate choice of the drug, the dose of the drug, and the source of the drug to the physician who is charged morally, ethically, professionally, and legally to treat the patient. If he assumes the full responsibility of treating any patient he must be free to prescribe the drug he wants.

Senator NELSON. May I interrupt a moment there, Doctor?

Dr. HAGOOD. Yes, sir.

Senator NELSON. So far as I know, no witness before this committee has suggested that the ultimate choice of the drug not be left to the physician. What puzzles me is that we have had several witnesses who put in this sentence which to me leaves the implication that somebody before this committee, or the committee itself, is suggesting that the responsibility for prescribing a drug be taken away from the physician. There has been no such testimony before this committee, and it has not been the position of anybody on this committee.

Dr. HAGOOD. I said this for emphasis, Senator Nelson, because I certainly hope this would never be given any serious consideration before this committee. This is a thing that must remain with the physician.

Senator NELSON. We have not, as I said, heard any testimony to this effect. The Pharmaceutical Manufacturers Association in some of its propaganda has left that implication, because I received a number of letters from practicing physicians who raised the same point. I just wanted to assure you that nobody before this committee has made that suggestion, and nobody on the committee has made that suggestion.

Dr. HAGOOD. Thank you.

May I proceed?

Senator NELSON. Yes, sir.

Dr. HAGOOD. Mr. Chairman, I have related in brief some of the more formal influences upon my prescribing practices. Now if I may, I should like to relate some other, secondary but real factors no physician concerned about medicine and people over the long range can com-

pletely ignore. These influences are somewhat analogous to a precinct, county, or township that repeatedly delivers the vote.

About 13 years ago a 3-year-old child was brought to me, the daughter of a man I know who farms near Clover, and who has a good old-fashioned farming family—a large one. This little girl had a sore ankle. We puzzled over it for a few minutes; it is not unusual to find the young child in a large family is more used to listening than talking, and this one was one of those who wouldn't say much about her problems. The thought struck me she might have an early case of osteomyelitis. I X-rayed the leg, did other tests and soon determined she did indeed have an infected bone. I put her on a drug called Signemycin.[1]

Now it is important in acute osteomyelitis to begin treatment promptly with an effective drug, prescribed in adequate dose and continued past the point of clinical healing. The infection is found in the bone and if unchecked, it spreads quickly, killing bone tissue as it proceeds, causing immense pain, leaving wrecked bones and destroyed joints in its wake.

I had some Signemycin in the office, and I gave what I had to the child. I wrote her a prescription for some more. Knowing her family's situation, I felt sure between cost of raising six other children and problems they were having with their farm, they would be hard put to bear the cost of this necessary cost of therapy.

When the detail man from J. B. Roerig and Co. came around, I explained the problem to him. I made it clear, eventually, this farmer would pay for the drug, but right now it would be difficult. I asked him if he could do something for this child. As it turned out, Roerig supplied gratis the entire amount estimated to retail at $350.00. That was a lot of money 13 years ago.

Fortunately, the little girl responded beautifully. I have a whole series of X-rays that show the gradual regression of the infection. I would like to show you the child now; she is now 16 and she has an interest in miniskirts, but for this experience, she might not otherwise have.

Gentlemen, I will not ignore memories like that, and I hope you don't think I should.

When I began practice 25 years ago, chronic osteomyelitis was fairly common. The resultant death of bone, the painful involvement and destruction of joints, the formation of large quantities of pus, and the unpleasant outlook all made for an exceptionally ugly situation. The antibiotic era has made chronic osteomyelitis an uncommon disease; it has the prompt and effective cure of acute osteomyelitis almost routine.

I can't forget things like that. Call it hearts and flowers if you wish. It is human to thank, and I thank the drug companies that discover these drugs. I am even more appreciative to find when the situation warrants, the best of them are more than willing to provide their products at a loss. This is responsible behavior, and it goes unheralded, except, of course, by the patient who benefits from it.

Another kind of example I mention is Aureomycin, made by Lederle Laboratories, the first tetracycline. I remember two things in particular about Aureomycin. The first, it caused a lot of my patients to vomit; and, it cost wholesale $1.50 per capsule when it was first introduced.

[1] See App. III, pp. 4795–4799, infra, with reference to Signemycin.

Whether there was a causal relationship between these two points I leave to your judgment. I used to tell my patients every time they failed to keep one down they were throwing $1.50 in the basin, that helped them keep it down.

Anyway, it wasn't long before the drug firms manipulated the tetracycline molecule and other tetracyclines came along. They corrected the two objections; very few people vomit the newer ones, and, through competition, the price is down to less than a tenth of what it was.

Senator NELSON. May I interrupt a moment?

Dr. HAGOOD. Yes, sir.

Senator NELSON. You see, this committee has been conducting hearings about what we consider to be some problems that need public discussion involving the drug industry and the medical journals and profession. The committee has not, of course, at any time taken the position that the drug industry has not made a great contribution to medicine. I think everybody on the committee, I think every witness we have had for 2 years, is willing to concede that the drug industry has made a great contribution to medicine, and that it is a very important industry.

But any time hearings are conducted involving an industry, the position of the industry usually is "we have done great things you aren't giving us credit for and you shouldn't expose to public view critical aspects." This happened to me when I introduced the tire and automotive safety legislation. The auto companies and others attacked me as criticizing a great industry. It is a great industry and we were criticizing it because the tire companies and auto companies were putting purposely, knowingly, rather unsafe tires on the highway, and still are. So the fact that we raise these questions about some practices that we consider improper does not mean we are making a general indictment of the drug industry.

We have raised questions on pricing practices which the industry can't answer. You mention on page 10 of your statement:

> I am even more appreciative to find when the situation warrants, the best of them are more than willing to provide their products at a loss.

Then you mention tetracycline on page 11.

I assume you are aware that Pfizer, Lederle, Bristol, Squibb, and Upjohn were found guilty in a criminal case of conspiring to fix prices, and that they just made an offer of settlement, a free offer of their own, of settlement of $120 million to the people they cheated for ten years. It was a criminal conspiracy; it was cheating. They were gouging the public and, of course, they could afford to give any doctor who asked for it for a patient, such as yours, free tetracycline because they were cheating the people so badly that it didn't cost them anything. This is the kind of thing that we have been exposing. I don't think you, or even the drug companies themselves, could defend price-fixing and price-gouging of the public, could you?

Dr. HAGOOD. Senator Nelson, may I go back for just a moment there? I read this piece in the paper you are referring to now, I guess it is 2 weeks or something ago. It was not my impression from the release that I read that these people had been found guilty of this. They had offered to set aside $120 million of dollars to pay off any claims that may be forthcoming by the 6th of March in this situation but it

was not my understanding that they had been proven guilty of this, and that they had purposely and willfully cheated.

Senator NELSON. That was the finding, December 1967, guilty of criminal conspiracy to fix prices. Guilty on three counts. It was a jury trial. This isn't the only one, but they were found guilty.

This is the point I would like to make with you, Doctor. This committee is conducting hearings on practices which we think, as they evolve, are inexcusable and the public is entitled to know them. That doesn't mean that a company doesn't also do some good research, but the posture taken by the Pharmaceutical Manufacturers Association in the propaganda they spread so effectively because they have vast amounts of money to do it, is that this committee is making a general indictment of doctors, a general indictment of the medical profession, a general indictment of the medical journals. That is not the case at all. We are raising those questions in those areas where there is an important public issue, and whereas a company is entitled to credit for research and healthful discoveries, they are entitled and should receive criticism when they gouge the public, and that is what these hearings are all about.

Thank you.

Dr. HAGOOD. Now that I have used the words Signemycin and tetracycline I will express myself on the subject of generic versus brand name.

I will continue to prescribe brand name drugs until I can be assured a generic drug is as effective, no more toxic, as convenient to give and is cheaper than the brand name drug. And these assurances must be present batch after batch after batch. Furthermore, I prefer these assurances be arrived at by a nongovernmental source or a source composed of representatives from the medical profession, the pharmaceutical industry and the Federal Government.

As far as price is concerned I am not knowledgeable enough to make a firm statement other than to say I don't believe you are going to set a price that will produce more than ephemeral satisfaction to the public. Doctors, hospitals, and drugstores have always been targets of dissent and they always will be because they represent sickness, bad health, unhappiness—something no one wants. True—many patients are grateful and probably the majority are at times. Nevertheless, nobody cares to be associated with any part of the medical profession any longer than absolutely necessary. Yet, when they are involved with the medical profession they expect good results.

And results leads to the much discussed subject of equivalency. To me, equivalency boils down to who is involved. If the drug is made by what I consider a reputable drug house I will accept it. If it is made by a drug firm unfamiliar to me but vouched for by my local pharmacist I have known for 15 years I will give it serious consideration, then decide whether I will accept it.

The third point on generic versus brand name drugs concerns the name of the drug. I would prefer to reduce confusion of drug names so a specific drug is known by the same name with the drug manufacturer's name following it. This suggestion opens up discussion for many other problems, such as, patent rights, royalties, profits, et cetera. And again, I am not knowledgeable in these areas—but would it be reasonable to allow the initial manufacturer to name the drug with

the approval of the organization that inspects his facilities and ascertains his quality control is what it should be?[1]

Senator NELSON. Let me say, Doctor, that is a proposal that other distinguished witnesses made as a suggestion to the committee. We have introduced legislation to that effect, and I think every distinguished person from the medical or pharmacy field who has appeared before the committee endorses this concept as suggested by you. I suspect that the drug companies will oppose it, but because brand name domination of the marketplace is their method of extending the patent long beyond the time a patent expired, but I think good prescribing practices according to professional witnesses before the committee would support the concept you suggest here.

Dr. HAGOOD. Thereafter, other firms manufacturing this drug would use this approved name followed by the secondary manufacturer's name. This would serve as an incentive to research. I realize this may well give the primary manufacturer a sales advantage which could be offset by changing the 17-year patent rights period.

Regardless of what is done this section of our incomparable free enterprise system, the drug industry, must be protected, preserved and promoted; else a disservice will have been done not only to Americans but the entire population of this globe.

Finally, let me say a word about promotional efforts of drug firms, which are, I am told, very costly, and which, no doubt, involve a degree of waste. I have every confidence in the earnestness of those who would reduce the cost of drugs by reducing this effort, but here again, as with the PDR, we have an established tool, the detail man, who in my opinion is not as effective as he could be.

In 1964 I had the privilege of addressing the public relations section of the Pharmaceutical Manufacturers Association. At that time I said the caliber of a physician's practice of medicine will be no larger than his continuing education effort. Time is limited. Therefore, every learning tool and every avenue through which learning can be projected must be large caliber to be effective. Please, don't send out any small bore detail men.

I still believe the detail man has a minor but important place in the well balanced continuing education program of the practicing physician. Those detail men I spend time with bring information about drugs—sometimes new drugs of major import, sometimes ones I will elect to forget, and he brings it in person. So I can challenge him and his company. So I can ask for and receive additional information, quickly. I don't know whether elimination of detail men would bring a significant reduction in drug cost, but I do know it

[1] Dr. Hagood subsequently submitted the following:

"On transcript page 5567, Senator Nelson interrupted, then stated my point had been made in several previous testimonies. He was referring to my statement: *I'd prefer to reduce confusion of drug names so a specific drug is known by the same name with the drug manufacturer's name following it.* And that's true. However, I don't believe I made my innovation, to this often repeated point, clear to the Senator. The innovation is this: *allow the initial manufacturer to name the drug with the approval of the organization that inspects his facilities and ascertains his quality control is what it should be.* An example of this innovation follows.

"Ciba discovers a drug that will cure hemophilia. Ciba consults with the organization that inspects Ciba's manufacturing process of the drug and they agree to name the drug Hemophiliam. Thereafter, the drug is officially called Hemophiliam with Ciba's name following—thus—Hemophiliam Ciba. Under the current patent laws Ciba would be the sole producer of this drug for 17 years. At the expiration of the 17 years other companies could produce the drug. However, the drug would be called Hemophiliam and the secondary manufacturer's name would follow the drug name. Now the drug could be prescribed Hemophiliam Ciba, Hemophiliam Lilly, Hemophiliam Abbott, etc."

would be a costly step in terms of the loss of communication. Incidentally, I doubt that elimination of the detail man would reduce cost of drugs to patients as much as the cost of merchandise to all Americans would be reduced if there could be a 50-percent reduction in shoplifting.

Senator NELSON. May I interrupt again, Doctor?

Dr. HAGOOD. Yes, sir.

Senator NELSON. We have here a bit of conflicting testimony on detail men, although I would guess from memory that most witnesses have taken the position you have, critical of detail men and some have testified that they made a valuable contribution.

I notice in the Virginia Medical Monthly, volume 94 of February 1967 on page 113, in an article[1] written by you, you stated that:

> If the ideal detail man exists he is clearly outnumbered by his imperfect brethren who reportedly interrupt the office routine, parrot stereotyped encomiums, hawk their wares in a truculent manner and talk without listening. This confrontation destroys one thing the physicians want, an opportunity to learn valuable information.

Dr. HAGOOD. What you have said exists in that paper but this is not the entire story there. I am searching here for the—there were other statements in there. In fact 80 percent of the group of people that I interviewed by questionnaire felt very kindly toward the detail man. They wanted to see him continued. Many of them said that his service could be improved, but to say this was a typical statement that has been made by the group is not entirely accurate.

Senator NELSON. I was not trying to suggest that. I was quoting your statement, not the statement of the people you polled. This was a quotation, as I understand it, from your article. It is on page 113 in an article written by you and John O. Owen, Jr., of Charlottesville. In the right-hand column, the bottom one third, this is on page 113. This is a statement which I assume you and Dr. Owen agreed upon in evaluating the detail man.

Dr. HAGOOD. This, I must accept the responsibility for, because my name is attached to this. I would say this simply in the way of explanation, that the writing of this was largely done by Dr. Owen because at that time I was engaged in some other activities, and I simply said to him, "John, if you write this you will have to do it yourself because I am busy at this time." He did send me copies of this for my comments and any corrections, and I must say that this statement here does not now reflect my feeling toward this. Had I, if I had my druthers, I would have done it differently, but nevertheless I wrote it, my name is signed to this. I will have to accept responsibility, but I feel differently.

Mr. GORDON. Dr. Hagood——

Dr. HAGOOD. Yes, Mr. Gordon.

Mr. GORDON (continuing). I notice you quoted a figure of 85 percent of the rural physicians giving the detail man a strong vote of confidence.

Now, in the same paper that the Chairman was discussing we are coming now to the younger doctors, 37.5 percent of the residents, had unfavorable opinions of detail men, and only 3 percent were favorable, and about 60 percent neutral.

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[1] See app. I beginning at p. 4789, infra.

In your survey of residents, interns and students only 9 percent of respondents were favorably disposed to the advertisements of the drug industry and 52 percent expressed gross dissatisfaction with advertisements.

Dr. HAGOOD. Mr. Gordon, let me explain, this paper is written from questionnaires, two questionnaires. One, the general practitioner, myself, sent out to a group of 200 rural general practitioners. A separate questionnaire, made by Dr. Owen, was circulated among the house staff and the medical students of the University of Virginia, and this is his portion of this paper there.

Mr. GORDON. But it is rather interesting to see how the rural practitioner differs from those at the university, the "Town and Gown" as you have named the article, the great disparity, the great difference in attitude toward the detail man. Would you say it is rather interesting?

Dr. HAGOOD. This is certainly interesting. I would think that the comment in the first paragraph of the comment should be brought out here, which says "it would be imprudent to attempt multiple interpretations of the responses to two different questionnaires distributed to two different and heterogeneous groups with such a variable percentage of replies."

Senator NELSON. Fine, Doctor. Go ahead. You were at the top of page 14.

Dr. HAGOOD. Yes. We must be realistic in viewing this form of communication. Obviously his basic function is to sell. Obviously he is not there to extol the competition's product any more than one would expect Republicans or Democrats to praise the opposition. The doctor isn't so foolish as to assume such things, and because of that the detail man is identified in the physician's mind as a biased, albeit honest, source. To be successful, the detail man must appreciate the fact he is seen with a bit of doubt, and he must therefore, if anything, be overly conscious of the need for honesty. A show of ignorance, of deception or fraud, and he may permanently damage his company in the doctor's view; and he certainly will be making his last visit to my office.

Going back to the 1964 talk I made to PMA people, I told them 80 percent of doctors practicing in rural areas in Virginia answering my questionnaire said they favored continuing use of detail men by drug companies. That questionnaire was mailed to 200 doctors in rural settings in Virginia. I received returns from 80 doctors in 55 counties, who had practiced medicine from three to 61 years in communities, varying in size from open rural country to a town of 4,200.

In general, I believe drug company promotions, and their representatives, are both helpful and reliable. Imperfect, of course. But their function is not without real value, and I know of no workable or less costly alternates. Lacking better substitutes, I suggest we concentrate on improving them, rather than deploring them.

Mr. Chairman, again I thank you for allowing me, a general practitioner from rural Virginia, to tell you my views on some of the knotty problems facing this committee. I earnestly suggest you hear more from practicing physicians from all over America. By practicing physicians I mean those who make their living daily by fee for service. That is where the action is. The National Center for Health

Studies said during the 1-year period from July 1966 to June 1967, an estimated 71.8 percent of all physician visits took place in the physician's office. This figure is growing because this represented an increase of 10 percent over the 1957–58 study year.

A further breakdown of NCHS figures shows general practitioners accounted for 64 percent of office visits and 85 percent of house calls. Patient visits to all physicians totaled 831.1 million.

That many millions of visits to doctors doesn't impress one until it is related to a concern of this committee. Mr. Chairman, every one of those visits to a physician represents at least one prescription written or refilled. And that means if all these prescriptions were written at once and distributed to the population of these United States each man, woman, and child would each have four prescriptions in their hand.

Senator NELSON. Are you saying there that every patient receives a prescription for a drug?

Dr. HAGOOD. I am saying this represents a prescription or a refill prescription. This is my assumption.

Senator NELSON. That everybody who visits a doctor gets a prescription for a drug or a refill.

Dr. HAGOOD. No, I was trying to relate this figure to something that was of concern to this committee, so that I simply used this to emphasize the number of patient visits to doctors throughout this country.

Senator NELSON. But you weren't saying that every patient who comes to your office gets prescribed a drug?

Dr. HAGOOD. No, I was not saying that.

Senator NELSON. I want to thank you very much, Doctor, again for taking the time from your busy practice to come here.

Just so that you won't have any misunderstanding about how this committee is proceeding, we have made it clear from the first day that, on every issue raised of any consequence before the committee, that the committee would invite the viewpoint, every viewpoint, as to that issue raised. That is what we have been following. A number of times the PMA has made attacks on the committee saying the witnesses are handpicked, the committee is unfair, the viewpoints aren't being heard, and that is a gross misrepresentation.

It shocks me to see how often the PMA representing this great distinguished industry would intentionally propagandize in this fashion.

Our position has been that first preference goes to the drug companies on any issue raised which concerns them. We have invited every drug manufacturer in America, publicly several times, to appear before this committee on any aspect of these hearings they wished. Very few of them have volunteered. We have invited them all repeatedly.

We have invited every company who is criticized before this committee, immediately, as soon as we could arrange it, to have an opportunity to appear to discuss the criticism that is made of them. I don't see how we could be more fair than that.

We have made it clear that we will hear the viewpoints of all medical organizations in this country, and including the Academy of General Practitioners because I happen to think it is a very important aspect of the practice of medicine in this country.

You may be assured there is not a single viewpoint group of any significance at all that won't be amply heard. If they think that the

time assigned to them isn't adequate we will welcome them back again. We are inviting them all. We have been attacked because some of them haven't been invited before others. But if we are going to hear witnesses over a period of 2, 3, 4 years, as I am sure you appreciate, you can't hear them all at once. You have to hear them in some order or another.

But I want you to leave here knowing that the general practitioners are going to be amply heard, including the American Academy of General Practitioners, all other major medical organizations, and any distinguished individuals who have something to contribute to it, as well as the PMA, which we have already heard, and have told they can come back again. I want to assure you that the hearings here are not stacked in any way.

There are now nine volumes printed, and any organization that has been involved, any medical organization, any medical journal, any industry, any company or any individual can read those hearings and if they wish to respond to something on it they can send in their statement on it or they can ask for hearing time and in due time they will be heard, so these will be balanced hearings, and that is one of the reasons you are here today.

Dr. HAGOOD. Thank you, sir.

Senator NELSON. Thank you very much, Doctor.

Counsel had one question on the advertising of the drug companies.

Mr. GORDON. In your statement, on page 14, you stated:

"A show of ignorance, of deception or fraud, and he may permanently damage his company in the doctor's view; and he certainly will be making his last visit to my office." You are referring to detail men here.

In an article [1] by Dr. Gourley of the University of Virginia entitled "Teaching the Evaluation of Drug Advertising to Medical Students," which appeared in the Virginia Medical Monthly in August of 1966, we find that students were particularly impressed with the number of quoted references which were not available even in a good medical library——

Senator NELSON. Was this in the advertising?

Mr. GORDON. The advertising, yes. But when they really got around to looking into it, they found that they couldn't even find 95 percent of the references.

Now, how is the practicing physician going to know whether he is really being had or whether they are proper references when he sees this advertising or even when a detail man gives you a whole line of references.

Dr. HAGOOD. Mr. Gordon, the only way I can answer this is from a personal standpoint. Advertising in itself means very little to me, and as far as checking on the references that are quoted in the advertising material, I don't recall ever once looking into this because I use other sources from which I have formed my opinion, and, of course, I have stated those in my statement here.

Senator NELSON. Again, thank you very much, Doctor, we appreciate your taking time to come here.

Senator McIntyre.

Senator MCINTYRE. Thank you.

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[1] See app. II beginning at p. 4793, infra.

I just want to say, Doctor, I read your statement last night and I found it to be most readable and I consider it an excellent statement overall. I am not sure that you are representative of the average doctor, but I certainly was impressed with it as a probative argument.

I think that your decision to enter in the medical profession was probably a loss that the legal profession had to sustain.

Thank you very much.

Dr. HAGOOD. Thank you, Senator, you are most kind.

I would like to make a statement if I might, please, sir.

Senator NELSON. Yes.

Dr. HAGOOD. First of all, I want to thank you for the opportunity of coming before this group. To me this represents, and this gives very positive evidence of, the great country that we have here. That an individual from a little hamlet in our country can come before a committee of the Senate of the United States of America and state his views. I thank you very much for this.

Senator NELSON. Thank you, too, Doctor. I think, it being my experience in committees of Congress, that almost all chairmen, given the time, are willing to hear all the viewpoints and try to get all the viewpoints although sometimes some people around the country have an impression we don't. But again thank you very much.

Dr. HAGOOD. Thank you.

(Whereupon, at 11:10 a.m., the committee was adjourned, to reconvene at 10 a.m., Thursday, February 20, 1968.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

THURSDAY, FEBRUARY 20, 1969

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

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

Present: Senator Nelson.

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

Senator NELSON. Our witness this morning is Dr. Robert Moser, chief, Department of Medicine, Walter Reed General Hospital.

Doctor, the committee is very pleased to have you come and present your testimony this morning.

You have submitted your biographical background, which will be printed in the record.

(The biographical sketch of Dr. Moser follows:)

CURRICULUM VITAE, ROBERT H. MOSER, COLONEL, MC, USA

Born: Trenton, N. J., 16 June 1923. Married to former Stella Neeson — 2 sons: Steven, age 19; Jonathan, age 16

College:
Loyola College of Baltimore, 1940–1942
Villanova College, 1942–1943 (B.S.)

Medical School: Georgetown University, 1944–1948 (M.D.)

Internship: District of Columbia General Hospital, 1948–1949

Residency:
Internal Medicine;
Fellow in Pulmonary Disease, D.C. General Hosptal, (Dr. Sol Katz) 1949–1950
Assistant Resident, Georgetown University Hospital, 1952–1953
Resident in Cardiology, Brooke General Hospital (with Colonel Weldon Walker), 1956–1957
Associate Professor of Medicine, Baylor University College of Medicine, 1958–1959
Fellow in Hematology, Salt Lake City Hospital (with Dr. Maxwell M. Wintrobe), 1959–1960

Military:
U.S. Navy, December 1943-July 1948
U.S. Army, July 1948 until present
Chief, Department of Medicine, U.S. Army Hospital, Salzburg, Austria, 1953–1955
Chief, Department of Medicine, U.S. Army Hospital, Wurzburg, Germany, 1955–1956
Physician to the American Delegation "Foreign Ministers Meeting," Geneva, 1956

Assistant Chief, Department of Medicine, and Director of Education, Brooke General Hospital, 1957–1959
Assistant Chief, Department of Medicine, and Director of Education, U.S. Army Tripler General Hospital, 1960–1964
Medical Flight Control Team—"Project Mercury"—participating in all suborbital and orbital missions, May 1959 until termination of program
Command and General Staff College—1964 (Fall Associate Course)
Chief, Department of Medicine, William Beaumont General Hospital, January 1965-June 1967
Chief, Department of Medicine, Brooke General Hospital, June 1967-July 1968
Chief, Department of Medicine, Walter Reed General Hospital, July 1968–

Certifications: Certified in Internal Medicine, 1955.

Organizations:
(1) American Medical Association
(2) Fellow, American College of Physicians, 1961—
(3) American Therapeutic Society, 1964–
(4) Assn. Mil. Phys. 1966–
(5) Bexar County Medical Society 1968

Journal Activities:
Book reviewer for Military Medicine, 1960–
Author of monthly column, "Diseases of Medical Progress" for "Clinical Pharmacology & Therapeutics" Journal 1962–
Author of monthly column "Of Tomes and Tangents" for "Medical Opinion & Review" Journal—July 1966–
Contributing Editor—"Medical Opinion & Review" 1966–
Editorial Board—"Military Medicine", Jan. 1967–
Book Review Editor (Editorial Board)—"Archives of Internal Medicine." Jan 1967–
Author of bi-monthly column "The Training Scene" for "The House Physician Reporter", Sep 1967–
Consulting Editor of the Medical Annals of the District of Columbia Oct 68–

Committees:
(1) Consultant In Internal Medicine to Queen's Hospital, Honolulu, 1960–1964
(2) Member, Advisory Panel of the Registry of Adverse Reactions, Council on Drugs, AMA, 1960–1967
(3) Consultant to AMA Council on Drugs publication "New Drugs," 1966–1967
(4) Consultant in Internal Medicine to "Medical Tribune," 1966
(5) Consultant in Internal Medicine to Manned Spacecraft Center, Project Gemini, NASA and Member of Medical Evaluation Team, Project Gemini—1964 until completion of project
(6) Consultant in Internal Medicine to Manned Spacecraft Center, Apollo Project—1967–
(7) Appointed to AMA Council on Drugs, March 1968
(8) Appointed to Editorial Board, Medical Opinion & Review, April 1968
(9) Appointed Editor of American Lecture Series in Medical Writing and Communication, Chas. C. Thomas Pub. Co., 1969

Teaching Affiliations:
Associate Professor, Baylor University College of Medicine, 1957–1959
Clinical Professor—Georgetown Univ Sch of Med 1968–

PUBLICATIONS

1. Diseases of Medical Progress, C. S. Thomas & Co., Springfield, 1960.
2. Diseases of Medical Progress, 2nd Ed., Edited by Col. R. H. Moser and 12 co-authors. C. S. Thomas & Co., Springfield, 1964.
3. "Steroid-Induced Adrenal Insufficiency Aggravated by Severe Medical illness," Amer. J. Med. Sci., 239, Mar 1960.
4. "Back Door" Digitalis Intoxication: Review and Report of a Case, U.S. Armed Forces Med. J. 11:391–402, Apr 1960.
5. "Renal Biopsy" 11:307–317, U.S. Armed Forces Med. J., Mar 1960.
6. "Malignant Carcinoid: Report of a Case Confined by Percutaneous Hepatic Biopsy," Texas State J. Med., (Jul) 1960.
7. "An Atlas of Sternheimer-Malbin Staining Technique in Examination of Urinary Sediments" What's New 218 (Summer) 1960 and 226 (Oct-Nov).

8. "Diseases of Medical Progress—Report", Clin. Pharm. & Ther. 2:446–522, (Jan) 1961.
9. "The Man in the Loop" Hawaii Med. J. 23:109–113, (Nov-Dec) 1963 (Editorial)
10. "On Speaking to Patients," Ann. Int. Med. 51, (Sept) 1964.
11. "Congenital Inclusion Body Hemolytic Anemia Associated with Epilepsy and Disordered Pyridoxine Metabolism," Blood 24, (Aug) 1964.
12. * "Of Plagues and Pennants," Mil. Rev. 45:71–84 (May) 1965.
13. "Are Drug Hazards Overstressed," Issues 1:1-14, (Dec) 1964.
14. "Man in Space," Southwestern Med. 1:45–48 (Feb) 1966.
15. "Hypertension and Hypercalcemia," Ann. Int. Med. 64:378–381, 1966. (co-author)
16. "Malaria," Southwestern Med. 47:213–219 (Aug) 1966.
17. "The Modern Aspect of Leprosy," Texas Medicine J. (Aug) 1966.
18. "Non-Spherocytic Hemolytic Anemia in Pyruvic Kinase Deficient Erythrocytes" (co-author) pending publication.
19. "Percutaneous Renal Biopsy in Chimpanzees" Am. J. Vet. Res. Vol. 28, No. 126, 1631–1634, Sep 1967 (co-author)
20. "Evidence for a Reservoir of Red Blood Cells in Man" by M. C. Nusynowitz, R. L. North, R. H. Moser (submitted to J. Clin. Invest.)
21. "To the Physician-Soldier"—commencement address to Medical Field Service School, August 1967.
22. Diseases of Medical Progress, 3rd Ed. Edited by Col R. H. Moser and 12 co-authors. C. S. Thomas & Co., Springfield (pending publication)
23. Urinary Sediment Handbook, Clay-Adams, Inc., September 1968.
24. "Iatrogenic Disorders" Medical College of Virginia Quarterly 3(2):91–100, 1967.
25. "ATP Metabolism in Pyruvate Kinase Deficient Erythrocytes" by Jeremiah J. Twomey, Floyd B. O'Neal, Clarence P. Alfrey and Robert H. Moser Blood, Vol XXX, No. 5, November 1967.
26. "Iatrogen Disorders" Animals and Clinical Pharmacologic Techniques in Drug Evaluation edited by Peter E. Siegler, M.D. and Hohn H. Moyer, III, M.D. Year Book Medical Publishers, Inc., Chicago, 1967.
27. Moser, R. H.: "Iatrogenic Disorders," in Proger, S.: The Medicated Society, New York, The Macmillan Company, 1968.
28. "Hereditary Chronic Nephritis Complicated by Nephrotic Syndrome." Arch Int Med, 122:156 (August) 1968 (Co-author)
29. Moser, R. H.: "The New Ethics" in Kutscher, A. H.: But Not to Lose, New York, Frederick Fell, Inc., 1968 (In press)
30. "Prospective Epidemiology Studies," Drug Information Bulletin, p. 92, July/September 1968
31. Editorial, "A Proposal from the Periphery," Military Medicine, 133:849 (Oct) 1968
32. "More . . . On Speaking to Patients" Medical Arts and Sciences, Vol 21, 2d Qtr, 1967

Senator NELSON. I have read your statement and I think it is an excellent presentation. It makes a very fine contribution to the committee's deliberations.

You may present your testimony in any way you see fit. If you find it best to read it, you may. If you wish to extemporize on any particular point, just feel free to do so. I assume that you have no objection to us interrupting with questions, as they might occur to us.

STATEMENT OF DR. ROBERT H. MOSER, CHIEF, DEPARTMENT OF MEDICINE, WALTER REED GENERAL HOSPITAL, WASHINGTON, D.C.

Dr. MOSER. Thank you, Senator Nelson.

Senator NELSON. Please speak into the microphone so they can hear in the back of the room.

*Awarded "Military writing achievement" by Military Review.

Dr. MOSER. At the outset, I would like to state that I am not a clinical pharmacologist. My subsequent remarks, sir, represent my personal opinion as a practicing internist interested in the drugs I prescribe. I am not speaking for the U.S. Army Medical Department, nor for the AMA Council on Drugs, of which I am a member.

My interest in drugs has centered primarily around the problem of adverse effects of drugs, drug interactions, and related areas.

Most of the comments I am about to make are quoted or paraphrased from sections of books, chapters of books, and papers I have written on this subject in the course of recent years.

The physician and his patient are the beneficiaries of the most dramatic expansion of medical capability in the long history of our art. But the rapid proliferation of medical knowledge has not been entirely benign.

Our reverses have been minor when contrasted to our advances, but negative effects cannot be ignored or derogated.

Pertinent to this evolution of medical capability has been the improvement in quantity and quality of drugs. In the early days new drugs came in a trickle. There was time for the physician to become familiar with their virtues and idiosyncracies.

Soon the trickle became a stream and there was less time for study and reflection. The stream has now become a torrent; it is impossible for the physician to keep pace. One might say his little black bag runneth over.

It has been stated that drug-induced adverse effects are the price we must pay for more effective and better medicaments, and there can be no quarrel with this statement; it is the high price we are haggling about. The thalidomide disaster indicated how expensive it can be.

By last count there were 2,625 amelic and phocomelic children born in West Germany—these were children with extremity deformities—between 1958 and 1962. About 1,000 of these deformed children will be obliged to remain under regular prosthetic care and supervision for the rest of their lives; about 100 with the most serious deformities will remain under medical supervision the rest of their lives. Fortunately between 80 and 90 percent of the deformed children were in school by the end of 1967, and 60 to 70 percent were attending regular schools.

From the financial aspect, the Health Ministry of West Germany has spent $2.8 million in research, treatment, rehabilitation, and developing facilities for the deformed children.

This sobering catastrophe had the effect of catalyzing international concern about adverse effects of drugs, a sentiment of rather amorphous configuration before thalidomide.

It is true that each year a mere handful of important new drugs ultimately emerge from the profusion of products offered to the physician. But it takes time and experience to sort out nuggets from gravel.

Senator NELSON. May I interrupt you, Doctor, for just a moment?

Dr. MOSER. Yes, sir.

Senator NELSON. In 1968, according to the statistics our committee has, there were 101 new drugs introduced, of which only 14 were new chemical entities, and of these five new single drugs and two biologicals had any significance. Do you have any comment to make

about the great profusion of new drugs, such as 101, of which only 14 were new entities?

What is the value of the other 90 or so drugs coming into the marketplace?

Dr. MOSER. That's rather difficult to answer, sir. The problem is that when a new drug emerges it is extremely difficult to figure out what its ultimate place is going to be, and it does take time to sort them out. It takes considerable clinical study before one can be sure that this drug is indeed going to be a valuable contribution. It is a bit more than the average physician can do without the help of some fine investigators. I hadn't thought about 14 specific drugs, but I would assume that is a fairly good average of what we would get each year. The effective new agents do represent a handful.

Senator NELSON. What about those 87 new drugs which are simply the same chemical entities that are already in the marketplace now introduced as new drugs in some other combination? What is the pattern historically of the value of these new combinations?

Dr. MOSER. Well, again, I think it is hard to generalize. I would suspect that many such drugs come out as a result of competitive drug manufacture. I don't know if combinations ever represent any significant contribution. Chlorothiazide when it first came out was superceded by hydrochlorothiazide. This was offered as a better drug, but ultimately it turned out to be quite similar.

I can't cite specific instances, but I think there are many cases where these combination drugs add very much to our ability to take care of patients.

Senator NELSON. Thank you.

Dr. MOSER. To continue, once the physician does manage to figure out which of the new drugs are indeed valuable agents—and this is not easy—the pressure may come from patients and often from one's own peers, this pressure to try a new, unfamiliar compound—that has been effectively merchandised—is an additional force to be considered in the therapeutic capability of the individual physician.

Yet I have observed an expanding spirit of skepticism and discontent with empiricism in therapeutics. I find more and more that modern practitioners demand drugs that have proper credentials. And this has precipitated a virtual renaissance in drug investigation.

The demands of the clinician to know more about drugs are being met by increasing capability in the laboratory. New insight and appreciation of the complexities of drug effects have come from several diverse avenues of investigation. Percutaneous biopsy, which is a technique using a needle where one can get a piece of tissue from the lung, liver, and so forth, and examine it on a microscope, electron microscopy, and immunofluorescent techniques have—which are techniques that can be used to identify specific substances within tissues that have been taken with biopsy, have resulted in dramatic revelations; the mysteries of intracellular morphology and physiology in the living organism has begun to yield.

Often, we are able to observe the specific site of drug action within the cell and subcellular structures. In other areas techniques continue to be perfected for assay of blood any tissue levels of drugs, intermediate products, enzymes, and hormones and thus we have come to learn more of the wonders and hazards of contemporary therapeutic agents.

The problems of adverse drug effects are many. Reduced to simplest elements, when drug A is introduced into the body, ultimately it or its intermediate products will be carried in blood and body fluids to bathe virtually all cells of the organism.

The effects of drug A become perceptible only when the function of certain organs is modified, by whatever mechanism, and this may be either beneficially or detrimentally, to the point of producing clinically perceptible changes, and it is by these phenomena that we learn to characterize the nature of drug A.

Yet as we focus attention upon the anticipated response of a specific organ (or organs), we are inclined to forget that drug A is also in contact with other tissues of the organism. Effects in these areas are not in immediate evidence, but subtle often nefarious influences may be at work, which become manifested clinically, at a much later date.

Such long-range effects may never be correlated with the antecedent administration of our drug A and if one were to add drugs B, C, D, E, F, and so forth, one begins to appreciate the endless combinations and permutations.

The identification of a significant adverse reaction follows a long but familiar pattern. First, scattered unsubstantiated reports—and these may come by hearsay, anecdote, word of mouth, in the cloakroom at the hospital—are encountered, hinting that a certain drug has caused a certain undesirable effect.

Then begins the tedious process of painstaking retrospective analysis. Many suspected cases must be scrutinized, and perhaps, ultimately the suspected culprit—the provocative drug will be revealed.

To depart from the text, there are several mechanisms whereby this is done. The most familiar, of course, is the FDA gathering of their forms 1639 where any physician, who encounters an adverse reaction may complete the form and send it to the FDA where it will be plugged into their computer system. The AMA Council on Drugs also collects similar types of reports from private physicians throughout the country, which again will be introduced to their computer. And if physicians in the North, South, East, or West, all unrelated and unknown to each other, seem to report the same kind of reaction occurring with a specific drug, then the wheels are set into motion for the beginning of an investigation.

Senator NELSON. May I interrupt you a moment?

Dr. MOSER. Yes.

Senator NELSON. How effective is the reporting system, that is, what percentage of the doctors around the country who discover a side effect from using a drug, report it to the FDA or AMA Council on Drugs?

Dr. MOSER. Senator, if you will bear with me, I will get to that toward the end.

At this point one must follow with a meticulously controlled prospective study which will involve provocative testing in animals and often in men, before we can prove that indeed it was the suspected drug that causes this difficulty. It is a tedious, frequently unrewarding process. But it is the only valid technique currently available to medicine.

This is a shadow world of pathophysiology, where relation of cause to effect is at best difficult to assess. I need only cite the still raging

controversy over analgesics and renal disease to demonstrate this difficulty, and there are other problems.

Perhaps the most careful, definitive study of adverse drug reactions is being conducted by Dr. Nelson Irey of the recently established Registry of Tissue Reactions to Drugs. In reviewing the first 509 cases discussed in the new registry, Dr. Irey cited four principal areas of difficulty in his investigations.

Senator NELSON. Who established the Registry of Tissue Reactions to Drugs?

Dr. MOSER. This was a joint effort, as I understand it, sir. The registry is sponsored by AMA, Food and Drug Administration, PMA, and NIH. But the organization operates independently, and Dr. Irey is an outstanding scientist. They were in the old Army Institute of Pathology, and at the present time they are in interim headquarters, and I am told that they will occupy a wing at the new Armed Forces Institute of Pathology on the campus at Walter Reed when that building is completed. That is where the new headquarters for the Armed Forces Medical Museum will be. Dr. Irey told me several months ago that that is where they ultimately will keep their registry.

So it is a very independent organization. I think it is a fine study.

Dr. Irey cited in one of his publications four principal areas where he is having difficulty identifying these types of reactions. One, there is incomplete time relationship between the drugs and the disease. Second, in most instances there is a multiplicity of drugs administered (this makes it difficult to pin down which drug or drugs is involved). Often there is a lack of objective means of demonstrating a correct relationship between the drug and the reaction.

And, finally, there is a limited number of reaction patterns of the body to the entire range of physical, chemical, and biologic causes of disease.

In other words, the body has a restricted number of ways in which it can respond to harmful stimuli regardless of their source whether it is bacteria or a drug or a climatic condition, et cetera.

The liver, for example, can only respond in a limited number of ways. Very frequently it is extremely difficult to say whether a drug or a virus has been the cause of a specific liver dysfunction, such as hepatitis.

Thus, following the appropriately rigid criteria demanded by the registry, it was observed that in only 8 percent could a specific drug be definitely called the causative factor. In 40 percent it was considered to be "probable"; in 32 percent "impossible"; and in 15 percent, "coincidental." In 4 percent there was no apparent relationship. The contribution of drug interactions to this complex milieu will be discussed later.

The widely quoted adverse reaction studies of Cluff and associates at the Johns Hopkins Hospital has pointed up dramatically, the "iceberg" nature of this problem. This was an intensive prospective assault on the question, conducted by highly motivated house officers; 714 such patients with adverse drug reactions were discovered during a 3-month period at the Hopkins.

Cluff has stated that 13.6 percent of patients acquired an adverse drug reaction during the period of hospitalization, and the other results that he found were also rather astonishing.

Senator NELSON. Are you saying 13 percent of all patients admitted?

Dr. MOSER. That is right; 13 percent of the patients who were in the hospital came in with an adverse reaction or acquired one while in the hospital.

Now, 4 percent of these patients were admitted to the general medical services with an adverse reaction. This was the cause of the mission, 4 percent. This was the admitting diagnosis. Of this particular group 30.4 percent acquired another drug reaction during the course of hospitalization. The Cluff team observed a 4.2-percent incidence of reactions among patients who were receiving six to 10 drugs while in the hospital, 24.2 percent with 11 to 15 drugs, 40 percent in patients who were receiving between 16 and 20 drugs, and astonishingly, 45 percent of patients suffered adverse reactions who were receiving 21 or more drugs in the hospital.

Now, this may seem like a lot of drugs but anytime this fact has been studied, it is found that many patients are receiving between 8 and 12 drugs while they are in the hospital, and this is a fair representation of the drugs being given to individual patients in fine university hospitals.

Now, in the Cluff study, antimicrobial agents (antibiotics), and cardiac drugs were implicated most often, accounting for 21.2 percent of all reactions each, or 42.4 percent of the total. Hypnotics, another word for sleeping medication, and sedatives, produced 13.0 percent reactions; insulin, 8.9 percent; and antihypertensive drugs, 8.2 percent.

The clinical manifestations of adverse drug reactions were: gastrointestinal, 35.6 percent; neuromuscular reactions (muscle aches and pains) 15.8 percent; metabolic disturbances, 13 percent; cardiovascular disturbance, 11.6 percent; skin rashes, 10.3 percent; hematologic, 4.9 percent; renal, 3.4 percent, and multiple systems (this would be heart, liver, kidneys, combinations of systems) were involved in about 2.7 percent. And, finally, pulmonary (that is, lung) and other miscellaneous types of reactions accounted for 1.4 percent each.

About 7 percent of all adverse reactions observed during this 3-month period of study were life threatening or fatal, and five deaths in this series were attributed to adverse drug reactions.

Over two-thirds of the in-hospital adverse reactions were detected within 4 days after the causative drug had been started. Allergic reactions usually developed between the fifth and 10th day, and some came on in an accelerated fashion. Nausea, vomiting, or diarrhea were the most common manifestations, and these occurred most frequently in women. Adverse reactions were more common in patients over 50; whites suffered more than blacks; women more than men. The average duration of hospitalization for patients with adverse drug reactions was 20.8 days. This is in contrast with 14.3 days for patients on the medical wards.

This is a significant increase.

In another well-known study of adverse drug reactions performed by five cooperating medical school hospitals in the Philadelphia area, namely, Hahnemann, Jefferson, Temple, Penn, and Women's 772 adverse drug reactions were reported during a 24-month period of study.

In this study dermatologic and allergic reactions were the most common and accounted for 65 percent of all case reports. Penicillin was

suspected in 101 reactions; phenobarbital and digitalis preparations in 21, and aspirin in 20.

In this study the overall incidence of adverse reactions was .49 percent of all hospitalized patients for the first year of the study, and .41 percent for the second year.

And, incidentally, it was during this Greater Philadelphia study that the first demonstration of a positive Coombs test in patients taking cephalothin sodium was detected.

The differences in incidence of adverse reactions between the Cluff study, the Schimmel report (in which 10 percent of hospitalized patients suffered adverse drug reactions) the Greater Philadelphia program, and others, may be related to techniques of data gathering and definition of what constitutes an "adverse drug reaction."

For example, the Philadelphia group and Koch-Weser at the Massachusetts General Hospital required that for admission to their protocol, a reaction must be "severe enough to be commented upon in the progress notes." And those familiar with the terse and often sparse progress notes written by the busy house officer might consider this to be a chancy qualification. Of course, this was not a determinant in the Cluff and Schimmel studies where the incidence figures of adverse reactions was much higher.

Finally, Cluff and Schimmel utilized a prospective method while other groups used a retrospective method. In other words, they set out to seek reactions on the wards while the others waited for them to occur and be reported.

The problems of adverse reactions to placebos or spontaneously occurring symptoms due to nondrug causes cannot be entirely discounted, especially when one is evaluating minor reactions to drugs.

However, I feel it is equally safe to assume that for every patient who becomes sufficiently ill with an adverse drug effect to trek to emergency room or physician's office, there are perhaps 10 who will not.

This is my own estimate.

Senator NELSON. In other words, are you saying that about one-tenth, one out of 10 cases of drug reactions are reported?

Dr. MOSER. No, not quite that. One out of 10 drug reactions are severe enough to bring them to clinical attention, to come to a doctor's office or to come to a clinic. And I think it is fair to say that with non-drug-induced illnesses it may be the same. But I think the point is that adverse drug reaotions represent illnesses just like other diseases, and the same ground rules apply. Probably one out of 10 come to clinical attention, and that is a fair guess.

The reasons are plentiful: The reaction may be mild, one may fear loss of time from the job, et cetera (the same reasons that one doesn't go to see a doctor for a non-drug-related disease). At the present time there are many studies underway throughout the country to gather more meaningful data on this subject. And I will comment upon these later.

Let's approach the problem from still another aspect. What is known of the role played by drugs in predisposing the organism to attack by micro-organisms or degenerative disease? One example is the effect of long-term corticosteroids in predisposing the leukemia or lymphoma patient to systemic fungus infections.

We have heard a great deal in medical literature about the so-called "opportunistic organisms." I consider this a semantically poor euphemism, but that's not the point. It is important to our thesis to mention the fungus *Candida albicans*. This is one of a group of saprophytes. A saprophyte is an organism that is normally found in the gut and usually does no harm; it is of limited pathogenicity under normal circumstances.

Candida may emerge as a systemic infection and seed into many organs during or following broad spectrum antibiotic therapy with or without concomitant corticosteroids or immunosuppressive drugs. This phenomenon has been related to suppression of susceptible intestinal bacteria with disruption of the normal ecologic balance. Everyone's intestinal tract exists in a state of balance between various groups of micro-organisms. We acquire these as soon as we begin to live; (literally), and they exist in symbiosis with the host throughout life. However, when one gives antibiotics occasionally this balance will be disrupted, and organisms that are not killed by this particular antimicrobial agent may gain ascendency. They will proliferate and often they will escape the intestinal confines, and if one is also receiving corticosteroids or immunosuppressive drugs, this occurs at a time when the normal defense mechanisms (to resist infection) are all but paralyzed, and one can get a systemic infection with fungus.

Another example is the devastating influence of prolonged——

Senator NELSON. Is there any drug that is effective against the fungus?

Dr. MOSER. Yes. There is amphotericin B which is a fairly effective systemic fungicide agent.

Another example is the devastating influence of prolonged corticosteroid therapy upon the elderly patient who is somewhat immobilized by cardiovascular disease or arthritis. In these individuals accelerated demineralization is encouraged through the antianabolic effect of corticosteroids. In other words, the corticosteroids will actually accelerate the normal tendency of the bones to lose calcium and some of their protein matrix. And again this is a classic demonstration of exacerbration, or making more severe, a degenerative process induced by a drug. In this situation we start with one disease, and our treatment for it produces another disease.

Let's modify the question again. What is known of the effects of drugs upon a previously diseased organ, with limited capability to metabolize or detoxify or otherwise cope with a drug given to treat another illness? Now, I have mentioned the phenacetin controversy. The discussion here revolves around the status of analgesic compounds in the provocation of a variety of interstitial kidney infection and destruction of papillary tips of the kidney in a normal organ. This is a longstanding controversy in which some of the analgesic drugs are thought to be able to cause specific disease of the kidney. But this discussion is about what they do in a normal kidney. And I ask what effect does phenacetin or aspirin or caffeine have upon a sick kidney, already poorly disposed to resist assault from either microorganisms or nephrotoxic drug?

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

Dr. MOSER. Yes.

Mr. GORDON. This is the APC tablets?

Dr. MOSER. Yes.

Mr. GORDON. These are also sold over the counter without a prescription? Isn't that right?

Dr. MOSER. Most of them have had phenacetin removed, according to my information. I think there may be a few companies that still produce it, but I think most of the APC's have the phenacetin removed.

Now, I want to say that this is a far from settled business. I don't mean to sit here and tell you that I know the answer to this problem, because many fine people have devoted a lot of time to trying to work this out. I don't want to take a stand on this because I really don't know. Let us say that there is perhaps an increased incidence of interstitial nephritis and papillitis in patients who have taken a variety of analgesic compounds. What the specific agent (or agents) is I don't really know.

I would like to go on to discuss now the phenomenon of delayed excretion of drugs or their active intermediate products (which we call metabolites), by an organ which is already diseased. In this situation the unanticipated high blood levels introduce a whole new spectrum of toxic effects. And what happens to the diseased kidney of itself, if the drug which it has been reticent to excrete, happens to be specifically toxic to the kidney and then becomes superconcentrated in the countercurrents of the kidney medulla.

All this means is that in the lower part of individual kidney units (in the lower part of the nephron) where there is exhaberant water absorption, any product that is coming through the kidney will be concentrated in this particular portion. And I pose the thought that in the event that the drug which with we are dealing happens to be nephrotoxic, the kidney may suddenly be receiving a very concentrated dose of this particular drug. It is an interesting area.

Or, consider the patient with a subclinical liver disease—a mild cirrhosis, if you will. What happens when he is given halothane or chlorpromazine or phenylbutazone, drugs known, occasionally, to be unkind to the normal liver? What happens when it is given to a previously diseased liver?

One could cite many examples wherein an organ with marginal function may be further insulted by a drug administered, most innocently, to treat another ailing system? The thought remains a continuing source of uneasiness in all drug therapy.

The mechanisms of adverse drug reactions have been a subject of many taxonomies, and I have selected one feasible classification as modified from a paper by Long, and he lists seven classifications:

Hypersensitivity or allergy; idiosyncrasy; immunological injury; enzyme induction (which means acceleration of the metabolism of a drug), enzyme potentiation (or inhibition of drug metabolism), carcinogenesis (which means cancer), teratogenesis and mutagenesis, which mean the induction of congenital conformities.

I don't feel it is pertinent to this presentation to delve in depth into the mechanisms of drug interactions or specific physiologic mechanisms that cause adverse reactions. However, a few general remarks may facilitate understanding of some of the problems that beset the practitioner in his effort to employ drugs effectively.

PHARMACOGENETICS

Perhaps the most fascinating new dimension in drug reactions was the identification of a relationship between enzyme systems and drug effects.

In 1959, Vogel introduced the term "pharmacogenetics" into clinical medicine. This was defined as "the study of genetically determined variations that are revealed solely by the effects of drugs."

The genetic aberration results in the absence or insufficiency of certain specific enzyme systems. This mechanism, the revelation of smoldering enzyme insufficiencies, has already been cited as one major explanation of the extraordinary human variability in response to conventional doses of conventional drugs.

Here we are discussing the effects of a single drug (A) upon a patient with congenital or inborn disorder of a specific enzyme or enzyme system. And I leave you to ponder the possibilities of what might happen if the drug (A) inhibits or stimulates enzymes responsible for the metabolism of Drug B or C. We will discuss this later in more detail, but I would like to cite a few notable examples of the phenomenon of pharmacogenetics.

The historical and classical prototype is the hemolytic anemia—this is a variety of anemia where the red cells burst—suffered by some members of certain ethnic groups, specifically Mediterranean basis dwellers, rare Scandinavians, and Negroes, individuals who have a quantitative or a qualitative deficiency of a critical enzyme that resides in red blood cells. Brisk rupture of these blood cells may follow exposure to many common therapeutic agents, and among these are certain antimalarials, certain sulfonamides, aspirin and perhaps a dozen other so-called "oxidant" type drugs. Even our old nemesis, the medical student's friend, the notorious Fava bean, continues to kill a few Sardinian children each year by triggering a catastrophic hemolytic anemia on the same basis.

And I might add whimsically that the excitement generated by the discovery that drugs could be employed to delineate specific enzyme insufficiency syndromes has done a great deal to increase the status of drug research as a respectable means of earning a livelihood. It is very respectable to do basic research in enzymes. Now that the drugs have been discovered to unmask such enzyme disorders, a lot of people are becoming interested in drug research.

The cause of this red cell destruction is a genetically transmitted defect that results in various degrees of deficiency, quantitative or qualitative, of this enzyme.

These patients are clinically normal. They have no apparent, either by appearance or by physiologic testing, abnormality of their red cells, until one of the provocative drugs is given, and then they will develop a brisk anemia.

Deficiency of this important red cell enzyme is somewhat of a problem in the chloroquine-primaquine antimalarial prophylaxis program in Southeast Asia. Soldiers known to suffer the clinical manifestations of this disorder are restricted from duty in endemic malarious areas, because we don't want to give them the chloroquine or primaquine tablets.

And there are dozens of other fascinating pharmacogenetic disorders, and new ones continue to emerge. If one reflects for a moment

upon the multitude of known enzyme systems as well as those suspected or latent or subclinical, but not as yet identified, one could predict that many drug effects that are now classified as idiosyncratic or even allergic will gradually be herded in the fold of pharmacogenetic disorders or perhaps enzyme insufficiencies that are acquired as the result of disease.

DRUG INTERACTIONS

One of the more complex, fascinating, and disturbing areas of pharmacology which has direct pertinence in any discussion of adverse drug effects is "drug interactions." Efforts to establish a feasible classification continue as new mechanisms are discovered. Dr. Hartshorn defines drug interaction as—and this is the best definition I could find—"The phenomenon which occurs when the effects of one drug are modified by the prior or concurrent administration of another—or the same—drug(s). Drug interactions may arise either from alteration of the absorption, distribution, biotransformation, or excretion of one drug by another or from combination of their actions or effects."

He makes a distinction between interaction and drug incompatibility. He reserves the latter form for reactions which occur either in the bottle as one mixes two drugs or in the syringe before they are given to a patient.

Dr. Irey has also been involved in interaction and he lists another classification of interaction in categories.

1. Interaction with other drugs or themselves. This is an induction process.

2. Then there may be interaction with endogenous physiologic chemical agents. And the example here is monoaminoxidase inhibitors and epinephrine.

3. Interaction of the drug with components of the diet, as in the administration of MAOI drugs with tyramine as one would get in cheddar cheese.

4. Interactions with chemicals used in diagnostic tests or the results of such tests. And an example of this would be the oral contraceptives which may modify the glucose tolerance tests.

Two of the more fascinating aspects of drug interactions have to do with enzyme induction and enzyme inhibition, and I would like to discuss these briefly, in turn, just to illustrate the magnitude of the problem.

ENZYME INDUCTION

Many drugs, when taken over a period of time, can cause a marked acceleration of their own metabolism or can accelerate the metabolism of other drugs being administered concomitantly or subsequently. This effect is mediated through stimulation of drug metabolizing enzymes in the liver. This process is called "enzyme induction," and it has become an extremely important aspect of drug toxicity. Induction can lead to an escalating requirement for maintenance doses of a given drug, each of which can be acutely toxic.

Fortunately, most drugs do not involve enzyme induction, but it must be conceded that not all drugs have been subjected to this rather difficult and time-consuming type of testing. Nor is it known if all individuals are susceptible to enzyme induction by a specific drug.

And this brings us to another aspect of this effect. Not only may a

drug accelerate its own metabolism, but it may affect others. The administration of drug A may stimulate hepatic enzymes which accelerate the metabolic breakdown of drug B. If this phenomenon is not appreciated and anticipated, it may result in lower than expected blood levels of drug B.

I would like to show a slide at this moment to illustrate this point, if I may.

The point is this. Here we have a patient who comes to see a doctor. The diagnosis is made, and the patient is started on a conventional dose of this drug. He is given one gram a day. Over a period of time over the next few days the patient gets the desired therapeutic effect, and the patient is going quite well.

However, by the fourth day the patient is seen by another doctor or by the same doctor and is then given drug B for some other complaint.

Now, drug B happens to be a drug capable of causing induction of drug A. In other words, it accelerates its metabolism, and the blood level of drug A rapidly falls off. So you see we have now a lack of effect. The patient comes back to the original doctor and says, "Doctor, I am certainly not getting the same response that I got from that drug (A) you gave me." But she neglects to tell him that she is also taking drug B; so he increases the dose of the first drug (A). After a few days she gets back up to the same therapeutic level, and then for one reason or another drug B is stopped, and this was the drug which was inducing and accelerating the metabolism of drug A. It is gone and suddenly we have a patient who becomes toxic from drug A. And if the physician does not know about this mechanism, he will become very confused and may think that the drug is no longer effective. And this is why enzyme induction is dreadfully important to us.

The cardinal principle involved is that individual doses of drugs may be required that are quite toxic in an effort to maintain blood levels that were achieved with much lower does earlier in the course of drug therapy. And the corollary is equally as important. One may consider that a drug is ineffective, when the actual fact is that the blood levels are too low, despite the administration of proper doses.

ENZYME INHIBITION

Now, the next phenomenon, one that is more familiar to physicians, that is antithetical to the concept of enzyme induction and accelerated drug metabolism. This is inhibition of the metabolic breakdown of one drug by another with a potentiation of its effect.

And we have another slide to illustrate this.

Now, here we have exactly the reverse situation. The patient comes in and is given drug A (drug A becomes more notorious as we proceed) and gets a therapeutic effect as anticipated.

At this particular time drug B is given by someone else. Drug B in this situation, rather than accelerate the metabolism of drug A, as occurred previously, now inhibits the metabolism. Therefore, drug A remains in the blood stream longer than was anticipated, begins to accumulate, and suddenly the patient develops toxic effects from drug A.

The physician at this point scratches his head and says, "Well, this patient may be unusually sensitive to this drug." So he drops the dose to half. And within a few days the blood level is back down, and the patient has lost the toxicity desired. A few days later drug B is stopped and inhibition of the first drug ceases. Now the physician is giving this patient an inadequate dose and the loss of therapeutic effect becomes evident. The importance is realization of the fact that two drugs can modify the effect of one upon the other.

It is a fairly common occurrence, can cause great consternation in any physician, if he does not appreciate this phenomenon. And we are just beginning to appreciate the complexities of drug interactions.

There are several other mechanisms involved, and I will not go into them in any great detail. Occasionally disease of the excretory organ, such as the kidney, can be made worse by a drug. This may cause inhibition of the excretion of another drug, and then drug B (the second drug), will persist in the blood for longer than anticipated periods of time.

Another mechanism is the physical displacement of drugs from blood protein (carriers). Most drugs are bound by circulating proteins, and therefore are relatively ineffective. They only become effective when released from their protein binding sites, and this is again calculated into the dosage requirements. But if you give a second drug that bumps the first drug off of its protein binding site, you will then have more of the free drug A circulating, and in this situation you can get toxicity.

DRUG EXCRETION

A few words about drug excretion seem appropriate. A prototype drug involved in this problem of excretion is phenylbutazone, which is an antiarthritic drug. When given in conjunction with a acetohexamide, a popular antidiabetes drug, the phenylbutazone will inhibit the excretion of the acetohexamide and one can get a higher than anticipated level of the latter. This can cause very low blood sugar levels and occasionally in an elderly patient can cause some hypoglycemic shock.

A drug that is known to inhibit the excretion of penicillin, through blocking kidney reabsorption, is probenecid. This is a drug normally used to accelerate uric acid excretion.

Now, this is a beneficial effect. In this situation we frequently employ penicillin with probenecid, specifically to maintain higher blood levels of penicillin than normal. This is frequently used in patients who have bacterial endocarditis with resistant micro organisms.

RESIDUAL DRUG EFFECTS

Residual drug effects remain another enigmatic area. For example, reserpine, an antihypertensive drug, continues to exert its influence in certain patients for several weeks after it has been discontinued. And it may cause unpredictable responses to general anesthesia. If the anesthesiologist is not very careful, he may get into some difficulty in the process of inducing anesthesia. It is a fine drug, but one must know that it may cause these responses.

In another area, elevated levels of iodine bound to protein were found to persist for 7 years in the sera of women who had received

iophenoxic acid, an agent used to take X-ray pictures of gall bladders. And babies born several years after their mothers had ingested this dye had extremely high levels of protein bound iodine, although they did not have any clinical manifestation of hyperthyroidism.

These agents may lie dormant in fat depots for many years, apparently innocuous but in curious contradiction to the usual tendency of the organism to rid itself of foreign substances.

One might ask what other drugs are stored for prolonged periods. Do they exert adverse effects? One might summarize the complex problem of drug interactions with this final diagram. This is a Venn diagram that I think summarizes the total picture.

It is a little hard to see, but the point can be made.

Here we have drug A at the top, drug B at the bottom. We have an enzyme system as it is involved in the metabolism of drug A and drug B, and finally we have the organ that is going to respond, the organ we are trying to treat with this combination. It is not just a simple matter of two circles, drug A and drug B acting upon the end organ. They are involved quite intimately with each other, with the enzyme system and with the end organ. And one could add on a whole sequence of circles that would intersect at various levels if you wanted to add enzymes B aand C which may be involved in the interaction. And all organs of the body are going to be involved. The physician is dealing with this, the middle of this complex situation, and therefore when drugs are being given it is not just a simple matter. It can be a rather complex business.

WHAT DOES ALL THIS MEAN?

Now that we have seen something of the broad introductory area of drug-induced diseases and drug interactions, a logical question might be, what will be the ultimate effect of these new therapeutic endeavors? And the answer must lie somewhere in the interface between philosophy and physiology.

The evolution of man is a continuing source of wonderment to students of physiology. Through the centuries of evolutionary metamorphosis, each challenge thrown at man by his environment was met by gradual genetic modulation that enabled him to survive. The species have arrived at the current state of advanced physiologic capability, admirably adapted to its environment.

We can dig diamonds at 9,000 feet in 123 degree heat and 100 percent humidity; we can spend a lifetime mining tin at 14,900 feet elevation; we can hike across the pole, and we can float weightless for 14 days in space.

But in the past few decades we have devised methods unprecedented in the entire previous experience of the species to challenge the adaptability of the organism. We have designed molecules unique to human physiology and insinuated them into blood and tissue by techniques that are also unique physiologic experiences.

Intravenous, intramuscular and subcutaneous injections, positive pressure inhalation, rectal administration, and agents facilitate passage of molecules through intact skin—all are unfamiliar modes of gaining access to the body.

Add radiation—by X-ray, beta ray, gamma ray and neutron, plus oxygen under greatly increased barometric pressure, and some other

modalities that I have doubtlessly forgotten—and one begins to appreciate the magnitude and genius of man's conspiracy to bypass the conventional avenues for introducing new environmental factors to the physiology of man.

In the past we only had to cope with naive nature and unsubtle environment. And they were confined to the gastro-intestinal tract, lungs, and occasionally the abraided skin, as avenues of access for alien materials to get at the core of man.

The implications of these ingenious tactics of assault, these strange manmade chemicals and emanations upon the beleagured human mechanism are fascinating to contemplate. One could speculate that this incredibly resilient physiologic engine of ours is sufficiently advanced in design to be able to cope with all environmental transgressors.

We have evolved defenses at all levels from the simplest reflex to the most complex immune reactions to meet the daily challenges of environment. And we have done very well in the matter of self-preservation.

Yet it is quite evident that some of these unprecedented therapeutic intrusions overtax the ability of the body to accommodate—and it will react with displeasure, if not violent rejection. And, of course, this is the heart of our thesis—drug-induced diseases.

CONCLUSIONS

Adverse Reaction Reporting

At this juncture I feel obliged to reiterate that these observations I am about to make are my own and do not necessarily reflect the opinion of the Army Medical Department or the AMA Council on Drugs.

Drug-induced disorders will be with us forevermore. They cannot be swept under the rug either by clinician or drug producer. My own naivite in the world of commercial enterprise is revealed by my admission that I think a fine new drug will become known to the profession on the basis of its merit. I am embarrassed when this noble commodity is demeaned by merchandising techniques, however subtle or artful, better suited to less vital products of commerce.

I do not feel that drugs should be propagandized to the medical profession. The pressure of commercial competition is not conducive to objectivity in the presentation of drug detailmen or in published advertisements. I feel that these factors add to the confusion in the already difficult problems of evaluating the efficacy and/or adverse effects of new drugs.

The requirement for an impartial agency that can provide current, reliable and objective data about the characteristics of new drugs, and alert the physician to their beneficial effects and toxic hazards is abundantly evident.

Senator NELSON. We have had testimony similar to your statement about the advertising and promotion of drugs. On the other hand, we have had claims by some doctors and the industry that promotion by detailmen is the most effective way of informing the American medical profession that the drug does exist.

Are you satisfied—I take it you are, from your statement—that if

there was not this wide drug promotion by advertising in medical journals and by promotion by detailmen that the medical profession would discover the drug and its merits and its appropriate uses just as well.

Dr. MOSER. Yes I do. And I will speak to that as we progress.

I will briefly summarize some of the efforts that have been made in this area. Both AMA and the FDA became immersed in the business of trying to obtain data on adverse drug reactions. The AMA had a potential information source of over 7,000 hospitals and 250,000 physicians. How many reports were received? The total as of December 1968 was 8,733.

Senator NELSON. From what date to what date?

Dr. MOSER. I think the study actually began in the early 1960s with the registry on blood dyscrasias and is still going on.

At times the quality and the accuracy of these reports was appalling. However, the original registry on blood dyscrasias fed information back to the profession in the form of semiannual tabulations. And these provided much helpful information. For example, knowledge of chloramphenicol and dipyrone toxicity was documented and facilitated through this mechanism.

Senator NELSON. We had rather extensive testimony here by a number of distinguished experts on the misuse or the use of chloramphenicol for nonindicated cases. Testimony, unrefuted thus far at least by any witnesses, including the drug industry was that anywhere from 90 to 99 percent of the patients who received chloramphenicol received it for nonindicated cases.

Now, if the toxicity of chloramphenicol was documented, why was there a failure to convey this information adequately to the medical profession?

Dr. MOSER. I can't answer that, Senator. I think the information has been abundantly available from many sources.

I am familiar with Dr. Best's report that received fairly wide dissemination in the Journal of the AMA and there has been information in the the Medical Letter. Virtually every publication that has come out in recent years has carried admonitions about careful selection of indications in the use of chloramphenicol.

It is difficult for me to understand how this information is not very broadly used. And I would be inclined to think—at least let's say I hope, that this misuse of chlormaphenicol is limited to a very few physicians. The actual indications are quite restricted and if the drug is used without proper indication, it is very bad. It is dreadful.

I can't answer your questions as to why it continues to be used without proper indication.

Senator NELSON. Well, if the testimony and the information we have is correct, approximately 4 million people are prescribed chloramphenicol annually. We have had estimates here from—I am not attributing this estimate to any one of these people—Dr. Dameshek from Mount Sinai, Dr. Best, Dr. Lepper, and two or three others, that anywhere from perhaps 10,000 or 15,000 to 20,000 out of the 4 million received this drug for an indicated case. This seems to me to involve a tremendous amount of misprescribing; if it is 4 million, the other 3,900,000 shouldn't have received it at all.

Have you followed, have you noticed, the advertising in the medical journals of chlormaphenicol?

Dr. MOSER. No, sir. I must confess that for the last several years I have not been reading the journal advertisements.

Senator NELSON. If a doctor opens up Goodman & Gilman, or any such source of information, and reads any article on the use of chloramphenicol, he will probably find that the specific limited indications of its use are listed very carefully, The package inserts that go with the medicine, which probably most doctors don't see because it goes to the pharmacist, lists the indicated uses and precautions and dramatic side effects in certain instances.

What I am curious to find out, if all this information is available, why has it been so widely misprescribed, if the testimony of these doctors is correct?

Dr. MOSER. Of course I cannot answer that, but one partial explanation resides in the fact that the average physician, in the course of a lifetime, may never see a case aplastic anemia. The incidence has been quoted at from 1 in 20,000 to 1 in 100,000 administrations of chloramphenicol. The rationale, as far as I can figure it, is that a physician may say, this is so rare it just isn't going to happen to me.

And chloramphenicol is a good drug. It is quite an effective drug. In fact, it is one of the most effective oral antibiotics that we have. Unfortunately, it has this potentially devastating complication.

I suspect that a physician will be tempted to prescribe this drug when it is not absolutely indicated because he just hasn't seen a case (aplastic anemia) himself. And there is a great tendency in medicine to rely on one's experience. This is dangerous; that is why we have the medical literature.

Senator NELSON. I think there is a problem with that statistic from the California study, which was about 1 in 20,000, I believe, nobody knows what percentage of cases are reported. Obviously, if a doctor uses it for acne, sore throat, headaches, upper respiratory problems, gum infections, hangnails, all of which are specific cases for which it has been used, and aplastic anemia results, which it has in all of these cases, he is not going to report it when he is liable in a lawsuit for the damage done. And there have been some very dramatic lawsuits in the past and many on the way now. We have testimony from doctors here that nobody is going to report that themselves.

So when you say 1 in 20,000 it may be 10 or 15 or 100 times that figure. The figure is high, but even so, even though the testimony is that it is an excellent drug, it is for such a limited number of indications that if you just read it once, you wouldn't use it as a broad spectrum antibiotic for which it obviously is being used.

Dr. MOSER. I do not feel that chloramphenicol should ever be used outside the hospital. It is a drug that should be used on inpatients for the treatment of very specific infections.

Senator NELSON. Thank you.

Dr. MOSER. Now, getting back to the discussion of the compilation of adverse reaction data, the AMA Registry continued to gather and tabulate its information until 1964, when it was decided that the data should be transferred to computer storage. And unfortunately this conversion never came to fruition. Also anticipated plans for free communication between the AMA and the FDA programs also never achieved a working reality. Through both programs it has been estimated that roughly 1 percent to 2 percent of adverse reactions that

were occurring in the United States were being reported. The FDA continues to receive reports from about 85 hospitals, mostly military and Federal, throughout the country.

The AMA Registry continues to receive reports from interested physicians who detect adverse reactions. At the present time, the council on drugs of the American Medical Association is in the process of devising an elastic prototype program that will enable hospitals of every size and mission to establish ongoing studies on adverse drug reactions and drug utilization practices.

As a working member of this committee, I can assure you that progress is being made. If such machinery can be established—and we have every reason to believe that it will be—and the data gathering made painless for the physician, yet pertinent to the statisticians, and we begin to help physicians learn more about drugs, this will certainly be worth the effort.

At this point I would like to say a word about the hospital pharmacist.

In this schema—and that's the one that we are devising for the AMA council to begin to do drug utilization studies—the hospital pharmacist will play an essential role. Under optimal circumstances, he should be integrated into the therapeutic team as an active member. While I feel it is inappropriate to have pharmacists participate in patient care decisions—an area which should remain the exclusive province of the physicians—pharmacists should serve as therapeutic advisers. The treatment of a patient includes too many variables beyond drug therapy. Social and psychologic perturbations, in addition to physiologic disruptions, add up to escalate the problems of "treatment" to a plane beyond consideration of drug therapy per se.

Nevertheless, the pharmacist has a vital role. In our hospital, pharmacists are active members of the therapeutic agents board and the drug utilization and adverse drug reactions committee. Teams of pharmacists visit all wards of the hospital twice each week and contact individual ward officers to inquire about adverse drug reactions that have occurred. The pharmacists then complete the FD 1639 form from information derived from the patient's chart and from direct communication with the responsible ward officer.

The FDA forms are reviewed by our drug utilization and adverse drug reactions committee, whch consists of one physician and three pharmacists; the pertinent data is presented at the next meeting of the therapeutic agents board, and then copies of FD 1639 are forwarded to the FDA and to the Army Surgeon General's Office.

In the future it is anticipated that our hospital, the Drug Utilization and Adverse Reactions Committee, will conduct drug utilization studies and ultimately drug efficacy studies.

In addition, the pharmacists—and this is the case at Walter Reed—maintain a ready file of FDA adverse reactions reports as a rapid information source for physicians. They also maintain current files of books and journals—available to physicians for immediate information on drugs, including efficacy, interactions, and toxicity.

Thus the pharmacist, with his special interest in pharmacology, has become an essential, permanent member of the therapeutic team. A logical question at this juncture might be, "What is the source of drug information utilized by most prescribing physicians?"

And I would like to preface my remarks by saying that I look upon all these statistics with some concern. The validity of a response by a given physician to this type of question from my personal observation is not necessarily candid.

In one famous national survey sponsored by the Pharmaceutical Manufacturers Association, the principal sources of drug information utilized by physicians was investigated: 61 percent said that they received the information from the Physicians' Desk Reference, a publication distributed free by the pharmaceutical industry; 37 percent of physicians said they received their information through personal experience and knowledge; 27 percent through journals and medical periodicals, and 19 percent from detail men. Other sources consisted of colleagues, consultants, medical society meetings, medical literature textbooks.

Compendia and drug reference books were the source utilized by 10 percent.

Senator NELSON. Didn't any doctor attribute his information to a drug ad?

Dr. MOSER. I assume that that was, sir, included in the 27 percent who said their information came from journals and medical periodicals. This was my assumption. It may not be valid.

Response to the question of the relative frequency with which sources of drug information were used: The Physicians Desk Reference was used by 82 percent; the Medical Letter by 2 percent, the Merck Manual by 2 percent. And there were 19 percent of the physicians in this group who had never heard of the Medical Letter.

One could quote many other studies done by private organizations which usually reveal that the principal source of drug information is derived from publications or visits that have their source material derived from the commercial drug industry.

On the 5th of February of this year, I had the privilege of participating in a meeting that was concerned with the problem of continuing education of physicians with regard to drugs. This meeting was held under the auspices of the Drug Research Board of the National Academy of Sciences in conjunction with the Food and Drug Administration and the regional health medical program of HEW. They had gathered about a hundred distinguished scientists from many disciplines representing clinical medicine, pharmacology, sociology, and psychology.

They were a conscientious, perceptive, dedicated group of men and women. From 9 o'clock in the morning until 10:30 that night we hammered away at the problem. It was quite reminiscent of other similar sessions I have attended in the chambers of the American Medical Association, Council on Drugs in Chicago and several other meetings throughout the country in recent months of equally concerned groups. And the theme was always the same.

We have a problem: There is urgent need to improve our methods of transmitting drug information to prescribing physicians at all echelons of medicine. And invariably at this point the discussion falters and usually founders on the matter of methods.

Some have suggested a drug compendium, a sort of grand formulary that would contain authoritative, current information about all drugs that a contemporary physician might seek. This, they say, would be a

significant first step. I feel a drug compendium would just be another big book that would gather dust on the shelf, standing next to several other unread tomes containing authoritative current information on drugs.

Others have championed the concept of a cadre of therapeutic consultants, a group of well-trained, practical-minded, clinical pharmacologists based at university teaching centers who would size up the needs of their local area and assist physicians or local hospitals in establishing practical programs on clinical pharmacology and therapeutics.

Still others have suggested periodic medical examination with successful passage being a requisite for relicensure.

I have personally favored the program I mentioned earlier, of activating or revitalizing therapeutics boards in hospitals of all sizes by initiating a program of continuing drug utilization surveillance. This would be a hospital committee that would undertake periodic review of therapeutic practices by individual members of the staff as a means to improve therapeutic practices.

Senator NELSON. What would you do about the doctor who is not hospital affiliated?

I think we had testimony that over one-third of the doctors in New York City have no hospital affiliation. And then you have thousands and thousands of others in rural areas or in cities who have no hospital affiliation. What is their source of information?

Dr. MOSER. Well, the cadre concept that has considerable appeal would bring such men into this program. The clinical pharmacologist who is based at the university hospital would work not only with the local hospitals but actually get out in the community and visit these physicians. Or, he will train others who will go out and do that sort of thing.

Physicians who are not hospital affiliated are a very difficult group to reach. I suspect that a personal type of approach would be the only way that they could be reached.

Another possibility would be that therapeutics agents boards in regional hospitals—and I am speaking of small hospitals of 75- to 100-beds. Such local hospitals could periodically invite these unaffiliated men in for sessions where they could give them information on contemporary advances in therapeutics.

I think these are all difficult things to do, and this unaffiliated group is indeed the hardest to reach.

I feel that all too often these individuals have been unduly singled out for criticism; I think that many of them are superb clinicians who do a very fine job. Many of my own acquaintances are men who are almost obsessive, compulsive readers. They keep themselves current because they know they are isolated, and these represent a significant proportion of American practitioners. I think what we are talking about is a minority, and I don't know how we can reach them. You can lead a horse to water but it is very hard to make him read.

Senator NELSON. What single objective source is there in the literature for a doctor to refer to?

Dr. MOSER. I will get to that.

Each of the plans that I have mentioned have their merits and its failings, as we have been discussing. The basic need is to motivate the

busy physician to learn more about the drugs he is using. And this is the heart of the problem. As I said, I feel that most physicians practice rational medicine. As a group they are intelligent, empathetic individuals, dedicated to the welfare of their patients. And I think we are speaking of a noisy but certainly an important minority.

In this same breath, I feel obliged to emphasize that effective drug therapy represents only one facet of the problem of postgraduate medical education in the United States. Admittedly, a proper knowledge of drugs is terribly important, but what about information about new diagnostic techniques, new physiologic principles, even new diseases and syndromes. The proliferation of medical information is not confined to therapeutics alone. If one were to solve this far broader problem of total continuing medical education, the enlightened use of therapeutic agents would fall into place.

Now, several months ago, in my column "Tomes and Tangents," which I write each month for the journal, Medical Opinion and Review, I outlined such a plan for continuing postgraduate medical education which I consider practical and feasible.

Mr. CUTLER. I was just wondering, would the availability of the price information be helpful to the physician on drugs?

Dr. MOSER. I don't quite understand—in what context?

Mr. CUTLER. In the context of prescribing medicines in the hospital, if he knew the cost of the individual drugs, price of one drug as opposed to another.

Dr. MOSER. Are we talking about physicians in the hospital or outside of the hospitals?

Mr. CUTLER. In either instance.

Dr. MOSER. I think it would be a factor, but I don't think it would be the sole factor. I think the most important thing that makes a doctor select a drug is will that drug work for him.

Now, if you show me two drugs; one is cheaper than the one I use now, better, and you can prove to me that the cheaper drug is just as good as the other, I will certainly switch. But if you come and say that these drugs are the same, but you cannot document this to me, I will not go for the cheaper drug. And I think this is common sense.

Senator NELSON. Your hospital has a formulary, doesn't it?

Dr. MOSER. Yes.

Senator NELSON. And you have a formulary committee and your hospital buys drugs on bids, I take it.

Dr. MOSER. Yes.

Senator NELSON. So that answers the question raised by minority counsel in the sense of cost to the patient, because all, I think all of the leading hospitals that use a formulary, have their own pharmacist and pharmacologist and their own clinical experience to draw upon and decide whether or not they are therapeutically equivalent and then accept the bids. And they may very well select the lowest bid or will select it, I assume, if they decide it is equivalent to all the rest of them.

I think the question raised by minority counsel refers to the fact that a practicing physician who isn't practicing with the use of a formulary in a hospital doesn't have that advantage. He does not know what the price is probably, or doesn't have the backup of a formularly committee that has evaluated the use of the drug.

I think that is the point that he is making.

Dr. MOSER. Well, I am certainly not qualified to speak from the aspect of a physician in private practice because this is not my area, but it would seem quite logical that a physician who is working in a community would know what the prices are on the drugs that he uses and have some feel for competitive pricing. But again, I am speaking with lack of personal experience.

Senator NELSON. That really doesn't help the physician in private practice in many instances because brand name identification is such that the only drug being prescribed is the brand name version. To use the example of prednisone, the market is dominated by Meticorten and is usually the one that the doctor prescribes. The Medical Letter listed 22 versions of this drug which were tested and then using the advice of their clinicians around the country concluded that they were all equivalent.

The price range was from Meticorten at $17.90 a hundred tablets to the pharmacist to Paracort at $17.88 a hundred to Merck's $2.20 to $1.80 to others at 59 cents. But you very seldom find the lower priced drugs in the drugstore because no one writes that on the prescription. They write Meticorten.

That is the problem here. So the patient is paying up to $33 to $40 for 100 tablets when he ought to be getting it for maybe $2.

That is the kind of problem I think minority counsel was raising.

Dr. MOSER. Sir, if that physician was getting the Medical Letter, he would know that, you see.

Senator NELSON. That's one of the problems, of course. The Medical Letter, from all the expert testimony we have, is a superb source of information, but I think the circulation is about 35,000 out of over 300,000 physicians.

Dr. MOSER. That is true, and I am about to comment on this matter.

This column that I spoke of, details this program of continuing postgraduate medical education, which I would really like to stress. This may not be the proper platform for this particular discussion.

Senator NELSON. Yes, it is. We have had testimony along that line previously and it is the right forum.

Dr. MOSER. I think all of us interested in medical education feel very strongly about this. The subject of therapeutics simply cannot be divorced from the big picture. It is perhaps the most essential aspect, but it must be included in the broad concept of continuing postgraduate medical education, which represents the most significant problem facing medicine today.

Senator NELSON. The lack of it?

Dr. MOSER. Sir?

Senator NELSON. The lack of adequate postgraduate education.

Dr. MOSER. I think that continuing postgraduate medical education should be a prime concern of all American physicians and all educators.

Let's get back to the subject of what sources does the average physician have to find out about new drugs.

As I said before, it is my conviction that every physician who treats patients should subscribe to the Medical Letter.

For $14.50 a year—less for House officers—one can obtain current, unbiased, candid information on new drug efficacy and toxicity.

This publication arrives about twice a month. It can be read and digested in about 15 minutes. It comes in looseleaf form and can be

filed with ease and the data retrieved with facility. Index issues arrive about four times a year. In addition, I would suggest that every prescribing physician own "Drugs of Choice" by Walter Modell, which comes out every other year, or "Current Therapy," by Howard Conn, which comes out every year, and one good current pharmacology text.

Sometimes in 1969, the comprehensive "American Medical Association Drug Evaluation" book will be available. This should serve as a most valuable adjunct to the physican who desirees to learn about drugs and should quell all dialog about the compendium. Of course, I would be delighted if everyone purchased a copy of my third edition of "Diseases of Medical Progress." But with this cluster of books within pivot-and-reach distance of his prescription pad, any physician will possess all the basic tools he needs to keep abreast of new drug developments and revised concepts of old drugs.

Gentlemen, drug information is abundantly available. The problem resides in kindling the initiative—in firing up the enthusiasm to get physicians to reach for that information.

Our remarkable therapeutic arsenal is a tribute to the commercial drug industry and the devoted chemists and pharmacologists of our medical schools. But neither AMA, FDA, nor the industry can solve the problem completely.

For the past 15 years, in lectures and articles my plea has been directed to the physician on the firing line, the doctor who prescribes the drug. It is farthest from my intention ever to suggest therapeutic timidity or homeopathy. Our predecessors in medicine had limited diagnostic and therapeutic resources.

The complement of nostrums in their little black bag was austere, but those drugs were regarded as old familiar friends. Some were worthless, others were dangerous; some were impure and unstandardized to the point of unpredictability.

The few effective drugs were trusted allies whose strengths and weaknesses were well known. The practitioner of the past attempted to compensate for lack of material resources with meticulous attention to his patients, personal charm, kindness and above all, a pervading equanimity.

His lonely hours of private hell, when he was tormented by his inability to come to grips with most of the severe illnesses that he encountered, constitute a long, bleak chapter in medical history.

The modern physician is afforded rare glimpses of this agony when faced wih terminal malignancy or severe degerenative disease or irreversible neurologic illness. Modern pharmacology has brought this unhappy era to an end, and today we enjoy the privilege of fine, powerful, well standardized therapeutic weapons.

Now we must work to create an atmosphere of rational caution and critical evaluation, where each physician will pause before putting pen to prescription pad and ask himself, "Do I know enough about this drug to prescribe it? Does the possible benefit I hope to derive from this drug outweigh its potential hazard?" I do not preach nihilism but rather therapeutic rationalism.

Thank you.

(The attachments to Dr. Moser's statement follow:)

TABLE NO. 1.—SOURCES WHICH SERVED AS THE FIRST NOTICE TO DOCTORS OF THE AVAILABILITY OF NEW DRUGS CONFERENCE ON CONTINUING EDUCATION FOR PHYSICIANS IN THE USE OF DRUGS

Source	Percent of doctors naming as first source— Caplow and Raymond	Ferber and Wales	Coleman, et al.
Detail men	31	38	52
Medical journals:	19		
Articles	6	25	9
Advertisements	16	19	22
Direct-mail advertisements	14	6	10
Colleagues	7	4	3
Medical meetings	7	8	3
Others	100	100	99
Number of doctors answering	182	328	87

Sources: Caplow, T., and Raymond, J. J.: Marketing 19:18–23 (July) 1954 Ferber, R., and Wales, H. G.: "The Effectiveness of Pharmaceutical Promotion, Urbana, Ill." 1958, p. 22. Coleman, J. S., Katz, E., and Menzel, H. "Medical Innovation" A diffusion study, Indianapolis, the Bobbs-Merrill Co., Inc., 1966, p. 59.

TABLE NO. 2.—SOURCES WHICH LED TO FIRST USE OF A DRUG

Source	Percent of doctors naming source Coleman and others	Ferber and Wales	Gaffin
Detail men	5	21	[1] 41
Medical journals:	[2] 42	28	15
Articles	2		
Advertisements	14	18	26
Direct mail advertisements	28	13	7
Colleagues	8	4	2
Medical meetings	1	16	9
Others	100	100	100
Total	87	328	1,011
Number of doctors answering			

[1] Some doctors named more than 1 source. Percentages have been adjusted to 100 percent
[2] This includes professional journals (21 percent) and periodicals published by drug companies (21 percent).

Sources: Coleman, J. S., Katz, E., and Menzel, H.: "Medical Innovation: A diffusion Study," Indianapolis, The Bobbs, Merrill Co., Inc., 1966, p. 59. Ferber, R. and Wales, H. G.: "The Effectiveness of Pharmaceutical Promotion," Urbana, Ill-1958, p. 24. "Attitudes of U.S. Physicians Toward the American Pharmaceutical Industry," Chicago, Ben Gaffin & Associates, Inc., 1959, p. C-13.

TABLE NO. 3.—*What is the most important source of drug information?*

	Percent
Detail men	68
Medical meetings	35
Journal advertisements	32
Direct mail advertisements	32
Colleagues	24
Journal articles	20

Senator NELSON. I would like to ask just one general question about drug combinations which have come into wide use.

We had testimony—and I will just quote a statement or two—from Dr. Calvin Kunin, of the University of Virginia Medical School, before this subcommittee in part 2, page 731 of these hearings:

A careful review of fixed-branded combinations on the market, including combinations of penicillin and sulfonamides, penicillin and streptomycin, tetracycline, and antifungal agents and tetracycline and novobiocin, does not

substantiate claims that the combination is superior to one of the agents used separately. These combinations are expensive, deny the physician flexibility in dosage, are primarily promotional devices, and have the inherent problem that the patient undergoes the risk of serious adverse reaction to two or more drugs rather than to a single defined agent. The physician cannot determine which component is causing trouble if a bad reaction is encountered. I personally believe that we would do much better without these preparations.

Then, as you know, the National Academy of Sciences under the Kefauver Act of 1962 has under review all of the drugs manufactured prior to then, and they have been making recommendations on various combination drugs that have been in the marketplace for a long time suggesting their—recommending their removal.

On Panalba, which is a combination of tetracycline, phosphate complex, and novobiocin sodium, evaluation "ineffective as a fixed combination," and then some "comments from the panel report. It does not seem rational to expose a patient to the hazards of two drugs when the beneficial effects are no greater than those resulting from the use of one. Again, it has not been shown each active ingredient makes a contribution to the effect of the combination claimed."

I am not reading the whole statement. The last sentences are:

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

This particular drug is among the top 200 most prescribed drugs. I think the National Academy of Sciences as of now has recommended removal of six of these combinations and is continuing its studies.

Do you have any comment from your experience or studies to make on the question of the developing, expanding production of combination drugs?

Dr. MOSER. Well, Senator, I guess the only thing that ever started the use of combination drugs was the simplicity of delivery where the patient takes one pill instead of two. But I am familiar with Dr. Kunin's statement, and I think this is reflected throughout the profession. You immediately hamstring yourself when you put two drugs in a fixed dosage together, and it is just not widely done in hospitals where I have been. I don't recall having used a drug combination in the last 5 years.

Senator NELSON. Does your formulary carry any fixed combinations?

Dr. MOSER. It carries one, to my knowledge. This is a combination of triameterene and hydrochlorothiazide.

Senator NELSON. You don't prescribe them yourself?

Dr. MOSER. No, I don't; because I like to adjust my doses, and I am not permitted by the fixed combination. And I think most physicians feel the same way. One prefers the elasticity that comes with being able to adjust dosages. Also, they are more expensive.

Senator NELSON. You mentioned a few moments ago what you considered an adequate source of information for physicians in prescribing drugs including the Medical Letter and some text and other sources. If the National Academy of Sciences is correct, and if your judgment about the use of them in your own practice is correct, on what basis do you suppose these drugs are so widely prescribed?

In other words, what source of information is the physician using, because they are widely prescribed and widely sold, and Panalba is one of the top 200—if all of these sources of information are so readily available to the physician, how do you account for the fact that these fixed combinations are so widely used?

Dr. MOSER. Well, I think it is because of the fact they are propagandized to the profession. I think that the detail men are well trained in the techniques of sales. They are very pleasant individuals who have time and give a very straight forward pitch. Their presentations are not cluttered by having to give you comparisons with other drugs. And I think there are other very effective means of promoting drugs. Drug advertisements are skillfully done and present a very straightforward approach. In the very same journal you occasionally find a very colorful, well done advertisement, and tucked away somewhere in bowels of the text will be an article that says exactly the reverse. But the advertisement is brief and simple, and it takes too long to read the drab article. It is very easy to flip the pages and come up with this attractive, arresting advertisement. It is just a matter of good salesmanship.

I think our problem is to encourage physicians to take the same amount of time that they do in listening to the detail men or reading these advertisements to read the Medical Letter or Modell or any of the other sources of drug information that are abundantly available. I think this is the problem, and it doesn't make sense to me that a physician would not utilize these sources of information.

I suspect we just have not told them about it. I think we have to educate physicians that there are good information sources available.

As I say, you can read the Medical Letter in 15 minutes. And this is a very worthwhile investment in time; One will learn about drugs. The time will be spent expeditiously.

Mr. GORDON. Doctor, throughout your paper you use only the official or generic names. Why didn't you use brand names? Why did you use only generic names?

Dr. MOSER. I guess it is because I am stubborn. I find it a challenge to try to get people to use generic names. I find that the trade names are used simply because they are more euphemistic. With the USAN committee now working very hard to create the generic names that have less than 25 syllables, we will begin to see a greater use of generic words.

I think it is more personal than anything else. I encourage all of my staff to use generic names unless a trade name represents the sole available drug form and is only known by that name. But it is just a personal idiosyncrasy, I guess. I just like the intellectual drill.

Senator NELSON. Dr. Modell and all others who have testified on this point before the committee have advocated the use of generic names in prescribing. It has been suggested before this committee on several occasions that all prescriptions that go to the patient should include the generic name. And, of course, if the doctor desires, he can indicate the brand name, too, unless there was some reason the patient, the doctor felt, shouldn't know what drug he was receiving.

The reason advocated for that was, in addition to good prescribing practice, the fact that there is such a multiplicity of brand names that nobody can keep up with them.

I asked a doctor who appeared before the committee whether he recognized a few brand names of thalidomide, none of which he recognized, none of which he would be expected to recognize. In the case of thalidomide, long after its harmful effects were known all over the world, it was still in the marketplace in South America and Spain and other places under brand names even though the profession knew it should not have been used. If it had said thalidomide, it wouldn't have been used. And many suspect that it is still on the shelves and in medicine cabinets around the world yet, simply because there is no identification.

Would you advocate the concept that the generic name be required on the label, with the doctor's choice as to whether he wants the brand name on, too?

Dr. MOSER. Yes, sir. I believe that. I think that prescriptions should be so written, unless the physician has a specific desire for the trade name product, based on his own experience or knowledge. And there are a few instances where physicians that I know, certainly feel quite strongly that they want a definite trade name; this product they feel is superior to another. I frequently challenge them to provie it, because often it proves to be more visceral than scientific. But for the most part we do order in generics. Our hospital pharmacist will notify us if someone does order by trade name and the pharmacist does not carry it. He will call the physician and notify him about substituting another drug.

My personal reaction is that we should use generic names, and if you desire to specify a company, it should be put in parentheses next to the generic name on the prescription pad.

I think this would solve the problem of trying to remember hundreds of trade names.

Senator NELSON. Well, Doctor, I want to thank you very much for your very valuable and thoughtful contribution to these hearings. We appreciate your taking time from your activities at Walter Reed Hospital to come here and testify today.

Dr. MOSER. Thank you, sir.

Senator NELSON. Thank you very much.

(Whereupon, at 11:45 a.m. the hearing was adjourned.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, FEBRUARY 26, 1969

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

The subcommittee met, pursuant to notice, at 10:20 a.m., in the Caucus Room, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

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

Senator NELSON. Today we resume our hearings on the drug chloramphenicol—widely advertised under the Parke, Davis brand name of Chloromycetin.

The drug is known to cause serious blood dyscrasias, including aplastic anemia. Though it is a valuable drug when properly used, all expert witnesses agree that it is indicated for use in an extremely limited number of cases—when the disease is serious, when no other drug is effective, and when the organism involved is susceptible to chloramphenicol.

In 1967, over 4 million people were administered this drug, though expert testimony before this committee is that 90 to 99 percent of these patients received it for nonindicated cases. That means that over 3½ million persons were being needlessly exposed to the threat of serious side effects.

As a result, many thousands have tragically and unnecessarily contracted blood diseases including aplastic anemia.

The widespread publicity given to this situation by these hearings resulted in a dramatic drop in the use of this drug in capsule form during the first 9 months of 1968—from 31.9 to 9.5 million grams—a decrease of 70 percent over the comparable period in 1967. Injectables decreased from 7.3 to 2.9 million grams, a decrease of 60 percent.

However, it is alarming to note that use of capsules has again increased during the last 3 months of 1968—from 3.6 to 4.9 million grams, an increase of 36.7 percent, as compared with the last 3 months of 1967. It is interesting to note that the use of the injectable form, usually confined to hospitals, went down during this 3-month period from 1.6 million to 500,000 grams, a decrease of 68 percent.

The purpose of these hearings is to continue to focus attention on this serious problem.

No other example that has come before this committee more dramatically demonstrates the ineffectiveness of the medical leadership of the Nation on drug education when measured directly against the pow-

er and persuasiveness of drug company promotion and advertising. Every medical journal, every reputable drug reference, and every authority on this drug has repeatedly cautioned against misuse of chloramphenicol. Yet, against the combined authorative voice of the whole medical profession, drug company promotion has carried the day hardly drawing a deep breath.

If this does not alarm the AMA, I fear that nothing ever will.

Our witness this morning is Dr. Paul F. Wehrle, chief physician, children's division, pediatrics and communicable diseases service at the University of Southern California School of Medicine. It that correct?

Dr. WEHRLE. In the Los Angeles County General Hospital.

Senator NELSON. Doctor, the committee appreciates very much your taking the time from your busy schedule to appear before the committee today to testify.

Your biographical sketch has been presented to the committee and will be printed in full in the record, prior to your statement.

(The biographical sketch follows:)

CURRICULUM VITAE—PAUL FRANCIS WEHRLE

Birthdate: December 18, 1921.
Birthplace: Ithaca, New York.
High School: Tucson Senior High School, Tucson, Arizona, 1937–1940,
Collge:
University of Arizona, 1940–1943 and summer session, 1946, B.S. (Zoology) 1947.
Tulane University of Louisiana, School of Medicine, M.D. 1947.
University of Illinois Graduate School, Chicago, Course in Virus Techniques–1949, no degree.
Johns Hopkins University, Baltimore, Immunochemistry—1954, no degree.
Internship: Scott and White Hospitals, Temple, Texas, 1947–1948.
Residency: University of Illinois, Research and Educational Hospitals (Pediatrics) 1948–1950.
Positions Held:
1950–1951:
(1) Assistant Medical Superintendent, Chicago Municipal Contagious Disease Hospital Jan. 1950–June 1951.
(2) Clinical Instructor in Pediatrics University of Illinois, College of Medicine July 1950——une 1951.
1951–1953:
(3) S.A. Surg (R) Public Health Service Epidemiology Intelligence Service, Communicable Disease Center, Atlanta, Georgia, July 1951–July 1953. (Promoted to Surg. (R) Inactive, 1958).
(4) Research Associate, Dept. of Epidemiology and Microbiology, University of Pittsburgh Graduate School of Public Health, Sept. 1951–July 1953.
(5) Lecturer in Public Health Administration, Duquesne University, Pittsburgh, Pa., 1951–1953.
(6) Staff Assistant for Allocation of Gamma Globulin, National Research Council, National Academy of Sciences, Washington, D.C. 1953.
1953–1955:
(7) Research Associate, Poliomyelitis Laboratory Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland, July 1953–June 1955.
(8) Attending Pediatrician, Baltimore City Hospitals July 1953–June 1955.
(9) Staff Assistant, Hepatitis Program, Committee on Sterilization of Blood and Blood Products, National Research Council National Academy of Sciences, April 1955–56.

1955–1959:
(10) Assistant Professor of Pediatrics, State University of New York, Upstate Medical Center, Syracuse, N.Y. July 1955–May, 1959.
(11) Assistant Medical Director City Hospital, Syracuse, N.Y., July 1955–April 1961 and Associate Attending Physician, Syracuse Memorial Hospital.
(12) Poison Control Officer, City of Syracuse, Department of Health, January 1957–April 1961.
(13) Acting Chairman, Department of Microbiology, State University of New York, Upstate Medical Center, Syracuse, N.Y., October 1959–April 1961.
1961–1968
(14) Hastings Professor of Pediatrics, University of Southern California School of Medicine, Los Angeles, April 1, 1961 to present.
(15) Head Physician, Communicable Disease Service, Los Angeles County General Hospital.
(16) Chief Physician, Children's Division (Pediatrics and Communicable Disease) July 1, 1964 to present.
(17) Lecturer, Epidemiology—Infections Disease and Tropical Medicine, University of California at Los Angeles Schools of Medicine and Public Health, 1966 to present.

Military Service:
U.S. Navy 1942–45 (much of this time in various training programs, no overseas service).
U.S. Public Health Service 1951–1953. Present rank is Surg. (R) Inactive.

Specialty Board Certificate:
American Board of Pediatrics 1953.

Personal Data:
Married 1944, 4 sons.

Professional Societies:
American Academy of Pediatrics
American Association for the Advancement of Sciences
American Association of Immunologists
American Association of University Professors
American Epidemiological Society
American Federation for Clinical Research
American Pediatric Society
American Public Health Association (Fellow)
American Society for Microbiology
California Medical Association
Infectious Diseases Society of American
International Epidemiological Association
Los Angeles Medical Society
Los Angeles Academy of Medicine
Los Angeles Pediatric Society, (President 66–67, Vice President 65–66)
Sigma Xi
Society for Pediatric Research
Western Society for Pediatric Research
Western Association of Physicians
Southwestern Pediatric Society

Organizations and Activities:
(a) *U.S.C. and Hospital:*
Member of Faculty Senate, U.S.C. (1962–1967)
Member of Faculty Executive Committee, U.S.C. School of Medicine 1961–present)
Member, U.S.C. Computer Advisory Committee (1963–65)
Member, Admissions Committee, U.S.C. School of Medicine 1962–68
Member, General Hospital Attending Staff Board of Directors (1962–present)
Secretary, Research Committee, Los Angeles County General Hospital Attending Staff (1963–present)
Member, Internship Advsiory Committee, Los Angeles County General Hospital (1964–present)
Consultant, Staff of Huntington Memorial Hospital, Pasadena (1968–present)
Consultant, Staff of Children's Hospital of Los Angeles (1968–present)
Member, Milk Commission, Los Angeles County (1968–72)

(b) *Local Medical Organizations:*
Chairman, Public Health Committee Los Angeles Pediatric Society and Southern California Chapter of the Academy of Pediatrics (1963–66)
Vice President, Los Angeles Pediatric Society, (1965–66).
President, Los Angeles Pediatric Society, (1966–67).
Member, Executive Committee, Southern California Chapter of Academy of Pediatrics (1962–63)
Member, Infectious Disease Committee, Los Angeles Tuberculosis and Health Association (1962–64)
Chairman, Los Angeles Virus Club (1963–64)
Scientific Advisor, Los Angeles County Medical Association Sabin Polio Vaccine Program (1962–63)

(c) *State Organizationss*
Consultant to the California State Health Dept.
1. Ad Hoc Advisory Committee on Phophylaxis of Poliomyelities (1962–1964)
2. Epidemiology, in Water Reclamation (1962–1967)
3. Air Pollution Medical Studies Unit (1962–1967)
Member, State Hospital Advisory Board, State of California (1965–69)

(d) *Other Universities:*
The Johns Hopkins University: Consultant to Health Resources Evaluation Program, Peru (Division of International Development) 1962–63.

(e) *National:*
1. Consultant, Human Resources and Development, Agency for International Development, U.S. State Dept. (1963–1967)
2. Member, Environmental Hazards Committee, Academy of Pediatrics (1962–1967) Chairman (1968 to present)
3. Member, Air Pollution Training Committee, Division of Air Pollution, United States Public Health Service, Washington, D.C. (1962–1966)
4. Member, Advisory Committee on Immunization Practices to the Surgeon General, U.S. Public Health Service (1964–1968)
5. Member, Program Area Committee on Child Health, American Public Health Association (1963–1967), Chairman, (1967 to present).
6. Member, Committee on Infections Within Hospitals, American Hospital Association (1964–present).
7. Consultant, to the Commanding General, Sixth U.S. Army (1965–present).
8. Member, Subcommittee on Epidemiologic Use of Hospital Data, subcommittee of the U.S. National Committee on Vital and Health Statistics 1965–present).
9. American Red Cross, Vaccine Immune Globulin Consultant Committee (1964–present)
10. Member, Committee on Diagnostic Standards in Respiratory Disease, American Thoracic Society, Medical Section of the National Tuberculosis Association (1965–present)
11. Consultant in Pediatrics & Infectious Diseases, Long Beach Naval Hospital (1968–present)
12. Member, Drug Efficacy Study Panel National Research Council, National Academy of Science (1966–1968)
13. Member, Epidemiology and Disease Control Study Section, Division of Research Grants, U.S. Public Health Service, National Institutes of Health, Bethesda, Md. (1967–present)

PUBLICATIONS

1. Wehrle, P. F. and Lepper, M. H.: Aureomycin Treatment of Pertussis, J. Ped. *39*:435–441, October 1951
2. Lepper, M. H., Wehrle, P. F. and Blatt, N.: Treatment of H. Influenza Meningitis, Am. J. Dis. Child. *83*:763–768, June 1952.
3. Hammon, W. McD., Coriell, L. L., Wehrle, P. F. and Klimt, C. R. and Stokes, J. Jrs.: Evaluation of Red Cross Gamma Globulin as a Prophylactic Agent for Poliomyelitis, III. Preliminary Report of Results Based on Clinical Diagnosis, J.A.M.A. *150*:757–760, October 25, 1952.
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5. Lepper, M. H., Blatt, N. H., Wehrle, P. F. and Spies, H. W.: Treatment of Bacterial Meningitis of Unusual Etiology and Purulent Meningitis of Unknown Origin, A.M.A. Am. J. Dis. Child., *85*:295–302, March 1953.

6. Hammon, W. McC., Coriell, L. L., Wehrle, P. F. and Stokes, J. Jr.: Evaluation of Red Cross Gamma Globulin as a Prophylactic Agent for Poliomyelitis, IV. Final Report of Results based on Clinical Diagnosis, J.A.M.A. *151*:1272–1285, April 11, 1953.

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8. Maclachlan, W. W. G., Crum, H. E., Kleinschmidt, R. F., Wehrle, P. F.: Psittacosis, Am. J. Med. Sci. *226*:157–163, August 1953

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11. Wehrle, P. F.: The Risk of Poliomyelitis Infection Among Exposed Hospital Personnel. Pediatrics *17*:237–246, February, 1956.

12. Hammon, W. McD., Coriell, L. L., Ludwig, E. H., McAllister, R. H., Sather, G. E., Greene, A. E. and Wehrle, P. F.: Effect of Passive Immunity on Infection with the Poliomyelitis Viruses, Poliomyelitis. Papers and discussions presented at the Third International Poliomyelitis Conference, pp. 159–166, I. B. Lippincott Co., Philadelphia, 1955.

13. Wehrle, P. F.: The Diagnosis and Management of Oral Infections, Pediatric Clinics of North America, *3*:871–884, 1956.

14. Wehrle, P. F., Feldman, H. A. and Kuroda, K.: Effect of Penicillins V and G on Carriers of Various Streptococcal Groups in a Children's Home, Pediatrics, *19*:208–216, 1957.

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16. Wehrle, P. F., Hammon, W. McD., Coriell, L. L. and McAllister, R. M.: Spread of Poliovirus Infection During an Epidemic of Unusual Severity. Am. J. Hyg. *65*:386–403, 1957.

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52. Portnoy, B., Leedom, J. M., Hanes, B., and Wehrle, P. F.: Factors Affecting ECHO 9 Virus Recovery from Cerebrospinal Fluid. Amer. J. Med. Sci. *248*:521–527, No. 5, November 1964.
53. Wehrle, P. F.: Meningitis, Acute, Bacterial. Current Therapy, W. B. Saunders Co., Philadelphia, pp. 24–25, 1965.
54. Wehrle, P. F.: Food Service Management on Communicable Disease Services. American J. Dietetics, *46*:465–467, No. 6, June 1965.
55. Wehrle, P. F.: Mumps. Current Diagnosis, W. B. Saunders Co., 1966, pp. 21–22.
56. Wehrle, P. F.: Current Immunization Methods and Precautions. Calif. Med., *101*:153–159, 1964.
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66. Wehrle, P. F. Landry-Guillain-Barre-Strohl Syndrome. Present Concepts of Etiology and Management. Bull. Los Angeles Neurological Society, (in press).
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68. Leedom, J. M., Ivler, D., Mathies, A. W., Thrupp, L. D., Portnoy, B., and Wehrle, P. F.; Importance of Sulfadiazine Resistance in Meningococcal Disease in Civilians. N. Eng. J. of Med., *273*:1395–1401, No. 26, Dec. 1965.
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PUBLICATIONS RESULTING FROM COMMITTEE WORK FOR VARIOUS ORGANIZATIONS

(Member of Committee, Collaborator or Editor)

1. The Student Health Project 1966; University of Southern California, 1967
2. Standards of Child Health Care: American Academy of Pediatrics, 1967
3. Guide for Services for Children with Eye Problems; American Public Health Association, 1968
4. Guide for Children with Communicative Disorders; American Public Health Association, 1968
5. Guide for Children with Cerebral Palsy; American Public Health Association, 1968
6. Tuberculosis Programs for Children; American Public Health Association (In Press)
7. Working Conference on Smallpox (Report); Office of International Research, N.I.H. Bethesda, 1968
8. Control of Infections Within Hospitals; American Hospital Association (In Press)
9. Use of Hospital Data for Epidemiologic and Medical Care Research; Report of Subcommittee on Epidemiologic Use of Hospital Data of National Center for Health Statistics (Submitted for final review)
10. Conference on the Pediatric Significance of Peacetime Radioactive Fallout; American Academy of Pediatrics, Lee E. Farr, Editor, Pediat. 41: Part 2, 165–378, 1968
11. Diagnostic Standards for Respiratory Disease; American Thoracic Society-National Tuberculosis and Respiratory Disease Association. (In Press)

Senator NELSON. You may present your statement in any way you see fit, and if at any time you wish to extemporize on any aspect of your statement and elaborate on it, we will be pleased to have you do so. I assume you have no objection to questions during the course of your testimony.

Dr. WEHRLE. No, sir; I do not.

Senator NELSON. Thank you very much, Doctor.

Dr. WEHRLE. Would you like to have me simply read the statement as——

Senator NELSON. That is probably the best way to approach it, and then any aspect of it that you would like to elaborate on, just feel free to do so, so that we get the best possible explanation in the record.

STATEMENT OF DR. PAUL F. WEHRLE, CHIEF PHYSICIAN, CHILDREN'S DIVISION, PEDIATRICS AND COMMUNICABLE DISEASE SERVICE, LOS ANGELES COUNTY-UNIVERSITY OF SOUTHERN CALIFORNIA MEDICAL CENTER

Dr. WEHRLE. Several important antibiotics have been developed since the licensure of chloramphenicol in 1949. Controlled studies have shown that the newer drugs have equalled or surpassed chloramphenicol in efficacy against most of the infections for which this drug had been used previously. At the present time, the only clear indications for the use of chloramphenicol appear to be in typhoid fever and in severe salmonellosis.

Senator NELSON. May I interrupt there just a moment? Do you know how many cases of typhoid fever occurred——

Dr. WEHRLE. Approximately 400 cases each year recently. There were 398 cases during the last year for which figures are available.

Senator NELSON. Is there any estimate on the number of cases of severe salmonellosis?

Dr. WEHRLE. Severe salmonellosis is very difficult to estimate. If one takes another totally different disease, measles, in years past where we had good data on cases reported to health departments and cases actually occurring by sample surveys, the reporting of measles is about ten percent. So that if you assume that salmonellosis is recorded in the same proportion as measles in contrast to the actual extent in the population, this would mean then that with 18,000 approximately reported in 1967, that this might be 181,000 or maybe 200,000.

Senator NELSON. Of severe cases?

Dr. WEHRLE. Well, here again, one has all gradations, and the 18,000 probably represents the most severe portion of what must be a much larger number.

In salmonellosis chloramphenicol may be particularly advantageous in debilitated patients with bacteremia, localized soft tissue or bone infections. It should be noted that even in these conditions other drugs are often effective.

Occasionally, serious diseases due to other organisms which are found to be susceptible in vitro to chloramphenicol but resistant to less toxic drugs may be treated with chloramphenicol. It should be emphasized that this latter situation is an unusual occurrence.

Until recently in pediatrics, chloramphenicol was considered the drug of choice for Hemophilus influenza infections, particularly in meningitis due to this organism. During the last few years, reports from our institution and others clearly indicate that Ampicillin, one of the newer penicillins, is at least as effective and is substantially safer. Consequently, we have not used chloramphenicol in the treatment of this condition in our hospital since the completion of our controlled evaluation in 1966.

Senator NELSON. Which hospital are you referring to?

Dr. WEHRLE. This is formerly the Los Angeles County General Hospital. It is now known as the Los Angeles County-University of Southern California Medical Center.

Senator NELSON. How large a hospital is that?

Dr. WEHRLE. It is a hospital of over 2,000 beds. It cares for approximately close to 200,000 inpatients per year, and the total inpatient and outpatient load is nearly a million patient visits per year.

Senator NELSON. Counting both outpatients and——

Dr. WEHRLE. Counting both outpatients and inpatients. It is in my understanding the largest acute hospital in the world.

Senator NELSON. Do you have any statistics on how many times during the past year or for any recent year chloramphenicol has been prescribed for children within your hospital?

Dr. WEHRLE. The use in children has been reduced substantially during the last 5 years, and at the present time, the use in children is negligible. This drug is used in our hospital most frequently on the obstetrical service and on the surgical services.

Senator NELSON. Are there any rules or practices followed within your hospital in the use of the drug; that is, if a prescription is written for the drug, does it have to be countersigned by anybody?

Dr. WEHRLE. If the prescription is written for this drug, the attending physician in charge of that service is expected to approve its use. In the Children's Division, we use it for cases of typhoid, which is seen most frequently among people who visit in Mexico and from Mexicans who develop the disease in Los Angeles County. For severe salmonellosis, we also use it. We rarely use it for other conditions on our service.

Senator NELSON. I am sorry I didn't follow you. You said if it is prescribed by whom, the attending physician must approve?

Dr. WEHRLE. The system that we have in our hospital is very similar to the system in other large teaching hospitals. The attending physician, whether he be a member of the full-time faculty or whether he be a well-qualified physician in practice in the community and our clinical faculty is in charge of his particular service in the hospital. Prescription orders written by the intern or the resident must be done with the approval of the attending physician on that service.

Senator NELSON. Is any record kept in your hospital of the use of chloramphenicol and the indications for which it was used?

Dr. WEHRLE. The Therapeutics Committee did this for a period of time. The usage of chloramphenicol has fallen substantially, and after monitoring it on a very careful individual basis for several years, this practice was delegated to the chief of each service about, I guess, 3 or 4 years ago.

Senator NELSON. Do you have any records which the hospital has kept over the past half dozen years on the use of chloramphenicol?

Dr. WEHRLE. Yes; I have figures that were supplied to me by Mr. Stanley Seibert, our chief pharmacist, on the usage of chloramphenicol. If you would like a copy of these——

Senator NELSON. Yes; I would like to see that.

Dr. WEHRLE. These records, I believe, are of particular interest, and if I may, I would like to call your attention to two things. First I would like to call your attention to two things. First I would call your attention to the fact that 250 milligram capsules are recorded in the first column on the left so that one must devide by four in order to determine the number of grams. Usage for the preparations in the intermediate three columns is negligible. In the column on the far right chloramphenicol for parenteral use is recorded in grams.

Senator NELSON. The far right column is grams?

Dr. WEHRLE. The far right column is grams. The far left is 250 milligrams individual capsules.

The two features these figures show very clearly are, No. 1, the peak usage of this drug was achieved in the 1958 through 1960 period when staphylococcal disease was a major problem and before the time when the semisynthetic penicillins were available to any extent or were well known.

Senator NELSON. Is that Ampicillin?

Dr. WEHRLE. This was Methicillin that came out first.

Senator NELSON. It is Ampicillin that is used now?

Dr. WEHRLE. Ampicillin came out later. I believe that Ampicillin was made available in 1963, I believe. Am I correct? Does anyone know?

I believe it was around 1963, possibly 1964.

The peak usage then was back sometime ago at a time when we didn't have many of the kinds of drugs that we have at the present time.

The other thing that I would point out is the sharp decline in the last several years, a progressive decline from 157,000 capsules in 1963 down to last year with some 32,000 capsules, which represents about 8,000 grams.

I would call your attention to the fact that the 8,000 grams in capsules is roughly equivalent to the 8,000 grams used in the parenteral form. These two are approximately equal at this time.

I would further point out that our hospital is one that is set up and designed expressly for the care of the desperately ill individual, and it is our responsibility to care for all patients in Los Angeles County that are deemed hazardous in terms of infectious problems for other hospitals in that area. We have the Communicable Disease Service.

Senator NELSON. What percentage of chloramphenicol is administered in your hospital by capsules vis-a-vis injectables, do you know?

Dr. WEHRLE. Parenteral use is equivalent to the capsule use in terms of numbers of grams of drugs dispensed. This would indicate to me that relatively little of this is used for the treatment of outpatients.

Senator NELSON. Very little of what?

Dr. WEHRLE. Very little of the drug is going into patients who are ambulatory and treated in our outpatient program.

The reason for this is that this drug is well absorbed. It is well tolerated by the gastrointestinal route and consequently after the initial serious, desperate illness is over, the physician is likely to change to the oral use of the drug while the patient is still in the hospital simply to save the discomfort of injection and the additional nursing time necessary for injection.

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

(The chart follows:)

CHLORAMPHENICOL PURCHASES OF LOS ANGELES COUNTY—UNIVERSITY OF SOUTHERN CALIFORNIA MEDICAL CENTER—UTILIZATION OF CHLORAMPHENICOL PRODUCTS

Year	Chloramphenicol 250 mg. capsules	Chloramphenicol solution 0.5 g./2 cc.	Chloramphenicol palmitate 125 mg./4 cc.	Chloramphenicol 1.0 g. I.M.	Chloramphenicol sodium succinate 1 gm./10 cc.
1952	25,104	348	598	(1)	(1)
1953	35,792	8,320	1,800	(1)	(1)
1954	27,600	15,548	2,278	106	(1)
1955	64,800	5,490	4,026	4,800	(1)
1956	118,700	10,250	4,896	1,500	(1)
1957	182,400	18,580	6,048	16,600	(1)
1958	271,800	32,340	7,272	24,882	(1)
1959	330,300	16,520	8,352	26,000	200,220
1960	395,200	(1)	8,768	23,200	355,000
1961	79,000	(1)	1,800	3,000	127,000
1962	104,200	(1)	2,007	4,250	25,802
1963	157,900	(1)	1,598	7,000	36,494
1964	147,600	(1)	2,016	4,000	42,924
1965	131,700	(1)	1,008	4,000	46,000
1966	119,600	20	1,440	5,000	35,000
1967	93,600	(1)	480	4,500	23,188
1968	32,400	(1)	48	1,000	8,000

[1] Data not available.

Senator NELSON. Please go ahead, Doctor.

Dr. WEHRLE. The continued widespread usage of chloramphenicol, often for what are apparently minor illnesses, or illness for which another drug is of at least equal or greater effectiveness, is difficult to understand in view of the mounting evidence of serious toxicity. While the specific toxicity of this drug to newborn infants can be controlled

by reducing the dosage—this is the gray baby syndrome—no method of predicting or preventing bone marrow depression has yet been found. The California Medical Association study, published more than 2 years ago, indicated a fatal outcome attributed to this drug in one of each approximately 20,000 patients treated with chloramphenicol. The continued pattern of frequent usage, despite the availability of other drugs of equal or greater effectiveness, appears to be due to at least five factors.

Senator NELSON. May I interrupt for a moment. I have been curious about the statistics in the California study in that we have had witnesses, doctors, testify that in a case where the doctor discovers that it was administered for a nonindicated case he obviously isn't going to report it because he's subject to a lawsuit. I don't know how they extrapolated or how they got this figure, one in 20,000, from the study. How accurate an estimate do you think this record represents?

Dr. WEHRLE. I think this is certainly subject to error in each direction. I think this is the best estimate that anyone has come up with to date, but it should be regarded as an estimate and one that may be inaccurate and presents only part of the picture in each direction. I simply don't know whether this is in the center or whether this is to one extreme, the high extreme or the low extreme. I simply don't know.

Senator NELSON. Are there any other blood dyscrasias that result as a result of administration of chloramphenicol?

Dr. WEHRLE. I think it should be recognized that this is based on fatal episodes, and this is a death certificate type of reporting. I would not—let me back up one moment. There are other kinds of problems that do occur. For example, in patients treated in the controlled evaluation when we were comparing chloramphenicol and Ampicillin in the treatment of meningitis, about 10 percent of the patients who received chloramphenicol had some evidence of marrow depression in terms of development of anemia or some lowering of the white count.

One of these patients developed a severe granulocytopenia; in other words, a very marked depression of the bacteria-fighting cells of the blood. He developed a staphlocci pneumonia, presumably as a consequence, which was an extremely serious infection. This was fortunately controlled by the use of the Methicillin.

Now, I have no idea in these one of 20,000 patients whether there are additional patients who may have died of asepsis secondary to marrow depression with the use of this particular drug. On the other hand, there is no way of knowing how many of these patients may have had a suppression of the marrow for presently unknown and unrelated reasons.

Senator NELSON. Is it possible that they may have had some bone marrow depression which they lived with a good many years without dying, of course, and not being reported in the statistics?

Dr. WEHRLE. I think this quite possible; yes.

Senator NELSON. Did I understand you to say that the one in 20,000 figure was based on death certificate——

Dr. WEHRLE. This was a survey of deaths or fatalities, and I am not certain whether this was from the vital statistics approach or a survey approach.

Senator NELSON. Well, obviously then, if these statistics were based on deaths as a consequence of aplastic anemia, they certainly don't

include any statistics of those physicians who didn't report that it was caused by chloramphenicol.

Dr. WEHRLE. This is certainly correct, and I think some of the problems in death certificate reporting are well known to the members of your committee. The death certificate reporting is as good as we have for many kinds of problems, but still such reporting is still not entirely accurate by any means.

Senator NELSON. You may proceed, Doctor.

Dr. WEHRLE. The five factors which may be at least in part responsible for the continued usage are:

1. The initial availability at a time when widespread staphylococcal disease was occurring and the preferred drugs, the newer penicillinase resistant penicillins, were not yet available.

2. Its preferred role by most pediatricians for the treatment of Hemophilus meningitis and other serious illnesses for many years.

Just parenthetically, it is apparent that a drug that can effectively treat a condition that is 100-percent fatal if untreated is a most impressive drug and develops an aura quickly that may spread to many other conditions.

3. The excellent diffusion, both in vitro and in vivo. This characteristic gives impressive zones of inhibition in the usual hospital bacteriology laboratory, whereas another antibiotic with smaller zones of activity may be equally effective clinically.

Mr. GORDON. Doctor, may I go back to No. 2. Do you think the pediatricians throughout the country are generally aware that Ampicillin is better for Hemophilus meningitis?

Dr. WEHRLE. I think there has been a considerable change in most hospitals around the country in the use of this drug for this condition.

Dr. Martha Yow in Houston has published on a number of occasions. There have been several Canadian hospitals that have reported their experiences with this drug, in Toronto particularly. One of the Boston hospitals has reported experience with this particular drug. My associates and I have made several reports, and I think have the largest experience with this particular drug. But I think as in anything else the physician's admonition of don't be the first to take up the new, nor the last to discard the old holds here. A change has taken place over the last 2 or 3 years and I think the acceptance of Ampicillin has made a profound difference in the consumption of chloramphenicol by pediatricians around the country.

Mr. GORDON. Would you know whether the manufacturers of Ampicillin are pushing that particular drug for this particular use with as great vigor as Parke, Davis pushed their drug?

Dr. WEHRLE. It is my impression that people who make Ampicillin are most anxious to sell it wherever they can.

Mr. GORDON. Your hospital did a study of relative efficacy between Ampicillin and chloramphenicol. Was it for this disease only or for what?

Dr. WEHRLE. This was the main and I think the most important one of the antibiotic controls of the control studies that we have done in recent years. We have done others, but this one I think is the one that bears directly on this problem.

Mr. GORDON. Can we get a copy of that?

Dr. WEHRLE. Yes, sir. I will have to mail you one. I seem to have forgotten my copies. The references are attached to the last page of my bibliography. We have also included the Houston studies, reference No. 6, by Barrett, Eardley, Yow, and Leverett; and the studies from our institution are items Nos. 3, 4, 5, 7, and 8.[1]

The first two references pertain to Drs. Burns, Hodgman, and Cass, and Drs. Hodgman and Burns concerning the problem with the gray baby syndrome in young infants who receive this drug in what we now consider excessive dosage. Those are also from the Los Angeles group.

In addition to the laboratory studies that I just mentioned where the extreme diffusibility of this drug is clearly evident, item 4 points out——

Senator NELSON. May I interrupt for 1 second. I have a question.

Dr. WEHRLE. Yes.

Senator NELSON. You say, "whereas another antibiotic with smaller zones of activity may be equally effective clinically," are you referring to the situation whereas chloramphenicol may be very effective, an invitro study may indicate that another antibiotic with a smaller zone of activity, as you put it, may be just as effective? Is that what you are referring to?

Dr. WEHRLE. Yes, sir. This is exactly what I mean. In other words, chloramphenicol is a drug that does diffuse very beautifully through tissues, into the eye, for example, into joints, areas such as this. It also diffuses very well through culture media used to test for antibiotic susceptibility. Consequently, two drugs that may have the same activity in tube dilutions where you have the drug already diluted may be different on an agar plate where diffusion plays a part in determining the disk or zone size.

So consequently, chloramphenicol, a drug that diffuses very beautifully, gives very impressive rings where the bacteria don't grow around the disk containing this particular antibiotic, whereas one that diffuses very poorly, like polymyxin, for example, may have the same tube activity, yet the zone is very difficult to see. It is a very small zone.

Now, this can mislead the hospital bacteriologist on occasion unless experienced in this problem, and can certainly mislead the physician if the physician stops and looks at the plates from the laboratory on his way to the patient's bedside.

Senator NELSON. Haven't clinical studies indicated over the past few years those instances where, say, Ampicillin would be as effective as chloramphenicol though less toxic?

Dr. WEHRLE. I personally feel so; yes sir.

4. A continuing aggressive advertising and detailing program, suggesting that the physician can "trust" this drug. This has continued to perpetuate the habit, established in earlier years, of prescribing this drug for both major as well as minor problems.

5. The availability of both oral and parenteral dosage forms which are comparatively free from minor gastrointestinal and local reaction.

I think it is apparent that a physician is interested in the welfare of his patient. This drug is so well tolerated by the intravenous route as well as by the oral route that in fact, I think, has often influenced the physician's judgment in prescribing it.

[1] See apps. IV–XI, pp. 4799–4857, infra.

The problem of continuing substantial usage of a potentially hazardous drug despite decreasing indications poses a problem with no easy solution. There are several possible avenues of approach and perhaps one or a combination of several may help place the future usage of this drug in a position more consistent with its indications. These are:

1. Limiting of availability to the hospital pharmacy. This drug could still be made available from such pharmacies to the occasional ambulatory patient for whom it might be indicated. The obvious disadvantages to this restriction are a likelihood of increased drug cost to the patient and considerable inconvenience to at least some of the patients, since in the rural areas particularly there are more neighborhood pharmacies than there are hospitals. The obvious inference to the physician with such a limitation would be that he should think of alternates if it were to be considered hazardous enough to require dispensing only by the hospital pharmacy. Regardless of these obvious disadvantages, this approach would seem preferable to the use of registry numbers on prescriptions as is the case with narcotics.

2. Restrictions on advertising and detailing of this product. Despite changes in recent years, the notice of hazards is often in smaller type and in a less conspicuous location than is the statement regarding real or presumed benefits.

Advertising should be restricted to illnesses for which the drug is preferred by a responsible group. Misleading illustrations, such as the bronchoscope, should be avoided. Such illustrations imply that chloramphenicol is useful for a variety of respiratory illnesses.

Senator NELSON. May I interrupt a moment there?

Dr. WEHRLE. Yes.

Senator NELSON. I have seen a number of those ads in which the bronchoscope is pictured. Are there any respiratory illnesses for which chloramphenicol is indicated?

Dr. WEHRLE. In my opinion, none whatsoever. I think we have less toxic drugs for these infections at the present time.

Senator NELSON. Is it indicated for any of the virus infections?

Dr. WEHRLE. Absolutely not.

Senator NELSON. It would seem to me, at least, that the FDA ought to prohibit the use of the picture of the bronchoscope which obviously indicates to the physician the area in which the drug is effective.

Dr. WEHRLE. This, in my opinion, would be a great step forward.

Physicians should indicate gross violations in claims by pharmaceutical house representatives, whose position is obviously dependent on sales of this particular drug. Such representatives have been well known to suggest antibiotic X for influenza. And by "antibiotic X," I do not mean chloramphenicol specifically but I mean any antibiotic that the particular representative is interested in selling.

I would also point out that there are extremely ethical detail people who present the facts very clearly and very fairly. There are people who tend to deviate, and I personally feel strongly that it is the responsibility of the physician to indicate such violations very clearly to the pharmaceutical house and as well perhaps to the FDA.

3. Improving data regarding hazards, and publicizing this information to the medical profession. Methods of improving both hospital and death certificate information should be considered. Individual physician reporting for infectious diseases has failed and it not likely

to be more effective for reporting drug reactions. Only the more severe drug reactions would be discovered from hospital and death reporting, but these instance are, of course, our greatest concern. The greater attention currently devoted to hospital organization and toward departmental program and function by the Joint Commission on Accreditation of Hospitals provides substantial assurance that hospital sources of information may be improved.

4. Surveillance of local or regional usage patterns of particular drugs. Given the authority and personnel to do so, the Food and Drug Administration might be able to detect factors which influence excessive usage of a drug in a region or in a local area. This approach appears to deserve study, as it may give a better insight as to why well-motivated and skillful physicians continue to persist in particular patterns of behavior after the factors establishing those patterns have ceased to operate. Comparative usage figures of an antibiotic such as chloramphenicol for several areas during a widespread influenza outbreak might be particularly revealing and may also be helpful in designing appropriate methods of approach.

Senator NELSON. Is it indicated for influenza?

Dr. WEHRLE. Absolutely not, but I think that this point might give a hint as to where the problem really is. One of the things that I would love to know, for example, is where the drug is going in Los Angeles, just as a matter of curiosity to see what types of physicians are using it and for what purposes.

I think that one of the responsibilities that medicine has is in terms of the education and the assistance of the members of the profession. And I would feel very strongly that such information would be most helpful to guide efforts on the part of either the Food and Drug Administration or the post graduate programs in medical education in many of the schools and hospitals. The staff in many of the hospitals is providing guidance, and indications as to drug usage. I would not restrict this to chloramphenicol. I think that these would be data that would be very helpful to those charged with the responsibility of post graduate education of physicians.

Senator NELSON. How would you find those statistics?

Dr. WEHRLE. These could be collected in several ways. The easiest way would be to simply look at the distribution of a drug in a community, and you know pretty well the physicians in the neighborhood and what pattern of practice they have. And if the usage is eight times or 10 times or 20 times as high in East Los Angeles as it is in San Gabriel or if you see other widespread differences in pattern, then I think it would be possible to be more selective in terms of who is prescribing and for what general kind of conditions.

This would give a lead for the first time as to where the drug is going within a community.

Senator NELSON. Well, mechanically, how would you collect it; how much is sold to the pharmacist in the area and how it was dispensed, that sort of thing?

Dr. WEHRLE. I would think that data on sales from pharmacies should be kept by the pharmacist. He's got to keep track of his stock and how much is going in and how much is going out. And I see no reason why such figures could not be made available.

Senator NELSON. But then you'd only be guessing, unless you did some survey about how it was used, wouldn't you?

Dr. WEHRLE. That is correct. But I think this gives at least a picture as to whether this is a uniform problem or a problem restricted to particular areas. It may be that most of the Nation's chloramphenicol is going into particular portions of ten of the major cities or maybe it is predominantly a rural problem for the practitioner who does not, because of one of several reasons, get into the medical center to see what is happening.

This technique is at least a step toward finding out where the problem really is. I simply don't know drug usage patterns even in Los Angeles.

In conclusion, the widespread usage of chloramphenicol, a drug with limited and decreasing usefulness, has continued during a period of substantial publicity and resulting greater awareness of its hazards. This poses a problem in designing the proper method of reducing usage without the establishment of unduly burdensome restrictions. Several methods of approach to this problem are suggested which may also have application for other particularly hazardous drugs in the future.

Senator NELSON. Your primary suggestion was, as I recall it, the same as Dr. Dameshek's, and perhaps some others, before the committee that it only be dispensed in a hospital or through a hospital pharmacy, is that correct?

Dr. WEHRLE. This is the easiest one I think to accomplish. There will be obvious objections to this, and I have indicated some of my concerns. But I think this would be the most workable of several different approaches.

As far as the usefulness of this and hampering its use by such a route, I would point out that about equal quantities of the drug have been used for some time in the oral and injectable forms in our hospital which would again indicate that the great bulk of this is going into hospitalized patients for inpatient use.

Senator NELSON. We've had some of the doctors, including one at the FDA, who expressed the view that most of the injectables are used in hospitals. We hope to have some statistics on that tomorrow. But at least that is what I was advised by a couple of different doctors. And if that is the case, that would explain the statistics of the past year—that is, the dramatic drop in the use in both capsule form and injectable, and then in the first 6 months of 1968 versus the first month of 1967. And then for some reason, and this may be the reason, capsule use in the last 3 months of 1968 increased from 3.6 million to 4.9 million grams, that is, 1968 over 1967, a 36-percent increase of 1968 over the last 3 months of 1967, whereas in injectable form it went down during this 3-month period from 1,600,000 grams to 500,000 grams, If, in your hospital, it was 50–50, that was typical of hospital administration, then something else has to account for the increase of the capsule use elsewhere.

Dr. WEHRLE. That is correct. And I wondered and speculated a bit about this. Now, if there is no artifact in these figures, in other words, if the producers of chloramphenicol are not getting large numbers of grams approved for next year's use, something like that, then I would think that it is most interesting that this is happening during the respiratory disease season and during the influenza outbreak, first the Hong Kong variety and currently the B which is beginning arise in some areas. So I think that this would indicate the need to at least

explore item 4 in the suggestions to find out where this drug is really going.

I would also like to urge you to think very carefully about the statement that most injectables are used in hospitals. There are some conspicuous drugs which don't follow this pattern. I cite particularly benzathine penicillin. Benzathine penicillin is one with a very long action. Intermediate doses provide low levels of penicillin for a period of 2 weeks approximately and larger doses for a period of about a month. This is a most popular drug for outpatient use in the treatment of streptococcal pharyngitis and in the prevention of rheumatic fever for the short and the longer periods respectively.

Senator NELSON. I was using the injectable cases applying solely to chloramphenicol.

Dr. WEHRLE. I would certainly agree.

Senator NELSON. I suppose there is some confusion about it. We have had testimony here from people like Dr. Lepper, Dr. Best, Dr. Dameshek and others, all of whom have stated it is widely overused, and I think Dr. Dameshek said it only ought to be administered in hospitals. If, in fact, it is used for the purposes, the limited purposes indicated, that is, in general that the disease must be very serious, no other antibiotic is effective, and chloramphenicol is effective against a particular organism, if that is the case, then you have, you probably have a patient who is or ought to be in the hospital. And hospital administration conforms much more consistently to the indicated use than outside the hospital. I believe the testimony was that Johns Hopkins, for quite some time, has simply had a rule that anytime it is prescribed, it has to be countersigned by the head of the service or someone else.

This is a difficult state to get to, but in any event, my statement, based on conversations with some of the doctors, referred only to chloramphenicol as to injectables.

Dr. WEHRLE. Yes.

Senator NELSON. We had testimony from the doctors I just mentioned and some others, all of whom estimated that chloramphenicol was much more widely used than it should have been and their estimates were that 90 to 99 percent of the chloramphenicol administered was in their judgment administered for a nonindicated case. Do you have any judgment or view on the administration of chloramphenicol in this respect?

Dr. WEHRLE. Yes, sir. I think I would like, though, to qualify this very carefully by indicating that it is difficult for a physician in one particular field to be completely comfortable about all of the indications and concerns that people in other fields have.

Now, the best estimate that I can come up with concerns an extrapolation of the pattern of usage in our particular institution. We might approach this from the standpoint of current usage and consider this drug to be used predominantly in inpatients. If we begin by indicating that the average of 1967–1968 usage was some 27,000 grams, about half parenteral and half oral, in the 798,000 patient visits to our hospital during the single year, this would work out to approximately 35 milligrams per patient visit. Obviously, relatively few patients are receiving this drug.

Now, if you further restrict this to only inpatients, these would average 188,000 patients for each of these 2 years. If all chloramphenicol

used were in inpatients, this would average approximately 140 milligrams per inpatient, that is per patient who was actually admitted to the hospital and remained for some time. Applying these data to the nearly 30 million hospital inpatients in the United States last year, as reported in the August 1968 issue of the Journal of Hospitals, published by the American Hospital Association, one would come to a total of approximately 2 million grams, about 1 million parenteral, about 1 million oral, for these 30 million patients admitted to hospitals all over the United States, including ours, providing our yardstick applied to the other hospitals. This figure takes account of the decreasing utilization in our hospital during recent years.

Now, if you further recall that this figure is based on a hospital that cares for more seriously ill, more long-neglected, more difficult to treat and referred patients than the average hospital in the United States, the figure of about 1 million oral and 1 million parenteral grams usage would be in my opinion a high level or a conservative level as far as total usage goes.

Senator NELSON. Do I understand you to be saying that if the same yardstick that is applied for the use of chloramphenicol in your hospital were applied to all hospitals in the United States, that would mean 30 million patients in all hospitals; is that correct?

Dr. WEHRLE. That is correct.

Senator NELSON. 30 million patients in all hospitals, during a single year would receive, would be administered 2 million grams, is that correct?

Dr. WEHRLE. This is correct, about half of which would be oral, about half of which would be parenteral.

Senator NELSON. In 1967, total number of grams used in the country was 42,800,000. In 1968, it dropped to 17,500,000. In 1967 and even in 1968, far and away most of the drug was being prescribed outside the hospital.

Dr. WEHRLE. Yes, sir. I would certainly agree. It looks as though the usage in the profession as a whole around the country is running approximately tenfold, at least tenfold higher than we are currently.

Senator NELSON. You mean in the whole profession?

Dr. WEHRLE. Pardon?

Senator NELSON. Who is using it tenfold higher, that is the average use in medicine in general is tenfold higher——

Dr. WEHRLE. Yes.

Senator NELSON (continuing). And in your hospital?

Dr. WEHRLE. Yes, sir; this is correct. This is what it would appear here. Obviously there are at least 10 times as many grams being marketed in respect to the numbers of patients admitted to other hospitals than to ours.

Senator NELSON. And this is despite the qualitative figure in terms of your patient, that is, that you have a high percentage of seriously ill patients, is that correct?

Dr. WEHRLE. This is correct, yes.

Senator NELSON. Well, thank you very much, Doctor, for your most valuable testimony. We appreciate your taking time to come here and appear before the committee. It has been most helpful to us.

We will recess until tomorrow morning at 10 o'clock.

(Whereupon, at 11:15 a.m., the subcommittee adjourned, to reconvene at 10 a.m., Thursday, February 27, 1969.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

THURSDAY, FEBRUARY 27, 1969

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

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

Present: Senator Nelson.

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

Senator NELSON. Our witness this morning is Dr. Herbert Ley, Commissioner of Food and Drugs.

Dr. Ley, the committee appreciates your taking time to come here this morning and present your testimony. You may proceed to present it in any fashion you desire. And if at any time you wish to elaborate on anything in your prepared text, feel free to do so. We may have some questions from time to time.

Go ahead, Dr. Ley.

STATEMENT OF DR. HERBERT L. LEY, JR., COMMISSIONER OF FOOD AND DRUGS, CONSUMER PROTECTION AND ENVIRONMENTAL HEALTH SERVICE, PUBLIC HEALTH SERVICE; ACCOMPANIED BY DR. B. HARVEY MINCHEW, ACTING DIRECTOR, BUREAU OF MEDICINE, FDA; AND WILLIAM W. GOODRICH, GENERAL COUNSEL, OFFICE OF GENERAL COUNSEL, HEW

Dr. LEY. Mr. Chairman, I appreciate the opportunity of appearing before your committee today to discuss the current status of the antibiotic, chloramphenicol.

Approximately 1 year ago, we came before you to discuss FDA's actions and intentions in regulating the interstate distribution of this drug. Today, I would like to report on the steps we have taken and the results of these actions.

Shortly after the hearing in February of 1968, we notified the Parke, Davis Co. which markets the antibiotic under the trade name Chloromycetin, that substantial revision in the labeling would be necessary. The new labeling was completed and approved in April 1968.

Senator NELSON. In preparing the new label, who does the original preparation?

Dr. LEY. The original preparation in this particular case was done

81-280 O—69—pt. 11——6

by the Bureau of Medicine's staff and then subsequently discussed with the firm. The firm had themselves prepared another draft so that actually the preparation was bilateral in this case.

Senator NELSON. What is the normal practice?

Dr. LEY. The normal practice, Senator, is for the firm to initiate the labeling change.

Senator NELSON. And if my recollection is correct, the firm prepares the labeling and at some stage the FDA reviews it, but ordinarily the FDA does not approve it prior to its being used?

Dr. LEY. That is correct, Senator.

Senator NELSON. In this particular case your department——

Dr. LEY. May I make one minor correction?

Senator NELSON. Yes, sir.

Dr. LEY. The labeling must be approved by FDA before it is used to accompany packages of the drug.

Senator NELSON. What about the indications and precautions and description of uses that are put in advertising?

Dr. LEY. The advertising claims and promotional claims need not be precleared by the FDA. However, they are based on labeling which is, and must be cleared by the agency before the labeling may be used as a basis for the advertisement or promotion.

Senator NELSON. Referring to that aspect of the advertising which lists the warnings and the precautions, does that have prior approval?

Dr. LEY. The body of information from which the warnings and precautions in an advertisement comes must have approval. Recent ads and the only current ad for this product features the entire package insert language for warnings and precautions.

Senator NELSON. On chloramphenicol, you mean?

Dr. LEY. Yes, sir.

Senator NELSON. Is this a special case?

Dr. LEY. This as it has evolved is a special case. With other drugs the manufacturer may prepare a brief summary which summarizes information in the package insert. That was not done in the case of this drug in any of the advertisements that were created after the committee hearing last year.

Senator NELSON. What about other ads where they are, of course, required to insert a warning and the precautions. Is that the language of the manufacturer, or is it language specifically approved by the FDA for all drugs?

Dr. LEY. In the case where specific warning statements are featured in the package insert and reproduced in the advertisements, that language must be approved by the agency.

Senator NELSON. But if they write an advertisement, do they have to include the warnings and precautions as are included in the package insert?

Dr. LEY. They must include these.

Senator NELSON. You may proceed.

Dr. LEY. The revised labeling included a carefully worded indications section expressed in restrictive terms. It included an estimate of the incidence of fatal aplastic anemia, based on a report made January 1, 1967, by the California Medical Association and State department of public health. It also states the desirability of hospitalizing patients being treated with chloramphenicol to facilitate observation during therapy.

Senator NELSON. The figure used on the incidents of aplastic anemia from the California study—I'm not exactly clear from my memory how that study achieved the statistics. It was the opinion, I believe, of Dr. Wehrle, who testified yesterday, that these statistics were gathered from death certificates. Is that correct?

Dr. LEY. If I may, Senator, I would like to outline the details of the California study leading to the determination of two separate risk incidents of aplastic anemia following chloramphenicol administration, and I'm referring specifically to the summary at the beginning of the California report.

The California group chose from death certificates filed in California for an 18-month period all those who were related to hematologic disorder. They then separated from these patients who had aplastic anemia and subsequently those that had fatal aplastic anemia. From this culling——

Senator NELSON. These were all death certificates?

Dr. LEY. These were all death certificates. That was the basic source of information. From this culling they uncovered 10 patients who had received chloramphenicol who died from aplastic anemia. This gives a numerator figure. For the denominator the total number of patients in California who had received chloramphenicol over the same period, they then made a survey of physicians and pharmacies to determine the usage. And they estimated that 220,000 patients had received chloramphenicol over the corresponding period.

There is one other computation which is critical here in arriving at the risk figure which the California group published in the determination of the average dosage per patient of chloramphenicol, I read directly from the report.

"If the risk is calculated on the average dose of 4.5 grams during 1965, the risk is one in 40,500."

Senator NELSON. Would you please start that sentence over again.

Dr. LEY. "If the risk is calculated on the basis of an average dose of 4.5 grams per patient"—that was my insert—"during 1965, the risk"—and I insert "of aplastic anemia developing"—"is one in 40,500." The next sentence, "If the risk is calculated on the basis of an average dose of 7.5 grams—I insert "per patient"—"it"—the risk—"is one in 24,200."

These were the two figures of risk identified by the California group which bracketed in their opinion the probability of the chloramphenicol-receiving patient developing aplastic anemia.

Senator NELSON. Well, doesn't this extrapolation made from these statistics have a built-in conservative factor; that is, you find 10 cases reported to have died from aplastic anemia. How often are you going to have cases in which the drug was prescribed for a nonindicated case and the physician simply isn't going to report that this was the case?

Dr. LEY. There is a possible bias here in the initial failure to report a death due to aplastic anemia. It could introduce a bias as you suggest. Death certificates are now required in all of our States and must indicate a specific diagnosis, primary diagnosis as the cause of death. The group chose those death certificates in which physicians had entered the diagnosis, aplastic anemia, as the cause of death. Now, it is possible that they may have been some death certificates that did not include this information. That is a possibility in the study.

Senator NELSON. Well, the statistics in the California report would be 10 more cases out of two hundred and some thousand and you've doubled the incidents.

Dr. LEY. That is correct, sir.

Senator NELSON. Please go ahead.

Dr. LEY. Cautionary information is included regarding use of the antibiotic in pregnancy and lactation. Leukemia is listed as an additional adverse reaction.

On May 7, 1968, following approval of the new labeling, we sent a "Dear Doctor" letter to every physician in the country calling attention to the proper indications for use and the strengthened warning about the hazards of this drug. The letter was also sent to all hospital administrators. The revised labeling was included with the letters, along with a facsimile of our Drug Experience Report form. Physicians were requested to report any adverse reactions associated with the use of chloramphenicol. I'd like to submit for the record a copy of this letter and the enclosures.

Senator NELSON. Thank you. Those will be included in the record.

(The information follows:)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

May 7, 1968

Dear Doctor:

Serious and often fatal blood dyscrasias are known to occur following the administration of chloramphenicol. Prominent warning to this effect has been part of the approved labeling for this drug since 1952, and this information has been disseminated in the medical and lay press, including editorials in the Journal of the American Medical Association.

Because the amount of chloramphenicol distributed exceeds that to be expected if the drug were prescribed only for its valid indications, the Food and Drug Administration believes that chloramphenicol is often prescribed for conditions for which it is not indicated, including trivial conditions such as acne, the common cold, and simple infections. Fatal reactions have been associated with use in these conditions.

To enlist your aid in ending the over-prescribing of this drug, the Food and Drug Administration asks that you carefully study the following "box warning" the substance of which has been and will continue to be part of the recently revised labeling of this drug:

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the "Indications" section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, 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, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.**

To clarify further the status of this drug in the therapy of infectious disease, the indications for use have been stated in the recently revised labeling as follows:

INDICATIONS: IN ACCORD WITH THE CONCEPTS IN THE "WARNING BOX" AND THIS INDICATIONS SECTION, CHLORAMPHENICOL MUST BE USED ONLY IN THOSE SERIOUS INFECTIONS FOR WHICH LESS POTENTIALLY DANGEROUS DRUGS ARE INEFFECTIVE OR CONTRAINDICATED. HOWEVER CHLORAMPHENICOL MAY BE CHOSEN TO INITIATE ANTIBIOTIC THERAPY ON THE CLINICAL IMPRESSION THAT ONE OF THE CONDITIONS BELOW IS BELIEVED TO BE PRESENT; *IN VITRO* SENSITIVITY TESTS SHOULD BE PERFORMED CONCURRENTLY SO THAT THE DRUG MAY BE DISCONTINUED AS SOON AS POSSIBLE IF LESS POTENTIALLY DANGEROUS AGENTS ARE INDICATED BY SUCH TESTS. THE DECISION TO CONTINUE USE OF CHLORAMPHENICOL RATHER THAN ANOTHER ANTIBIOTIC WHEN BOTH ARE SUGGESTED BY *IN VITRO* STUDIES TO BE EFFECTIVE AGAINST A SPECIFIC PATHOGEN SHOULD BE BASED UPON SEVERITY OF THE INFECTION, SUSCEPTIBILITY OF THE PATHOGEN TO THE VARIOUS ANTIMICROBIAL DRUGS, EFFICACY OF THE VARIOUS DRUGS IN THE INFECTION, AND THE IMPORTANT ADDITIONAL CONCEPTS CONTAINED IN THE "WARNING BOX" ABOVE:

1. ACUTE INFECTIONS CAUSED BY SUSCEPTIBLE STRAINS OF *SALMONELLA TYPHI*
   Chloramphenicol is a drug of choice.* It is not recommended for the routine treatment of the typhoid "carrier state".
2. SERIOUS INFECTIONS CAUSED BY SUSCEPTIBLE STRAINS IN ACCORDANCE WITH THE CONCEPTS EXPRESSED ABOVE:
   a. *Salmonella* species
   b. *H. influenzae,* specifically meningeal infections
   c. Rickettsia
   d. Lymphogranuloma-psittacosis group
   e. Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
   f. Other susceptible organisms which have been demonstrated to be resistant to all other appropriate anti-microbial agents.
3. CYSTIC FIBROSIS REGIMENS

* In the treatment of typhoid fever some authorities recommend that chloramphenicol be administered at therapeutic levels for 8-10 days after the patient has become afebrile to lessen the possibility of relapse.

The revised labeling suggests that patients being treated with chloramphenicol be hospitalized where indicated to facilitate observation during therapy. It also includes cautionary information regarding use in pregnancy and lactation, and the listing of leukemia as an additional adverse reaction. An estimate of the incidence of fatal aplastic anemia is included based on a report to the California State Assembly and Senate by the California Medical Association and State Department of Public Health, January 1, 1967.

The revision of the labeling of chloramphenicol was approved by a special committee of experts in hematology, infectious diseases and other medical fields convened by the Food and Drug Administration on February 26, 1968. A copy of the revised labeling is enclosed for your attention.

To assist us in further evaluation of this problem, the Food and Drug Administration requests that you report to us any adverse reactions associated with the use of chloramphenicol. A facsimile of our Drug Experience Report (FD 1639) is reproduced on the reverse side for your information. If you wish a supply, please write to the Food and Drug Administration, Bureau of Medicine, Washington, D.C. 20204.

Sincerely yours,

James L. Goddard, M.D.
Commissioner of Food and Drugs

Enclosure:
Revised Labeling

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

DRUG EXPERIENCE REPORT

BUDGET BUREAU NO. 57–R0004
Approval Expires December 31, 1970

DATE SENT TO FDA (Mo, day, yr) | 1. ☐ INITIAL REPORT ☐ FOLLOW UP REPORT | 2 PATIENT INITIALS AND IDENTIFICATION NUMBER | 3. ACCESSION NO. (For FDA use only)

SECTION I. BASIC REACTION DATA

4. SEX ☐ M ☐ F | 5. HEIGHT ins. / WEIGHT lbs. | 6. DATE OF BIRTH mo / day / yr | 7. ORIGIN ☐ CAUC ☐ NEGRO ☐ ORIENTAL ☐ AMERICAN INDIAN ☐ OTHER | 8. DATE OF REACTION ONSET mo / day / yr

9. SOURCE OF REPORT (Mfg, Hospital, etc)(Name of reporting Physician is optional.)

10. ADDRESS OF SOURCE (Give Street, City, State, and Zip Code.)

11. DESCRIBE SUSPECTED ADVERSE REACTION(s) AND ANY POSSIBLE ASSOCIATION WITH THE DRUG(s) INVOLVED

12. OUTCOME OF REACTION TO DATE
- ☐ ALIVE WITH SEQUELAE
- ☐ RECOVERED
- ☐ STILL UNDER TREATMENT
- ☐ DIED (Give date and cause)

13. LIST ALL THERAPY IN ORDER OF SUSPICION (Manufacturer; List NDA or IND No.)

NAME OF DRUGS TRADE (Generic)	MANUFACTURERS CONTROL NO.	DOSAGE FORM (tab, cap, etc.)	TOTAL DAILY DOSE	ROUTE (po, im, iv, etc.)	DURATION OF THERAPY	DATES OF ADMINISTRATION	14. DISORDER OR REASON FOR USE OF DRUG

SECTION II. IMPORTANT MODIFYING DATA

15. SUBSTANTIATING LABORATORY STUDIES (Clinical Laboratory, Autopsy, X-Ray, etc.)
CLINICAL LAB: ☐ DONE ☐ ATTACHED ☐ NOT DONE
BIOPSY/AUTOPSY: ☐ DONE ☐ ATTACHED ☐ NOT DONE

16. LIST POTENTIALLY NOXIOUS OR ENVIRONMENTAL FACTORS (Include household products, industrial and agricultural chemicals)

17. EXISTING OR PRIOR DISORDERS AND PAST DRUG REACTION OR ALLERGIC HISTORY
PREVIOUS EXPOSURE TO SUSPECTED DRUG OR RELATED COMPOUND ☐ YES ☐ NO

18. (a) IF FEMALE GRAVIDITY ☐☐ PARITY ☐☐ (b) IF PREGNANT WEEKS OF GESTATION ☐☐

19. MAY THE SOURCE OF THIS REPORT BE RELEASED TO THE ARMED FORCES INSTITUTE OF PATHOLOGY? ☐ YES ☐ NO

FOR FDA USE ONLY | **FOR MFG USE ONLY**

20. REACTION FACTORS (Check all applicable boxes)
☐ DECOMPOSITION OF DRUG ☐ INTERACTION OF TWO OR MORE DRUGS ☐ DRUG NOT USED ACCORDING TO LABELING ☐ DRUG OUTDATED
☐ DRUG MISUSED BY PATIENT ☐ OVERDOSAGE ☐ DRUG MISLABELED ☐ CONTAMINATION OF DRUG ☐ OTHER DRUG MISUSE (Specify)

GPO : 1968 O - 288-415

FORM FD–1639 (Rev 8/67)

Use additional sheet if necessary.

PACKAGE INSERT FOR CHLORAMPHENICOL

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the "Indications" section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, 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, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.**

DESCRIPTION: Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for,* serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see "Indications" section).

ACTIONS AND PHARMACOLOGY: In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group and *Vibrio cholerae.* It is particularly active against Salmonella typhi and *Hemophilus influenzae.* The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg./kg./day, a dosage of 1 gm. every 6 hours for 8 doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg./ml. one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg./ml. after the fifth dose of 1 gm. Mean serum levels ranged from 8-14 mcg./ml. over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68 percent to a high of 99 percent over a three-day period. From 8 to 12 percent of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg./ml. in patients receiving divided doses of 50 mg./kg./day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS: IN ACCORD WITH THE CONCEPTS IN THE "WARNING BOX" AND THIS INDICATIONS SECTION, CHLORAMPHENICOL MUST BE USED ONLY IN THOSE SERIOUS INFECTIONS FOR WHICH LESS POTENTIALLY DANGEROUS DRUGS ARE INEFFECTIVE OR CONTRAINDICATED. HOWEVER CHLORAMPHENICOL MAY BE CHOSEN TO INITIATE ANTIBIOTIC THERAPY ON THE CLINICAL IMPRESSION THAT ONE OF THE CONDITIONS BELOW IS BELIEVED TO BE PRESENT; *IN VITRO* SENSITIVITY TESTS SHOULD BE PERFORMED CONCURRENTLY SO THAT THE DRUG MAY BE DISCONTINUED AS SOON AS POSSIBLE IF LESS POTENTIALLY DANGEROUS AGENTS ARE INDICATED BY SUCH TESTS. THE DECISION TO CONTINUE USE OF CHLORAMPHENICOL RATHER THAN ANOTHER ANTIBIOTIC WHEN BOTH ARE SUGGESTED BY *IN VITRO* STUDIES TO BE EFFECTIVE AGAINST A SPECIFIC PATHOGEN SHOULD BE BASED UPON SEVERITY OF THE INFECTION, SUSCEPTIBILITY OF THE PATHOGEN TO THE VARIOUS ANTIMICROBIAL DRUGS, EFFICACY OF THE VARIOUS DRUGS IN THE INFECTION, AND THE IMPORTANT ADDITIONAL CONCEPTS CONTAINED IN THE "WARNING BOX" ABOVE:

1. ACUTE INFECTIONS CAUSED BY SUSCEPTIBLE STRAINS OF *SALMONELLA TYPHI*

   Chloramphenicol is a drug of choice.* It is not recommended for the routine treatment of the typhoid "carrier state".

   * In the treatment of typhoid fever some authorities recommend that chloramphenicol be administered at therapeutic levels for 8-10 days after the patient has become afebrile to lessen the possibility of relapse.

2. SERIOUS INFECTIONS CAUSED BY SUSCEPTIBLE STRAINS IN ACCORDANCE WITH THE CONCEPTS EXPRESSED ABOVE:

   a. *Salmonella* species
   b. *H. influenzae,* specifically meningeal infections
   c. Rickettsia
   d. Lymphogranuloma-psittacosis group
   e. Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections
   f. Other susceptible organisms which have been demonstrated to be resistant to all other appropriate anti-microbial agents.

3. CYSTIC FIBROSIS REGIMENS

CONTRAINDICATIONS: Chloramphenicol is contraindicated in individuals with a history or previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

PRECAUTIONS:

1. Baseline blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.
2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.
3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.
4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.
5. There are no studies to establish the safety of this drug in pregnancy.
6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).
7. Precaution should be used in therapy of premature and full-term infants to avoid "gray syndrome" toxicity. (See "Adverse Reactions.") Serum drug levels should be carefully followed during therapy of the newborn infant.

8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.
9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS:

1. **Blood Dyscrasias**

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol.

An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed. A reversible type of bone marrow depression, which is dose related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding 1) the size of the population at risk, 2) the total number of drug-associated dyscrasias, and 3) the total number of non-drug associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There are reports of aplastic anemia terminating in leukemia attributed to chloramphenicol.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. **Gastrointestinal Reactions**

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. **Neurotoxic Reactions**

Headache, mild depression, mental confusion, and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. **Hypersensitivity Reactions**

Fever, macular and vesicular rashes, angioedema, urticaria, and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. **"Gray Syndrome"**

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the "gray syndrome". One case of "gray syndrome" has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

(1) In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life.
(2) Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol.
(3) The symptoms appeared in the following order:
  (a) abdominal distension with or without emesis;
  (b) progressive pallid cyanosis;
  (c) vasomotor collapse, frequently accompanied by irregular respiration;
  (d) death within a few hours of onset of these symptoms.
(4) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
(5) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg./ml. after repeated doses).
(6) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

DOSAGE AND ADMINISTRATION

DOSAGE RECOMMENDATIONS FOR ORAL CHLORAMPHENICOL PREPARATIONS

The majority of micro-organisms susceptible to chloramphenicol will respond to a concentration between 5 and 20 mcg./ml. The desired concentration of active drug in blood should fall within this range over most of the treatment period. Dosage of 50 mg./kg./day divided into 4 doses at intervals of 6 hours will usually achieve and sustain levels of this magnitude.

Except in certain circumstances (e.g., premature and newborn infants and individuals with impairment of hepatic or renal function) lower doses may not achieve these concentrations. Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Close observation of the patient should be maintained and in the event of any adverse reactions, dosage should be reduced or the drug discontinued, if other factors in the clinical situation permit.

Adults—Adults should receive 50 mg./kg./day (approximately one 250 mg. capsule per each 10 lbs. body weight) in divided doses at 6-hour intervals. In exceptional cases patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg./kg./day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under "Newborn Infants.") Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children—Dosage of 50 mg./kg./day divided into 4 doses at 6-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (e.g., bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg./kg./day; however, it is recommended that dosage be reduced to 50 mg./kg./day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants—(See section titled "Gray Syndrome" under "Adverse Reactions.") A total of 25 mg./kg./day in 4 equal doses at 6-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg./kg./day equally divided into 4 doses at 6-hour intervals. *These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants.* This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature, (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes—In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg./kg./day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

Dr. LEY. As a result of this letter, we received approximately 275 letters or notes from physicians. Most important, we received 22 adverse reaction reports, as follows—and if I may, let me read them—five cases of aplastic anemia, fatal; three cases of pancytopenia, fata; three cases of pancytopenia, persistent (not fatal); four leukopenia, transient, recovered; one nosebleed and paresthesias, recovered; two cases anemia, recovered; three cases aplastic anemia, still under treatment; and one case of erythema multiforme, recovered.

At the time the "Dear Doctor" letter was mailed, we also contacted various professional publications—Medical Tribune, Medical World News, AMA News, and the journals of every State medical society—asking their cooperation in publicizing the proper use of the drug and the hazards associated with its use. The labeling revisions and the warning letter also were widely publicized in the general news media.

Senator NELSON. Doctor, did the FDA do a specific check of all the State society journals and the AMA and various other medical journals to see what they did say and do about this.

Dr. LEY. We did not do a specific check of all State society journals. I have here, if the Senator wishes, a listing of all journals to whom we supplied this information which can be made available for the record, if you choose.

Senator NELSON. This is a list of the journals that you requested?

Dr. LEY. Yes, sir.

Senator NELSON. Do you have any list of the journals that responded to the request positively?

Dr. LEY. We have not, sir, as of this date doublechecked all of these journals to determine whether or not they did make specific references to the letter and material which we provided them. In some of the more widely distributed medical publications, the letter and the enclosures received considerable publicity, and I am speaking of "AMA News," "Medical World News," "Medical Tribune," and so forth.

Senator NELSON. They did that?

Dr. LEY. They did indeed feature it, and we have copies of the articles that appeared in those publications which we would be pleased to submit for the record.

Senator NELSON. Including JAMA?

Dr. LEY. I will have to check with the staff to determine whether "JAMA" is included in that list or not.

We were unable to find any reference within "JAMA" itself. However, "AMA News," which is published by the AMA as a weekly news magazine, did feature the item significantly.

Advertisements for chloramphenicol—particularly the "reminder" ads which include no warning information—were also of concern in connection with the excessive use of this drug.

On April 25, 1968, Dr. James L. Goddard, then Commissioner of Food and Drugs, sent Parke, Davis & Co. a letter requesting them to discontinue such reminder advertisements and reminder labeling for chloramphenicol. With your permission, I would like to submit a copy of this letter for the record.

Senator NELSON. You are talking solely about reminder ads of the kind such as "when it counts, Chloromycetin?"

Dr. LEY. Yes, sir.

Senator NELSON. You requested the discontinuance of this kind of ad and the company complied with the request?

Dr. LEY. That is my belief; yes, sir.

Senator NELSON. None of these reminder ads are being run on Chloromycetin any longer?

Dr. LEY. The only ad copy of which we are aware today is this ad copy here which carries that same front page that you illustrated there but is accompanied by the full prescribing information including the warning in the label.

Senator NELSON. Well, doesn't the company, in many instances achieve the same results it was seeking to achieve with the reminder ads for all those who don't bother to read the fine print?

Dr. LEY. The first page of this spread carries an additional statement, "See following page for prescribing information." If a physician is to use the drug, unless he has had experience with the dosage in the past, he would usually refer either to the information in the advertisement or to the Physicians' Desk Reference, which carries exactly the same information. So that he would be reading the warning and all of the other information. I cannot however, guarantee that he does this.

Senator NELSON. But if the FDA felt it was important enough to stop the company from using the reminder ad as it stands alone—such as the example here—it seems pretty obvious to me that the purpose sought in the ad is to get the benefit of the reminder ad since many people might not carefully read the fine print. Isn't there a problem though in that the indications for the use of chloramphenicol have been changing rapidly in the past half dozen years? And I think, if I remember correctly the National Academy of Science Report—it does not specifically list chloramphenicol as the drug of choice in any case.

Dr. LEY. It does not carry the words, "The drug of choice" in any case in the present labeling—a drug of choice, yes, with typhoid.

Senator NELSON. Pardon?

Dr. LEY. There is the wording, "a drug of choice" for typhoid fever.

Senator NELSON. So here you have a situation in which the testimony of all the experts appearing before the committee—unrefuted by the company or any other witnesses—is that chloramphenicol continues to be widely prescribed for nonindicated uses. Some of these nonindicated uses were, I would guess, indicated uses prior to, say, Ampicillin and some of the newer drugs. So that when a practicing physician who has been using the drug 5 or 6 years, prior to the revised judgment of what its indications are—sees the labeling in the ad, he just doesn't bother to read it—since he may have read it many times years ago. So isn't this, then, really, in effect, a reminder ad with the same effect on that physician—why read this fine print again for the 10th time?

Dr. LEY. I acknowledge that the physician may not read the fine print. However, that same physician was exposed to a letter from Dr. Goddard the text of which specifically highlighted the significant and important changes in the labeling. Again, I cannot guarantee that the physician read the letter. But the combination of the letter and the considerable publicity given after your hearings of last year in "Medical World News," "AMA News," and "Medical Tribune," I think must have had an effect of reeducating the physician concerning the indications of use for this drug.

Senator NELSON. Well, there is no question but that the statistics demonstrate a dramatic drop in the use of the drug, comparing the

first 6 months of 1967 vis-a-vis the first 6 months of 1968. And, of course, you have and are presenting the statistics of what happened the last 3 months of 1968 versus the last 3 months of 1967 when there was a dramatic increase in the use of the capsule form as contrasted with the injectable which went down.

The point, it seems to me, still is that it is widely misprescribed for nonindicated uses, and every conceivable effort has been made to assure that it will not be used for nonindicated uses. In the wording of the package insert, FDA, including Dr. Goddard and yourself, takes the position of the use of the drug should be limited to hospitals. The committee has had a number of distinguished experts who took that position. Yet FDA has not been prepared to confine it to hospital use. If it were administered only in hospitals, there is no question but that there would be much more significant control, and a more significant factor in educating the doctor about the precautions of this drug.

But since the FDA isn't prepared to do that, and since it continues to be prescribed widely for nonindicated cases, it seems to me that FDA ought to be doing every thing else within its power to stop it. And it seems to me this use of the reminder ad with the fine print attached still promotes the drug for nonindicated cases. You really ought to consider whether this type of ad—even with the fine print—can be justified.

(The information previously referred to follows:)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Washington, D.C., April 25, 1968.

DR. AUSTIN SMITH,
Parke Davis & Co.,
Detroit, Mich.

DEAR DR. SMITH: Under the existing regulations pertaining to advertisements for prescription drugs, producer sponsored advertisements have been permitted an exemption from the requirement of providing a statement of information in brief summary relating to side effects, contraindications and effectiveness if an advertisement contains no information as to indications or dosage recommendations. In the case of Chloromycetin, we are aware of your use of so-called reminder advertisements for that product which contain no "Brief Summary."

Taking into account the recent disclosures regarding the broad use of chloramphenicol and the urgent need to bring warning information regarding the drug to the attention of physicians by every means feasible, I am asking that your firm immediately discontinue using so-called reminder advertisements and reminder labeling in the promotion of chloramphenicol, whether or not any such promotion is entitled to exemption under the reminder advertising or reminder labeling provisions of the existing regulations.

While we believe that we could require prior approval of chloramphenicol advertisements under the terms of section 1.105(j) of the regulations, I would prefer not to consider proceeding under that concept at this time.

Will you please let me have your comments as soon as possible concerning your willingness to meet the above request.

Sincerely yours,

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

[From The Journal of the American Medical Association, Jan. 22, 1968, pp. 162–163]

may be indicated in certain severe respiratory infections

Because of its wide antibacterial spectrum and its ability to diffuse into infective foci, CHLOROMYCETIN may be of value in the treatment of selected severe respiratory tract infections due to susceptible microorganisms. However, as with any antibacterial agent, the administration of CHLOROMYCETIN must be adjunctive to the overall therapeutic approach to this family of diseases. Appropriately treated, good results can be expected in bacterial pneumonia and empyema; in bacterial complications of bronchiectasis and bronchitis; all of which are severe disorders often chronic and difficult to eradicate.

The decision to choose CHLOROMYCETIN from among a group of antibiotics suggested by *in vitro* studies to be potentially effective against a specific respiratory tract pathogen(s) should be guided by severity of infection, relative susceptibility of the pathogen(s) to the various antibacterial drugs, relative efficacy of the various drugs in this family of infections, and the important additional concepts contained in the "warning box."

Patients with respiratory tract infections usually become afebrile in 18 to 72 hours on recommended doses; roentgenographic clearing may be slower.

Neoplastic, fungal, and mycobacterial disease as a cause of persisting respiratory disease should be ruled out by appropriate means.

Chloromycetin

Detailed information, including indications and dosage, appears in the package inserts of CHLOROMYCETIN products for systemic use. Consult the appropriate package insert.

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.

CHLOROMYCETIN, an antibiotic having therapeutic activity against a wide variety of organisms, must, in accordance with the concepts in the "warning box" above, be used only in certain severe infections.

Contraindications: Chloramphenicol is contraindicated in individuals with a history of previous sensitivity reaction to it.

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 and Side Effects: Untoward reactions in man are infrequent; however, they have been reported with both short-term and prolonged administration of the drug. Among the reactions reported are blood dyscrasias as mentioned in the warning. When, during the course of therapy, blood counts show unusual deviations which may be attributable to the drug such as reticulocytopenia, leukopenia, or thrombocytopenia, therapy with chloramphenicol should be discontinued. Also reported are certain gastrointestinal reactions resulting in glossitis and stomatitis, which are indications to stop the drug. On rare occasions, superimposed infection by *Candida albicans* may produce widespread oral lesions of the thrush type. Diarrhea and irritation of perianal tissues have been reported. Pseudomembranous enterocolitis has been reported in a few patients. Hypersensitivity reactions manifested by angioneurotic edema and vesicular and maculopapular types of dermatitis have been reported in chloramphenicol-sensitive patients. Urticaria and vesicular lesions have been observed. They are usually mild in character and ordinarily subside promptly upon cessation of treatment.

Febrile reactions have been reported.

A reaction of the Jarisch-Herxheimer type has been reported following therapy in syphilis, brucellosis, and typhoid fever. Typhoid fever patients have exhibited a "shock-type reaction" characterized by circulatory collapse attributed to sudden release of endotoxin. Neurotoxic reactions, including optic and peripheral neuritides, headache, mild depression, "dazed feelings," internal ophthalmoplegia, mental confusion, and delirium have been reported. Symptoms of peripheral neuritis or decreased visual acuity call for prompt withdrawal of the antibiotic and the possible use of large doses of oral or parenteral vitamin B complex. When prolonged high dosage is necessary, toxic side effects may occur which call for dosage reduction or discontinuance of chloramphenicol therapy. Adults and children with impaired liver or kidney function, or both, may retain excessive amounts of the drug. In such instances, dosages should be adjusted accordingly.

Toxic reactions, the signs and symptoms of which have been referred to as the "gray syndrome," with some fatalities, have resulted from high concentrations of the drug in the premature and newborn age groups. One case of "gray syndrome" has been reported in an infant born to a mother having received chloramphenicol during labor. The following summarizes the clinical and laboratory studies that have been made on these patients: (1) In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life. (2) Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol. (3) The symptoms appeared in the following order: (a) abdominal distention with or without emesis; (b) progressive pallid cyanosis; (c) vasomotor collapse, frequently accompanied by irregular respiration; and (d) death within a few hours of onset of these symptoms. (4) The progression of symptoms from onset to exitus was accelerated with higher dose schedules. (5) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol after repeated doses. (6) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

Precautions: See "warning box" for precautions.

The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. Constant observation of the patient is essential. If new infections caused by nonsusceptible organisms appear during therapy, the drug should be discontinued and appropriate measures should be taken.

Monitoring of liver and kidney function should be accomplished during therapy in patients with existing liver or kidney disease.

Supplied: CHLOROMYCETIN is available in a variety of forms including Kapseals® of 250 mg.

960R67

PARKE-DAVIS

when it counts

CHLOROMYCETIN® Kapseals®

(CHLORAMPHENICOL CAPSULES)

PARKE-DAVIS

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the "Indications" section. It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, 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, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

DESCRIPTION

Chloramphenicol is an antibiotic that is clinically useful for, and should be reserved for, serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see "Indications" section).

ACTIONS AND PHARMACOLOGY

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group and *Vibrio cholerae*. It is particularly active against *Salmonella typhi* and *Hemophilus influenzae*. The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg./kg./day, a dosage of 1 gm. every 6 hours for 8 doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg./ml. one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg./ml. after the fifth dose of 1 gm. Mean serum levels ranged from 8-14 mcg./ml. over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8 to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg./ml. in patients receiving divided doses of 50 mg./kg./day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS

IN ACCORD WITH THE CONCEPTS IN THE "WARNING BOX" AND THIS INDICATIONS SECTION, CHLORAMPHENICOL MUST BE USED ONLY IN THOSE SERIOUS INFECTIONS FOR WHICH LESS POTENTIALLY DANGEROUS DRUGS ARE INEFFECTIVE OR CONTRAINDICATED.

HOWEVER, CHLORAMPHENICOL MAY BE CHOSEN TO INITIATE ANTIBIOTIC THERAPY ON THE CLINICAL IMPRESSION THAT ONE OF THE CONDITIONS BELOW IS BELIEVED TO BE PRESENT; *IN VITRO* SENSITIVITY TESTS SHOULD BE PERFORMED CONCURRENTLY SO THAT THE DRUG MAY BE DISCONTINUED AS SOON AS POSSIBLE IF LESS POTENTIALLY DANGEROUS AGENTS ARE INDICATED BY SUCH TESTS. THE DECISION TO CONTINUE USE OF CHLORAMPHENICOL RATHER THAN ANOTHER ANTIBIOTIC WHEN BOTH ARE SUGGESTED BY *IN VITRO* STUDIES TO BE EFFECTIVE AGAINST A SPECIFIC PATHOGEN SHOULD BE BASED UPON SEVERITY OF THE INFECTION, SUSCEPTIBILITY OF THE PATHOGEN TO THE VARIOUS ANTIMICROBIAL DRUGS, EFFICACY OF THE VARIOUS DRUGS IN THE INFECTION, AND THE IMPORTANT ADDITIONAL CONCEPTS CONTAINED IN THE "WARNING BOX" ABOVE:

1. Acute infections caused by susceptible strains of *Salmonella typhi*

Chloramphenicol is a drug of choice.* It is not recommended for the routine treatment of the typhoid "carrier state."

*In the treatment of typhoid fever some authorities recommend that chloramphenicol be administered at therapeutic levels for 8-10 days after the patient has become afebrile to lessen the possibility of relapse.

2. Serious infections caused by susceptible strains in accordance with the concepts expressed above:

a. Salmonella species
b. *H. influenzae*, specifically meningeal infections
c. Rickettsia
d. Lymphogranuloma-psittacosis group
e. Various gram-negative bacteria causing bacteremia, meningitis or other serious gram-negative infections
f. Other susceptible organisms which have been demonstrated to be resistant to all other appropriate anti-microbial agents.

3. Cystic fibrosis regimens

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.

PRECAUTIONS

1. Baseline blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.
2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.
3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.
4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.
5. There are no studies to establish the safety of this drug in pregnancy.
6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).
7. Precaution should be used in therapy of premature and full-term infants to avoid "gray syndrome" toxicity. (See "Adverse Reactions.") Serum drug levels should be carefully followed during therapy of the newborn infant.
8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.
9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding 1) the size of the population at risk, 2) the total number of drug-associated dyscrasias, and 3) the total number of non-drug associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the "gray syndrome". One case of "gray syndrome" has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3 month infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

(1) In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life.
(2) Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol.
(3) The symptoms appeared in the following order:
  (a) abdominal distension with or without emesis;
  (b) progressive pallid cyanosis;
  (c) vasomotor collapse, frequently accompanied by irregular respiration;
  (d) death within a few hours of onset of these symptoms.
(4) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
(5) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg./ml. after repeated doses).
(6) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

DOSAGE AND ADMINISTRATION

DOSAGE RECOMMENDATIONS FOR ORAL CHLORAMPHENICOL PREPARATIONS

The majority of microorganisms susceptible to chloramphenicol will respond to a concentration between 5 and 20 mcg./ml. The desired concentration of active drug in blood should fall within this range over most of the treatment period. Dosage of 50 mg./kg./day divided into 4 doses at intervals of 6 hours will usually achieve and sustain levels of this magnitude.

Except in certain circumstances (e.g., premature and newborn infants and individuals with impairment of hepatic or renal function) lower doses may not achieve these concentrations. Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Close observation of the patient should be maintained and in the event of any adverse reactions, dosage should be reduced or the drug discontinued, if other factors in the clinical situation permit.

Adults

Adults should receive 50 mg./kg./day (approximately one 250 mg. capsule per each 10 lbs. body weight) in divided doses at 6-hour intervals. In exceptional cases patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg./kg./day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg./kg./day divided into 4 doses at 6-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (e.g., bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg./kg./day; however, it is recommended that dosage be reduced to 50 mg./kg./day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants

(See section titled "Gray Syndrome" under "Adverse Reactions.")

A total of 25 mg./kg./day in 4 equal doses at 6-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg./kg./day equally divided into 4 doses at 6-hour intervals. These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants. This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg./kg./day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

PACKAGE INFORMATION

Kapseals No. 379, Chloromycetin (chloramphenicol capsules), each contain 250 mg. chloramphenicol, supplied in packages of 16 and 100, and Roll-Pak* of 100.

Capsules No. 477, Chloromycetin (chloramphenicol capsules), each contain 50 mg. chloramphenicol, supplied in packages of 25 and 100.

Capsules No. 480, Chloromycetin (chloramphenicol capsules), each contain 100 mg. chloramphenicol, supplied in packages of 25 and 100.

Oral Suspension Chloromycetin (chloramphenicol) Palmitate, each 4 cc. represents 125 mg. chloramphenicol, (each cc. contains chloramphenicol palmitate equivalent to 31.25 mg. chloramphenicol with 0.5% sodium benzoate as preservative), in bottles of 60 cc.

Chloramphenicol Palmitate is hydrolyzed to chloramphenicol before absorption. Resulting blood concentration is similar to that produced by the oral administration of chloramphenicol.

CHLOROMYCETIN, brand of chloramphenicol, Reg. U.S. Pat. Off.

*Trademark for dispensing package

Parke, Davis & Company, Detroit, Michigan 48232

PARKE-DAVIS 48268

Senator NELSON. Please go ahead.

Dr. LEY. In a letter dated May 1, 1968, the firm notified us that it had discontinued all "reminder advertisements" in March of 1968, with the exception of those ads that were too far along in the publication process to be cancelled.

Dr. L. M. Lueck, of Parke, Davis, also said in this letter that the distribution from Detroit of all "reminder" pieces—such as rulers, pencils, and calendars—had been discontinued. He said this practice also was being discontinued in the field as rapidly as possible. Since that time, ads for the drug have carried essentially the full disclosure information from the package insert of the dangers and side effects associated with the use of chloramphenicol and the "box warning" that is part of the labeling.

On June 27, 1968, we issued a revision of the prescription drug advertising regulations applicable to "reminder" advertising which took into account our experience with chloramphenicol. Under these regulations, if the Commissioner finds there is evidence of a significant incidence of fatalities or serious side effects associated with the use of a particular drug, he can, by notifying the firm forbid the use of "reminder" advertisements that omit warning information.

On March 12, 1968, we met with representatives of Parke, Davis and the Pharmaceutical Manufacturing Association to determine whether the advertisement which appeared in the Reader's Digest issue of February 1968 "was caused to be disseminated" by the drug firm. This ad, in our view, recommended the drug for uses that were not warranted and seriously understated the hazards, side effects, and contraindications.

As a result of the meeting, we learned that the idea for this ad originated with the advertising agency handling the public relations program for PMA. The copy was reviewed and approved by PMA. Parke, Davis was subsequently asked to review the copy and to give permission for the use of the names of Dr. Payne and Dr. Burkholder. Funds for the advertising program which included this ad were contributed by approximately 100 members of PMA. Dr. Goddard accepted the explanation that PMA, not Parke, Davis was responsible for the ad.

Senator NELSON. May I interrupt for a moment.

We discussed this at great length with Dr. Goddard in the spring of 1968 and I raised the point that it didn't seem rational to permit Parke, Davis as a contributing member of the PMA to sort of duck its responsibility since it was the advertising firm and PMA that paid for the ad with Parke, Davis, in fact, reviewing the ad. There is a further question—as a member of the PMA any member company must have imputed to it responsibility for whatever the corporation is that they really own and control. If that is not the case, then any company can escape responsibility for an ad, which really violates FDA rules and regulations, by simply saying, well, it was the advertising firm and the PMA; although they all run the PMA, in this way they escape responsibility. I thought it was a very inappropriate ruling on the part of FDA.

My question is, What is the policy as to future situations such as this? Will the company be held accountable or will they be excused?

Dr. LEY. I would like to ask our General Counsel, Mr. Goodrich to respond to this question, if I may, Senator.

Mr. GOODRICH. When we were here last spring we did have this conversation about imputing the responsibility to the company Dr. Goddard and I concluded that before making any recommendations we should get PMA and Dr. Smith, the president of Parke, Davis, in to find out what the relationship was. The facts that we developed are as stated in this statement. It is possible legally to argue that mere membership, contribution to this PR fund is the causing tof the dissemination of the ad, but this would be a very difficult point to make in a criminal case, and Dr. Goddard accepted the explanation on this ad.

In the future, of course, we are going to try to avoid this sort of thing. We expressed both to Parke, Davis and to PMA our displeasure with this ad, and you had done the same thing. I do not think it will occur again, and it has not in the future advertisements of this type which appeared after this ad in the Reader's Digest.

Senator NELSON. Well, I suppose as lawyers we may have a difference of opinion as to what may or may not be difficult to prove.

Mr. GOODRICH. Right.

Senator NELSON. I would think it would be almost automatic if the facts are as stated here, where the company itself, and 99 or so other associates own the PMA; it is their creature; next, all the ads are paid for by contributions to the PMA, it has no independent status of its own at all, then the ad is reviewed by Parke, Davis, and it makes broader claims than the FDA would approve. I don't think there would be any question in the world but what the firm would be assigned a responsibility for that ad in any kind of a lawsuit. You may, of course, differ on that. My concern would be, at least, that they be notified that in any future case you will try it.

Mr. GOODRICH. Right.

Senator NELSON. You will try a lawsuit and then find out what the law is.

Mr. GOODRICH. That was done.

Senator NELSON. You did try it?

Mr. GOODRICH. That we have told them that this kind of practice in the future would be considered for possible prosecution.

Senator NELSON. I see. All right. Please continue.

Dr. LEY. Let me turn now to another problem associated with chloramphenicol. In May 1968, after reviewing all the blood-level data in our files on chloramphenicol for parenteral use, we concluded that chloramphenicol sodium succinate injection produced lower blood levels than the oral preparations. We suspended certification of chloramphenicol succinate pending resolution of the question about the therapeutic effectiveness of these lower blood levels. Certification was resumed in September 1968, as will be explained shortly when I discuss revision of the labeling of parenteral forms of chloramphenicol.

Senator NELSON. May I interrupt for a moment?

Dr. LEY. Certainly.

Senator NELSON. As I recall it, the issue was raised a year ago in December; is that correct?

Dr. LEY. September 1967.

Senator NELSON. Yes. The question raised was that the other chloramphenicols in the marketplace did not achieve the same blood level at the same time as Parke, Davis' chloramphenicol, is that correct?

Dr. LEY. That is correct, sir.

Senator NELSON. Is there any clinical evidence at all that demonstrates that one blood level has a better therapeutic aspect than the others?

Dr. LEY. There is no evidence of this sort currently in our files. I would like, if I may, to trace the history of that particular incident because it might be valuable in further discussion here this morning.

Senator NELSON. Fine.

Dr. LEY. In October of 1966, the date the chloramphenicol patent protection expired, several other firms petitioned us to approve certification for competing brands of chloramphenicol. In retrospect, the decision that was made at that time was in error. The staff of scientists at FDA considered that with a drug which could be synthesized, such as chloramphenicol can, which can be analyzed carefully and accurately, that permitting marketing on the basis of purely chemical standards of purity, identity, et cetera, would provide a product which was comparable in every respect to the original product in the marketplace. This assumption was subsequently found to be false.

At this point, when we recognized the blood levels from the later competing manufacturers of the product were at variance, in that they appeared more slowly than the blood levels from the Parke, Davis product, we faced the question of whether we could clearly define a blood level as being effective for this condition or that condition.

The decision which we finally made in December of 1967, Mr. Chairman, was a decision that each one of the competing firms could have one or the other of two choices. Either they could demonstrate by testing in human substance that the blood level which their product produced was equivalent to the same blood level of the Parke, Davis product which was supported by adequate clinical data in the past, or as their second choice, they could collect and submit to us clinical data demonstrating the efficacy of their product even though it had a lower blood level. None of the manufacturers elected to take the second course; all chose the first course of action. So that at this point in time, the three manufacturers of chloramphenicol who are currently marketing their product all have blood levels which are essentially identical when tested in human substance.

Senator NELSON. So there is no positive clinical evidence that one blood-level achievement in x period of time is more effective than another.

Dr. LEY. The information of this sort is extremely rare, and there are several studies in progress at the moment that might eventually prove that a lower dosage of chloramphenicol would be effective in treating, let's say, typhoid fever than the dosage which was first given in the literature, but these data are not yet in. This is the extent to my knowledge—and I'll have to ask Dr. Minchew to be absolutely certain—of the type of data that are available linking blood levels with clinical efficacy for this product. Is this correct?

Dr. MINCHEW. Yes.

Senator NELSON. Because the claims made by the PMA at that time, you know, were that this just proves the case that generics or that

the brand names are better, and so forth, when, in fact, it didn't prove anything except they achieved different blood levels. You could have, I suppose, a situation where the companies that came in last were, in fact, companies who discovered the drug and then along came another company that achieved a higher blood level 17 years later. Without some clinical tests, it doesn't prove anything one way or another; is that correct?

Dr. LEY. That is the position we have taken. I believe it is a sound one.

Senator NELSON. Mr. Gordon.

Mr. GORDON. Mr. Chairman, I have just one question.

Concerning the succinate form of chloramphenicol, am I correct that the intramuscular and the subcutaneous forms are effective only through the intravenous route?

Dr. LEY. We came a little later to this point in discussing the Academy recommendations. Let me say that current labeling for the succinate labeling that is currently being distributed with new succinate entering the market, limits in its indication the use of succinate through the intervenous route. The instramuscular and subcutaneous routes are not recognized on the basis of clinical data submitted to us as appropriate routes for administration of succinate form at this point in time.

Mr. GORDON. Are there any drugs on the market now of chloramphenicol which is labeled intramuscular and subcutaneous?

Dr. LEY. Material which was distributed into the market prior to the revision of the labeling still contains in the package for that product labeling which was prepared under the old set of guidelines before we received the Academy comments. The other means of getting information on succinate; namely, the Physicians' Desk Reference, and current package inserts which may be requesed from the firm by physicians, are all revised to include the intravenous route only.

Mr. GORDON. If you have a mislabeled drug on the market, you generally recall it, don't you?

Dr. LEY. This is a question that depends upon the particular circumstances. If there is an immediate and clear-cut hazard in the taking of such a drug by a patient, let's say contamination, superpotency or subpotency, the drug itself would be recalled. In this case, we do not question the drug itself.

It is the insert that accompanies the drug which has been modified in the subsequent period since this drug was put into warehouses, pharmacies, and so forth.

Mr. GORDON. What happened with the products of the smaller companies that were on the market when there was mislabeling?

Dr. LEY. That was not simply a question of mislabeling. That was a question in which our laboratory tests demonstrated that the product of the smaller companies, without exception, as nearly as we could determine, had a drug on the market, irrespective of the labeling, which was not capable of performing in a comparable fashion to the original reference product, the Parke, Davis product. That was a defective drug.

Mr. GORDON. Are you speaking of the injectables?

Dr. LEY. No, I am speaking of the oral in that case.

Mr. GORDON. We are now talking about the succinate form, the injectables.

Dr. LEY. All right.

Mr. GORDON. How were the smaller companies treated?

Dr. LEY. There is only one other firm besides Parke, Davis which is marketing succinate at this point in time. That firm's application for approval of the product was submitted—do you remember the exact date that came in?

Dr. MINCHEW. It was in, I think, late 1967.

Dr. LEY. Approximately late 1967—and approved following the receipt of the Academy recommendations on the succinate product. All labeling for that product is the new labeling revised along the lines of the Academy recommendations.

Senator NELSON. Please proceed, Doctor.

Dr. LEY. As a part of the overall review of drug efficacy being conducted for FDA by experts selected by the NAS–NRC, the Panel on Anti-Infective Drugs has been studying the various dosage forms of chloramphenicol. On August 9, 1968, we received reports from the Academy giving the results of this study. I submit copies for the record.[1] These reports showed that the Panel on Anti-Infective Drugs:

(1) Endorsed the warnings that FDA required in the labeling of chloramphenicol.

(2) Emphasized the toxicity of the antibiotic.

(3) Recommended the use of less hazardous agents where they could be expected to accomplish the desired therapeutic effect.

FDA reviewed the Academy reports and agreed with them.

We also reviewed, in the light of these reports, the labeling we had developed in May for the various chloramphenicol preparations and concluded that:

(1) The labeling of chloramphenicol capsules was consistent with the Academy's recommendations.

(2) The labeling of chloramphenicol palmitate oral suspension was consistent with the recommendations.

(3) The labeling for parenteral forms of chloramphenicol required further revision. The panel had noted the higher and preferable blood levels obtained by intravenous use, compared with intramuscular administration. It also recommended a change to the oral chloramphenicol as soon as possible since these gave better blood levels. The new labeling reflecting these recommendations, was approved on September 3, 1968. I submit a copy of the revised labeling for the record.[1]

The Academy reports also discussed the effectiveness, or probable or possible effectiveness, of chloramphenicol in treating a variety of specific conditions for which it had been promoted—such as various surgical infections, respiratory tract infections, and urinary tract infections—but none of these are listed specifically in the drug's current labeling, which is oriented to causative organisms rather than sites of infection.

Senator NELSON. Do I understand, then, that this kind of ad, which shows a bronchoscope, is now prohibited?

Dr. LEY. That ad is no longer running. We would not look with favor upon such an ad.

Senator NELSON. Was there any valid medical reason for using the

[1] See information, pp. 4407–4476.

bronchoscope associated with chloramphenicol at any time in the history of this drug?

Dr. LEY. This is difficult to say. In the 1950's perhaps this might have been a very reasonable correlation, bronchoscopy, severe pulmonary infection, lung abcess, and chloramphenicol. We have very carefully looked at this and the similar cystoscope ad, and although the text is absolutely word-for-word as stated in the package insert, we feel at this point in time that that type of visual display with that copy is inappropriate.

Senator NELSON. The drug has never been indicated, has it, for any upper respiratory diseases?

Dr. LEY. No, sir. It is not so indicated now. However, in the very early days in antibiotic therapy, chloramphenicol, tetracycline, and so forth, were widely used for many infections. That was in the late 1940's and early 1950's. Times have changed.

Senator NELSON. It is well known in the scientific community that if the ad were ever justified, it was many, many years ago, is that correct?

Dr. LEY. We believe that statement is correct.

Senator NELSON. And this ad was run on February 5, 1968?

Dr. LEY. I'm aware of that. It has since terminated.

Senator NELSON. So this ad was run many years after any conceivable claim could have been made for this kind of indication?

Dr. LEY. I would agree.

Senator NELSON. Fine.

Dr. LEY. The same orientation, I might add, will be used for other antibiotics as labeling is revised to carry out efficacy recommendations of the National Academy. The rational choice of an antibiotic should be predicated on the judgment of the prescribing physician as to the causative organism. It also should take into consideration the possible adverse effects of an antibiotic as well as its established efficacy. The current package insert for chloramphenicol, as I indicated a moment ago, illustrates this approach. The indications section is basically oriented to causative organisms and the labeling also highlights the serious adverse effects of the drug.

I know that the committee is specifically interested in the overall use of this antibiotic. After the hearing before this committee last February, the issuance of the FDA "Dear Doctor" letter, and the discontinuance of "reminder" advertising for the drug, the quantities of chloramphenicol certified dropped materially. In calendar year 1968, we certified for all dosage forms for systemic use slightly less than half as much as in 1967.

This is still, in our opinion, more than is needed for all of the approved uses of the drug and we are exploring further measures that may be in order.

Senator NELSON. Yesterday, Doctor Wehrle—I hope my memory is correct—in making some judgment about the use of chloramphenicol and using the statistics from his hospital and extrapolations from there, concluded that of the 30 million hospitalized patients annually, if the same standards for use were applied as were established for his hospital, about 2 million grams a year would be used on hospitalized patients. I am sure you are aware this was formerly Los Angeles Gen-

eral, now associated with the university. I think it is the largest hospital in the United States.

He made the further point that they had a much higher incidence of very serious illness in that hospital than the ordinary hospital had. So they would use more of the drug on the average per patient than most hospitals would.

Anyway, his conclusion was, extrapolating from their usage and the controls they have established over usage, that about 42 million grams, or slightly over, were used in 1967.

Dr. LEY. That is correct.

Senator NELSON. Then it dropped to 17, is that correct?

Dr. LEY. Our figures on certification for systemic forms of therapy—that would be parenteral and oral capsules—are approximately, within a few hundred thousand, 20 million grams certified for last year.

Senator NELSON. Versus 42 million grams for 1967?

Dr. LEY. Yes, sir.

Senator NELSON. Do you have any statistics that might be in any way comparable to Dr. Wehrle's showing how many grams of chloramphenicol would be indicated if it were confined to its proper use?

Dr. LEY. This is a very difficult question to answer, Senator Nelson. We have put considerable thought on this particular question within the past several weeks. We have certain focal points that we can be reasonably certain of. For example, the fact that there were in 1967, 396 cases of typhoid fever in this country which would be suitable candidates for therapy. There were reported—and this is just a small fraction of the total—18,120 salmonellosis severe enough to warrant the attention of physicians.

Senator NELSON. May I interrupt for just one second?

Dr. LEY. Yes, sir.

Senator NELSON. Dr. Wehrle's extrapolation from that was, assuming that 10 percent of those were reported, you get a figure then of 180,000 cases that might indicate its use. Is that, in your judgment, a reasonable estimate?

Dr. LEY. This would be a rough estimate of the nature of salmonellosis in this country that conceivably could need therapy.

We included in the labeling a strong insistence of the Cystic Fibrosis Association, a specific use of the drug in cystic fibrosis regimens. There are according to the foundation 7,000 such children and young adults who may require continuous antibiotic prophylaxis to prevent serious infection and death in this rather tragic disease.

Senator NELSON. That doesn't mean that chloramphenicol is indicated for all 7,000, does it?

Dr. LEY. Not necessarily, Senator, although the drug is preferred in many of these infants and children because of the problems of giving multiple drugs and because the risk of death due to infection is very high in this group. But if we take these figures, we have a total of 396, 180,000, and 7,000, which would be roughly 190,000, 200,000 patients.

Senator NELSON. And as I recall it, estimates were that in 1967 about 4 million people were administered chloramphenicol, is that about correct?

Dr. LEY. This is based upon the assumption of an average dose per patient and the total certification. The total certification does not nec-

essarily represent sales for the same time period, although the two are closely related over a longer time span.

Senator NELSON. I would assume that is the case, since in June of 1968, you certified zero, which we assume meant that it was still used in the United States, but that some had been left on the shelf.

Dr. LEY. That is correct. The California data indicated that on the average in the patients who have received chloramphenicol there are a very small amount of the drug was given, approximately four to four and a half grams. However, in treatment of typhoid fever and salmonellosis, a very typical total dosage for an adult would be a total of 50 grams of the drug, approximately 4 grams per day over an extended period of 10 to 12 to 14 days.

Senator NELSON. Was that a small number of people percentagewise?

Dr. LEY. That is a small number of people. In terms of salmonella infections, amounts in the order of 30 grams over a period of a week would be typical. The estimates of how many people received the drug are based, to my best knowledge—and Mr. Gordon, I think is well aware of this—on dosage levels of the order of 4 grams per patient.

Senator NELSON. Pardon me?

Dr. LEY. The estimate of the number of patients receiving the drug is made on the basis of an average dose of about 4 grams per patient.

Senator NELSON. It was my understanding 9.5.

Dr. LEY. 9.5?

Senator NELSON. I may be wrong about that. My memory was 9.5. There is a significant difference.

Mr. GORDON. The California study showed that the average dose was 9.55 grams.

Senator NELSON. I suppose none of these statistics are very firm.

Dr. LEY. They're not.

Senator NELSON. I notice some dosages are as low as 4 grams and you have cited instances of 30 and 50. In any event, a very large number of people are receiving it?

Dr. LEY. However, I would point out, Senator, that if you take a dosage for the material certified last year, for example, and if you accept for the systemic form of therapy an average dose of 10 grams, the number of patients who would be treated by that amount would be somewhat less than the 4 million figure. I would be between 1 and 2 million on the basis of last year's certification.

Senator NELSON. And the year before that?

Dr. LEY. The year before that would be close to 4 million.

Senator NELSON. Doesn't that dramatic drop indicate that it was being more widely used in 1967 for nonindicated cases than in 1968?

Dr. LEY. I cannot draw any other conclusions, Senator.

We know from discussions between our staffs, Mr. Chairman, that you are interested in a month-by-month listing of the quantities of the drug certified. I submit such a listing for the record.

Senator NELSON. It will be printed in the record.

(The information follows:)

TOTAL CHLORAMPHENICOL CAPSULES CERTIFIED FROM 1966 TO PRESENT ON A MONTH-BY-MONTH BASIS

[In grams]

Month	1966	1967	1968	1969
January	3,323,275	4,566,323.0	1,045,900.0	248,575
February	2,817,750	4,954,775.0	2,855,325.0	
March	2,064,525	5,109,650.5	256,900.0	
April	2,329,800	3,938,725.0	513,475.0	
May	2,437,920	2,120,100.0	259,950.0	
June	2,050,675	2,371,955.0	0	
July	1,024,975	2,599,725.0	[1] 1,702,250.0	
August	1,797,800	4,206,550.0	2,618,927.5	
September	2,049,925	2,026,219.0	291,150.0	
October	2,704,875	[2] 1,836,925.0	[3] 1,992,466.0	
November	3,371,675	1,779,900.0	1,927,561.0	
December	[4] 5,805,702	0	1,023,307.0	
Annual total	31,778,897	35,510,847.5	14,487,211.5	

[1] Includes certification of generic chloramphenicol for Rachelle Laboratories.
[2] Certification of generic chloramphenicol discontinued because of low blood levels.
[3] Includes certification of generic chloramphenicol for McKessen Laboratories.
[4] This includes initial certification of a total of 3,441,852 grams of chloramphenicol from firms other than Parke, Davis.

TOTAL CHLORAMPHENICOL INJECTIONS CERTIFIED FROM 1966 TO PRESENT, ON A MONTH-BY-MONTH BASIS

[In grams]

Month	1966	1967	1968	1969
January	502,503	796,456.5	385,635	0
February	430,307	651,646.0	602,619	
March	36,475	562,053.0	525,680	
April	1,981,253	894,380.0	191,116	
May	1,321,105	620,122.0	341,655	
June	934,244	748,484.0	[1]	
July	215,752	48,809.0	[1]	
August	842,420	646,709.0	125,707	
September	715,779	753,732.0	[2] 275,328	
October	728,666	533,007.0	92,883	
November	1,534,408	583,898.0	319,686	
December	1,325,461	481,300.0	98,990	
Annual total	10,568,373	7,320,596.5	2,959,299	

[1] Certification of chloramphenicol injection temporarily discontinued while FDA evaluated blood-level studies for drug.
[2] Includes initial certification of injectable of chloramphenicol from firms other than Parke, Davis.

TOTAL CHLORAMPHENICOL ORAL SUSPENSION CERTIFIED FROM 1966 TO PRESENT, ON A MONTH-BY-MONTH BASIS

[In grams]

Month	1966	1967	1968	1969
January	265,913	560,754.0	674,721.0	0
February	688,969	181,980.0	0	
March	87,195	361,434.4	271,162.5	
April	362,633	628,000.0	131,310.0	
May	270,233	0	0	
June	769,466	682,066.3	0	
July	88,875	274,841.0	272,216.0	
August	378,583	0	0	
September	0	80,145.0	0	
October	891,126	0	0	
November	451,450	0	0	
December	454,680	0	266,640.0	
Annual total	4,709,123	2,769,220.7	1,616,049.5	

TOTAL CHLORAMPHENICOL OPTHALMIC AND OTIC VIALS CERTIFIED FROM 1966 TO PRESENT, ON A MONTH-BY-MONTH BASIS

[In grams]

Month	1966	1967	1968	1969
January	1,833	1,796.2	1,023.7	3,431
February	1,931	2,028.5	1,735.5	
March	2,591	2,039.8	2,540.3	
April	1,806	6,530.0	4,906.9	
May	4,971	2,292.0	2,760.9	
June	1,102	1,215.5	678.3	
July	1,448	1,540.0	1,842.9	
August	6,542	4,105.7	1,327.0	
September	2,513	809.0	704.7	
October	1,099	1,936.0	666.0	
November	1,152	2,104.0	1,507.0	
December	3,092	1,313.0	4,110.0	
Annual total	30,080	27,709.7	23,803.2	

TOTAL CHLORAMPHENICOL OINTMENT CERTIFIED FROM 1966 TO PRESENT, A MONTH-BY-MONTH BASIS

[In grams]

Month	1966	1967	1968	1969
January	1,378	3,328.9	18,409.8	11,334
February	9,244	1,639.0	897.0	
March	5,265	8,463.6	9,239.9	
April	3,440	3,409.2	6,823.6	
May	7,093	4,687.6	5,904.9	
June	6,977	9,440.3	6,912.4	
July	6,385	15,583.5	13,714.0	
August	6,760	17,008.8	14,657.0	
September	3,511	22,605.5	11,097.5	
October	2,625	11,540.0	5,894.0	
November	10,800	12,856.0	875.0	
December	2,603	18,259.0	5,711.0	
Annual total	66,081	128,821.4	100,136.1	

Dr. LEY. In January 1969, we decided to again convene our ad hoc committee on chloramphenicol. It had been approximately a year since this advisory group had last met. We wanted the committee's evaluation of the steps taken in regard to chloramphenicol during this time, as well as its consideration of additional measures for the future. The meeting took place on February 20, 1969.

After reviewing the certification figures for 1968, the committee concluded that the publicity concerning chloramphenicol had had significant impact upon its use. The committee took note of the increase in the number of capsules certified in the last quarter of 1968, but noted also the sharp drop that occurred in January of 1969.

Senator NELSON. May I ask a question at this points, Dr. Ley?

Dr. LEY. Certainly.

Senator NELSON. There was, as you know, a dramatic increase in the use of capsules, chloramphenicol capsules, in the last 3 months of 1968 over the last 3 months of 1967. Our statistics from your agency are that it increased from 3.6 million grams in the last 3 months of 1967 to 4.9 million grams in the last 3 months of 1968, which is a 36.7 percent increase. Are thse figures correct?

Dr. LEY. I believe the figures are correct, Senator, but there is an additional factor which must be considered in making such a comparison. This is noted in footnotes with the material which we have

submitted for the record, and I believe the same data was also provided at an earlier request from a member of your staff.

In 1967, beginning on the month of October, certification of generic chloramphenicol was discontinued because of the low blood level that I previously mentioned, and during the month of December no chloramphenicol at all was certified for any manufacturer until we resolved this question of equivalency among the oral products.

Senator NELSON. I had forgotten that. I do recall now. How does the last 3 months of 1968 compare with the last 3 months of 1966.

Dr. LEY. They were considerably lower in 1968 than in 1966. I would have to do a quick addition here. It is approximately 3 million grams for 1968 and for the last 3 months of 1966—then this is not a good comparison because in the month of December of 1966 the generic manufacturers appeared on the scene—but the total for the months of October and November of 1966 is 6 million grams for those 2 months alone without the generic.

Mr. GORDON. May I interrupt here?

Dr. LEY. Certainly.

Mr. GORDON. What percentage of the total did the small manufacturers contribute? As I understand it, it is a very, very small percentage

Dr. LEY. It was a small proportion for the entire period. There were certain months immediately after the small manufacturers began to apply for certification in which they represented a significant part of certification for a single month. I think the significant point here is that if we go so far as to exclude the month of December altogether, the total for October and November of 1966 is 6 million grams. For October, November, and December of 1968, it is 3 million grams. I think that the comparison of 1966 and 1968 again demonstrates—four, I'm sorry.

Senator NELSON. 4.9.

Dr. LEY. Four. I'm sorry.

Senator NELSON. 4.9, isn't it?

Dr. LEY. Right.

Mr. GORDON. And you think that the small companies made up that 36.7 percent——

Dr. LEY. We have more detailed information on the graphic——

Senator NELSON. Are you saying that nobody manufactured in December of last year?

Dr. LEY. There were no certifications of chloramphenicol in the month of December 1967.

Senator NELSON. For any company?

Dr. LEY. Oral capsules.

Senator NELSON. Oral?

Dr. LEY. Oral capsules.

Senator NELSON. How much in injectables?

Dr. LEY. Half a million grams, roughly. Four hundred eighty-one thousand grams of injectables in that month.

Senator NELSON. This had nothing to do with FDA. It was just a question of Parke, Davis not submitting any batches for testing in December for capsules.

Dr. LEY. I'm afraid, Senator, it did have something to do with the FDA. Until we reached our eventual decision on the 20th of December, we chose not to certify any that month.

Senator NELSON. I see. That was action of the FDA then?

Dr. LEY. That is right.

Senator NELSON. So then I would guess that you have to conclude from this that you just about have to measure year versus year rather than particular months, although at certain times of the year, there is a rise in the number of certifications which I assume is associated with the incidence of the cases for which it may be indicated; is that correct?

Dr. LEY. Yes.

Senator NELSON. Please go ahead.

Dr. LEY. The committee saw no need for any further labeling changes in the warning section or in the indications for use of the drug. A number of other suggestions which had been made in the past for controlling the use of this antibiotic were also considered by the committee. This includes such steps as restricting the use of the drug to hospitals, requiring a procedure of countersigning prescriptions, or licensing the drug as a narcotic. The committee was unanimously opposed to such restrictions. Neither did the committee consider it advisable to add warning information on the labeling provided the patient. The commitee did, however, recommend the exploration of further means of emphasizing to the medical community the proper uses for this drug and its possible adverse effects.

On the basis of the committee's recommendations and our own consideration of this matter, we have started, or will promptly initiate the following actions:

1. We have asked the American Medical Association for assistance in communicating at the county medical society level information as to the misuse of chloramphenicol, the limited areas of its proper usefulness, and the grave hazards associated with the drug.

2. The AMA News has agreed to give further publicity to the chloramphenicol problem in an early issue.

3. Both the American Hospital Association and the Joint Commission on Accreditation of Hospitals will be asked to support and encourage the broader use of pharmacy and therapeutic committees in hospitals, a point that Dr. Wehrle made in his testimony to you yesterday.

4. The AMA Council on Drugs has proposed that these committees exercise more effective control over drug use and improve the reporting of adverse reactions. We intend to fully support the council in this recommendation.

5. We have received the Parke, Davis promotional material, noting the discontinuance not only of the "reminder" ads, but also of a group of ads headlined to promote the drug for respiratory and urinary infections, which we discussed here earlier.

6. We have checked the detailing piece used by Parke, Davis in the promotion of the drug and it is in conformity with the package insert.

In summary, Mr. Chairman, I believe we have made considerable progress in dealing with an exceedingly difficult problem. I intend to make every possible effort in the months ahead to assure that this progress continues.

I thank you for your time and attention, and if there are any questions, I will be happy to answer them.

Senator NELSON. The only statistics we have as of now showing the reduction in the use of the drug are statistics of 1967 versus 1968. If I interpret what you have said correctly, it still is the judgment of the FDA, or of you, that it is still more widely prescribed than it should be; is that correct?

Dr. LEY. This is my belief Senator.

Senator NELSON. Now supposing next year—as the president of Parke, Davis predicted last June, that once the hearings were forgotten, the use would rise again—suppose that occurs, what steps does the FDA intend to take?

Dr. LEY. At that point in time, I would be forced to reconsider this whole matter. I wish in the coming year to place very strong pressures on additional means of communicating the facts relating to the adverse reactions to chloramphenicol to the people who prescribe the drug. And I hope to be able to elicit the help of such groups as the AMA in this effort.

Assuming that this does take place, fine. If it is not possible to obtain assistance from this group, I think we in FDA are going to have to consider our own means of getting significant information of this sort before the medical profession—possibly including still another letter.

But I would say that we should give the steps I've outlined here a trial to see what they are capable of doing, because I do not believe these steps have ever been taken before.

Senator NELSON. I suppose one of the problems here is, or has been from the beginning, to actually bring this matter of the indicated uses directly and forcefully to the attention of the prescribing physician in such a way that he ends up being persuaded.

We had some testimony here on one occasion from a very fine doctor who knew what chloramphenicol was used for but did not realize at the moment that the National Academy of Sciences had revised the indicated uses. In other words, there were substitutes, and so forth, and he wasn't quite aware of that. I think this is part of the problem that one might use this over a period of years. We have had some testimony on its use among the pediatricians to the effect that, because of the historical factor, they know about the drug and they use it. Then the indicated uses change for various reasons and that fact isn't brought home to them. How are you going to bring it home to the physicians of the country that the National Academy of Sciences now says it is not "the" drug of choice for any condition? How do you get that home to them?

Dr. LEY. I think it can be covered in two separate ways; each will have its impact, and yet with both. I cannot assure you that every physician will receive the message. We have plans scheduling an interview between the AMA News and myself in the near future. I wish to feature in that interview not only the types of adverse reactions which have been reported to us over the past several years, but also the appropriate indications for use. And I think we can even support the estimates that have been given by several previous people who have appeared before you, that as nearly as we can tell the drug is appropriately called for perhaps in roughly 10 percent of the patients who receive it.

Senator NELSON. In your judgment that statistic still stands?

Dr. LEY. That statistic is as good an estimate as we can make, and I believe your prior witnesses here could get no better statistic. We have not been able to find anything closer ourselves.

Senator NELSON. If I understand you correctly, about 90 percent of the people receiving chloramphenicol are getting it for nonindicated cases. Is that what you are saying?

Dr. LEY. Nonindicated cases under present labeling, that is correct.

Senator NELSON. And that is in 1968 as well as 1967?

Dr. LEY. It is too early, Senator, to really make this judgment. The course of aplastic anemia is a protracted one. We would normally not receive the report until the patient's death which may be a year after the initiation in the fatal cases.

Senator NELSON. Let me understand this. The question of whether or not somebody died from aplastic anemia may not have anything to do with others who received it for an indicated case? You might receive it for a sore throat or infected gums or acne, without getting aplastic anemia, and it is still prescribed for a nonindicated case?

Dr. LEY. That is correct. Yet, we have to enter the data system at some point and the only point available to us to enter it is the terms of the adverse reactions reported to us. In other words, we see the adverse reaction reports. In looking over the adverse reaction reports, it is our best judgment at this point in time that about 10 percent of the patients reported as having reactions of a whole spectrum of types receive the drug on appropriate indications. The indications are also outlined telegraphically in the reports.

Now, if we are to see any change with time in the incidence of aplastic anemia as a result of your committee hearings last year and the increased interest this year, it will take us at least a year because of the delay in reporting such tests to have any evidence statistically of a change in incidence of aplastic anemia. That was the point I was trying to make earlier.

Senator NELSON. Of course, the only study that has been called to the attention of the committee is the California study which heaven knows is skimpy enough when you are dealing with a factor of 10 deaths and trying to extrapolate from them. The other factor, of course, is that literally tens of thousands of people may receive chloramphenicol for a nonindicated case, and get no reaction at all, and that statistic is nowhere to be found. I don't suppose it would be possible.

Dr. LEY. Dr. Best in his review several years ago of serious side reactions, I believe, arrived at the same figure of appropriate usage of 10 percent, 10 percent of the patients who were reported to him as having reactions had been given the product on the basis of what would be an acceptable indication.

Senator NELSON. I was thinking it was 1 percent, but I believe it was Dr. Weston, the pathologist, who thought that 99 percent received it for nonindicated cases. And as I recall his testimony from a year ago, he had never seen a case in which death resulted from aplastic anemia in which the drug had been given for an indicated case, not one.

Well, now, what concerns me is getting the information out. It is perfectly understandable that doctors become acquainted with the drug at some period in history—there are thousands of drugs—and they may not have reason or have gotten around to keeping up on the changes for its use.

Now, the National Academy of Sciences has made their report. As I understand it, FDA agrees with that report.

Dr. LEY. We have not only agreed, but we have taken definite action with reference to this product.

Senator NELSON. The literature will certainly carry references about this. There will be some news here and there in the medical journals. But the fact is one reason for advertising is to promote the drug. General Motors made a public announcement calling back 4,900,000 cars on the ground that it is a public hazard. This is a matter of public health. Shouldn't Parke, Davis be required now to say it is a different ball game; there are other drugs, this is not the indicated drug, the drug of choice in any disease, and run ads in the medical journals saying that? This is what General Motors did. And we all agree, all the experts agree, and you do, that it appears that 90 percent of the people are getting this drug for nonindicated cases. It is no greater tragedy to die from an automobile accident than from this drug unnecessarily. General Motors has made the front page announcement. That is what the law requires. Why shouldn't Parke, Davis be required now to advertise what the fact is?

For whatever purpose the ads were valid in the past, they aren't now, and it is not the drug of choice for any disease and it ought to be called to the attention of the medical profession by ads in all the journals. Why shouldn't that be done? We aren't willing to restrict their practice, saying they can only use it in the hospitals, but a lot of doctors should be told about this. Well, you aren't doing that. Just make them tell the truth. What is wrong with that?

Dr. LEY. We have essentially through our own letters last year said, look, to the physician recipient, the indications of this product have changed. It is a different ball game. Parke, Davis has not said this. And I'd have to turn to the General Counsel to see if there is any way that FDA could be instrumental in arriving at such a statement from Parke, Davis. I have doubts whether we could.

Mr. GOODRICH. Well, I think we have required them to do that in this very ad. If you will read the box warning, it does tell them that the ball game has changed, that the indications have changed, that the warnings are stronger, and we have, by telling them to discontinue the reminder ads, required that this message go with all promotional material.

Now, we do not have the specific authority of the Automobile Safety Act to require notification of defects, but this went to every physician in the United States and keeps going in every ad used, in the detailing piece and in the Physicians' Desk Reference. So I believe we've done more than just say, just modified the labeling in terms of indications. The indications were written in a very special way in a box form, and the side effects and hazards were emphasized both in wording and in outlay and display.

Senator NELSON. Well, we are talking, of course, about two different things: One is the package insert, that aspect of the fine print in the ad that you require, and the other is to counteract the history of a whole page stating, "when it counts."

Mr. GOODRICH. That was the purpose of the letter to every physician in the United States, and rather than have Parke, Davis send it out we sent it out. We made sure it went not only to every physician but

to every hospital administrator, and we have followed that up by following the promotion to make sure that those defects which we have outlined in the statement did not appear, such as that cystoscope and the headline series on respiratory infections, serious urinary tract infections, that now the message on chloramphenicol be oriented to its use only on the basis of an identified causative organism, not to be used where another less potentially hazardous product is available, and not to be used except in these specific indicated cases.

This is the kind of message I think you are talking about that should be sent to the physician, and since we send it ourselves, first-class mail, with a notice on the front of the envelope, we think we communicated that to the physicians. They need to be told again, and as Dr. Ley's statement says, we are planning to try to communicate with them through the AMA at their local county medical society meetings to see if we can't emphasize this, too.

Senator NELSON. But the test is the result?

Mr. GOODRICH. Right.

Senator NELSON. The testimony still is that 90 percent of the people receive it for a nonindicated case. It really wouldn't have done any good for General Motors to have announced that a whole lot of these cars have this defect, including a carburator that might induce lethal gases from the exhaust into the car, had a story on that, and that is all. It would have about the same effect as what the FDA is saying to the doctors. Some people would notice it and do something about it and most would not. And most apparently haven't done aything about this.

Mr. GOODRICH. Well, there's been a substantial reduction in the use of the drug. I think we have started by agreeing with that.

Senator NELSON. Correct.

Mr. GOODRICH. And our point was that while some progress, some very good progress had been made, much remains to be done, and we've suggested a program of going at it.

Senator NELSON. What I am getting at is, whether or not it is adequate.

Now, it is a fact that it is no longer the drug of choice in any case. At one time it was the drug of choice in certain circumstances. And millions and millions of dollars were spent to demonstrate that it was the drug of choice. Apparently as a consequence of this kind of promotion, it was much more widely used than its indications warranted. This is a matter of public health. It is a matter of life and death to anybody who gets it for a nonindicated case and dies.

Why shouldn't Parke, Davis be told that they should now run an ad in all journals saying "here is what the National Academy of Sciences now says—it is not the drug of choice for any disease, and here is specifically how to use it?" They got to the doctors in promoting it. Why shouldn't they get to the doctors in depromoting it, is my question?

Mr. GOODRICH. That was the point of the statements in the indications sections: "Chloromycetin must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated."

Senator NELSON. Even the package insert doesn't tell the case. Why shouldn't the package insert say right at the top, this is no longer the

drug of choice for any disease in this country? It doesn't say that. I know what happens. I have had doctors say, "who reads these package inserts!" In the first place, they don't see them. They all go to the pharmacists. They see them if they get a free drug. So they really aren't seeing the ad anyway but they do see that ad in the medical journals.

So, what you are really saying is we've gotten reasonably tough about the package insert which never goes to the doctor who prescribes it. I don't think this is fair to the consuming American public.

Mr. GOODRICH. We have put into the record a copy of the package insert which is a detailing piece that goes with the free samples. We've also put into the record the ads. Now, if that is not satisfactory, then it is not satisfactory, but that is what's been done.

Senator NELSON. Well, I don't think it is satisfactory because I think we have to go by the test of results. All the distinguished witnesses, including Dr. Goddard and Dr. Ley, and all the other experts who have testified have said in public that about 90 percent of the people are getting this drug for nonindicated cases. And Dr. Goddard sat in that witness chair and said "I am at wits end," to quote him precisely, "on how to stop the use of this drug." Well, I'm not at my wits end. I'll give you some suggestions.

I think they ought to have to run an ad saying this is what it is now indicated for. I would think in the package insert, which most physicians don't really see, it should say right at the top in a box, quote:

> Not the drug of choice in any case. Here is what it is to be used for: Never to be used except in a case where the disease is serious; never to be used except when no other antibiotic will do the job, and never to be used unless the organism involved is susceptible to chloramphenicol.

Not a whole lot of print, just concise and to the point. And then in the ad that goes in the paper, I would think you ought to print at the top, exactly what I've said. You know, if we had accomplished our purpose with what we had done a year ago, what Dr. Goddard did, I think there would be no argument, but we haven't. We've come a long way. There is no question about that. We have reduced the usage from 42 million grams to 20, but we are talking about people who are going to unnecessarily die. And I think that we ought to tell every doctor in America, in ads and package inserts, that here is the present status of the recommended use of the drug.

Are you, for example, going to send out the "Dear Doctor" letter saying here is what the National Academy of Sciences says—not the drug of choice?

Dr. LEY. This is a perfectly satisfactory option for us to consider, and I will weigh this very carefully. We have, Senator, also embarked on another effort which is broader in scope than this but very similar.

Early this month, we cosponsored a conference with the NIH on the continuing education of physicians in which Dr. Dowling chose chloramphenicol as a beautiful example of the difficulty in updating the physicians' knowledge on drugs. His remarks were very similar to your own a few moments ago. He pointed out that there are a variety of influences operating on the physician. None of these are perfect. Public interest, newspaper publicity, to some extent the labeling, all are important in molding his reaction. However, the response which he indicated here is attractive in terms of the decrease in certification

over the past year, is one which must be continually pressed for by new means and more effective means of communication between us and the community at large.

Senator NELSON. Well, now, I hope you will consider a "Dear Doctor" letter. I know that there will be those who get it for headaches and acne and flu and die from it, but these people are entitled to the most vigorous protection possible.

Then it seems to me the advertising should contain what the National Academy of Sciences now says and with which the FDA agrees—this ought to be boxed in a very prominent place. I know enough from political advertising about how to cover up the warts and exaggerate the good qualities, but it would seem to me the FDA ought to require a very prominent place in the whole medical journal advertising. This is new. It is not the drug of choice.

Now, why shouldn't that be considered? You can approve the advertising. All you are doing is saying tell the doctors what the National Academy of Sciences says.

Dr. LEY. This is a possibility to consider that has wider ramifications than merely this product. There are at present, and will soon be many more, examples of drugs whose indications are being drastically revised by the Academy's action and review. I think that the problem of communication of such changes of appropriate indication for the older class of drugs marketed between 1938 and 1962 is a very important problem for us to consider. How may we get this information, not just for chloramphenicol, but for the entire spectrum of drugs marketed between 1938 and 1962 effectively before the physician population of this country?

It is a difficult problem, one that we have been looking at and exploring possible avenues of approach. We do not have an answer as of this time.

Senator NELSON. I am sure it is a difficult problem. I'm sure you know how much more difficult a problem it is than this committee does. But I am concerned that we vigorously pursue it. And it does seem to me that the medical profession is entitled now to be told what the National Academy says. I am not critical—nobody conceivably could be critical of a practicing physician who doesn't know what the National Academy of Sciences now says. How is he going to know that? And the continuing education problem is certainly a tough one. I think the friends I have in the medical profession are very conscientious people. Some have a complicated, difficult problem to keep up on all these matters. But it seems to me in a case like this the situation is clear, though the FDA has done a lot, there is more it ought to do in terms of the advertising and the packaging insert and notifying the doctors, otherwise I think we'll have the tragedy of a rising use of the drug again. We will have more at the end of next year and we will still be talking about it at the end of next year.

I wonder if perhaps you would take a look, when it is printed, at Dr. Wehrle's testimony, in which he made a suggestion about trying to find out just where geographically chloramphenicol is being used, for what purpose, and what doctors are prescribing it. He thought that you could perhaps set up some sample areas and do a survey of how much is being used in this area and what are the reasons for its use.

I don't know whether you would consider that a useful enterprise or not, but it might very well be. I don't know whether you have the facilities to do that, but perhaps they may be available in NIH or HEW. I believe it would be valuable because nobody seems to be able to tell us, you know, what the variations are, nor why.

Dr. Wehrle raised the question yesterday, for example, whether or not chloramphenicol was prescribed widely or not at all or in fair amount during the flu epidemic? Does anybody know that?

Dr. LEY. No. This is a question we asked our consultants and they had no firm answer at this time.

Senator NELSON. I wish you would take a look at it. It may well be that you could get some helpful information.

It isn't indicated for influenza, is it?

Dr. LEY. No, sir, it would not be indicated for influenza under any condition.

Mr. GORDON. Coming back to the Reader's Digest of February 1968, you stated the ad recommended the drug for uses that were not warranted and seriously understated the hazards, side effects, and contraindications. Could anything have been done along these lines to make the Reader's Digest perhaps run a remedial ad?

Dr. LEY. This is a question I would like to turn over to our General Counsel.

Mr. GOODRICH. We have no direct authority to require any type of remedial ad. We have required some by persuasion, if you might call it that, where we had a choice of taking action against the company or its drug, but we would not have authority over Reader's Digest at all.

Mr. GORDON. How about moral or ethical authority? Couldn't you, for example, approach the Reader's Digest and say, look, this is a false and misleading ad. How about correcting it for the sake of the public welfare?

Mr. GOODRICH. Sure, that could be done.

Mr. GORDON. That wasn't done, though, was it?

Mr. GOODRICH. That was not.

Mr. GORDON. Thank you.

Senator NELSON. I want to thank you, Dr. Ley, for your very valuable testimony. I wouldn't want you to feel that because we might have had some differences that I do not think the FDA in the past—since Dr. Goddard's administration and yours—hasn't been doing a superior job.

Dr. LEY. Thank you, very much.

Senator NELSON. Thank you, Doctor.

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

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

DRUG EFFICACY STUDY

Form A

(To be submitted in duplicate by applicant)

1. NDA Number 6D307 (9021H) 2. Date Originally Approved December 3, 1953 3. Rx ☒ OTC ☐

4. Brand Name Chloromycetin Solution

5. Applicant's Name Parke, Davis & Company

and Address Joseph Campau at the River; Detroit, Michigan

6. Quantitative Formula

Established (Non-Proprietary) Name of Active Ingredients (in order shown on label)	Amount (per tablet, per ml., etc.)
Chloramphenicol	0.5 Gm./2 cc. vial

7. Dosage Form (tablets, etc.) ampoule

8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) parenteral

9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.

12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).

Panel on Anti-Infective Drugs (III)

INDICATIONS

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

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

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

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

III. Typhoid fever.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

IV. Other salmonelloses.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

V. Urinary tract infections.

EVALUATION: Effective, but . . . .

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

are often susceptible only to chloramphenicol.

DOCUMENTATION:

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

VI. Surgical infections: postoperative wound infections.

EVALUATION: Possibly effective.

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

DOCUMENTATION: Most favorable report is reference 1 (Altemeier).

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

VII. Surgical infections: cellulitis.

EVALUATION: Possibly effective.

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

DOCUMENTATION: Same as for Indication VI.

VIII. Surgical infections: infected sinus tract.

EVALUATION: Possibly effective.

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

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

DOCUMENTATION:

1. Altemeier, W.A., and W.R. Culbertson. Chloramphenicol (chloromyceti and aureomycin in surgical infections. J.A.M.A. 145:449-457, 1951.
2. Bloomer, W.E., S. Giammona, G.E. Lindskog, and R.E. Cooke. Staphyloccal pneumonia and empyema in infancy. J. Thorac. Surg. 30: 265-274, 1955.
3. Carmichael, D.B., Jr. Fatal bacterial endocarditis due to staphylococcus aureus. U.S. Armed Forces Med. J. 4:287-294, 1953.
4. Hausmann, W., and A.J Karlish. Staphyloccal pneumonia in adults. Brit. Med. J. 2:845-847, 1956.
5. Kanof, A., B. Epstein, B. Kramer, and I. Mauss. Staphylococcal pneumonia and empyema. Pediatrics 11:385-392, 1953.
6. Lepper, M.H., P. Tillman, and R. Devetsky. Patterns of transmission of staphylococci. Ann. N.Y. Acad. Sci. 128: 404-427, 1965.
7. Martin, C.M., C.M. Kunin, L.S. Gottlieb, and M. Finland. Asian influenza A in Boston, 1957-58. II. Severe staphylococcal pneumonia complicating influenza. A.M.A. Arch. Intern. Med. 103: 532-542, 1959.
8. Wallman, I.S., R.C. Godfrey, and J.R.H. Watson. Staphylococcal pneumonia in infancy. Brit. Med. J. 2:1423-1427, 1955.
9. Woodward, T.E., and C.L. Wisseman, Jr. Chloromycetin, pp. 122-124. Antibiotics Monographs No. 8. New York: Medical Encyclopedia Inc., 1958.

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

EVALUATION: Possibly effective.

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

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

DOCUMENTATION: Same as for Indication VIII.

X. Respiratory tract infections.

EVALUATION: Possibly effective.

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

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

DOCUMENTATION:

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

XI. Meningeal infections.

EVALUATION: Probably effective.

COMMENTS: The three most common causes of meningitis are the meningococci, pneumococci, and Hemophilus influenzae. All are susceptible to chloramphenicol, as are many staphylococci and the gram-negative aerobic rods that often infect newborns. Moreover, it is true that the drug does get into the spinal fluid well. As a drug of choice

for empiric use, however, it is probably not first, because it is likely to be less effective in pneumococcal disease than is penicillin. Although many believe it is first choice in Hemophilus infections, tetracycline is probably as good and ampicillin is, too. It is likely that this claim (drug of choice in H. influenzae meningitis) is no longer justified. In menigitis of the newborn kanamycin is preferred as the drug of choice for empiric treatment. In older patients, when a diagnosis has been made and the organisms shown to be more susceptible to chloramphenicol than to other agents, it may be the drug of choice. As indicated, in the insert, initial treatment should be parenterally administered.

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

DOCUMENTATION:

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

XII. Brucellosis.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

XIII. Bartonellosis.

EVALUATION: Probably effective.

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

DOCUMENTATION:

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

XIV. Relapsing fever.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

XV. Granuloma inguinale.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

XVI. Plague.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

XVII. Ornithosis.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

GENERAL COMMENTS

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

Tissue distribution appears to be favorable. The distribution into the cerebrospinal fluid is good, as pointed out in the insert, and is reasonably good into brain tissue, which is important when cerebrit accompanies meningitis. The distribution into bile is not as high as that of the tetracyclines and some of the penicillins. The very small amount in the feces is of interest as is the fact that the fecal content is higher when the palmitate has been given.

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

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

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

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

It may be less ambiguous if there were a specific package insert that eliminated the references to the succinate and the intramuscular form. The lag in the use of the succinate is probably of little clinical importance, but if the insert were designed specifically for this form of the drug there could be little difficulty in making clear that there is a little lag in hydrolysis with a somewhat lower level of antibacterial activity at 15 min. Only the paragraph on page 3 (concerning ampoule No. 258) is needed in this insert.

Approved by Wm Kerr
Chairman JHW

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

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

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

DRUG EFFICACY STUDY

Form A
(To be submitted in duplicate by applicant)

1. NDA Number 6D315 (90142) 2. Date Originally Approved February 20, 1959 3. Rx ☒ OTC ☐

4. Brand Name Chloromycetin Sodium Succinate Steri-Vial, 1 Gm.

5. Applicant's Name Parke, Davis & Company

and Address Joseph Campau at the River; Detroit, Michigan

6. Quantitative Formula

Established (Non-Proprietary) Name of Active Ingredients (in order shown on label)	Amount (per tablet, per ml., etc.)
Chloramphenicol Sodium Succinate	1 Gm. base/vial

7. Dosage Form (tablets, etc.) steri-vial

8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) parenteral

9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.

12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).

Panel on Anti-Infective Drugs (III)

INDICATIONS

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

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

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

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

III. Typhoid fever.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

IV. Other salmonelloses.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

V. Urinary tract infections.

EVALUATION: Effective, but . . . .

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

are often susceptible only to chloramphenicol.

DOCUMENTATION:

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

VI. Surgical infections: postoperative wound infections.

EVALUATION: Possibly effective.

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

DOCUMENTATION: Most favorable report is reference 1 (Altemeier).

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

VII. Surgical infections: cellulitis.

EVALUATION: Possibly effective.

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

DOCUMENTATION: Same as for Indication VI.

VIII. Surgical infections: infected sinus tract.

EVALUATION: Possibly effective.

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

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

DOCUMENTATION:

1. Altemeier, W.A., and W.R. Culbertson. Chloramphenicol (chloromycetin) and aureomycin in surgical infections. J.A.M.A. 145:449-457, 1951.
2. Bloomer, W.E., S. Giammona, G.E. Lindskog, and R.E. Cooke. Staphyloccal pneumonia and empyema in infancy. J. Thorac. Surg. 30: 265-274, 1955.
3. Carmichael, D.B., Jr. Fatal bacterial endocarditis due to staphylococcus aureus. U.S. Armed Forces Med. J. 4:287-294, 1953.
4. Hausmann, W., and A.J Karlish. Staphyloccal pneumonia in adults. Brit. Med. J. 2:845-847, 1956.
5. Kanof, A., B. Epstein, B. Kramer, and I. Mauss. Staphylococcal pneumonia and empyema. Pediatrics 11:385-392, 1953.
6. Lepper, M.H., P. Tillman, and R. Devetsky. Patterns of transmission of staphylococci. Ann. N.Y. Acad. Sci. 128: 404-427, 1965.
7. Martin, C.M., C.M. Kunin, L.S. Gottlieb, and M. Finland. Asian influenza A in Boston, 1957-58. II. Severe staphylococcal pneumonia complicating influenza. A.M.A. Arch. Intern. Med. 103: 532-542, 1959.
8. Wallman, I.S., R.C. Godfrey, and J.R.H. Watson. Staphylococcal pneumonia in infancy. Brit. Med. J. 2:1423-1427, 1955.
9. Woodward, T.E., and C.L. Wisseman, Jr. Chloromycetin, pp. 122-124. Antibiotics Monographs No. 8. New York: Medical Encyclopedia, Inc., 1958.

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

EVALUATION: Possibly effective.

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

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

DOCUMENTATION: Same as for Indication VIII.

X. Respiratory tract infections.

EVALUATION: Possibly effective.

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

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

DOCUMENTATION:

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

XI. Meningeal infections.

EVALUATION: Probably effective.

COMMENTS: The three most common causes of meningitis are the meningococci, pneumococci, and Hemophilus influenzae. All are susceptible to chloramphenicol, as are many staphylococci and the gram-negative aerobic rods that often infect newborns. Moreover, it is true that the drug does get into the spinal fluid well. As a drug of choice

for empiric use, however, it is probably not first, because it is likely to be less effective in pneumococcal disease than is penicillin. Although many believe it is first choice in Hemophilus infections, tetracycline is probably as good and ampicillin is, too. It is likely that this claim (drug of choice in H. influenzae meningitis) is no longer justified. In menigitis of the newborn kanamycin is preferred as the drug of choice for empiric treatment. In older patients, when a diagnosis has been made and the organisms shown to be more susceptible to chloramphenicol than to other agents, it may be the drug of choice. As indicated, in the insert, initial treatment should be parenterally administered.

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

DOCUMENTATION:

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

XII. Brucellosis.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

III. Bartonellosis.

EVALUATION: Probably effective.

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

DOCUMENTATION:

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

XIV. Relapsing fever.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

XV. Granuloma inguinale.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

XVI. Plague.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

XVII. Ornithosis.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

GENERAL COMMENTS

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

Tissue distribution appears to be favorable. The distribution into the cerebrospinal fluid is good, as pointed out in the insert, and is reasonably good into brain tissue, which is important when cerebritis accompanies meningitis. The distribution into bile is not as high as that of the tetracyclines and some of the penicillins. The very small amount in the feces is of interest as is the fact that the fecal content is higher when the palmitate has been given.

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

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

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

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

It would be less ambiguous if there were a specific package insert that eliminated the references to the buffered I.V. and the intramuscular form. The delay in achieving peak blood levels in the use of the succinate form is probably of little clinical importance, but if the insert were designed specifically for this form of the drug there could be little difficulty in making it clear that there is a little lag in hydrolysis with a somewhat lower level of antibacterial activity at 15 min.

Approved by Wm Kerr
Chairman JHW

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

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

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

DRUG EFFICACY STUDY

Form A
(To be submitted in duplicate by applicant)

1. NDA Number 6D306 M(90136) 2. Date Originally Approved October 5, 1951 3. Rx ☒ OTC ☐

4. Brand Name Chloromycetin Palmitate Oral Suspension

5. Applicant's Name Parke, Davis & Company

and Address Joseph Campau at the River; Detroit, Michigan

6. Quantitative Formula

ablished (Non-Proprietary) Name of Active Ingredients (in order shown on label)	Amount (per tablet, per ml., etc.)
hloramphenicol Palmitate	125 mg./4 cc.

Dosage Form (tablets, etc.) suspension

Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) oral

Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.

In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).

Panel on Anti-Infective Drugs (III)

INDICATIONS

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

EVALUATION: Possibly effective.

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

DOCUMENTATION:

1. Bloomer, W.E., S. Giammona, G.E. Lindskog, and R.E. Cooke. Staphylococcal pneumonia and empyema in infancy. J. Thorac. Surg. 30:265-274, 1955.
2. Carmichael, D.B., Jr. Fatal bacterial endocarditis due to staphylococcus aureus. U.S. Armed Forces Med. J. 4:287-294, 19
3. Hausmann, W., and A.J. Karlish. Staphylococcal pneumonia in adults. Brit. Med. J. 2:845-847, 1956.
4. Kanof, A., B. Epstein, B. Kramer, and I. Mauss. Staphylococcal pneumonia and empyema. Pediatrics 11:385-392, 1953.
5. Lepper, M.H., P. Tillman, and R. Devetsky. Patterns of transmi sion of staphylococci. Ann. N.Y. Acad. Sci. 128:404-427, 1965
6. Martin, C.M., C.M. Kunin, L.S. Gottlieb, and M. Finland. Asian influenza A in Boston, 1957-58. II. Severe staphylococcal pneumonia complicating influenza. A.M.A. Arch. Intern. Med. 103:532-542, 1959.
7. Wallman, I.S., R.C. Godfrey, and J.R.H. Watson. Staphylococcal pneumonia in infancy. Brit. Med. J. 2:1423-1427, 1955.

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

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

III. Typhoid fever.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

IV. Other salmonelloses.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

V. Urinary tract infections.

EVALUATION: Effective, but . . . .

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

are often susceptible only to chloramphenicol.

DOCUMENTATION:

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

I. Surgical infections: postoperative wound infections.

EVALUATION: Possibly effective.

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

DOCUMENTATION: Most favorable report is reference 1 (Altemeier).

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

I. Surgical infections; cellulitis.

EVALUATION: Possibly effective.

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

DOCUMENTATION: Same as for Indication VI.

VIII. Surgical infections: infected sinus tract.

EVALUATION: Possibly effective.

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

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

DOCUMENTATION:

1. Altemeier, W.A., and W.R. Culbertson. Chloramphenicol (chloromyce and aureomycin in surgical infections. J.A.M.A. 145:449-457, 1951.
2. Bloomer, W.E., S. Giammona, G.E. Lindskog, and R.E. Cooke. Staphyloccal pneumonia and empyema in infancy. J. Thorac. Surg. 30: 265-274, 1955.
3. Carmichael, D.B., Jr. Fatal bacterial endocarditis due to staphylococcus aureus. U.S. Armed Forces Med. J. 4:287-294, 1953.
4. Hausmann, W., and A.J Karlish. Staphyloccal pneumonia in adults. Brit. Med. J. 2:845-847, 1956.
5. Kanof, A., B. Epstein, B. Kramer, and I. Mauss. Staphylococcal pneumonia and empyema. Pediatrics 11:385-392, 1953.
6. Lepper, M.H., P. Tillman, and R. Devetsky. Patterns of transmission of staphylococci. Ann. N.Y. Acad. Sci. 128: 404-427, 1965
7. Martin, C.M., C.M. Kunin, L.S. Gottlieb, and M. Finland. Asian influenza A in Boston, 1957-58. II. Severe staphylococcal pneumonia complicating influenza. A.M.A. Arch. Intern. Med. 103: 532-542, 1959.
8. Wallman, I.S., R.C. Godfrey, and J.R.H. Watson. Staphylococcal pneumonia in infancy. Brit. Med. J. 2:1423-1427, 1955.
9. Woodward, T.E., and C.L. Wisseman, Jr. Chloromycetin, pp. 122-124. Antibiotics Monographs No. 8. New York: Medical Encycloped Inc., 1958.

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

EVALUATION: Possibly effective.

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

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

DOCUMENTATION: Same as for Indication VIII.

X. Respiratory tract infections.

EVALUATION: Possibly effective.

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

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

DOCUMENTATION:

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

XI. Meningeal infections.

EVALUATION: Probably effective.

COMMENTS: The three most common causes of meningitis are the meningococci, pneumococci, and Hemophilus influenzae. All are susceptible to chloramphenicol, as are many staphylococci and the gram-negative aerobic rods that often infect newborns. Moreover, it is true that the drug does get into the spinal fluid well. As a drug of choice

for empiric use, however, it is probably not first, because it is likely to be less effective in pneumococcal disease than is penicillin. Although many believe it is first choice in Hemophilus infections, tetracycline is probably as good and ampicillin is, too. It is likely that this claim (drug of choice in H. influenzae meningitis) is no longer justified. In menigitis of the newborn kanamycin is preferred as the drug of choice for empiric treatment. In older patients, when a diagnosis has been made and the organisms shown to be more susceptibl to chloramphenicol than to other agents, it may be the drug of choice. As indicated, in the insert, initial treatment should be parenterally administered.

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

DOCUMENTATION:

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

XII. Brucellosis.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

XIII. Bartonellosis.

EVALUATION: Probably effective.

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

DOCUMENTATION:

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

XIV. Relapsing fever.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

XV. Granuloma inguinale.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

XVI. Plague.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

XVII. Ornithosis.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

GENERAL COMMENTS

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

Absorption after oral administration is good, in that 75-90% of a dose can be accounted for by metabolic products found in the urine. Tissue distribution appears to be favorable. The distribution into the cerebrospinal fluid is good, as pointed out in the insert, and is reasonably good into brain tissue, which is important when cerebrit: accompanies meningitis. The distribution into bile is not as high as that of the tetracyclines and some of the penicillins. The very small amount in the feces is of interest as is the fact that the fecal content is higher when the palmitate has been given.

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

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

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

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

Approved by W. E. Kerby
Chairman JHW

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

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

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

DRUG EFFICACY STUDY

Form A

(To be submitted in duplicate by applicant)

1. NDA Number 6D315 (90149) 2. Date Originally Approved September 20, 1963 3. Rx ☒ OTC ☐

4. Brand Name Chloromycetin Sodium Succinate - Infant, 250 mg.

5. Applicant's Name Parke, Davis & Company

and Address Joseph Campau at the River; Detroit, Michigan

6. Quantitative Formula

Established (Non-Proprietary) Name of Active Ingredients (in order shown on label)	Amount (per tablet, per ml., etc.)
Chloramphenicol Sodium Succinate	250 mg. base/vial

7. Dosage Form (tablets, etc.) steri-vial

8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) parenteral

9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.

12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).

Panel on Anti-Infective Drugs (III)

INDICATIONS

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

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

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

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

III. Typhoid fever.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

IV. Other salmonelloses.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

V. Urinary tract infections.

EVALUATION: Effective, but . . . .

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

are often susceptible only to chloramphenicol.

DOCUMENTATION:

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

VI. Surgical infections: postoperative wound infections.

EVALUATION: Possibly effective.

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

DOCUMENTATION: Most favorable report is reference 1 (Altemeier).

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

VII. Surgical infections: cellulitis.

EVALUATION: Possibly effective.

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

DOCUMENTATION: Same as for Indication VI.

VIII. Surgical infections: infected sinus tract.

EVALUATION: Possibly effective.

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

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

DOCUMENTATION:

1. Altemeier, W.A., and W.R. Culbertson. Chloramphenicol (chloromycetin) and aureomycin in surgical infections. J.A.M.A. 145:449-457, 1951.
2. Bloomer, W.E., S. Giammona, G.E. Lindskog, and R.E. Cooke. Staphyloccal pneumonia and empyema in infancy. J. Thorac. Surg. 30: 265-274, 1955.
3. Carmichael, D.B., Jr. Fatal bacterial endocarditis due to staphylococcus aureus. U.S. Armed Forces Med. J. 4:287-294, 1953.
4. Hausmann, W., and A.J Karlish. Staphyloccal pneumonia in adults. Brit. Med. J. 2:845-847, 1956.
5. Kanof, A., B. Epstein, B. Kramer, and I. Mauss. Staphylococcal pneumonia and empyema. Pediatrics 11:385-392, 1953.
6. Lepper, M.H., P. Tillman, and R. Devetsky. Patterns of transmission of staphylococci. Ann. N.Y. Acad. Sci. 128: 404-427, 1965.
7. Martin, C.M., C.M. Kunin, L.S. Gottlieb, and M. Finland. Asian influenza A in Boston, 1957-58. II. Severe staphylococcal pneumonia complicating influenza. A.M.A. Arch. Intern. Med. 103: 532-542, 1959.
8. Wallman, I.S., R.C. Godfrey, and J.R.H. Watson. Staphylococcal pneumonia in infancy. Brit. Med. J. 2:1423-1427, 1955.
9. Woodward, T.E., and C.L. Wisseman, Jr. Chloromycetin, pp. 122-124. Antibiotics Monographs No. 8. New York: Medical Encyclopedia, Inc., 1958.

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

EVALUATION: Possibly effective.

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

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

DOCUMENTATION: Same as for Indication VIII.

X. Respiratory tract infections.

EVALUATION: Possibly effective.

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

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

DOCUMENTATION:

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

XI. Meningeal infections.

EVALUATION: Probably effective.

COMMENTS: The three most common causes of meningitis are the meningococci, pneumococci, and Hemophilus influenzae. All are susceptible to chloramphenicol, as are many staphylococci and the gram-negative aerobic rods that often infect newborns. Moreover, it is true that the drug does get into the spinal fluid well. As a drug of choice

for empiric use, however, it is probably not first, because it is likely to be less effective in pneumococcal disease than is penicillin. Although many believe it is first choice in Hemophilus infections, tetracycline is probably as good and ampicillin is, too. It is likely that this claim (drug of choice in H. influenzae meningitis) is no longer justified. In menigitis of the newborn kanamycin is preferred as the drug of choice for empiric treatment. In older patients, when a diagnosis has been made and the organisms shown to be more susceptible to chloramphenicol than to other agents, it may be the drug of choice. As indicated, in the insert, initial treatment should be parenterally administered.

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

DOCUMENTATION:

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

XII. Brucellosis.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

XIII. Bartonellosis.

EVALUATION: Probably effective.

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

DOCUMENTATION:

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

XIV. Relapsing fever.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

XV. Granuloma inguinale.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

XVI. Plague.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

XVII. Ornithosis.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

GENERAL COMMENTS

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

Tissue distribution appears to be favorable. The distribution into the cerebrospinal fluid is good as pointed out in the insert, and is reasonably good into brain tissue, which is important when cerebritis accompanies meningitis. The distribution into bile is not as high as that of the tetracyclines and some of the penicillins. The very small amount in the feces is of interest as is the fact that the fecal content is higher when the palmitate has been given.

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

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

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

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

The unique feature of the succinate is the delay in achieving peak concentrations of active drug because of the hydrolysis required. The material (about Steri-Vial 148) on page 2 of the insert points out the unique features of the design for the infant and instructions for each route. The instructions and dose recommendations are good. In this case, the insert pertains to the one preparation and is also good from that point of view.

Approved by Wm Kerr
Chairman JHW

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

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

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

DRUG EFFICACY STUDY

Form A
(To be submitted in duplicate by applicant)

1. NDA Number 6D302 (6655) 2. Date Originally Approved December 8, 1950 3. Rx ☒ OTC ☐

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

5. Applicant's Name Parke, Davis & Company

and Address Joseph Campau at the River; Detroit, Michigan

6. Quantitative Formula

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

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

8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) oral

9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.

12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).

81-280 11329

Panel on Anti-Infective Drugs (III)

INDICATIONS

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

EVALUATION: Possibly effective.

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

DOCUMENTATION:

1. Bloomer, W.E., S. Giammona, G.E. Lindskog, and R.E. Cooke. Staphylococcal pneumonia and empyema in infancy. J. Thorac. Surg. 30:265-274, 1955.
2. Carmichael, D.B., Jr. Fatal bacterial endocarditis due to staphylococcus aureus. U.S. Armed Forces Med. J. 4:287-294, 1
3. Hausmann, W., and A.J. Karlish. Staphylococcal pneumonia in adults. Brit. Med. J. 2:845-847, 1956.
4. Kanof, A., B. Epstein, B. Kramer, and I. Mauss. Staphylococca pneumonia and empyema. Pediatrics 11:385-392, 1953.
5. Lepper, M.H., P. Tillman, and R. Devetsky. Patterns of transm sion of staphylococci. Ann. N.Y. Acad. Sci. 128:404-427, 196
6. Martin, C.M., C.M. Kunin, L.S. Gottlieb, and M. Finland. Asia influenza A in Boston, 1957-58. II. Severe staphylococcal pneumonia complicating influenza. A.M.A. Arch. Intern. Med. 103:532-542, 1959.
7. Wallman, I.S., R.C. Godfrey, and J.R.H. Watson. Staphylococca pneumonia in infancy. Brit. Med. J. 2:1423-1427, 1955.

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

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

III. Typhoid fever.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

IV. Other salmonelloses.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

V. Urinary tract infections.

EVALUATION: Effective, but . . . .

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

are often susceptible only to chloramphenicol.

DOCUMENTATION:

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

[. Surgical infections: postoperative wound infections.

EVALUATION: Possibly effective.

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

DOCUMENTATION: Most favorable report is reference 1 (Altemeier).

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

[. Surgical infections; cellulitis.

EVALUATION: Possibly effective.

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

DOCUMENTATION: Same as for Indication VI.

VIII. Surgical infections: infected sinus tract.

EVALUATION: Possibly effective.

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

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

DOCUMENTATION:

1. Altemeier, W.A., and W.R. Culbertson. Chloramphenicol (chloromyc and aureomycin in surgical infections. J.A.M.A. 145:449-457, 1951
2. Bloomer, W.E., S. Giammona, G.E. Lindskog, and R.E. Cooke. Staph yloccal pneumonia and empyema in infancy. J. Thorac. Surg. 30: 265-274, 1955.
3. Carmichael, D.B., Jr. Fatal bacterial endocarditis due to staphylococcus aureus. U.S. Armed Forces Med. J. 4:287-294, 1953
4. Hausmann, W., and A.J Karlish. Staphyloccal pneumonia in adults. Brit. Med. J. 2:845-847, 1956.
5. Kanof, A., B. Epstein, B. Kramer, and I. Mauss. Staphylococcal pneumonia and empyema. Pediatrics 11:385-392, 1953.
6. Lepper, M.H., P. Tillman, and R. Devetsky. Patterns of trans- mission of staphylococci. Ann. N.Y. Acad. Sci. 128: 404-427, 196
7. Martin, C.M., C.M. Kunin, L.S. Gottlieb, and M. Finland. Asian influenza A in Boston, 1957-58. II. Severe staphylococcal pneumonia complicating influenza. A.M.A. Arch. Intern. Med. 103: 532-542, 1959.
8. Wallman, I.S., R.C. Godfrey, and J.R.H. Watson. Staphylococcal pneumonia in infancy. Brit. Med. J. 2:1423-1427, 1955.
9. Woodward, T.E., and C.L. Wisseman, Jr. Chloromycetin, pp. 122- 124. Antibiotics Monographs No. 8. New York: Medical Encyclope Inc., 1958.

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

EVALUATION: Possibly effective.

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

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

DOCUMENTATION: Same as for Indication VIII.

X. Respiratory tract infections.

EVALUATION: Possibly effective.

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

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

DOCUMENTATION:

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

XI. Meningeal infections.

EVALUATION: Probably effective.

COMMENTS: The three most common causes of meningitis are the meningococci, pneumococci, and Hemophilus influenzae. All are susceptible to chloramphenicol, as are many staphylococci and the gram-negative aerobic rods that often infect newborns. Moreover, it is true that the drug does get into the spinal fluid well. As a drug of choice

for empiric use, however, it is probably not first, because it is likely to be less effective in pneumococcal disease than is penicillin. Although many believe it is first choice in Hemophilus infections, tetracycline is probably as good and ampicillin is, too. It is likely that this claim (drug of choice in H. influenzae meningitis) is no longer justified. In menigitis of the newborn kanamycin is preferred as the drug of choice for empiric treatment. In older patients, when a diagnosis has been made and the organisms shown to be more susceptibl to chloramphenicol than to other agents, it may be the drug of choice. As indicated, in the insert, initial treatment should be parenterally administered.

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

DOCUMENTATION:

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

XII. Brucellosis.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

XIII. Bartonellosis.

EVALUATION: Probably effective.

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

DOCUMENTATION:

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

XIV. Relapsing fever.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

XV. Granuloma inguinale.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

XVI. Plague.

EVALUATION: Effective, but . . . .

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

DOCUMENTATION:

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

XVII. Ornithosis.

EVALUATION: Possibly effective.

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

DOCUMENTATION:

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

GENERAL COMMENTS

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

Absorption after oral administration is good, in that 75-90% of a dose can be accounted for by metabolic products found in the urine. Tissue distribution appears to be favorable. The distribution into the cerebrospinal fluid is good, as pointed out in the insert, and is reasonably good into brain tissue, which is important when cerebritis accompanies meningitis. The distribution into bile is not as high as that of the tetracyclines and some of the penicillins. The very small amount in the feces is of interest as is the fact that the fecal content is higher when the palmitate has been given.

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

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

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

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

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

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

The dose recommendations are accurate.

Approved by Wm Kerby
Chairman JHW

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SPECIMEN

FOR INTRAVENOUS ADMINISTRATION

CHLOROMYCETIN®
(CHLORAMPHENICOL)
SODIUM SUCCINATE

PARKE-DAVIS

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the "Indications" section. It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, 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, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

IMPORTANT CONSIDERATIONS IN PRESCRIBING INJECTABLE CHLORAMPHENICOL SODIUM SUCCINATE

1. Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate blood levels compared with the base given intravenously.
2. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
3. Patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable.
4. Chloramphenicol sodium succinate is recommended for intravenous use only.

Use of this product by the intramuscular route in emergency situations has been described, but this route is not recommended, because lower blood levels are attained and there is a lack of evidence that it is effective when given by this route.

DESCRIPTION

Chloramphenicol is an antibiotic that is clinically useful for, and should be reserved for, serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see "Indications" section).

HH

CHLOROMYCETIN
(CHLORAMPHENICOL)
SODIUM SUCCINATE

ACTIONS AND PHARMACOLOGY

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group and *Vibrio cholerae*. It is particularly active against *Salmonella typhi* and *Hemophilus influenzae*. The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg./kg./day, a dosage of 1 gm. every 6 hours for 8 doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg./ml. one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg./ml. after the fifth dose of 1 gm. Mean serum levels ranged from 8–14 mcg./ml. over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8 to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg./ml. in patients receiving divided doses of 50 mg./kg./day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS

IN ACCORD WITH THE CONCEPTS IN THE "WARNING BOX" AND THIS INDICATIONS SECTION, CHLORAMPHENICOL MUST BE USED ONLY IN THOSE SERIOUS INFECTIONS FOR WHICH LESS POTENTIALLY DANGEROUS DRUGS ARE INEFFECTIVE OR CONTRAINDICATED. HOWEVER, CHLORAMPHENICOL MAY BE CHOSEN TO INITIATE ANTIBIOTIC THERAPY ON THE CLINICAL IMPRESSION THAT ONE OF THE CONDITIONS BELOW IS BELIEVED TO BE PRESENT; *IN VITRO* SENSITIVITY TESTS SHOULD BE PERFORMED CONCURRENTLY SO THAT THE DRUG MAY BE DISCONTINUED AS SOON AS POSSIBLE IF LESS POTENTIALLY DANGEROUS AGENTS ARE INDICATED BY SUCH TESTS. THE DECISION TO CONTINUE USE OF CHLORAMPHENICOL RATHER THAN ANOTHER ANTIBIOTIC WHEN BOTH ARE SUGGESTED BY *IN VITRO* STUDIES TO BE EFFECTIVE AGAINST A SPECIFIC PATHOGEN SHOULD BE BASED UPON SEVERITY OF THE INFECTION, SUSCEPTIBILITY OF THE PATHOGEN TO THE VARIOUS ANTIMICROBIAL DRUGS, EFFICACY OF THE VARIOUS DRUGS IN THE INFECTION, AND THE IMPORTANT ADDITIONAL CONCEPTS CONTAINED IN THE "WARNING BOX" ABOVE:

CHLOROMYCETIN
(CHLORAMPHENICOL) SODIUM SUCCINATE

1. Acute infections caused by *Salmonella typhi*

Chloramphenicol is a drug of choice.* It is not recommended for the routine treatment of the typhoid "carrier state".

2. Serious infections caused by susceptible strains in accordance with the concepts expressed above:

a. Salmonella species

b. *H. influenzae,* specifically meningeal infections

c. Rickettsia

d. Lymphogranuloma-psittacosis group

e. Various gram-negative bacteria causing bacteremia, meningitis or other serious gram-negative infections

f. Other susceptible organisms which have been demonstrated to be resistant to all other appropriate anti-microbial agents.

3. Cystic fibrosis regimens

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infection.

PRECAUTIONS

1. Baseline blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.

2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.

3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.

5. There are no studies to establish the safety of this drug in pregnancy.

6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).

7. Precaution should be used in therapy of premature and full-term infants to avoid "gray syndrome" toxicity. (See "Adverse Reactions.") Serum drug levels should be carefully followed during therapy of the newborn infant.

8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.

*In the treatment of typhoid fever some authorities recommend that chloramphenicol be administered at therapeutic levels for 8-10 days after the patient has become afebrile to lessen the possibility of relapse.

CHLOROMYCETIN
(CHLORAMPHENICOL)
SODIUM SUCCINATE

9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding 1) the size of the population at risk, 2) the total number of drug-associated dyscrasias, and 3) the total number of non-drug associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the "gray syndrome". One case of "gray syndrome" has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3 month infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

CHLOROMYCETIN
(CHLORAMPHENICOL) SODIUM SUCCINATE

(1) In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life.
(2) Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol.
(3) The symptoms appeared in the following order:
  (a) abdominal distension with or without emesis;
  (b) progressive pallid cyanosis;
  (c) vasomotor collapse, frequently accompanied by irregular respiration;
  (d) death within a few hours of onset of these symptoms.
(4) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
(5) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg./ml. after repeated doses).
(6) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg./kg./day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

AS SOON AS FEASIBLE AN ORAL DOSAGE FORM OF CHLORAMPHENICOL SHOULD BE SUBSTITUTED FOR THE INTRAVENOUS FORM BECAUSE ADEQUATE BLOOD LEVELS ARE ACHIEVED WITH CHLORAMPHENICOL BY MOUTH.

The following method of administration is recommended:

Intravenously as a 10% solution to be injected over at least a one-minute interval. This is prepared by the addition of 11 cc. of an aqueous diluent such as water for injection or 5% dextrose injection.

The "Infant Size" package (Steri-Vial No. 148) contains 250 mg. This should be reconstituted with 2.75 cc. of diluent.

DOSAGE

Adults

Adults should receive 50 mg./kg./day in divided doses at 6-hour intervals. In exceptional cases patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg./kg./day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg./kg./day divided into 4 doses at 6-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (e.g., bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg./kg./day; however, it is recommended that dosage be reduced to 50 mg./kg./day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

CHLOROMYCETIN
(CHLORAMPHENICOL)
SODIUM SUCCINATE

Newborn Infants

(See section titled "Gray Syndrome" under "Adverse Reactions.")

A total of 25 mg./kg./day in 4 equal doses at 6-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg./kg./day equally divided into 4 doses at 6-hour intervals. These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants. This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg./kg./day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

PACKAGE INFORMATION

Steri-Vial No. 57, Chloromycetin (chloramphenicol) Sodium Succinate provides the equivalent of 1 Gram chloramphenicol in a rubber-diaphragm-capped vial. Available individually and in packer units of 10.

CHLOROMYCETIN, brand of chloramphenicol, Reg. U.S. Pat. Off.

PARKE, DAVIS & COMPANY
121 865000
A DETROIT, MICHIGAN, U. S. A.
Aug. 1968

FOR INTRAVENOUS ADMINISTRATION

CHLORAMPHENICOL SODIUM SUCCINATE, STERILE, U.S.P.

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the "Indications" section. It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, 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, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

IMPORTANT CONSIDERATIONS IN PRESCRIBING INJECTABLE CHLORAMPHENICOL SODIUM SUCCINATE

1. Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate blood levels compared with the base given intravenously.
2. The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
3. Patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable.
4. Chloramphenicol sodium succinate is recommended for intravenous use only.

Use of this product by the intramuscular route in emergency situations has been described, but this route is not recommended, because lower blood levels are attained and there is a lack of evidence that it is effective when given by this route.

DESCRIPTION

Chloramphenicol is an antibiotic that is clinically useful for, and should be reserved for, serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see "Indications" section).

DSA-HH

ACTIONS AND PHARMACOLOGY

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group and *Vibrio cholerae.* It is particularly active against *Salmonella typhi* and *Hemophilus influenzae.* The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg./kg./day, a dosage of 1 gm. every 6 hours for 8 doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg./ml. one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg./ml. after the fifth dose of 1 gm. Mean serum levels ranged from 8-14 mcg./ml. over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8 to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg./ml. in patients receiving divided doses of 50 mg./kg./day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS

IN ACCORD WITH THE CONCEPTS IN THE "WARNING BOX" AND THIS INDICATIONS SECTION, CHLORAMPHENICOL MUST BE USED ONLY IN THOSE SERIOUS INFECTIONS FOR WHICH LESS POTENTIALLY DANGEROUS DRUGS ARE INEFFECTIVE OR CONTRAINDICATED. HOWEVER, CHLORAMPHENICOL MAY BE CHOSEN TO INITIATE ANTIBIOTIC THERAPY ON THE CLINICAL IMPRESSION THAT ONE OF THE CONDITIONS BELOW IS BELIEVED TO BE PRESENT; *IN VITRO* SENSITIVITY TESTS SHOULD BE PERFORMED CONCURRENTLY SO THAT THE DRUG MAY BE DISCONTINUED AS SOON AS POSSIBLE IF LESS POTENTIALLY DANGEROUS AGENTS ARE INDICATED BY SUCH TESTS. THE DECISION TO CONTINUE USE OF CHLORAMPHENICOL RATHER THAN ANOTHER ANTIBIOTIC WHEN BOTH ARE SUGGESTED BY *IN VITRO* STUDIES TO BE EFFECTIVE AGAINST A SPECIFIC PATHOGEN SHOULD BE BASED UPON SEVERITY OF THE INFECTION, SUSCEPTIBILITY OF THE PATHOGEN TO THE VARIOUS ANTIMICROBIAL DRUGS, EFFICACY OF THE VARIOUS DRUGS IN THE INFECTION, AND THE IMPORTANT ADDITIONAL CONCEPTS CONTAINED IN THE "WARNING BOX" ABOVE:

1. Acute infections caused by *Salmonella typhi*

Chloramphenicol is a drug of choice.* It is not recommended for the routine treatment of the typhoid "carrier state".

2. Serious infections caused by susceptible strains in accordance with the concepts expressed above:

a. Salmonella species
b. *H. Influenzae*, specifically meningeal infections
c. Rickettsia
d. Lymphogranuloma-psittacosis group
e. Various gram-negative bacteria causing bacteremia, meningitis or other serious gram-negative infections
f. Other susceptible organisms which have been demonstrated to be resistant to all other appropriate anti-microbial agents.

3. Cystic fibrosis regimens

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infection.

PRECAUTIONS

1. Baseline blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.

2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.

3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

4. Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.

5. There are no studies to establish the safety of this drug in pregnancy.

6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).

7. Precaution should be used in therapy of premature and full-term infants to avoid "gray syndrome" toxicity. (See "Adverse Reactions.") Serum drug levels should be carefully followed during therapy of the newborn infant.

8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.

*In the treatment of typhoid fever some authorities recommend that chloramphenicol be administered at therapeutic levels for 8-10 days after the patient has become afebrile to lessen the possibility of relapse.

9. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS

1. Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding 1) the size of the population at risk, 2) the total number of drug-associated dyscrasias, and 3) the total number of non-drug associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. Neurotoxic Reactions

Headache, mild depression, mental confusion and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. Hypersensitivity Reactions

Fever, macular and vesicular rashes, angioedema, urticaria and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. "Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the "gray syndrome". One case of "gray syndrome" has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3 month infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

(1) In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life.
(2) Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol.
(3) The symptoms appeared in the following order:
  (a) abdominal distension with or without emesis;
  (b) progressive pallid cyanosis;
  (c) vasomotor collapse, frequently accompanied by irregular respiration;
  (d) death within a few hours of onset of these symptoms.
(4) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
(5) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg./ml. after repeated doses).
(6) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg./kg./day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

AS SOON AS FEASIBLE AN ORAL DOSAGE FORM OF CHLORAMPHENICOL SHOULD BE SUBSTITUTED FOR THE INTRAVENOUS FORM BECAUSE ADEQUATE BLOOD LEVELS ARE ACHIEVED WITH CHLORAMPHENICOL BY MOUTH.

The following method of administration is recommended:

Intravenously as a 10% solution to be injected over at least a one-minute interval. This is prepared by the addition of 11 cc. of an aqueous diluent such as water for injection or 5% dextrose injection.

The "Infant Size" package (Steri-Vial No. 148) contains 250 mg. This should be reconstituted with 2.75 cc. of diluent.

DOSAGE

Adults

Adults should receive 50 mg./kg./day in divided doses at 6-hour intervals. In exceptional cases patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg./kg./day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants.) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children

Dosage of 50 mg./kg./day divided into 4 doses at 6-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (e.g., bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg./kg./day; however, it is recommended that dosage be reduced to 50 mg./kg./day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants

(See section titled "Gray Syndrome" under "Adverse Reactions.")

A total of 25 mg./kg./day in 4 equal doses at 6-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg./kg./day equally divided into 4 doses at 6-hour intervals. These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants. This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg./kg./day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)

PARKE, DAVIS & COMPANY
121 852250
A DETROIT, MICHIGAN, U.S.A. DSA-HH
Aug. 1968

Steri-Vial® No. 57

CHLOROMYCETIN®
(CHLORAMPHENICOL)
SODIUM SUCCINATE

FOR INTRAVENOUS ADMINISTRATION

Equivalent to **1 GRAM** chloramphenicol

CAUTION—Federal law prohibits dispensing without prescription.

PARKE-DAVIS

Stock 35-57-1

WARNING—Blood dyscrasias may be associated with the use of chloramphenicol. It is essential that adequate blood studies be made. See enclosed warnings and precautions.

Parke, Davis & Company
Detroit, Michigan 48232 U.S.A.

Not suitable for laboratory diagnostic use.

To prepare a 10% solution, add 11 cc. of sterile aqueous diluent such as Water for Injection or 5% Dextrose Injection.

USUAL ADULT DAILY DOSE—50 mg. per Kg.
See package insert.

Sterile solution may be kept at room temperature for 30 days without significant loss of potency. A cloudy solution should not be used.

WARNING—Keep out of the reach of children.

Patient:

Room:

S-V No. 57

CHLOROMYCETIN®
(CHLORAMPHENICOL)
SODIUM SUCCINATE

FOR INTRAVENOUS ADMINISTRATION

EQUIVALENT TO
1 GRAM
CHLORAMPHENICOL

PARKE-DAVIS
Stock 35-57-1

Steri-Vial® No. 57

CHLOROMYCETIN®
(CHLORAMPHENICOL)
SODIUM SUCCINATE
FOR INTRAVENOUS ADMINISTRATION
1 GRAM

Expiration Date and Lot

Steri-Vial® No. 57

CHLOROMYCETIN®
(CHLORAMPHENICOL)
SODIUM SUCCINATE
FOR INTRAVENOUS ADMINISTRATION
1 GRAM

Stock 35-57-1

Strength:
Date: Room
Patient:

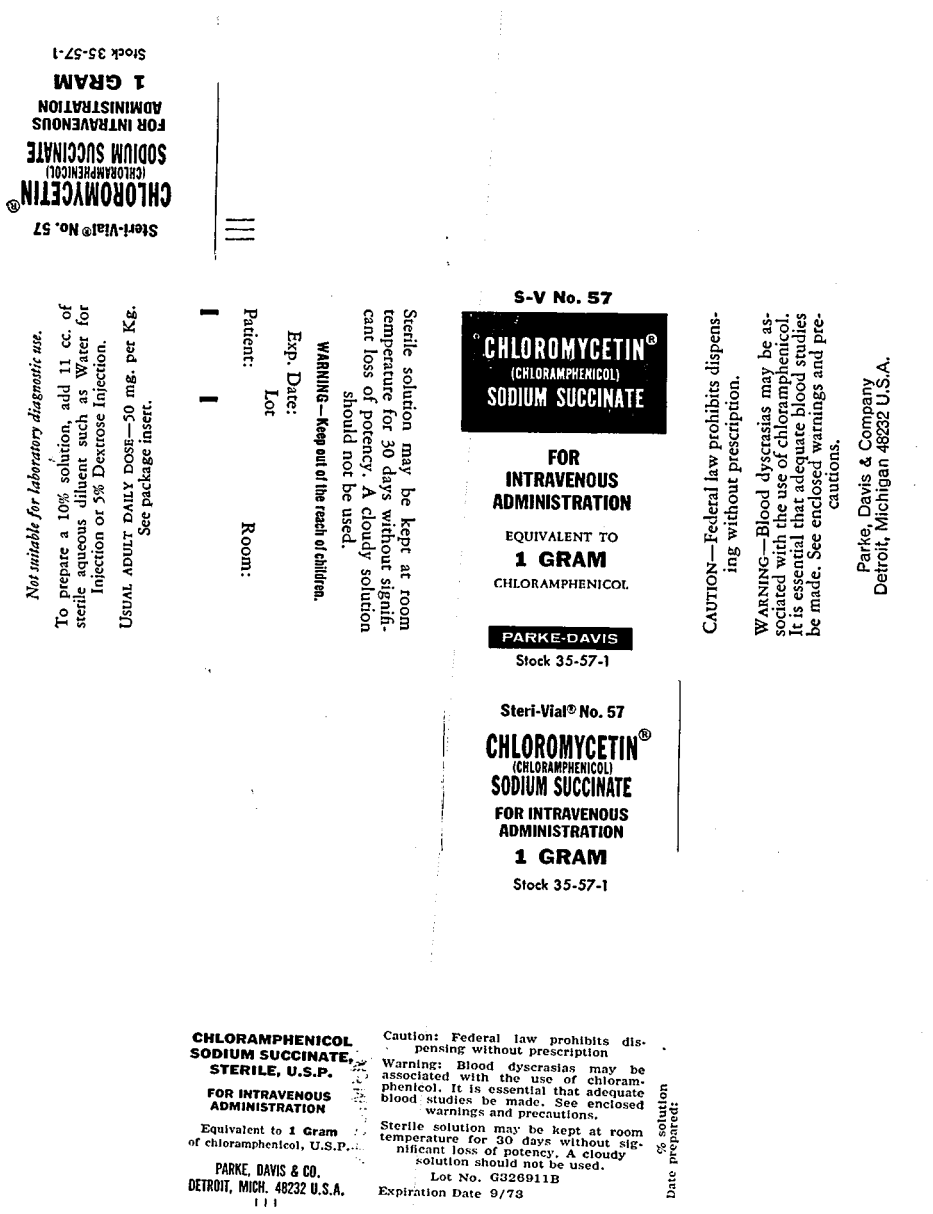
Parke, Davis & Company
Detroit, Michigan 48232 U.S.A.
Exp. Date:
Lot

WARNING—Blood dyscrasias may be associated with the use of chloramphenicol. It is essential that adequate blood studies be made. See enclosed warnings and precautions.

Usual adult daily dose
50 mg. per Kg. See package insert.

To prepare a 10% solution, add 11 cc. of sterile aqueous diluent such as Water for Injection or 5% Dextrose Injection. Solution should be used within 30 days. A cloudy solution should not be used.

WARNING—Keep out of the reach of children.


Steri-Vial® No. 57
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(CHLORAMPHENICOL)
SODIUM SUCCINATE
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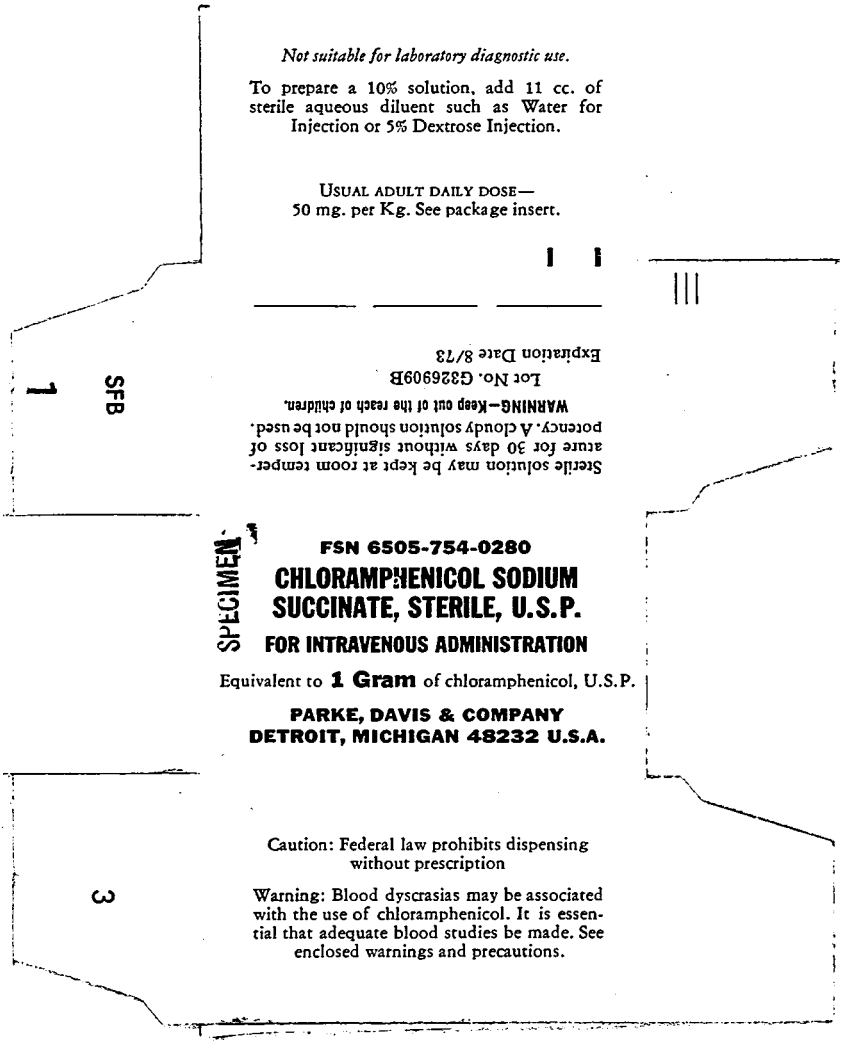

(Whereupon, at 11:45 a.m., the subcommittee adjourned.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

THURSDAY, MARCH 13, 1969

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

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

Present: Senators Nelson and Hatfield.

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

Senator NELSON. I regret that our hearing yesterday had to be cancelled. Dr. Dale Console, who was to be our witness, was unable to come because of ill health. His work within the drug industry as former medical director for E. R. Squibb and Company and his experience in private practice make him especially well qualified to comment on the various matters which have been dealt with in the course of our continuing study of the drug industry.

Dr. Console's biographical sketch and prepared statement, which was submitted to us, will be made a part of our hearing record. The questions I had planned to ask will be sent to Dr. Console, and his answers will be placed in the record immediately following his statement.

(Dr. Console's biographical sketch, prepared statement, and supplemental information follow:)

BIOGRAPHY, A. DALE CONSOLE, M.D.

Born: 1915.
Training:
B. S. Cornell University 1937.
M.D. Cornell Medical College 1941 (Polk Prize for General Efficiency).
Intern, Asst. Res., Resident Surgeon, New York Hospital 1941–1946.
Resident Neurosurgeon, New York Hospital 1946–48 (John and Mary Markle Foundation Grant).
Research Fellow in Psychiatry, Pennsylvania Hospital 1957–1958.
Research Fellow in Psychiatry, Payne Whitney Clinic 1958–1959.
(Psychiatric Division of Cornell-New York Hospital)
Experience:
Consultant to Surgeon General (Neurosurgery), Fort Dix.
Asst. Clinical Professor of Surgery, (Neurosurgery), Cornell Medical College.
Attending Surgeon (Chief of Neurosurgery), St. John's Hospital.
Research Consultant, New Jersey Neuropsychiatric Hospital.
Director of Research and Training, N.J. State Hospital at Marlboro.
Psychiatric Consultant, Douglass College.
Assoc. Medical Director and Medical Director, E. R. Squibb & Sons.
Research Assoc. in Psychiatry, Cornell Medical College.

Certification:
Diplomate of the American Board of Surgery.
Diplomate of the American Board of Psychiatry and Neurology (Psychiatry).
Memberships:
American Psychiatric Association.
Society of University Surgeons.
American Group Psychotherapy Association.
New Jersey State and Mercer County Medical Societies.
Alpha Omega Alpha.
Publications:
15 Papers dealing primarily with Hypertension and the Sympathetic Nervous System.

STATEMENT BY A. DALE CONSOLE, M.D.

INTRODUCTION

Before presenting my prepared statement I should like to make some introductory comments. I have prepared my statement with the understanding that representatives of the drug industry, the PMA and the AMA either have had or will have their days in court. The drug industry and its friends have demonstrated in the past that they are more than able to speak for themselves. I do not exect them to support my views of the problems. I feel no need to support theirs.

I also wish to make it clear that I am not an academician. For almost ten years I have devoted 90% of my time to the private practice of psychiatry, and my contact with the so-called "white towers of medicine" has been minimal. During those ten years I have held only one academic position and that is a part-time one, Research Association in Psychiatry at Cornell Medical College.

I speak for myself and myself only. The primary justification for my appearance here derives from a degree of expertise I gained during the six and one-half years I spent as Associate Medical Director and Medical Director of E. R. Squibb & Sons.

LICENSING AND INSPECTION

I have always found it curious that a process that started in late 1959 as an investigation of "administered prices in the drug industry" ended in 1962 with the passage of legislation that had no effect on drug prices. Actually no one who was knowledgeable expected that the Kefauver-Harris Amendments of the Drug Act would affect prices and it seems clear that the late Senator Kefauver accepted the bill in its final form only because it was the best compromise he could get at the time. Even so he made a last-ditch effort to introduce a patent amendment and was defeated.

The record is clear and it demonstrates that the attack on drug prices had two prongs. One of these was contained in the patent provisions. The other was directed against the allegation that generic equivalents are inferior and unreliable drugs. In drafting S. 1552, Kefauver and his staff sought to increase price competition by encouraging generic prescribing. Realizing that they could not accomplish this unless assurance was given that any drug on the market had to meet standards of purity, safety, and efficacy determined by the FDA, they drafted Section 508. Let me quote some of the pertinent language: "Paragraph (b) provides that no license shall be granted unless the applicant demonstrates that the establishment . . . meets such standards . . . to insure . . . the purity, safety, and efficacy of the drug. . . . When the Secretary (of HEW) determines that the establishment no longer meets the standards, he shall revoke or suspend the license."

The intent of the language is crystal clear, and it was emphasized in Kefauver's opening statement in the first session of the hearings on S. 1552. Referring to the licensing and inspection provisions, he said, "These provisions *put real teeth into the Food and Drug Act.* By realizing that any firm which produces inferior drugs can have its license to do business suspended or revoked, the physician should gain assurance that any drug sold in the country, whether produced in this country or abroad, whether made by large companies or small companies, and whether marketed under a brand name or generic name, *is of adequate and acceptable quality*" (emphasis mine).

Perhaps Kefauver and his staff were naive in thinking that these provisions would effectively neutralize the mountain of propaganda produced by self-professed reliable drug companies and by the PMA. They may have been naive in believing that the average physician's prescribing habits could be changed that easily. In any case, the theory never has been tested. During the process of legislative hocus-pocus, Section 508 disappeared and a toothless version appeared in its place. It calls for registration of name and place of business. The inspection provisions are so vague that they defy interpretation.

It has taken some five years for other to recognize the need to put more teeth into the Food and Drug Act. I have studied the Interim Report and recommendations of the Task Force on Prescription Drugs, published in August 1968, with great care. No one in my opinion has made so exhaustive a study of the many problems posed by the ethical drug industry and expressed the findings in such balanced and temperate language. Among its recommendations it urges consideration of a registration and licensing system and strict quality control. Recognizing that this might raise the prices of some drugs, it feels that the increased quality would offset any increase in prices. While I am not an economist, I share the view that was held by Kefauver and his staff, namely that, overall, increased price competition would tend to lower prices and at the same time ensure the quality and efficacy of all drugs.

The need to strengthen the existing law has also received support from an unexpected quarter. It has been the practice of *Medical Tribune* to commission a Professor of Governments, Joseph D. Cooper, Ph.D. to write extensive series of articles on the FDA, Generic Equivalency, and other subjects of interest to physicians. The tenor of Professor Cooper's comments and the editorial policy of *Medical Tribune* are quite obvious: It would require a rather remarkable distortion to characterize either as hostile to the drug industry. For this reason alone, it is of interest that a series of articles on the FDA that appeared in mid-1967, Professor Cooper called for a system that he labeled "licensed self-regulation." In describing the system, he went on to say, "the power of this method of control lies in the fear of the company that part or all of its license might be revoked." One can almost hear the ghost of the late Senator Kefauver.

I strongly urge that Congress give early consideration to licensing and inspection provisions similar to those proposed in the original S.1552. If the 1962 legislation had contained these provisions we probably would not find ourselves in the generic equivalency mess that now exists. In any case, the search for adequate guidelines would have started five years earlier than it did.

MONETARY REWARDS AND OBJECTIVITY

In his letter inviting me to appear before this Committee, Senator Nelson mentioned "growing concern that the medical profession has forfeited too much responsibility for the continuing education of physicians to the pharamaceutical industry and that the increasingly close financial relationship between the industry and the profession may be contrary to the best interests of the medical profession and the public."

I, too, share this concern; I have shared it for almost 18 years. It is now almost nine years since I appeared before the "Kefauver Committee" and said: "Unfortunately drugs are not always prescribed wisely, and while the physician and patient among others must share the responsibility for this with the pharmaceutical industry, it is the industry that carefully nurtures and encourages the practice. . . . The pharmaceutical industry is unique in that it can make exploitation appear a noble purpose. It is the organized, carefully planned, and skillful execution of this exploitation that constitutes one of the costs of drugs which must be measured not only in terms of dollars but in terms of the inroads the industry has made into the entire structure of medicine and medical care. With the enormous resources at its command, it has usurped the place of the medical educator and has successfully substituted propaganda for education." At another point in the same statement, I said, "The abdication of leaders and educators in medicine is disturbing. Postgraduate medical education is their province, not the pharmaceutical industry's."

I am also disturbed, however, over the tendency to focus on financial relationships. While I feel that this is important and requires attention and correction, I am also convinced that we would be making a grave error if we decided that the total problem could be corrected simply by cutting financial ties. The well-known articles by Dr. Charles May and Dr. William Bean cover the problems of "payola" and other financial entanglements. I believe I can accomplish more

if, instead of repeating what they have already said so well, I try to draw your attention to an area of equal importance; perhaps even of greater importance.

The relationship that exists between the medical profession and the drug industry is an unhealthy one and in many ways a corrupt one. It is important to remember, however, that it is not only money that has the power to corrupt. Having spent more than six years in the business of influencing doctors and investigators, and some five years as a member of Fellowships and Grants Committee, I can assure you that while large grants and other monetary rewards play an important role, that role is minor relative to other inducements and techniques that can be used to destroy objectivity. An incident that will always remain fresh in my memory will perhaps illustrate the point I wish to make.

Sometime in 1956, when I was still a Medical Director, the lagging sales of one of our products led management to decide that the product needed a boost. The boost took the form of obtaining an endorsement from a physician who was a prominent authority in the field. We knew that the particular physician was being subsidized by another drug company and so management decided that it would be simple for me as Medical Director to "buy" him. I objected since I felt that the doctor was incorruptible and because I felt the product did not deserve endorsement. My business colleagues overruled me and I was left with a blank check to win his favor. I was free to offer him a large grant to support any research of his choice "without strings" or to retain him as a consultant with generous annual compensation. I was quite certain that the doctor would throw me out of his office if I approached him with any of the techniques suggested by my colleagues. They all had the obvious odor of a bribe. I decided, therefore, to use a strategem that was more likely to be effective and that I thought (at the time) would be easier on my own conscience.

I took the doctor to lunch, and after the usual two Martinis, I told him exactly what had been going on and of my disagreement with my colleagues. In this manner we established a physician-to-physician relationship in which we were both deploring the questionable tactics used by the drug industry. Conversation gradually shifted to the product and, to make a long story short, we got our endorsement almost as a personal favor. My travel expenses and the price of the lunch made up the entire cost to the company.

I recall this out of a hundred similar incidents only because the doctor was, and still is, a highly respected authority. My attitude toward him still is one of profound respect and admiration, since I must confess that the device that gulled him would have fooled me had I been in his place.

We are still human in spite of being physicians. As humans, we are vulnerable to all forms of flattery, cajolery, and blandishments, subtle or otherwise. The drug industry has learned to manipulate this vulnerability with techniques whose sophistication approaches perfection. It was this knowledge that led me to write a letter that appears in the record of the "Humphrey Hearing" (p. 2289). Referring to the methods that can be used to destroy objectivity I said, "Any employee of a drug firm who is worth his salt has an expert's appreciation of their power, a gourmet's taste for their subtleties, and the deft delicate touch that leads the doctor to hang himself." These techniques are used not only by physicians employed by a drug company but also by more experienced detailmen.

I know of no effective way to deal with this type of hanky-panky that goes on every day between the medical profession and the drug industry. It seems impossible to convince my medical brethren that drug company executives and detailmen are either shrewd businessmen or shrewd salesmen, never philanthropists. They make investments, not gifts.

As further evidence of this manipulation of the physician's vulnerability, let me quote from the literature that was uncovered during the thalidomide scandal. A document written by the William S. Merrell Company was sent to "special representatives" before Kevadon (thalidomide) was approved for marketing. It set up minimum goals and objectives, including contacting teaching hospitals and the chiefs and senior members of hospital departments "for the purpose of selling them on Kevadon and providing them with a clinical supply." In the instructions the representatives were told: "Appeal to the doctor's ego—we think he is important enough to be selected as one of the first doctors to use Kevadon in that part of the country" ("Humphrey Hearings," p. 1918). I can assure you that even this simple device will open many doctor's doors.

Let me hasten to add that during my time as Medical Director I worked with many physicians who were incorruptible. Many of them received large

grants but they produced studies that were models of objectivity. These were truly cooperative efforts in which both the drug industry representatives and the investigators were seeking the truth. There is no doubt in my mind that similar cooperative efforts exist today.

On the other hand, during my time as Medical Director, I can remember only six to eight drugs that were truly exciting and interesting. I also remember a hundred humdrum concoctions and combinations that would bore any doctor to death. These, however, must also be studied and in trying to find "investigators" who are willing to do the job, one must scrape the bottom of the barrel. As a result, the drug industry doctor must rub shoulders not only with the giants in medicine but also with its dregs. In my 1960 statement I called the latter "stables" using the vernacular of the industry.

Drug testing is a costly, burdensome, and often a boring chore. Those who do the work well should receive adequate compensation. Both because there are doctors who are incorruptible and because someone must pay for drug testing, I think it is wrong to damn monetary rewards in a blanket fashion. I do believe, however, that clinical testing and the choice of investigators should be taken out of the hands of the drug industry. So long as we have a system that allows drug companies to buy the claims that will sell a drug, we have a potentially corrupt system.

I am convinced that the public interest will be best served when we devise a system that preserves anonymity between the drug company that has a proprietary interest in a drug and the investigator whose research results may or may not supply the claims that will sell the drug.

During the writing of this statement I learned that many physicians who preceded me recommended a "Drug Institute" or a similar central agency. I do not believe the recommendation can be repeated too often. A central agency, supported both by federal funds and by fees paid by drug companies, should serve as an impartial intermediary between drug companies and clinical investigators. By preserving anonymity and by selecting investigators on the basis of their qualifications, we could raise drug testing to a level it has never known. Since I believe in the theory of the unconscious (as well as the existence of incorruptible physicians), I am convinced that any thing that falls short of this system cannot insure objectivity.

The larger problem of destroying objectivity by appealing to the doctor's ego is as old as man. I do not intend to offer a solution. I think it is important that we remain aware of its existence and of the fact that physicians are just as human as everyone else. Unfortunately, what I said on this matter in my statement of 1960 is as true today as it was then. "There are far too many physicians who must still be taught the difference between a free golf ball, the magnetic personality of a detailman, and a scientific fact as criteria for the evaluation of a drug."

THE PHYSICIAN'S PRIVILEGES AND PREROGATIVES

The ease with which objectivity can be destroyed is only one of many signs that the relationship between the drug industry and a considerable segment of the medical profession is contaminated. Both the AMA and individual physicians have demonstrated that they are quite willing to pull the drug industry's chestnuts out of the fire when they can, at the same time, serve their own interests. Both the AMA and the PMA have long paid lip service to the principle of upgrading the scientific stature of the FDA. Yet each time this principle has been tested, either the AMA or the PMA or both have demonstrated that they are not prepared to practice what they preach. They have proposed instead glib anti-scientific solutions.

The AMA probably represents the majority of the nation's more than 200,000 physicians. Whether it speaks for them is not clear. In any case, the cozy "you scratch my back and I'll scratch yours" relationship that exists between the AMA and the drug industry raises some serious questions.

One of the first major confrontations between government and medicine (regarding drugs) came in the "Kefauver Hearings." At that time, to use the words of Dr. William Bean, ". . . the AMA in its fear . . . euchred itself into [an] astonishing posture . . ." It suggested a solution that made "every physician his own Pasteur." Even after the bill became law, anti-science still reigned, and the AMA House of Delegates resolved that "the AMA attempt to have removed from the Kefauver-Harris Amendments those provisions which author-

ize the U.S. Food and Drug Administration to determine the effectiveness of drugs." Anti-science is still with us.

Another major confrontation came in 1963 when the FDA, following the recommendations of a panel nominated by the prestigious National Academy of Sciences proposed banning the sale of antibiotics in combination with cold preparations intended for symptomatic relief. The response of the drug industry, the PMA, the APA, and individual physicians constitutes one of the most shocking episodes in the history of American medicine. Although it is documented in the record of the "Humphrey Hearings" (pp. 1502–1530) and has been described by Morton Mintz in *By Prescription Only*, it has received little attention in the medical community.

I had intended simply to mention this episode and give the references. During the preparation of this statement, however, it became clear that we were heading into another major confrontation between the FDA and the drug industry, which is almost exactly the same as the confrontation that took place in 1963. In the hope that it might help to prevent a repetition of the 1963 episode, it seems worthwhile to give some account of the genesis, the life and the death of the proposed ban.

Sometime in 1962 became concerned about the inclusion of antibiotics in mixed cold preparations intended for symptomatic relief and in throat lozenges and troches. Concern about these products had been expressed in the medical literature since 1953. The FDA finally decided that these uses of antibiotics were irrational and should be studied. It requested nominations for a panel of experts from the NAS and selected from the nominations a panel chaired by Dr. Harry Dowling, an internationally recognized expert on infectious diseases and antibiotics.

The report and recommendations of the panel led Dr. Ralph Smith of the FDA to write to his superior recommending (as the law requires) publication in the *Federal Register* of a proposal to remove antibiotic containing cold preparations from the market. In his letter, Dr. Smith said, "the proposal is likely to be met by substantial industry opposition." This will probably stand as one of the greatest understatements of all time.

I doubt that more than a handful of practicing physicians read the *Federal Register* and so the information reached physicians through other channels. These were accounts in the media controlled by the AMA, in throw-away journals that subsist on drug advertising, and in letters mailed to physicians by a large drug company.

I have a clipping from the *J.A.M.A.* of November 23, 1963 which is typical of accounts that help to mold the opinions of the medical profession. It is too long to read it in its entirety, but I request that it be made part of the record. In it both the PMA and the AMA take turns labeling the proposed ban "unauthorized interference with the practice of medicine . . . government fiat . . . governmental dictation . . . regulatory fiat . . . (and) coercion."

To expect the average physician to consider any issue dispassionately when presented in such inflammatory language is equivalent to expecting a bull to become reasonable by waving a red flag at him.

The response of physicians was hardly surprising. One account (*The Pink Sheet* September 16, 1963) stated that "over 100 letters of protest" were received by the FDA. Another account (John Troan, *Washington Daily News*, November 12, 1963) stated "about 1,000 physicians have filed protests with the FDA." This larger figure may reflect the difference that appeared in the month that separated the two reports. It appears that only one physician, Dr. Joseph K. Ackerman, wrote to the FDA approving its proposed action. His letter appears in the record of the "Humphrey Hearings", (p. 1523) and I quote part of it: "The opinion of a minority of experts is of much greater value than the opinion of a majority of practitioners who have had an irregular and inadequate exposure to competent and objective pharmaceutical literature. Whether their opinion has the political leverage is another thing again."

There was one other letter that supported the FDA position but it was sent to *Medical World News* rather than the FDA. I wrote the letter in response to a news article entitled "Curb on Cold Remedies Faces Fight" which appeared in the September 13, 1963 issue of that journal. The letter appears in the record of the "Humphrey Hearings", (p. 1523) and I quote it in part from that source. "If the drug industry is successful in urging medical leaders to lodge a formal protest against the proposed ban on antibiotic mixtures . . . the caduceous should be at half mast . . . If 'thousands of physicians' have found these mixtures useful, it should be easy to collect conclusive data demonstrating that

utility. The drug industry can answer the FDA's objections better by collecting and submitting those data than by blowing up an emotional storm over 'interference' with the physician's prerogatives . . . the real need is for data not protest."

At the same time I sent a personal letter to one of the members of Dr. Dowling's panel in which I exhorted him to stand fast and to urge the panel not to be swayed by irrational protest regardless of its volume. I pointed out that if the panel and the FDA capitulated they would set a precedent for an incredible policy, namely drug evaluation by mass protest and by testimonial.

Subsequent events demonstrated that the majority of practicing physicians with "irregular and inadequate exposure" had the "political leverage" and prevailed. The FDA retreated and extended the period for filing comments for two months. Subsequently, it appears, both the FDA and the panel did capitulate and this bold, but rational, step toward sound medical practice came to naught. Capitulation in the face of voluminous and vehement protest is understandable, but nonetheless regrettable. It is incredible that testimonials and irrational protest can be so effective.

If scientific data ever were presented I have no knowledge of such data. Even the AMA (in the article quoted above) gave a pathetically weak and specious argument to justify the continued use of these irrational combinations of drugs. In defense of these products the AMA said: "It seems that many phsyicians in practice prefer to prescribe such a mixture of drugs because they believe that each drug in the mixture will have a specific desirable purpose." The AMA still clings to the fiction that every physician is his own Pastuer. It would probably prefer to forget that there was a time when it refused to accept advertising for drug combinations.

The AMA also gave its usual glib solution as the answer to the problem of irrational antibiotic-cold preparations. According to the AMA the answer lies not in FDA action but in "education of physicians" and "labeling." If the experience with chloramphenicol is an example of what can be accomplished by physician education and labeling, it is high time we began to search for other solutions.

The weight that should be given to the average practitioner's concept of the problem is reflected in one of the letters to the FDA quoted by John Troan. The latter came from a small local medical society and said: "We deeply resent this proposed usurpation of our prerogative to *treat and diagnose* our individual patients and our prerogative to err if that be the case." I have added the emphasis because as a psychiatrist I have always found the Freudian slip that reverses the order of the terms *diagnose* and *treat* of special interest. I am still awed by the arrogance the latter expresses.

According to the PMA and the AMA these views should be given the same or greater weight than that given to scientific evidence derived from controlled studies. Testimonials are still testimonials regardless of their numbers. The irrational does not become rational by virtue of volume.

If the entire antibiotic combination episode is an illustration of how the drug industry, the medical profession, and their chosen representatives the PMA, and the AMA seek to enhance the scientific stature of the FDA and how they seek to promote sound medical practice, it leaves much to be desired.

Curiously, all the sound and fury was over nothing since the proposed ban did not interfere with the physician's prerogative to prescribe as he chooses. It did proscribe the marketing of certain irrational mixtures, but the physician was still free to prescribe a cold preparation and to write a prescription for any antibiotic of his choice in those cases where it was indicated.

If the FDA cannot proscribe the marketing of irrational mixtures of drugs because that proscription infringes on the privileges of physicians, Congress and the people should re-examine those privileges. This is clearly an abuse of privilege and should not be tolerated. According to a Supreme Court decision the people give privilege to professions and the people may take it away.

The stage for the pending confrontation between the FDA and the drug industry was set in 1962 when Congress approved the efficacy provisions of the Kefauver-Harris Amendments of the Drug Act. At that time Congress had a clear choice between exempting drugs approved for safety only during the period between 1938–1962, under a grandfather clause, or making the efficacy provisions retroactive. In choosing the latter course Congress gave the FDA a clear mandate to re-evaluate all such drugs for efficacy and unleashed forces of explosive potential.

Probably because the leaders of the FDA recognized this explosive potential they elected not to exercise the authority given them by Congress until 1966. At that time the FDA, under the inspired leadership of former Commissioner Goddard, accepted the assistance of the FAS–NRC and select panels began the long review. The findings and recommendations of these panels have begun to filter down and the FDA either has published or plans to publish its intention to ban the marketing of certain irrational combinations. The most recent decisions deal with irrational antibiotic mixtures. While these steps are rational they fail to make allowance for the irrationality of the drug industry, the AMA, and a segment of the medical profession. The drug industry and its friends operate under a different set of rules which can be stated quite simply. Whenever a drug, through rational or irrational usage, has acquired a place in the Art of Medicine it is no longer subject to any scientific scrutiny. Morton Mintz caustically labelled this the "Hussey-Stetler Test of Time." Any attempt to subject a drug that is already on the market to sicentific scrutiny is met with howls of protest over interference with the privileges of physicians. If we accept this abuse of privilege we set scientific concepts of drug therapy back to the Middle Ages.

The spectacle of the drug industry acting as the champion of the privileges and prerogatives of the physician would be amusing if it did not have such serious consequences. The drug industry is interested in encouraging irrational prescribing and thereby increasing sales volume, not the rights of the physician. In my statement of 1960 I said: "The incidence of disease cannot be manipulated and so increased sales volume must depend, at least in part, on the use of drugs unrelated to their utility or need or, in other words, improperly prescribed." Today I would go a step further than I did in 1960. Probably the major part of the sales volume of many drugs (and especially combinations) is dependent on their being prescribed improperly or irrationally.

We can only hope that the FDA and the panels will not be swayed as they were in 1963. We have had more than enough of drug evaluation by mass protest. We have had more than enough of political leverage. We have had more than enough of irrational prescribing, and of anti-science. If there is such a thing as a science of medicine then let us behave as if we believe it. The pharmacologic action of drugs is a Science not an Art. Those who believe it is an Art should limit their prescribing to innocuous placebos whose activity does indeed depend on art.

Unfortunately there are rumors that the FDA may be returning to the doldrums it was in for more than 30 years prior to Dr. Goddard's leadership. Dr. Goddard was a realist and recognized that the industry had to be dealt with as an adversary. To deal with the drug industry in any manner than as an adversary is not only unrealistc; it is nonsense.

IRRATIONAL PRESCRIBING

The Task Force on Prescription Drugs simply accepts the existence of irrational prescribing. For obvious reasons it makes no attempt to answer the all-important question about the incidence of irrational prescribing. It does state: "We find that few practicing physicians seem inclined to voice any question of their competency in this field. We have noted, however, that the ability of an individual to make sound judgments under these quite confusing conditions is now a matter of serious concern to leading clinicians, scientists and medical educators."

There are two quite different ways to practice medicine. One calls for precise, pinpoint diagnosis and the aiming of a handloaded rifle bullet at the center of the target. Unfortunately, this method is not always available; an overwhelming potentially fatal infection is an obvious exception, but this is the primary method taught in medical schools. The other method, which is not taught in medical school, seeks only some general categorization of the patient's illness, such as anemia, infection, or gastro-intestinal disorder and either letting loose a shotgun blast in the hope that one of the pellets will find the mark, or firing one or more rifle bullets in random fashion hoping, again, that one will reach the bull's eye. These are examples of irrational prescribing and unsound medical practice.

This latter method of practice requires far less skill, much less time, and uses much more medication than sound medical practice. Because it is easier, it has more and more appeal as the physician becomes more hurried, more harried, and more confused. Because it uses more drugs, the drug industry encourages the practice in the "education" it gives in its advertising and promotion efforts. It is easier than you will believe to fall into the habit of thinking fever equals infection equals a prescription for chloramphenicol. Viewed in this light, the misuse of chloramphenicol becomes more understandable since chloramphenicol is

one of the biggest shotguns of them all. As I said in my statement of 1960: "Too many physicians, pressed for time, would like to believe that medicine can be practiced with a clinical thermometer and a bottle of pills."

There is nothing new or unique in this description of irrational prescribing. As far back as 1953 Dr. Maxwell Finland, an eminent authority on antibiotics, dealt with the problem in a scientific paper. Under the heading "Omnibiotics" Dr. Finland said: "The physician in practice, and many of his patients as well, are constantly on the lookout for some simple substance or formula which they can apply with universal success. The busy practitioner is particularly desirous of having some major weapon on which he can always rely to be successful in all types of infections, and would thus relieve him of the responsibility and trouble involved in the complicated or even simple diagnostic procedures" ("Humphrey Hearings" p. 1507).

In addition to precision in diagnosis (and treatment), medical schools also teach the painful and anxiety provoking process of watchful waiting when the diagnosis is not clear and a laissez faire attitude when the complaint is not serious. Watchful waiting does provoke anxiety and requires much more continuous attention to the patient's changing condition. Laissez faire leads many patients to object because they feel their complaint has not been taken seriously. In either case, only too often, the physician feels compelled to write a prescription, even though the prescription does more good for his anxiety or his convenience than it does for the patient's illness. It also exposes the patient to the additional hazard of drug induced illness which may or may not obscure the underlying cause of the original illness, and may or may not make the cure worse than the disease.

Because it feels that rational prescribing and sound medical practice cannot be legislated, the Task Force leans heavily on education, at both the medical school and the post-doctoral levels, for a partial solution of the problem. While I cannot gainsay the value of education I am dubious about the effectiveness of physician education in this particular area. I am forced to ask the question I asked in 1960. Since it is a long one, I will paraphrase it. Is it reasonable, I asked, to expect legitimate education to compete with modern methods of advertising and promoting drugs? My answer was then, and still is, an unqualified no. Education is not enough and I believe the experience with chloramphenicol, among other drugs, proves it. I agree that rational prescribing and sound medical practice cannot be legislated. We can, however, enforce legislation that exists and consider new legislation, if necessary, to choke off at least part of irrational prescribing and thereby contribute to sound medical practice.

The irrational use of drugs has at least two facets. On one hand we must deal with single drug entities which have specific but limited use and, while they may be irrationally prescribed, are still the drugs of choice in some disorders. Chloramphenicol and penicillin are examples of drugs that have specific uses but are often improperly prescribed for disorders for which they are not indicated. On the other hand, we have irrational combinations of drugs which serve only to encourage irrational prescribing. If the use of these drugs were limited to those occasional cases where they might by stretching reason, be indicated they would wither on the vine and their sale would become unprofitable. Invariably the purpose of these drugs can be served equally or better by prescribing the ingredients separately in those rare cases where more than one drug is indicated. Antibiotic containing cold preparations and the combination of amphotericin B with tetracycline are examples of combinations in this category. We cannot ban products in the first category. We will have to accept the mususe and abuse of these drugs until education or publicity or both reduce such improper use. We should, however, ban the marketing of irrational combinations even if it requires new legislation. We probably will have to interfere with the privilege of the medical profession arrogates to itself but rational prescribing and sound medical practice must take precedence over the AMA's the PMA's or the individual physician's concept of privilege.

Naturally it woul be preferable if the medical profession policed itself. If the AMA could cure itself of its phobia over government control it could serve a useful purpose in contributing to sound medical practice. So long as it adopts astonishing postures it invites regulatory control. Experience has demonstrated that the AMA is phobic and that neither the drug industry nor a considerable segment of the medical profession is prepared to police itself. Actually the AMA and the medical profession should serve as the first line of reserves behind the FDA in the battle to curb the excesses of the drug industry. Instead of supporting the FDA, the AMA and a segment of the medical profession have joined

forces with the drug industry and as allies they wage war against a common enemy, the FDA. The combined efforts of the drug industry and its allies make the anti-regulatory forces so powerful that it is doubtful that the FDA alone can deal with them. Reform and tighter regulation of drugs (and especially combinations) is clearly required. Firm action and support of the FDA by Congress, the people, and the leaders and educators in medicine is in order.

In conclusion, let me quote Senator McCumber, who, arguing for the Food and Drug Act passed in 1906, said: "You cannot, for years, surround a people with crime and deceit and imposition on every side without it, in time, affecting the moral character of the people. Constant association with crime and deceit dulls our senses to offenses of that nature." I do not believe that his language is anachronistic. We have come dangerous close to repeating the conditions he described.

PRINCETON, N.J., *March 26, 1969.*

Hon. GAYLORD NELSON,
U.S. Senate, Washington, D.C.

DEAR SENATOR NELSON: Let me take this opportunity to express my regret that I was unable to be present at the hearing.

Under separate cover I am sending you the answers to the questions raised by you and by Mr. Gordon regarding my prepared statement. Whereas my statement was, indeed, prepared and went through several drafts and revisions before it took on a form I was partially satisfied with, I have not used this method in answering the questions.

I have simply sat with a typewriter and allowed myself to reminisce allowing the flow of one thought to lead on to the next. This gives the answers a random and sometimes even a repetitive quality. Nevertheless, it is essentially what I would have said had I been present at the hearing. I have added exhibits and source material which brings this part of my statement up to date.

If there are questions that remain unanswered, or if the answers raise further questions or need clarification, please do not hesitate to let me know.

Sincerely,

A. DALE CONSOLE, M.D.

DR. CONSOLE'S ANSWERS TO QUESTIONS SUBMITTED BY SENATOR NELSON

Question. (a) How can legitimate education compete with the millions upon millions of dollars spent on advertising and promotion, gifts and financial grants to physicians, financing of journals and meetings and gifts to students? Wouldn't you say that this is a rather uneven struggle? (b) What has been the role of the medical organizations in helping the doctors get scientific, unbiased information?

Answer. The struggle is indeed, an uneven one. As I pointed out in previous testimony, industry alone commands the resources necessary to make propaganda effective. How can legitimate education compete with the carefully contrived distortions driven home by the triphammer effect of weekly mailings, the regular visits of the detailman, the two page spreads, and the ads that appear six times in the same journal; not to mention the added inducement of the free cocktail party and the golf outing complete with three golf balls stamped with the name of the doctor and the company in contrasting colors? Drug advertising and promotion efforts encourage the doctor to believe that there is an easy way to practice medicine. They offer larger and larger shotguns which make pinpoint diagnosis, or for that matter any diagnosis at all a pedantic exercise and a troublesome inconvenience that only the less informed academician bothers with. The sound practice of medicine is a rigorous discipline. There are no short-cuts. There are no easy ways to achieve the necessary goals. There are no omnibiotics or shotguns that eliminate the need to think, and to worry. The disparity between legitimate education and drug advertising and promotion is not only in the quantity of the blandishments the drug industry offers, but also in the quality of the piece of candy dangled in front of the physician's nose.

With respect to the role played by medical organizations, it is difficult to generalize. There are thousands of such organizations ranging from county medical societies to the select clubs consisting almost exclusively of blue bloods. I have maintained my membership in the Society of University Surgeons primarily because it tends to fall in the latter category. Although I have been a

member for almost 20 years I have never known it to offer a program intended for drug promotion. This is in contrast to the New York Academy of Science from which I, among others resigned because it began to sponsor obviously biased "symposia" which were nothing more than grandiose promotion programs intended to push a particular product.

So long as the average practioner is the captive of the drug industry, and I am convinced he is, and medical organizations are made up of physicians who are captive, it follows that the organizations are in turn captive. The real question is not whether they are captive but rather the degree to which they are captive. Those who publish a journal and derive income from drug advertising are probably even more captive that the average practitioner. Those who derive such income cannot deny that a conflict of interest exists. The AMA's contention that it is not a party in a tacit conspiracy with the drug industry is not convincing. Its denial fails to explain the astonishing, unscientific, pro-drug industry positions it has taken. It has given shelter to the drug industry under the cloak of immunity given to physicians, and the drug industry has been more than willing to accept the shelter since it gives the industry an ethical image while it uses the same profit-oriented tactics of any big busines. It pays well for the shelter by buying advertising pages. As I suggested in my prepared statement, the AMA is serving its own interests and the support it gives the drug industry is secondary. In my opinion this is simply a definition of conflict of interest. I would not expect the AMA to put the drug industry's interests before its own. I wish to make it clear that I have used the term propaganda to describe the drug industry's "education", in terms of one of Webster's definitions of propaganda; "any systematic, widespread, deliberate indoctrination, or plan for such indoctrination; now often used in a derogatory sense connoting deception or distortion".

As we speak of propaganda as opposed to education I am reminded of recent reports in which the AMA, trying to keep its significant income derived from drug advertising tax free, has quoted Dr. Goddard to the effect that drug advertising is educational. I do not know the source of this quotation or whether the quotation is being used in or out of context. If it is accurate and in context, I can only say that I disagree with Dr. Goddard. The concept that the merchant who hawks his wares serves an educational purpose is a travesty.

Finally let me point out that I devoted a major portion of my 1960 statement to exploding the myth that drug advertising is educational. I enclose a mimeographed copy of that statement which you may wish to make a part of the record of these hearings.

Question. On page 3 of your statement you refer to your experience in getting the endorsement for a particular product. Was the product worthy of an endorsement? What form did the endorsement take?

Answer. I have deliberately kept this part of my statment vague since I would not want, under any circumstances, to reveal the name of the physician involved.

I have said in my statement that I did not believe the product deserved endorsement at the time of the incident. Since that time nothing has happened to change my opinion. I can add, that it was a combination product which as a fixed combination was rarely, if ever indicated. The doctor involved was a vocal opponent of all such products and frequently mentioned our product by name. The "endorsement" was actually an agreement on his part to discontinue this practice. I essentially promised that we would limit our claims, but over the years the promise was not kept. The doctor did not know that the mere fact that we could market it with any claims at all had already led to widespread misuse.

Question. When you were a drug company medical director, did you ever instruct detail men in how to sell drugs? What kind of techniques of selling did you present to the detail men? How effective were these techniques on the physicians? Was the aim to make physicians prescribe more intelligently?

Answer. During my time in the drug industry I had a close ongoing relationship with detailmen. It was from one of them that I learned the simple maxim I drew attention to in my 1960 statement; "If you can't convince them, confuse them". During my time I attended detailing "clinics" and "workshops" and I played an important role in introducing new products to the entire detail staff (I believe it was about 500 men at that time).

The primary purpose of detailing (as is true of all advertising and promotion efforts) is to sell the company's products. Any and all other goals are secondary. The company that has exclusive rights to a new drug that is truly useful is fortunate, indeed. This is a rare occurrence and those companies (e.g. Smith, Kline and French) who have been in such a position even for a few years have

made a fortune. Even so SKF made a strong bid for the Miltown market in its detailing, advertising and promotion.

Most often the new product is a duplicative "me too" that resulted from patent evading molecular manipulation, a combination that has, at best, an extremely limited market, or an uninspired drug that must compete with a host of competitive drugs already on the market. Not infrequently a drug that represents a real breakthrough is useful only in a very small number of patients (simply because the disorder is a rare one) and there is always the temptation to increase its sales volume by extending the indications to include patients who do not need the drug. In teaching and instructing detailmen one must attempt to instruct and inspire them over a product that is, more often than not, uninspiring in order to increase sales volume to its maximum point.

A detailman is a salesman and, as is true of any salesman, his enthusiasm about the product he is selling plays an important role in how many sales he makes. The members of my staff and I were only a part of the manpower used to whip up enthusiasm over a humdrum concoction. In addition, innumerable prizes ranging from cutting boards to sets of monogrammed glasses are given to those detailmen who reach or exceed a pre-set quota of sales. Since I was the confidant of many of the detailmen I learned that many of them had convinced, or confused, a doctor to prescribe one of our products by telling the doctor that they were only one step away from winning a prize.

It is my considered opinion, regardless of what may be said by even a majority of average practitioners, that detailmen are nothing more or less than extremely expensive parasites. The Task Force estimates that there are 20,000 detailmen employed by the drug industry. I estimate that the cost of maintaining a detailman is somewhere near $20,000 per year. This is a minimum rather than a maximum estimate, and so we are speaking of an expenditure on the order of one half billion dollars. This amount is, of course, deducted as part of the cost of doing business when income tax is calculated. In brief, the public pays a large part of the expense for the support of the detail man and pays it twice.

I went into psychiatry on the crest of the wave of psychopharmacology and so I am psychopharmacologically oriented. I use drugs when they are indicated and I use many of them. In almost 10 years of practice I have never seen a detailman and only about a half dozen have called my office trying to make an appointment. My refusal to see detailmen is based both on my experience in training them and on their confiding to me the methods they use to make a sale. I am not aware that my ability to practice psychiatry or my knowledge of the many drugs used in psychiatry have suffered by the absence of the detailman. I would rather take the advice of an uninvolved, impartial expert than be guided by the claims made by the merchant hawking his wares. I can express my overall opinion about detailmen best by paraphrasing Oliver Wendell Holmes; if all detailmen were dumped into the sea it would result in the betterment of mankind and detriment to the fishes. The primary purpose of the detailman is to make a sale even if it involves irrational prescribing and irrational combinations that contain a prophylactic ingredient furnish an ideal path to confusion. There are drugs whose merit is such that there is no need to mislead or confuse the physician.

If the physician does any reading at all, he has no need for the detailman. If we could legislate the detailman out of existence this could well prove to be the most important piece of drug legislation enacted. The detailman is not the expert both the industry and the apologists claim he is. His detail is often "canned" or is at best a paraphrasing of what he has been told to say. A standard answer to a question he has not been drilled on is to be modest and claim he would not want to tell the doctor how to practice medicine (not much). Or the detailman tells the doctor that he will forward his question to the home office. In this case an expert does the confusing rather than the inexpert detailman.

Question. Dr. Paul Lowinger of Wayne State University recommended to the committee that investigators working on a drug know who the other investigators are and the results of their work. This could save a lot of time by pointing out failures and pitfalls. What do you think of this idea?

Answer. In any kind of large scale research, proper coordination of the research is almost as important as the research itself. My suggestion that a central agency act as an impartial intermediary between the drug company and the investigators was predicated on the assumption that the central agency would serve as a coordinator. So long as rights regarding publication are respected, failure to follow Dr. Lowinger's suggestion would be foolish.

Question. The AMA testified before the Kefauver Committee (Pt. I, p. 87 Drug Industry Antitrust Act):

"* * * *inevitably a useless drug will not be used because of the training and experience of physicians because of their experience with this useless drug, if it is permitted to be marketed.*

"* * * *We feel that a profession fully knowledgeable in a free market economy will soon bring about the withdrawal from the market of a useless drug.*"

What do you think about this?

Answer. I believe this is much more a semantic exercise than a statement that requires refutation. In the first place, if we use the AMA's definition of utility, there is no such thing as a "useless drug". Milk sugar or any other inert ingredient when put into the form of a tablet, a capsule, a solution for injection, or any other dosage takes on the properties of any placebo. Administered as a drug it can produce temporary relief in a host of disorders and even cure in disorders that are self limited. It can also produce side effects that lead the patient to refuse to take the "medication". If we use a *pharmacological* definition, milk sugar is a useless drug. If, on the other hand, we use changes that may be observed in some patients by physicians who do not know that it is an inert substance, and especially if they have been preconditioned to expect beneficial effects, milk sugar becomes a useful drug. This is the yardstick used by the AMA.

A combination of meprobamate and benactazine (Deprol) has been marketed as a useful agent in the treatment of depression for at least ten years. Most experts agree that it has no demonstrable value in the condition for which utility is claimed. Yet it has withstood the "Hussey-Stetler Test of Time" which the AMA, by its own admission, feels is the ultimate test of the utility of any drug.

Vitamin B 12, especially in the form of 1,000 microgram injections, has an extremely limited use. If its use were restricted to those patients who really need it I would guess that the amount now used in one year would be enough to treat patients with true Vitamin B 12 deficiency for almost one hundred years.

The absurd limits to which average practitioners go is illustrated by my own experience with Vitamin B 12 during the time I was Medical Director. Because claims for its utility in many neurological disorders ranging from peripheral neuritis to trigeminal neuralgia and herpes zoster, as well as claims for utility in loss of appetite, underweight, poor growth, etc, were based purely on testimonial evidence I refused to approve such claims in our literature on the drug. I answered the detailmen's immediate complaint by pointing out that our brand of Vitamin B 12 was therapeutically equipotent with any brand on the market. If the doctor believed that it was indicated in any condition other than true Vitamin B 12 deficiency, our brand would meet the need as well as any other brand. For many months after I made this decision I received letters of complaint not only from detailmen but also from practitioners (who were probably told by detailmen that I would like to hear from them). Our sales volume fell off, and there is adequate reason to conclude that many practitioners actually believe that the pharmacological effects of a drug are dependent upon the labeling that accompanies a drug. This is true not only of labeling that makes claims but also of labeling that does not make claims. Many physicians obviously believe that a drug that is identical with competitive drugs becomes inferior by virtue of the fact that it makes fewer claims than the competitive products. This is one of the more obvious illustrations of the irrationality of practitioners and the irrationality of their prescribing habits.

The rapid rate of obsolescence of drugs is dependent not on the wisdom imputed to the average practitioner by the AMA, but rather on his lack of wisdom. "Since so much depends on novelty, drugs change like women's hem-lines and rapid obsolescence is simply a sign of motion, not progress as the apologists would have us believe . . . with a little luck, proper timing, and a good promotion program any bag of asafoetida with a unique chemical side chain can be made to look like a wonder drug. The illusion may not last, but it frequently lasts long enough. By the time the doctor learns what the company knew at the beginning it has two new products to take the place of the old one." Not infrequently the doctor never learns and the obsolete drugs remain on the market. Oral Mephenesin is a good example.

The "Hussey-Stetler Test of Time" deserves the contempt that Morton Mintz heaped on it. The uncontrolled observations of average practitioners constitute testimonials and as such have zero validity in the scientific evaluation of a drug. Whether we multiply zero by 1,000, 10,000, or 300,000 the answer is still zero. The contention that the fate of a drug in the market place is an accurate index of its value as a drug simply is not true.

Actually my first exposure to the principle of the test of time and the market

place came at least five years before the AMA gave its incredible testimony in the "Kefauver hearings."

The position taken by the AMA was criticized by several medical experts including Dr. Bean, Dr. Butler, and Dr. Goodman, among others. Perhaps the clearest (and the most humorous) description of the AMA's position is that given by a layman, Miss Barbara Yuncker, a reporter for the New York Post. I enclose a photostat of her article entitled "AMA Delirium" and have marked it Exhibit #5. I request that the entire article be made part of the record or that the portion bracketed in pencil be quoted as part of my statement.

I believe it was in 1953 that Squibb arranged an exclusive licensing agreement with a German firm that gave us rights to market some of their products. They were asked to send me supporting data that would permit me to decide which products I could approve. The supporting data they sent were sales volume figures for various countries where the drugs were marketed and the advertising and promotional material found most successful. When I asked for scientific data consisting of laboratory studies and controlled clinical trials they behaved as if I were mad. I still find myself chuckling when I am reminded that the Germans did not use the terms advertising and promotion. All such material was labeled "propaganda" and one needs only to give the word a Germanic inflection to understand how it was used. The word is obviously borrowed from English and the Germans either did not know or did not care about the connotation the word has in English. They actually believed that the test of time and the marketplace plus the suggestive effect of their "propaganda" was an adequate basis for my evaluation of the drugs. Broken down to simple language this is exactly what the AMA suggests. In this particular area I, in contrast to the average practitioner, was an expert. While it is shocking, it is probably true that the chances that an average patient will get the right drug, in the right amount, at the right time is in the order of fifty percent. Ineffective drugs, drugs that are not indicated, drugs that are effective in disorders different from the patient's illness, unnecessary ingredients in combinations, and placebo doses are only some of the pit-falls. The unluckiest patient of all is the one who needs no drug since, if he has a complaint it is almost impossible to get out of the average practitioner's office without a prescription.

Question. Isn't it true that there have been dangerous drugs put on the market? And many of them have been taken off the market? Do you know of any case in the last ten years of the AMA urging that a drug be taken off the market because of lack of safety or efficacy?

Answer. The list of drugs that are dangerous and have had to be taken off the market is long. Some of them unfortunately are still on the market and should be removed. Off hand I think of MER/29, Orabilex, and Marsalid in the first category. Parmate (tranylcypromine) is, in my opinion, in the second category. We may have reached the point where chloramphenicol is also in that category.

If in the last ten years the AMA has initiated action to take a drug off the market because of lack of safety or efficacy that action has not come to my attention. It has played an important role in fighting quackery (e.g. Krebiozen), but it seems to be determined to deny that quackery exists in the ethical drug industry.

Question. (a) What is the role of testimonials in the advertising and promotion of drugs with respect to efficacy and safety?

(b) How about reprints of articles in journals which subsist only on the purchase of reprints by the industry?

(c) Do you know of cases when independent doctors signed their names to articles and letters written by the drug company?

(d) How did you get testimonials (when you were a medical director)?

(e) Did you pay for them?

(f) Were they included under research or advertising?

(g) Have you had any experience of distinguished physicians and scientists turning down a drug and then by sending the drug to the "right type" of doctor, "proof" of the drug's usefulness was finally secured?

(h) Is it a common practice for drug firms to purchase reports in favor of drugs?

Answer. Before answering this question I wish to make it clear that I bear no malice toward Squibb. Actually, I regret the need to implicate Squibb at all, but if my testimony is to carry any weight I must choose between mentioning them or remaining silent. Since I interviewed innumerable physicians who had served other companies as possible candidates for my staff, and had other dealings with