COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

HEARINGS

BEFORE THE

SUBCOMMITTEE ON MONOPOLY

OF THE

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

NINETY-FOURTH CONGRESS

SECOND SESSION

ON

PRESENT STATUS OF COMPETITION IN THE PHARMACEUTICAL INDUSTRY

PART 32

MAY 26 AND 27, 1976

PHARMACEUTICAL COMPANY PRACTICES IN LABELING AND PROMOTING PRESCRIPTION DRUGS SOLD IN LATIN AMERICA

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APPENDIX

HEARING DATES

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

WEDNESDAY, MAY 26, 1976

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

The subcommittee met, pursuant to notice, at 10 a.m., in room 318, the Russell Senate Office Building, Senator J. Glenn Beall, Jr. presiding.

Present: Senator Beall.

Also present: Benjamin Gordon, staff economist; Judah C. Sommer, minority counsel; and Karen Young, research assistant.

Senator BEALL. The subcommittee will come to order.

At the outset let me apologize for keeping everybody waiting. When Senator Nelson graciously asked me to preside on his behalf, we had to readjust our schedule.

As you can note, there is one light on above us which indicates there is a vote on the Senate floor. I will make a brief opening statement. We will start the testimony. I will disappear briefly while you are giving your testimony and I will be right back after I vote, however.

The Monopoly Subcommittee of the Senate Small Business Committee is holding hearings today and tomorrow on drug company practices in the promotion and labeling of drugs in the United States and Latin America.

The subcommittee has accumulated considerable evidence over the years that the drug companies are not telling the same story about their drugs in all countries. Claims for their effectiveness and the extent of disclosure of hazards vary from country to country. A particularly blatant example is the well-known antibiotic chloramphenicol. While the labeling in this country mentions serious side effects, including aplastic anemia, grey syndrome (which causes death) and says that this drug should be used only when less dangerous drugs are not effective, the labeling in Italy stated that:

> It is a very significant fact that Chloromycetin therapy is conspicuously devoid of side effects. The medication enjoys a high degree of tolerance with both adults and children. In the few cases where reactions have occurred, these are generally limited to mild nausea or diarrhea and only rarely does their gravity impose suspension of treatment.

It is interesting to note that at the annual meeting of the stockholders of the Warner-Lambert Company in 1972, 97 percent of

the stockholders voted "no" to a resolution that the corporation change its policy by divulging to foreign doctors what U.S. law now demands that it tell U.S. doctors about the toxicity of its Chloromycetin, a product of its Parke-Davis division.

Many drugs have been removed from the market in the United States—about 6,000 of them in the last few years—because of lack of efficacy or unreasonable risks to the public. Yet these same drugs are still being sold in foreign countries. The effect of these practices on the people of these countries, especially Latin America, as well as on the U.S. public, will be discussed by our panel of distinguished witnesses today and tomorrow.

The first witness is Dr. Milton Silverman, who is a lecturer in pharmacology, the schools of pharmacy and medicine, and the senior faculty member of the health policy program at the University of California in San Francisco.

Dr. Silverman, it is a pleasure to have you with us this morning and we look forward to receiving your testimony. You may proceed. And, as I said, during the course of your testimony I will slip out to go vote but I will be right back. But do not let my departure deter your testimony in any way. You may proceed as you wish.

STATEMENT OF MILTON SILVERMAN, PH. D., LECTURER IN PHARMACOLOGY, SCHOOLS OF PHARMACY AND MEDICINE, AND SENIOR FACULTY MEMBER, HEALTH POLICY PROGRAM, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, CALIF.

Dr. SILVERMAN. Thank you, Mr. Chairman.

I am pleased to be able to respond to your invitation and to meet with you today to report on how the multinational drug companies promote their prescription drug products to physicians in this country and to physicians and other health professionals in a number of Latin American countries.

I must note at the outset that I am not a physician myself or a pharmacist. I am a pharmacologist. And I must further note that any views I may express here today are entirely my own, and do not necessarily represent those of my university.

And, as a final prefactory statement, let me acknowledge that without the dedicated and courageous pioneering investigations conducted by this committee, and especially by Senator Nelson and Benjamin Gordon, much of the work that my colleagues and I have been able to accomplish over the past few years in our own investigations would have been far more difficult if not totally impossible.

The research on which I am prepared to report today will be officially published tomorrow by the University of California Press under the title "The Drugging of the Americas." It involves an indepth study of the promotion to the medical profession of 26 different drugs—active ingredients—marketed in the form of some 40 products by 23 global drug companies.

Most of these companies are based in the United States, but it is important to note that some of them are based in Europe, notably in Switzerland, France, and West Germany.

The drugs that we selected for investigation are, beyond doubt, valuable and in some cases lifesaving. There can be no question that they

have saved many lives, not only in this country but in the Latin American countries. But their effective use depends on their appropriate use. Although each is demonstrably effective in one or more conditions, each has equally demonstrable hazards. Some of the side effects may be only annoying, like a stuffy nose or a rash, others may be serious or fatal. And it is only with the knowledge of both, the good and the bad, the advantages and the potential hazards, can a physician in any country select the right drug to prescribe for each patient to get the maximum benefit with the least possible risk.

In the United States physicians are given such information—the good and the bad—in the package insert or in what is known as "Physicians' Desk Reference," or PDR, with which I know some of you are quite familiar. The drug company is not obliged to publish in PDR; he may elect to do so in the form of paid advertising. This book, sometimes called the "bible for prescribers," is distributed annually at no cost to every practicing physician of this country.

Although the statements in both the package insert and PDR are prepared and paid for by the drug industry, no firm can make any statement it wants. The claims for efficacy or usefulness are restricted to those for which the company has submitted what is known as convincing scientific evidence to the Food and Drug Administration; and all potential hazards must be fully and openly disclosed. In some cases, the company is required to include a special warning which may read something to the general effect of: "Do not use for trivial conditions."

It is important to emphasize that this information, required by law, is intended only to inform the physician. The physician, if he wants, may use the drug for any indication, approved or not. He may ignore the warnings partially or entirely.

For many years, as you pointed out, it has been known that the situation in other countries is somewhat different. As this committee disclosed at its hearings almost a decade ago, the Parke-Davis brand of chloramphenicol—known as Chloromycetin—carried warnings that were very strict in the United States but far more relaxed in Great Britain. And some of us, I am sure, will recall that when this discrepancy was called to the attention of a company official, he offered the defense that full disclosure of hazards was not required by British law, and, in fact, he went on to say that in his mind, British physicians would be insulted if full disclosure of hazards were included in advertising.

That revelation before this committee was a brief but tremendously important prelude to what we can report today.

In our own studies, we investigated these 26 drugs as they were promoted in the United States, and also in Mexico, the six Central American countries—Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, and Panama, along with the Dominican Republic—and in Colombia, Ecuador, Brazil, and Argentina.

Mr. GORDON. Dr. Silverman, why did you not also include other countries like Venezuela, Bolivia, Peru, or Chile?

Dr. SILVERMAN. Because, Mr. Gordon, in these other countries, there is no such comparable volume. The drug information is included almost entirely in the form of catalogs, which gives dosage forms,

concentrations, and price. The countries that we selected are those that have books comparable to PDR.

Essentially, we conducted a comparison of what each company said about its product to physicians in the United States through PDR, and what it said about its identical product to Latin American physicians in somewhat comparable—but not entirely comparable—Latin American reference volumes.

Two points are important here.

In the first place, I personally am in no position either to support or to condemn the policies and the decisions of FDA as these are reflected in PDR. But PDR, I think, may be viewed as a rather useful standard for comparison. It has the virtual blessings of an important governmental agency; it is based in large part on the advice of distinguished governmental and nongovernmental experts; it is widely distributed to physicians, and frequently used by them. And the drug industry in this country, although it may continue to dispute certain FDA decisions, has learned to live with them and to live with them without substantial financial trauma.

In the second place, it must be understood that PDR and the Latin American books are not exactly the same. In PDR, the statements presumably have governmental approval. The promotional statements in the Latin American books, however, do not have approval from any governmental agency; they say what the company wants to say.

Among the books that we have looked at is one known as the "Diccionario de Especialidades Farmaceuticas," which is published in one edition for Mexico—published in Spanish—another edition for Central America, and still a third edition for Ecuador and Colombia. Another, published in Portuguese, is the "Index Terapeutico Moderno," in Brazil, and another which I brought along with me is the Argentine "Therapia Vademecum," which also is somewhat different. In the case of the other Latin American books, the company says what it wants, and this is generally published without any formal or informal governmental approval or blessing.

For the Argentine book, the material is written not by the companies but by the board of editors and, accordingly, the company has no responsibility for what is published. We have included it in our study if only to indicate to our readers what kinds of information are presented to physicians in Argentina.

A second fact came out very quickly.

In the United States, the list of the contraindications, and warnings, and potential adverse reactions is lengthy and detailed. Virtually every unhappy, serious, or possible lethal side effect to which a physician should be alert is included.

But in striking contrast, the potential hazards published in the Latin American volumes are usually minimized or glossed over or totally ignored. In some instances, the company may disclose that the drug may perhaps cause stuffiness of the nose, but neglects to mention that the drug can kill you. In some cases, not a single danger is disclosed.

Let me cite a few examples.

ANTIBIOTICS

Consider first the antibiotic chloramphenicol, which has figured so prominently in the hearings of this committee. It is unquestionably a potent and useful drug, but its known dangers are such that it is promoted in the United States for only such serious infections as typhoid fever and a few other life-threatening but relatively infrequent infections in which the causative organism is shown to be susceptible to the drug.

Physicians in this country are advised not to use it in trivial infections, or when other effective but less dangerous drugs are available.

In Mexico and Colombia, the Parke-Davis brand marketed as Chloromycetin is promoted for use not only for life-threatening conditions but also for tonsillitis, pharyngitis, bronchitis, urinary tract infections, ulcerative colitis, pneumonia, staphylococcus infections, streptococcus infections, eye infections, yaws, and gonorrhea.

In Central America, a competitive brand marketed by McKesson is recommended for whooping cough.

In the United States, the Parke-Davis product carries a long list of contraindications, warnings, and adverse reactions. Perhaps the most alarming of these include aplastic anemia and other serious or fatal diseases of the blood-forming system.

In Mexico, the Parke-Davis product carries only a limited list of warnings. In Central America, no contraindications or warnings are given, and no adverse reactions are disclosed.

The McKesson product statement discloses a few hazards in Central America but none in Colombia and Ecuador.

In the case of tetracycline, marketed by Lederle under the name of Achromycin, numerous adverse reactions are given in the United States, a few in Mexico and Brazil, and none in the Central American countries.

For Squibb's amphotericin B, marketed as Fungizone, physicians in this country are told that this valuable but potentially toxic antibiotic should be used primarily for the treatment of progressive and potentially fatal forms of fungal infections. No such warning is listed in the Latin American promotion.

Schering's Garamycin carries roughly the same indications in the United States and Latin America, but the warnings are minimized in the Latin American promotion.

ORAL CONTRACEPTIVES

A similar situation was discovered in the case of a number of oral contraceptives—Ovulen marketed by Searle, Norlestrin or Prolestrin marketed by Parke-Davis, Ortho Novum marketed by Otho, Novulon marketed by Johnson, Norinyl marketed by Syntex, and Ovral or Anfertil marketed by Wyeth.

In PDR, all of these are described as indicated for only one use—contraception. In the Latin American countries, they are openly recommended for contraception, and also for the control of premenstrual

tension, menstrual pain, problems of the menopause, and a host of other conditions.

In the United States, physicians are warned of the possibility of many side-effects, especially thromboembolic changes that can lead to serious or fatal blood clots.

In Latin America, for all the products studied here, the risk of thromboembolic changes is ignored. No adverse reactions of any kind are given for the Searle product in Ecuador, Colombia, or Brazil, for the Parke-Davis product in Central America, and for the Wyeth product in Ecuador, Colombia, or Brazil.

Mr. GORDON. I might remind you that the labeling in the United States says that one out of every 2,000 women who take the oral contraceptives is hospitalized because of blood clots. That statement is not used in foreign countries?

Dr. SILVERMAN. To my knowledge, Mr. Gordon, this is not made known to Latin American physicians.

ANTI-ARTHRITICS

For Ciba-Geigy's anti-arthritis drugs Butazolidin and Tandearil, only a few indications for use are approved in the United States but many in Mexico, Central America, Colombia, and Ecuador. In contrast, the warnings are numerous in this country but few in Latin America.

No adverse reactions of any kind are disclosed for McKesson's competitive brands in Central America, Colombia, or Ecuador.

United States physicians are cautioned against the use of such drugs for prolonged periods. The result may be serious or fatal adverse reactions. A somewhat similar warning is given in Mexico, but the matter is not mentioned in the other countries.

In the United States, Merck's Indocin is approved for use in four serious forms of arthritic disease. In Latin America, many other indications are recommended.

In the case of this product, it seems noteworthy that the hazards listed in the Latin American countries are approximately the same as those given in this country.

CORTICOSTEROIDS

Four widely-used corticosteroid hormones were included in our investigation—Schering's Meticorten and Celestone, Lederle's Aristocort or Ledercort, and Upjohn's Medrol. All can be of great value in the control of arthritis, asthma, and a variety of other conditions. But all of them, especially if used for excessive periods, may cause unpleasant or deadly side-effects—a flare-up of latent tuberculosis, bone-softening and fractures of the vertebral bones, peptic ulcer with perforation and hemorrhage, psychic changes, and many others.

Few of these hazards are disclosed for Meticorten in Latin America, and none of Celestone in Central America, Colombia, Ecuador, and Brazil. For both Aristocort and Medrol, the major hazards are glossed over or given in nonspecific terms.

The promotion of another steroid hormone, Winthrop's Winstrol, offers even more striking inconsistencies. It is described to Latin

American physicians as useful to increase weight, appetite, and strength. Such indications are not listed in PDR.

What is disclosed in PDR is the risk of such adverse reactions as stunting the growth of children, jaundice, interference with normal sexual development in children, and undesirable sexual changes in adults. Few of these are disclosed in Mexico and Brazil, still fewer in Central America, and none in Colombia and Ecuador.

TRANQUILIZERS

Among the so-called major or antipsychotic tranquilizers included in our study were Sandoz's Mellaril and SKF's Stelazine. As with other drug classes, the approved indications for use are few in the United States and numerous in Latin America. Among the indications not approved in this country but listed for the Sandoz product in Central America is use of the drug for the treatment of children with behavioral disorders, hostility reactions, inability to adapt in school, insomnia, sleep walking, bed-wetting, and nail-biting. Many adverse reactions for Mellaril are disclosed in the United States, a few in Mexico, but none in Central America, Colombia, or Ecuador.

In the case of Stelazine, physicians in the United States are warned of the risk of the development of tardive dyskinesia—a disorder marked by involuntary movements of the lips, tongue, hands, fingers, and feet. Speech may be seriously affected, the face distorted, and maintenance of body position impossible. In some patients, the condition may become irreversible. No effective treatment is known.

In the promotion of Stelazine, the danger of this development is disclosed to physicians in the United States. It is not listed in the reference works in Mexico, Central America, or Brazil. In fact, no adverse reactions are listed for Stelazine in the Central American countries or Brazil.

ANTIDEPRESSANTS

With the antidepressants, the story is the same—rigorously limited indications for use in the United States, with full disclosure of hazards. The reverse is obvious in Latin America—many recommendations, but few hazards disclosed. This holds for Ciba-Geigy's Tofranil and Lakeside's Norpramin. In the case of Lilly's Aventyl, however, indications for use are limited in both the United States and Mexico, and the disclosure of hazards is similar in the two countries.

With Warner-Chilcott's Nardil, a member of the particularly dangerous group of MAO-inhibitor antidepressants, a long list of contraindications, warnings, and adverse reactions is disclosed to physicians in the United States, only relatively minor dangers are noted in Mexico, and none is disclosed in the Central American countries.

ANTICONVULSANTS

Our last group includes three anticonvulsants widely used for the control of epilepsy. One is diphenylhydantoin, or phenytoin, marketed by Parke-Davis as Dilantin and by McKesson as Kessodantin. The promotion of the Parke-Davis product discloses only a few hazards in Mexico, fewer still in Colombia and Ecuador, and none in Central America. Only one warning is presented for the McKesson product in

Central America, Colombia, and Ecuador, and no adverse reactions are disclosed.

A similar situation was found for Sandoz's Mesantoin, with only one warning presented to physicians in the Central American countries, and no adverse reactions disclosed.

With Ciba-Geigy's Tegretol, numerous adverse reactions are disclosed to physician in the United States, a few to their colleagues in Mexico, Colombia, and Ecuador, but none to physicians in Central America or Brazil.

Mr. GORDON. Dr. Silverman, do you have any idea on what basis a company decides which indications to promote in each country and which hazards to disclose?

Dr. SILVERMAN. Obviously this represents company policy. But we were told by drug promotion experts in some Latin American countries that generally they work on the basis that if your competitor is claiming five effective uses for his product, you have got to claim at least six for yours. And if he discloses three hazards, you are out of your mind if you disclose four.

Mr. GORDON. Well, these global drug companies that you have been discussing were informed of your investigations annd your findings, were they not?

Dr. SILVERMAN. Yes, sir.

Mr. GORDON. You have discussed it with them?

Dr. SILVERMAN. We have discussed it in considerable detail with them.

One of the problems that we have all faced is the difficulty to estimate with any precision the prices that patients are forced to pay for this kind of promotion. They pay not in terms of pesos or quetzals or colones, but in needless injury and needless death.

Information on the frequency of adverse drug reactions in Latin America is far from adequate, just as it is far from adequate in the United States and in Europe. Nevertheless, in every country in which we have worked, medical experts—especially hematologists, pathologists, and microbiologists—have expressed to us their dismay, their frustration, and their anger at what one described to us as "this whole sickening business."

They have described to us the rise of resistant strains of bacteria, due probably and almost certainly to the excessive and irrational use of antibiotics. And with our own eyes, we have seen physicians and pharmacists distributing these potent drugs as if they were popcorn.

They have described the rate of fatal aplastic anemia in Mexico, now one of the highest reported in the world, related in substantial part to the use of chloramphenicol. In Guatemala, one leading expert told us that when a child is given chloramphenicol for typhoid fever, and it dies from aplastic anemia, this is a tragedy but perhaps an unavoidable tragedy. But where it happens when the drug is used to treat a case of virus pneumonia, or an undiagnosed respiratory infection, or a sore throat, this is unconscionable.

Others have told us of serious reactions to amphotericin B when it is given to treat minor fungus infections without any of the precautions made known to U.S. physicians.

They have told us of serious or fatal blood disorders, including agranulocytosis and aplastic anemia, following prolonged use of antiarthritis drugs.

They have told us of the excessive use of steroids resulting in perforated peptic ulcer or explosive flareups of tuberculosis and other diseases.

They have told us of cases of permanent brain damage caused by excessive use of antipsychotic tranquilizers, and sometimes by such tranquilizers given to control bed wetting or nailbiting in children, or an inability to get along in school.

We do not know how often such tragedies occur. In most cases, it seems, neither the patient nor his family, nor even the physician, is aware that the irrational use of a drug was responsible.

One fact that may possibly be related is that generally throughout the Latin American countries there is no such thing as medical malpractice. Malpractice suits are unknown.

Another related factor may be the influence and the numbers of detail men, or the visitadores. In the United States, we calculate that there is one detail man for every 10 physicians. In Ecuador, there is one for every eight physicians. In Columbia, there is one for every five. And in Guatemala, Mexico, and Brazil, there is one for about every three. There are some physicians in Latin America who take advice from none of these visitadores, whom they call visiting professors of therapeutics. In some cases, they will not even let the detail men into their offices or their hospitals. There are other physicians who take advice only from these company representatives.

Senator BEALL. Are these educated people?

Dr. SILVERMAN. Well, they are educated. In some countries they are required to have a high school diploma. In other countries, the requirements are a little more vigorous. And I believe it is Costa Rica that is now implementing a law that they must have a degree either in pharmacy or in medicine.

Senator BEALL. But primarily they are salesmen. Is that correct?

Dr. SILVERMAN. Yes, sir.

Senator BEALL. Thank you.

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

Is there any possibility that any of these drugs, like chloramphenicol, for instance, might be less dangerous for people in Latin America than for those in the United States?

Dr. SILVERMAN. Mr. Gordon, this arose when the first reports came, I believe, from Bogota, Colombia. Somebody wrote a letter to the New England Journal of Medicine saying,

> Isn't it marvelous that Chloromycetin produces these horrible results in Europe and North America but it does not happen in Colombia. It must be something in the genetic system of Colombians that protects them.

And this brought on a torrent of letters from hematologists and pathologists who said that this is a lot of nonsense; that there had been many, many deaths from aplastic anemia. And he said "All you have to do is start looking for them and you will find them."

The best information we can get now—and this comes primarily from hematologists in Mexico—is that there is a higher susceptibility to aplastic anemia that may be related in part to the proportion of Indian blood in the national blood pool. We are certainly not aware of any genetic protection that keeps Latin Americans immune from these unhappy side effects.

Senator BEALL. I notice on page 12 you were talking about "physicians and pharmacists"—but more importantly, physicians—"physicians are distributing these potent drugs as if they were popcorn."

Dr. SILVERMAN. Physicians and pharmacists, Mr. Chairman?

Senator BEALL. All right.

Dr. SILVERMAN. This is another factor that intensifies the problem.

Senator BEALL. I read your testimony. But is the implication that physicians are distributing them so freely because they are not aware of their effects or because they just are anxious to distribute them?

Dr. SILVERMAN. Mr. Chairman, I do not know the reasons for their actions. All I know is what their actions are. They are distributing them with or without prescriptions.

Senator BEALL. With respect to the drugs we are discussing, is the situation such that they require a prescription in the United States for some of them but do not require a prescription elsewhere? Is that right?

Dr. SILVERMAN. No, sir. They require a prescription in the United States. And in most of the Latin countries, there are laws saying that they also require a prescription. It has been the feeling of my associates and myself that with the probable exception of the morphine alkaloids and a few other drugs, you can obtain any prescription drug that you want in almost any Latin American country with or without a prescription.

Senator BEALL. You can get a prescription drug without a prescription in a Latin American country?

Dr. SILVERMAN. Yes, sir.

Senator BEALL. Would improved drug information remedy the situation?

Dr. SILVERMAN. We would hope it would, yes, sir.

Senator BEALL. Why would it? Is that the most effective way to remedy the situation in South America?

Dr. SILVERMAN. I think it is one of the requirements. The information that goes to physicians, in our mind, is inadequate. The pharmacists, who also prescribe and dispense, have even less information available.

Senator BEALL. As a practical matter, although these drugs are made in the United States, this is a marketing practice of the drug companies. Is that correct?

Dr. SILVERMAN. These drugs may or may not be made in the United States.

Senator BEALL. Well, as a practical matter, to what extent do we have the authority to require manufacturers here or elsewhere to provide information outside the United States?

Dr. SILVERMAN. To the best of my knowledge, Mr. Chairman, there are no laws in the books which would control what a drug company based in this country must say to physicians in a foreign country.

Dr. LEE. Mr. Chairman, following the hearings of this committee in 1967 and 1968 on chloramphenicol, with widespread publicity to the public, the use of chloramphenicol declined dramatically in the United States. The laws regarding the promotion of chloramphenicol were not changed. The behavior of physicians, however, changed dramatically as the information about the adverse effects of the drug was

disseminated, not only more widely to physicians and to the general public. The public became aware of the problem just as they have with oral contraceptives thanks to public hearings. It is not a matter just of disseminating the information to the profession, but the general public must also be made more aware of the possible hazard. The way the drugs are promoted in Latin America, the physicians and the pharmacists are not adequately informed of the possible adverse effects of the drugs which Dr. Silverman has described.

Dr. SILVERMAN. In some countries, Mr. Chairman, we found that no one is allowed to practice as a pharmacist unless he has considerable advanced training. In some cases, this could be comparable to training in pharmacy in the United States. In other countries, the requirements are so loose that an individual can become a licensed pharmacist providing he has served 5 years as an assistant to a pharmacist and can show that he is of good moral character. He is not required to take any examination of any kind.

I can cite one instance which always will be memorable to us. We were in San Jose, the capital of Costa Rica, and for some reason—we needed some over-the-counter drug—we went into what is the largest pharmacy in the country. There was a long counter with a great many people in white jackets waiting on the customers. I stood in line behind one nice little old lady. If I had to make a curbstone diagnosis, I would probably say that she was suffering from a severe thyroid disease. She was nervous, tense, and jittery, and very thin. When she came up to the man to wait on her, she reached into her dress and brought out a scrap of paper—it was not a prescription; it was a piece of butcher paper, I think, on which she had written something recommended by somebody or other—and she asked for a drug called Largactil, which is one of the trade names for a very effective, very potent tranquilizer used in the control of psychosis.

The pharmacist's assistant said, if my translation was right, that he had something much better. I watched him carefully. He did not look at any book, he did not consult with any of his colleagues. He went to a shelf behind him, and he brought down a bottle of one of the more potent antithyroid drugs. It is widely used, very effective, but it has known hazards. Ordinarily, physicians in the United States would not prescribe a drug like this unless they had subjected the patient to thorough diagnostic studies. Some physicians will even hospitalize their patients before they start them on this drug. But in this case, the clerk just counted out the prerequisite number of tablets, collected the proper number of colones from the lady, who walked out. And we watched this in amazement. After we got out of the store, my colleague and I still cannot agree whether this assistant was aged 14 or 13 or 12. I know he had not begun to shave yet.

Senator BEALL. Well the question I have is, whose fault is that?

Dr. SILVERMAN. I think this fault has to be shared.

Senator BEALL. By whom?

Dr. SILVERMAN. Partly by the drug industry, partly for not making available more accurate information to physicians and pharmacists.

Senator BEALL. Well, wait a minute. I can understand a situation of a physician giving a drug to an individual, and he might not have accurate information. But here you have a case of a minor working

behind a drug counter selling a drug. And I have no difficulty blaming that on the licensing authorities in the country where the sale was made. I have a little difficulty in shifting that blame back to somebody here in the United States, however. I think that it is reprehensible that people in those countries do not have better standards for the people who are going to dispense these drugs. But you said that in this instance the danger of the drug was fairly common knowledge to physicians, but a 14-year-old kid was dispensing it.

Dr. SILVERMAN. Right.

It would be very easy to point the finger to examples of this sort—and there are many like this—in which a law has clearly been violated. But as a citizen of the United States, I do not feel that I can point a finger at any other country for failures to enforce its laws.

Senator BEALL. Well, I can understand bad marketing practices and over-aggressive marketing factors, but the example you gave me I think is one where the fault clearly rests with the individual who was dispensing the drug, who was not equipped to handle the job that he is performing. And I have a hard time putting that responsibility back on somebody some place else other than the people that are running the pharmacy and perhaps those charged with the licensing of the pharmacy.

Dr. SILVERMAN. Well, let us match that with the use of this drug Largactil, also called chlorpromazine, which is prescribed by physicians down there who are unaware of the known hazards of the drug. This is legal. The physician is not violating any national laws. But he has not been presented with adequate information by the manufacturer.

Senator BEALL. That is a reprehensible marketing practice.

Dr. SILVERMAN. I think it might be considered so.

Senator BEALL. All right.

But I think we have to disassociate those two. You have to talk about the marketing practices, on the one hand, which we may or may not be able to do something about, and licensing standards in foreign countries, on the other hand, which I do not think we can do anything about, as bad as they are, except perhaps create the kind of international discussion that would cause people to come up with better standards.

Excuse me, doctor, please go ahead.

Dr. SILVERMAN. All right.

When these inconsistencies—inconsistent between what the company is saying about its product in this country and what it is saying in Latin America—became apparent to us, we showed them to the heads of some of the American and European countries involved, and we asked how these could be explained. I think it is important to emphasize that in no instance did the company spokesman deny the differences. Their responses usually included a number of different defenses. For example, they would tell us that Latin American physicians do not need any warnings; they are already aware of any hazards. Such a claim, we learned, totally infuriates Latin American medical specialists, particularly those teaching in medical schools, and clinical pharmacologists, and by pathologists and hemotologists, who by the nature of their specialties, are most aware of the damage done and where the bodies are buried.

Another defense is that they make more full disclosure in their package inserts, but we found there are also discrepancies in these inserts, which are not always full or complete. Furthermore, many physicians do not see these package inserts, and usually they are quickly thrown into the wastepaper basket. And at least in some areas, the use of package inserts themselves, even for physicians, is prohibited by law.

We have been told it is their detail men who gives each physician full information on hazards. This, as Mr. Gordon will recall, is a defense we have long heard in this country, but in Latin America, as in the United States, it is generally held that you do not knock your own product, particularly if you are working on commission. I should point out here that the Latin American situation is somewhat different in that many, if not most, of the Latin American physicians are employed by the government. We have been told that, in most of these countries, a physician cannot possibly expect to earn an income of more than $6 or $7 thousand a year. The average detail man makes far more.

We have also been told that physicians know that if they write to the company, it will be glad to send them more complete information. This is one defense that I do not think deserves even the dignity of a comment.

We have been told that no drug manufacturer would engage in such shoddy practices, that would tamper with the truth or cover up dangers, because in the long run this would cost him the confidence of the medical profession. I do not know the answer to this one so far as Latin American physicians are concerned. I do not know that much about the Latin American medical profession. But I do know that where the profession in this country is concerned, such a defense is nonsense.

Over the years, we have witnessed the record of the so-called "Dear Doctor letters," through which many major drug companies were required by FDA to notify every physician in the country that they had, in fact, tampered with the truth, or made claims that could not be supported, or they failed to disclose hazards. We have seen the remarkable cases of Chloromycetin and MER/29, both of which were investigated by this committee, and all the resultant civil suits for damages. And we have also found out what happened to the good name of the companies, to their reputation with the medical profession, and to their annual sales and their annual profits. And what happened? The answer is distressingly clear; by and large, nothing happened.

There are two additional defenses that perhaps are more noteworthy.

The companies tell us that the differences in promotion represent honest differences in opinion. That is to say, "We are honestly convinced from the scientific data we have that we are right and FDA is wrong." A drug, for example, might be proposed for use in the condition such as acne and FDA may turn it down. But the company says, "Well, we are convinced it is good and safe for acne, and we propose to so market it and promote it in Latin America."

We have also found out that the idea of such differences of honest opinion would be more palatable if we could find that a company said one thing in the United States, where FDA is constantly looking over

its shoulder, and something else throughout Latin America. But we find it a little more difficult to accept when it is obvious that what a company says about its product in Mexico City is not the same as what it says in Guatemala City or in San Jose de Costa Rica, which in turn is different from what it says in Colombia or Ecuador or Rio de Janeiro.

And, finally, there is the statement: "Each of our foreign subsidiaries is managed by a citizen of the country. He knows the laws and regulations, and he abides by them. We are not breaking any laws."

This defense has apparently been impenetrable. The hearings of this committee, Mr. Chairman, were effectively blocked from further investigation on Chloromycetin. One of the reasons is now clear. It is not easy to obtain copies of Latin American drug laws in this country. Fortunately, it became possible for us to work on the spot in a number of Latin American countries to acquire up-to-date copies of the laws, and to analyze them with the aid of Latin American attorneys and drug specialists, both governmental and private.

The legal situation may be summarized as follows:

In a number of countries, when the companies say they are not breaking any laws, they are telling the truth. They are not breaking any laws because there are no laws requiring disclosure of hazards. Each company can follow its own conscience and its own ethical standards, and that is the end of it.

In a few countries, there is a kind of a grey zone; the picture is not so clear. Governmental officials believe they probably have the legal authority to require full disclosure, but the authority has never been spelled out in adequate detail, and the laws have not been enforced.

But in some countries—notably Colombia—there is no lack of clarity. The laws are on the books. They require full disclosure of all hazards to all physicians. And these laws are now being flaunted. If the companies say they are not breaking the laws in Colombia, they are lying.

Let me, if I may, Mr. Chairman, recite a portion of the Colombian laws. In one section, the National Health Code says, "In the labels of the products there must be included the name of the product, the number of the license, the dosage, the manner of use, the contraindications, the name of the producing laboratory and the sales price to the public." And even more potent and completely clear is this regulation passed in 1963:

> In the text of propaganda, whatever the medium used, in the literature to the medical profession, in the labels, in the package, and in the literature or package inserts accompanying the drugs, there should always appear the contraindications, secondary effects, and precautions for use.

Senator BEALL. Doctor?

Dr. SILVERMAN. Yes, sir.

Senator BEALL. Now, you are saying in the case of Colombia, the law is on the books and you are saying that the people are breaking the law. Why does not Colombia enforce the law?

Dr. SILVERMAN. That is a matter for the Colombian Government to determine.

Senator BEALL. I know; but what bothers me about our discussion here is what can we do about that? If a country has a law that says that it is illegal to do something, and a U.S. company is making some-

thing and selling it in that country in violation of its laws, what can we in the United States do about that, other than publicize it?

Dr. SILVERMAN. It is my understanding that there is nothing that the Food and Drug Administration or the U.S. Congress can do.

Senator BEALL. Why is not the United Nations' World Health Organization more active in this field?

Dr. SILVERMAN. I think this is a matter that Dr. Wegman can address with much more competence than I, Mr. Chairman.

Senator BEALL. All right; we will wait for his testimony.

Dr. SILVERMAN. Incidentally, one internationally famed health educator, Dr. Jose Felix Patino, the former Minister of Health in Colombia, put it this way to us. He said, "U.S. manufacturers would be put to shame if the U.S. public knew how they are promoting their products in Latin America."

Colombia is only one of the countries that has perfectly clear laws on the books. The other three are El Salvador, Honduras, and Panama. Even within some of the multinational companies, top medical scientists are beginning to discover the situation for themselves, and they have told us that they are appalled to find what their own firms have been doing. I believe that when this record is disclosed to company boards of directors and to company stockholders, at least some of them, too. will be appalled.

Senator BEALL. In order to make sure we actually have the record clear, what percent of these drugs that we are talking about this morning are produced in the United States and what percent are produced in wholly owned and partially owned subsidiaries in South America?

Dr. SILVERMAN. So far as I am aware, Mr. Chairman, none of them is produced in final dosage form in the United States.

Senator BEALL. They are all produced elsewhere?

Dr. SILVERMAN. I understand that they are put in final dosage form and bottled elsewhere.

Senator BEALL. Would that mean that the FDA would have no authority over them at all since they are not produced here in final dosage form?

Dr. SILVERMAN. That is my understanding, Mr. Chairman.

Senator BEALL. So there is no way anybody in the United States can reach these drugs, legally.

Dr. LEE. The only way I think that anything can be done by the FDA, Mr. Chairman, would be if the Agency for International Development provided a loan or a grant for the purchase of drugs in the United States, which then would be shipped to a Latin American country.

Senator BEALL. And put in final form.

Dr. LEE. The drugs would be put in final form in the United States and shipped abroad.

Senator BEALL. I see.

Dr. LEE. We would have to find out from AID how much of that is done, but I would question whether much of it is done.

Senator BEALL. Would the FDA have authority over any drug put in final form regardless of where it goes in the United States?

Dr. SILVERMAN. In the United States? Yes, sir, I believe it does.

Dr. LEE. Yes, sir.

If it is manufactured in the United States, it would.

Senator BEALL. If manufactured.

Dr. SILVERMAN. And bottled and labeled here.

Senator BEALL. And if put in final form here, the FDA has authority.

Dr. LEE. Yes.

Senator BEALL. And you are distinguishing between drugs bought with and without AID funds?

Dr. LEE. The FDA could do something about that.

Senator BEALL. You can do that whether AID buys it or not?

Dr. LEE. Yes, I believe so.

Senator BEALL. It has been pointed out by the staff here that the law says that "So long as it is not in conflict with the laws of the country to which it is intended for export it is legal." So if it does not violate the laws of that country it is all right for them to produce it and ship it out.

Excuse me. Go ahead.

Dr. SILVERMAN. One other aspect that I think deserves a little more attention, Mr. Chairman, is that the medical care system in Latin America is not the same as that in the United States. There are many Latin American patients who, for whatever reason, do not have ready access to a physician. If they or their children are stricken by an illness, they can get care at low or no cost in many instances by going to a social security hospital. Unfortunately, the supply of physicians in most of these countries is not adequate to meet the needs. Accordingly, if you need medical care for yourself or one of your children, you may have to go to a hospital and stand in line for many hours, starting maybe at 5 or 6 o'clock in the morning, and waiting for many hours and sometimes many days before you can get in to see a physican. Under such conditions, if you have a serious acute illness, or if your child is seriously ill and possibly dying, you have two alternatives. You can go to a private physician—and there are some excellent private physicians in Latin America—but for this you have to pay cash. You might have to pay a large doctor bill amounting to perhaps as much as $2 a visit. This does not sound like much, but if you are living on a per capita income of $200 a year, it is a lot of money.

The only other alternative the patient has is to go directly to a pharmacist. And even though, as we mentioned before, this may be against the national laws, the pharmacist not merely dispenses the drug, he prescribes it and he diagnoses. In some instances, particularly in the smaller villages, there is no physician. The only health professional available is the pharmacist, and he has no recourse except to do the best he can. And in some instances, the pharmacist practices everything up to and including surgery.

Still further out, in the more remote parts of the country, there are not even pharmacists, and the medical care is given by the village witch doctor, who may prescribe herbs or incantations or whatever. In some instances—and we are not sure how this comes to pass—he may dispense potent antibiotics.

The crux of the problem, as we see it, is not whether a physician or a pharmacist will be influenced in his prescribing decisions by such factors as poverty or cultural attitudes, the incidence of disease, and so on. It is whether or not he is given ready access to the scientific facts

on which he can base the appropriate precribing decision. It is whether or not the drug companies tell the truth and all the truth.

Again, the problem is not simply a matter of violating laws in the developing nations, as important as that may be. It is that what should be the objective presentation of knowledge is being twisted by the morals of the marketplace. That is, if it is possible and you can get by with it, it is ethical. The problem is that medical science is being prostituted.

There are, Mr. Chairman, many related aspects on which others far more competent than I may wish to comment.

There are matters of drug prices and the handsome profits that some of these global drug companies have been extracting by means of their promotional practices in Latin America. This may be blood money, indeed.

There are the matters of ethics and morality, and how drug companies view their social responsibilities and to whom they feel responsible, whether it is to their corporate officers, their stockholders, or patients here and abroad.

And there is the matter of telling the truth, all the truth, and of deciding whether the truth depends on international borders, whether what is truth in one country may be untruth in another. For example, I find great difficulty in comprehending how a company can describe one of its products as dangerous in San Diego but safe a few miles across the border in Tiajuana, or how it can promote the product as effective in only 4 conditions in Washington, D.C., in 10 in Mexico, and in 17 in Central America.

There is another aspect that I am sure has not escaped the attention of this committee. Over the years, we have all heard American drug companies individually complain bitterly in public that the present FDA laws are excessively harsh and, in fact, are totally unnecessary. The companies insist they would live up to their moral and social responsibilities, laws or no laws.

The record of their performance in Latin America, where the laws have been safely bent, or broken, or ignored, or where there are no legal restrictions on drug promotion, might, to coin an expression, make a person wonder.

Remaining for consideration is what can be done about this unpleasant affair. As I noted earlier, so far as I can determine, there is nothing that FDA can do under existing law, especially if the product is put into final dosage form and bottled outside of the United States. And even though the Congress is empowered under the Constitution to regulate foreign and domestic commerce, it is my understanding that the Congress cannot enact any laws to regulate this kind of foreign commerce. Instead, it is my belief that there are a number of things that must not be done. There are some that could be done and some that must be done.

Among the steps that must not be taken is to attempt in anyway to act as Big Brother, to try and export the policies and practices of FDA to Latin America, to export our clinical or social standards, or to tell Latin American physicians and pharmacists how they should practice their professions. We must never tell Latin American legislators what drug laws they should enact. Any such efforts on the part of this or any

other country would be impracticable, morally indefensible, and impertinent.

Then there are certain steps that might be taken. Most important, I believe, would be to alert, mobilize, and support the world medical-scientific community, the health scientists, and the health professionals of every nation. I believe very strongly that the international medical-scientific community has the unavoidable responsibility, not merely to recommend, but to assure that full and objective information on drug products is made available to all nations in which they are marketed, and to all physicians and all pharmacists who may prescribe or dispense. It should be the responsibility of this world medical-scientific community to resolve the differences of opinion that will inevitably arise and to set at least minimum guidelines.

Now this international medical-scientific community has no formal structure—it has no officers, no bylaws, no official delegates—but it is far from impotent. Even without any legal powers, it has already played a key role in having controls placed on the use of human subjects in medical research, assuring more humane treatment of prisoners, reducing enviromental pollution, slowing the world population explosion, and placing at least some safeguards on so-called genetic engineering.

Although it should not—and probably cannot—dictate to a physician how he prescribes, it should see to it that each physican has available to him full and honest information.

And, finally, there is one thing that must be done. The existence and the nature of the problem must be made fully known to all countries, their physicians, their pharmacists, and their patients. It should be made fully known to all drug companies—their officers, their boards of directors, and their stockholders.

In your committee hearings today and tomorrow, Mr. Chairman, in the publishing of our findings, I believe we have taken the first step to achieve this goal.

Thank you, sir.

Senator BEALL. Thank you, Doctor.

I think we should be concerned about problems of this sort. It seems to me that it, as a matter of public interest or for public health, we establish policies in this country relating to the admonitions or the warnings that are placed on the drug containers as a matter of policy, then I think it is reasonable to assume that the producers of the drugs should also produce those same warnings for people wherever they live, even outside the United States. And I would hope that the drug companies would feel compelled to do that. At the same time, I think that we have to be careful that we do not tar American producers with the inadequacies of local government regulations or local laws.

Dr. SILVERMAN. I agree.

Senator BEALL. And I think there is too much of that around the world. And I would hope that as a result of using world health organizations and other international organizations we could get some influence brought to bear on that problem and improve licensing and training that is available for people in these governments who are dispensing drugs.

Dr. Lee is next, I believe.

STATEMENT OF PHILIP R. LEE, M.D., PROFESSOR OF SOCIAL MEDICINE, DIRECTOR, HEALTH POLICY PROGRAM, SCHOOL OF MEDICINE, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, CALIF.

Dr. LEE. Mr. Chairman, I am pleased to have this opportunity to appear before the Subcommittee on Monopoly, Small Business Committee, to respond to the committee's request to discuss the results of Dr. Silverman's studies on drug product promotion in Latin America. Like Dr. Silverman, the views I express are my own and do not necessarily represent those of my colleagues at the University of California.

Although I have had the opportunity of reviewing the results of Dr. Silverman's studies in detail, I focus on the statement which I would like to submit for the record, and the remarks that will summarize that statement, on one problem, specifically, the development of drug-resistant pathogenic bacteria and the relationship of this problem to drug promotion, physician and pharmacist prescribing and dispensing in Latin America. Specifically, in the statement I discuss in detail the problems that arose in Central America because of an epidemic of Shiga dysentary due to *Shigella dysenteriae* strains resistant to chloramphenicol, tetracycline, streptomycin, and sulfonamides, and the problems that arose in Mexico because of an epidemic of typhoid fever caused by chloramphenicol-resistant *Salmonella typhi*. Until the epidemic of typhoid fever in Mexico in 1972, chloramphenicol was the drug of choice for this disease throughout the world. In Mexico, it proved ineffective because of drug resistance.

The development of pathogenic bacterial resistance to antimicrobial drugs has been a serious problem in the United States since the development of penicillin-resistant staphylococci in the 1950's. In the 1960's resistant strains of meningocoocci appeared causing meningitis in members of the Armed Forces. Patients with bacillary dysentery in various parts of the world were found to harbor strains of Shigella resistant to several antimicrobial drugs. In the late 1960's the epidemic of Shiga dysentery in Central America was caused by Shigella resistant to chloramphenicol and other antimicrobial drugs.

In the 1970's a typhoid fever epidemic in Mexico was found to be due to *Salmonella typhi* strains resistant to chloramphenicol. Recently, in the United States and in Egypt, cases of meningitis due to Hemophilus influenza strains resistant to ampicillin and penicillin have been reported. In 1975, physicians at the U.S. Naval Medical Research Unit No. 3, in Cairo, Egypt, reported for the first time isolation of chloramphenicol-resistant *Salmonella paratyphi A* in a patient admitted with chronic enteric fever. The problem is not limited to the United States, it is a worldwide problem.

The increasing prevalence of drug-resistant strains of bacteria is apparently related to the widespread use of antibiotics and other antimicrobial agents. This is due, to a considerable extent, to irrational prescribing by physicians, irrational dispensing by pharmacists where they are permitted to dispense antibiotics without a physician's consent, and to the promotional practices by the drug companies that encourage irrational prescribing and dispensing.

I should note here—and I think Dr. Wegman will also emphasize—that the promotion is not only by U.S. multinational corporations but

by corporations based in Switzerland, Germany, France, and England. So that it is not exclusively a U.S. problem.

Senator BEALL. Are the promotional practices generally the cause of the irrational dispensing and prescribing of drugs?

Dr. LEE. I think they are, in part, related to that. In Latin America, I think that the educational programs for physicians and pharmacists are inadequate, as they are in the United States. The promotional practices by the pharmaceutical companies also foster irrational prescribing and dispensing. The continuing education of physicians in the United States is largely dependent on the drug companies. That is also true in Latin American countries. After physicians complete their basic training they continue to get information which is not fully accurate. They are not provided the information that they need to prescribe rationally and for the pharmacists to dispense rationally.

Dr. Silverman in his testimony dealt at some length with the promotion of chloramphenicol in Latin America, and in my statement I discussed this in detail.

What are the consequences of the type of promotion that we see for antibiotics, specifically chloramphenicol, in Latin America?

First, physicians and pharmacists will be more likely to prescribe and dispense chloramphenicol either when it is not needed, when it is contraindicated, or when other drugs would be more appropriate. Patients will be more likely to take chloramphenicol without particular concern for the possible hazards or they may be totally unaware of the hazards, and some will undoubtedly suffer serious, indeed fatal, side effects.

The regulation of the manufacture, promotion and marketing of drugs is the responsibility of the government in each country where the drugs are made, sold and promoted. Drug companies may, and indeed do, adopt standards that exceed the requirements in many countries. The regulations of the drug industry in Mexico, Guatemala or any other country should, however, be a matter of concern for the United States because inadequate regulations poses a hazard both for the citizens of the countries involved and for the visitors to those countries, and potentially for those who never traveled to the countries. In short, inadequate regulation poses a potential threat to world health and this is particularly true because of the emergence of drug resistant strains of bacteria.

In my statement I detailed some of the history, the pharmacology and the microbiology that is involved in this problem.

In Latin America there are, of course, millions of residents of those countries who are exposed to these hazards. It is also important to note that 2½ million residents of the United States travel to Mexico annually. Millions more travel to Central America and to other Latin American countries, as do travelers from Europe, Asia and Africa. At least one-third of the travelers to Mexico and many other Latin American countries are likely to suffer an episode of gastroenteritis during or following their trip. If they develop that they are very likely to be prescribed a potentially dangerous drug, chloramphenicol, as an example. They then may develop a serious side effect either during or subsequent to that treatment.

In addition to the hazards to the visitor, we have noticed in the United States the development of an increasing number of cases of Shiga dysentery due to drug resistant organisms. In Guatemala, the epidemic of Shiga dysentery killed 12,500 people; in El Salvador, 2,000 additional deaths occurred. Many of those who died were young children or old people. We have not seen that kind of high mortality rate in the United States but we have seen an increase in the number of cases. In 1965 there was one case of Shiga dysentery in the United States. In 1968—this was before the epidemic in Central America—there were five cases. In 1972, there were 70 cases, and 58 of those were in the border States of California, Arizona, Texas and New Mexico. I am sorry I do not have more recent information, but it may well be that those cases have continued to increase.

Perhaps even more important than the Shiga dysentery epidemic was the epidemic of typhoid fever in Mexico which illustrates the problems that arise when the organisms causing the disease are resistant to the drug of choice, in this case, chloramphenicol.

In May 1972, Mexican authorities announced the existence of a widespread outbreak of typhoid fever. A total of 6,342 cases were reported in 1972, a 100 percent increase over the 1971 total. The epidemic subsided in mid-1973. Many of the early cases were treated with chloramphenicol and many of them died because it was not known initially that the drug was resistant to chloramphenicol, a drug that had been used for more than 20 years to treat the disease and treat it very effectively.

In addition to the thousands of cases of chloramphenicol resistant typhoid fever reported in Mexico during the epidemic, cases due to the Mexican epidemic strain of *Samonella typhi* were also later reported in the United States and Great Britain.

There have been isolated cases of chloramphenicol resistance to *Salmonella typhi*—that is the cause of typhoid fever—since 1950. But prior to the Mexican epidemic in 1972, no epidemic was caused by a resistant strain. There have been cases reported in England, India, West Africa, Greece, Israel, Chile, Kuwait and Spain. And in the cases from Kuwait, for example, they arose in at least three different places: one in Aden, one in Cairo, and one in Pakistan.

The resistance to chloramphenicol is due to a resistance factor that can be transmitted to other bacterial strains so that it can spread to other enteric organisms and produce other cases of drug resistant infection with interric bacteria.

Senator BEALL. What, if anything, did you find about chloramphenicol in China?

Dr. LEE. Well it is interesting. Dr. Wegman and I went to China together on a mission in 1973, and I was really appalled at the way they use chloramphenicol. It was used frequently in out-patient clinics and hospitals. It was used even by barefoot doctors to treat febrile illness, much as it is used in many other developing countries. There was little evidence that the prescribers were sufficiently aware of the possible adverse effects. It is interesting that some of the articles that have appeared in Chinese medical journals have decried the misuse of antibiotics in out-patient clinics, specifically the overuse and misuse of chloramphenicol. So that some of the people there are aware of the

problems. But it appeared to be misused there as it is misused in many other parts of the world.

Myron, would you agree with that observation?

Dr. WEGMAN. I would agree entirely, Mr. Chairman. I too was struck by the overuse. It seems that the knowledge of the danger simply has not penetrated into that vast country. One of the problems is that China, we found to our surprise, had no single, monolithic health system; there are a whole series of health systems, making communication more difficult.

Senator BEALL. They cannot communicate. They have great problems.

Mr. GORDON. Do they not have access to the PDR and the material that we have in this country?

Dr. LEE. Not out in the rural areas, Mr. Gordon. Certainly, the academic physicians and the people in the major hospital centers that we talked to were well aware of the hazards.

Senator BEALL. The medical elite, so to speak.

Dr. LEE. Right.

But that information was not disseminated widely, as it should have been.

Dr. SILVERMAN. Mr. Chairman, if I might, I think it is important to recognize that the rationality of the use of chloramphenicol may depend on other circumstances. For example, I think Dr. Lee and Dr. Wegman would be horrified at the way chloramphenicol is used in some of the larger metropolitan areas in Latin America. There, we hope the use is beginning to drop off. But out in the jungles, this is a different situation. The physicians or the pharmacists or even the witch doctors practicing there do not have access to a whole arsenal of different antibiotics. They have miserable systems of preserving materials. They have very limited transportation facilities. They have essentially no laboratory facilities to culture which type of organism is involved. And there, I think, the health practitioners take what is clearly a calculated risk. They recognize that if they use chloramphenicol they possibly cause a few hundred cases of serious or fatal aplastic anemia. But on the other hand, they may save the lives of thousands or tens of thousands of patients from dying from an infectious disease.

Senator BEALL. Am I correct? You are talking about chloramphenicol, about a drug where everybody seems to know, or everybody who is trained seems to know the consequences of the use of this drug. Are you suggesting that in the case of this drug the drug companies are not adequately warning people as to its effects? You indicate that although in the medical centers the people do know, they have not told the people for whom they are prescribing the drug what the side effects are.

Dr. LEE. In Latin America that certainly is the case. Even in the United States part of the problem is the continued irrational prescribing of chloramphenicol by physicians who do get the warnings and do have the information available. There is still some misuse of it here, but it does not compare to the extent of the misuse that we have now seen in Latin America. When we see the development of epidemics of typhoid fever or Shiga dysentery caused by chloramphenicol resistant organisms, that is evidence of a possible consequence of the misuse in a developing country where the sanitation is not as adequate and

where these diseases are more endemic than they are in the United States.

Senator BEALL. Well my question is, is it the fault of the producer of the drug or is it the fault of the medical fraternity in those countries that this is taking place?

Dr. LEE. It is all three. It is the fault of the pharmacy profession, the medical profession, and the drug industry.

Senator BEALL. But in no particular order.

Dr. LEE. I would say in no particular order.

Dr. SILVERMAN. A partial answer to that question, Mr. Chairman, is that in the offices of some of the finest practitioners in Latin America, particularly in the medical schools and their great hospitals, they have on their shelves not merely the Latin American books, but they also have PDR, which they brought in themselves from the United States, and that is where they got their information.

Senator BEALL. In very limited numbers.

Dr. SILVERMAN. I said only the very best practitioners.

Dr. LEE. Let me just turn to my recommendations, Mr. Chairman, which begin on page 16. In my statement I address myself to the problems of the regulatory policies particularly related to the promotion and dispensing of drugs because I think that is a basic problem. We can do less about medical education and less about pharmacy education.

First, I think that all major U.S. pharmaceutical firms that market drugs in Latin America should be asked to review their present promotional practices or those of their affiliates and adopt a standard of promotion and marketing throughout the world that is fully consistent with, if not identical to, the practices required in the United States.

Second, the American public should be made aware of the hazards posed by the misuse of antibiotics, particularly the problems posed for travelers, where antibiotics may be dispensed without a prescription and the individual receiving the drug need not be informed about the potential hazards. Perhaps the U.S. Public Health Service could develop an informational document for international travelers on the problems posed by the misuse of antimicrobial agents. You can get information about immunization, but I have not seen comparable information about the hazards posed by the misuse of antimicrobial drugs.

Third, the Center for Disease Control (CDC) should be given the resources necessary or needed to carry out the clinical, epidemiological and laboratory studies necessary to determine the nature and extent of the health hazards posed by the emergence of drug resistant pathogenic organisms. The CDC should have the staff, facilities and equipment to monitor the emergence of resistant strains, to work with local health departments and hospitals and others to study the problems as they arise. The Director of CDC should be asked to report annually on the problem of drug resistant pathogenic organisms, the hazards posed and what actions are appropriate to reduce or eliminate the hazards.

Fourth, the Department of State and the Department of Health, Education, and Welfare should be fully appraised of Dr. Silverman's findings and requested to propose policies to deal with the problem to

the World Health Organization, particularly to the office for the Western Hemisphere Region, the Pan American Health Organization.

Fifth, the FDA should be asked to review its authorities and report to the Congress what measures, including new legislative authority, might be taken to restrict the use of critically important antibiotics, such as chloramphenicol, to those patients where its use is essential.

Finally, Mr. Chairman, let me join with Dr. Silverman and commend you, Senator Nelson, and other members of this committee, and the committee staff, particularly Mr. Ben Gordon, for again bringing to the attention of the Congress and the American people a serious problem related to the promotion, marketing, prescribing, dispensing and use of drugs that poses a very real hazard to our health.

Thank you.

Senator BEALL. Thank you, Dr. Lee. I appreciate your suggestions because it seems to me that your suggestions are very reasonable and very practical. This is more than just a local problem as far as we in the United States are concerned. This does appear to be something that will have to be handled through international organizations and certainly something that deserves high priority and consideration in those international organizations.

Dr. LEE. We have an expert on that on my right.

Mr. GORDON. Dr. Lee, Dr. Silverman found that the oral contraceptives were not promoted properly in Latin America and no notice was given about blood clotting and so forth. Do you have any comments to make on that?

Dr. LEE. Yes; it poses a very great problem for the women who receive those drugs. It poses a problem for the physicians who prescribe the drug who may really be unaware of the hazard. As we have learned in the United States, as physicians became aware of the hazard here, and as the general public became aware of it, thanks to, among others, this committee and Morton Mintz of the Washington Post, the use of oral contraceptives dropped dramatically, and people were able to make choices. I think the same choices ought to be available to physicians and to patients in Latin America who receive oral contraceptives, because otherwise they are exposed to undue risks.

Mr. GORDON. Well, my understanding from your testimony is that it really is not a Latin American problem, but it is a world problem because it does affect us here, too.

Dr. LEE. Absolutely.

Mr. GORDON. So the U.S. Government is concerned to some extent. Is that not right?

Dr. LEE. Yes; the Government should be concerned because any American traveler to Mexico may develop diarrhea and may go to a physician or a pharmacist and get a prescription for chloramphenicol without being aware that it is chloramphenicol. The same thing can happen in Spain, the same thing can happen in Egypt where chloramphenicol is the drug of choice for fevers of unknown origin. It can happen almost anywhere in the world.

Senator BEALL. I think you have provided an answer for this committee in that respect, Doctor. I think this committee should write a letter to the Public Health Service suggesting they publish a document—we can do that today—that warns American foreign travelers of the kind of situations they might run into if they get into a foreign

country and a certain drug is given to them for their use. That is one of your suggestions at the top of page 17, and I think we ought to follow through on that suggestion.

Thank you very much, Dr. Lee. I appreciate your testimony.

Dr. Wegman?

STATEMENT OF DR. MYRON E. WEGMAN, JOHN G. SEARLE PROFESSOR OF PUBLIC HEALTH AT THE UNIVERSITY OF MICHIGAN AND DEAN EMERITUS OF THE SCHOOL OF PUBLIC HEALTH

Dr. WEGMAN. Mr. Chairman, I am Myron E. Wegman, John G. Searle professor of public health at the University of Michigan and dean emeritus of the school of public health.

I have a prepared statement, Mr. Chairman, which I have submitted for the record. I should like to elaborate on it orally.

Let me explain, first, that my presence here has two bases. In the first place, I have spent a great many years in the international health field. Before coming to Michigan I was for almost 9 years a full-time staff member of the Pan American Sanitary Bureau, which serves as the regional office for the Americas of the World Health Organization. During the last 4 years I was Secretary-General and have traveled throughout Latin America.

The other base is that I am chairman of an ad hoc seminar group in Ann Arbor, which is attempting to bring together a group of people from a number of fields—medicine, dentistry, nursing, law, pharmacy, psychology, and ethics—to work on ways of achieving rational use of medicine. The stimulus for bringing of our group together was a tragedy that was suffered by Professor and Mrs. Zander of our faculty, whose daughter, while traveling in Spain, was given a drug for a completely irrational use. She came back to Ann Arbor, and despite many, many blood transfusions, died of aplastic anemia. The Zanders have devoted themselves to preventing recurrences of this tragedy and a good deal of my own knowledge comes from the efforts of Mrs. Zander and Professor Zander in providing information.

Our committee has gone into many of the problems involved—one having to do with the ethical values. We have also tried to look at commercial aspects, educational aspects, professional education, and education of the public.

I ought to point out, however, Mr. Chairman, that my presence here is as an individual because our seminar has not reached conclusions or formulated its recommendations yet.

I want first to call attention to something perhaps already known to most people in this room. Latin America is an area of the world that is particularly sensitive in regard to drugs. There are a number of reasons for this. The pharmaceutical industry is very poorly developed, so most of Latin America is particularly susceptible to imported drugs. There is, however, some promise for change. Recently, as you may know, the Andean Pact countries—the six countries along the range of the Andes—have come together in a variety of ways; among them Peru is trying to take the lead in providing a center for manufacturing generic drugs and drugs that will be more readily available.

There is one other important fact. In most of the countries of Latin America, as has been brought out in previous testimony, the analog

of the Food and Drug Administration, usually in the Ministry of Health, is far less powerful and far more susceptible to outside pressure. Furthermore, in any developing economy there is a general tendency to put marketplace considerations ahead of welfare aspects.

As you made clear in your own remarks, Mr. Chairman, a very important way to get at this problem is through professional education of physicians. Professional education is sharply limited in Latin America through lack of resources. One phase in which I am intimately concerned now has to do with providing textbooks. In many Latin American countries up to recently, most of the students in medical school used, instead of textbooks, mimeographed notes or notes that they took themselves. I am a trustee of the Pan American Health and Education Foundation, which, with a loan from the InterAmerican Development Bank, is providing textbooks to students at half price. I believe this can be an exceedingly important measure for achieving better use of drugs, among other aspects of medical education.

Mr. Chairman, you asked earlier in this hearing about why the WHO and PAHO are not doing more in this field. Actually they have done quite a lot. Last year, our seminar had the privilege of a long session with Dr. Marcolino Gomes Candau, the Director-General Emeritus of the World Health Organization. A Brazilian, he was Director-General for 20 years. He is a member of our faculty and in residence with us in Ann Arbor roughly 5 weeks a year. He summarized for us the various actions and resolutions of the World Health Organization that have been taken in regard to use of medicinal drugs.

Let me cite just a few of those. Perhaps one of the most important was in 1963 when World Health Assembly resolution 16.36 asked the member states to inform the organization immediately of problems with drugs and asked the Director-General to transmit this information to all governments. As one instance our Food and Drug Administration notified WHO in 1971 of a tightening of regulations regarding chloramphenicol and on June 25, 1971, the Director-General sent a circular to every country of the world giving full details of this warning. Sad to say, little action resulted.

In May of 1968, 8 years ago, the 21st World Health Assembly adopted a resolution on ethical and scientific criteria for the advertising of drugs. I have included in my formal statement a reprint of that resolution as adopted. More recently, WHO has set up a unit in Geneva for monitoring adverse reactions reported by the governments of the world. I am quoting from the Annual Report by the Director-General for 1975, presented to the World Health Assembly this very month. There was a total of roughly 100,000 reports received on about 12,000 drugs, but from only 21 of the 150 member countries of WHO.

Of even greater significance for the future was a discussion at the World Health Assembly in 1973 ending with a request to the Director-General to study (1) the feasibility of an international reporting system which would provide data on the scientific basis and conditions for registration and withdrawal of individual drugs and (2) whether practical minimum requirements could be established internationally. These might be problems in any international agreement because it probably would require ratification by the various parliaments of the different countries. But it is hoped that in the end the World Health Organization would be able to introduce such a reporting system.

It is of interest, Mr. Chairman, that in the debate on this resolution every single one of the countries that took part in the debate supported the idea more or less vigorously. But there was an interesting kind of division: The small countries all supported it wholeheartedly; the big countries gave slightly less enthusiastic support, warning of the dangers and problems of interfering with confidentiality involved in reporting.

More recently, just a year ago the 1975 Assembly adopted a resolution on standards for quality control of drugs, another area in which WHO has worked intensively. You may know that it was only some 5 years after establishment of the World Health Organization that, in 1952, the first International Pharmacopeia was adopted.

All of these efforts, unfortunately, Mr. Chairman, have accomplished very little and emphasizes your earlier question: Why don't they do more? I think it goes back, in essence, to the fact that the World Health Organization and the Pan American Health Organization are intergovernmental units. They can pass resolutions which may be noble and high sounding. They can distribute information. They can give advice. They can outline better procedures. But in the end it falls upon the Ministry of Health of each country and these Ministries simply do not have the clout to compete with other parts of their own government when commerical interests are involved.

Fundamentally, Mr. Chairman, as Dr. Silverman and Dr. Lee and you yourself have pointed out, what goes on in any country is the responsibility of that country. When a manufacturer says it is not illegal to make exaggerated claims in a country that has no laws against doing so, he is absolutely correct, legally. But, Mr. Chairman, here is where the problem of ethical and moral values comes in. It just seems to me, as a professional person, absolutely indefensible for a company to say that because there is a high incidence of typhoid fever in a given country one ought to treat every case of diarrhea with chloramphenicol.

Mr. Chairman, I have lived in the era when we did not have antibiotics or chemo-therapeutics. When I was a medical student and an intern I had the experience of seeing case after case of influenza bacillus meningitis die. When I was Pediatrician-in-Chief at Charity Hospital in New Orleans, the first time I used chloramphenicol in a child with influenza bacillus meningitis was one of the most dramatic incidents in my medical career. This was an 18 month old baby with the highest fever that I have seen anywhere. The child had a temperature of 109.2 on admission to the hospital, and this was confirmed with any number of thermometers. The child was treated with chloramphenicol, and within 36 hours the baby was standing up in bed yelling for food.

This kind of experience is a very powerful influence on a physician who has seen children get well from a disease he always considered fatal. But it is still dangerous nonsense to use chloramphenicol routinely for every case of meningitis. You must know what you are dealing with.

Diarrheal disease is a prime example. In 1973, the year after the tragic death of their daughter, Professor and Mrs. Zander traveled in Spain and brought home this poster which was on the drugstore counters, Chlorostrep, a product of Parke-Davis of Spain. The poster says, in effect, "Don't allow diarrhea to interfere with your vacation. Take Chlorostrep at the first problem." This drug is a combination of chlor-

amphenicol and dihydroestreptomicine. As you may know, streptomycin, although not commonly in small doses, carries the risk of causing deafness. Thus, if you take this fine combination, you run the risk of becoming deaf before you die. And its usefulness for most causes of diarrhea commonly seen is negligible.

Senator BEALL. Is that drug available in the United States?

Dr. WEGMAN. I do not know, but as far as I know it is not.

Senator BEALL. It would not be permitted to be made available in the United States?

Dr. WEGMAN. I believe so because the FDA is opposed to fixed combinations of antibiotics.

But the chloramphenicol is far the more dangerous drug.

Mr. Chairman, Mrs. Zander has prepared a listing of their own investigation and copies of some of the material, copies of this ad, copies of the letters written by the drug companies to doctors and to pharmacists urging the use of this combination and other formulations of chloramphenicol.

Senator BEALL. We will receive that for the record and we will also print it in the record of these hearings.

Dr. WEGMAN. Thank you, sir.[1]

In our seminar at Ann Arbor we recognized that, in any free-market society, it is the ethical duty of management of a company to make profit for its stockholders, but it seems to us there is equal ethical responsibility to present to all physicians and pharmacists objective and complete information not just on the utility but on the dangers of its products. Every physician knows that every single drug he uses, even the salt that he uses, has risks that go with benefits. The problem is getting the balance between these two. It seems to us that in the advertising and the promoting of these drugs human considerations must come before profit considerations.

It may be, Mr. Chairman, that this conflict is irreconcilable. It may be that the profit motive is never going to let the companies give out every bit of information, some of which is going to interfere with their profits. If that is so, then it seems to me that the kind of pressures that can be built-up through public hearings such as this, through the measures that Dr. Lee suggested in his testimony, can keep the subject constantly before the public and keep constant pressure on the pharmaceutical houses.

What can the U.S. Government do? I am told by my colleagues in the Pan American Health Organization and in the World Health Organization that our Food and Drug Administration has cooperated well with international health organizations in supplying information. I think FDA ought to be encouraged in those efforts and asked to help even more. It would be very useful if other parts of Government—the Department of Commerce, Department of the Interior, Department of Agriculture, and other parts of Government involved in international export—would also recognize that health considerations for human beings everywhere have great significance for us right here.

Now I am aware—I think you brought this out yourself—there is little that can be done through our laws to control a foreign subsidiary

[1] See letter dated May 31, 1976, to Senator Gaylord Nelson, from Mrs. Alvin F. Zander, page 15485.

of one of our countries that is working entirely abroad. It is equally true that Swiss, German, French and other manufacturers are probably as guilty as the U.S.-based companies in terms of inadequate information.

It seems to me, Mr. Chairman, however, that for us to use the argument that because our competitors do something we are absolved of criticism is absolutely shameful. I think a country that prides itself on leadership cannot be justified in saying because our competitors engage in reprehensible practice we have to follow suit, or even show the way. I have often wondered whether there is a feasible approach through the tax laws. I am told that there are investigations being made of using our tax laws, in making allowances for taxes paid abroad, to achieve some control of U.S.-based national companies. But this is a matter on which I am a complete novice and there are many experts in Government who might be motivated to look into the matter.

But let me talk a little about what can be done through PAHO and WHO. Mr. Chairman, the major motion for bringing the international health organizations into being was foreign quarantine, the attempt, going back to the Middle Ages, to keep preventable disease out of a country by stopping it at the border. Modern experience has taught us that this approach is essentially futile for most diseases. There are now only four diseases, fortunately, over which are included in the international quarantine regulations of the World Health Organization. We have recognized that the much more important way to prevent disease from entering a country is through controlling it at its source and increasing use has been made of the advisory work of the World Health Organization. It seems to me that this approach has great promise in the area we are discussing and there are a number of things there that can be done to strengthen the work of PAHO and WHO for this purpose. For example, it seems to me not unreasonable for your committee to ask the U.S. Delegation to the World Health Assembly to sponsor a resolution which would call on all manufacturers, everywhere in the world, at least to make their advertising in any one country basically the same as the advertising in others. As Dr. Silverman has pointed out, how can a company justify advertising one thing in San Diego and another thing in Tijuana? If we could at least make this kind of moral pressure, for what it is worth, on the companies of the world, it might be helpful.

I might point out that there are a number of international associations that are in what the World Health Organization calls "Official Relations." They are known as Non-Government Organizations (NGO). Among them are the International Union of Pharmacology, the International Pharmaceutical Federation, and even more interesting, the International Federation of Pharmaceutical Manufacturers Associations.

They would have the privilege of participating in the discussion on the resolution I suggest and would I hope, exert some sort of moral pressure on their own members for more humanitarian behavior.

Further attention might be given to education of the health professions. I would hope that this committee might make pressure for additional support to the Pan American Health Organization and to the Pan American Health and Education Foundation for the textbook

program and for improving the training of all people in the health professions. Pharmacists may be as important as physicians. Pharmacists are prescribing drugs, legally or illegally, but they are fundamentally human beings with an interest in saving lives, and with better education they will do a better job.

Finally, one very important aspect has to do with international information system. The World Health Assembly is going on right now in Geneva. I am not sure whether the Director-General's report on the feasibility study will have come before this Assembly or not, but it is sure to be discussed at the next Assembly a year from now. This gives ample time for the United States to prepare a position of strong support. My own feeling is that, although the legal aspects need to be pursued, information, education, and moral pressure, are exceedingly important.

Mr. Chairman, I want again to echo the words of my predecessors in congratulating you and the committee on bringing this matter before the public.

Thank you.

Senator BEALL. Thank you, Dr. Wegman, for your testimony.

It seems to me that you make a very important point about communications. I think obviously it is necessary for us to do everything we can to impress upon the conscience of the producers the necessity of making the same information available all over the world wherever they are marketing the drug. And I also think that by our example, hopefully, we can get other producers in other countries to follow us and come up to our standards as we do in so many things rather than have us be dragged down to theirs. But it seems to me that for the immediate future we also have to spend a great deal of our effort in improving communications through the international organizations so that the word gets out to people who are dispensing drugs poorly because of lack of training. You are suggesting, I believe, that we devote some time to strengthen the organizations so that they can develop better means of communicating with professionals and semiprofessionals and unskilled dispensers, particularly in South America. And I think that is a very worthwhile suggestion.

Dr. WEGMAN. We also see, I think, Mr. Chairman, the value of strengthening our own abilities in the United States. The example of smallpox eradication will have very great benefits throughout the world. The leader in the World Health Organization for that program happens to be from the CDC in the United States, Dr. D. A. Henderson. The major impetus to that program was given by the U.S. Government with a regional program in Africa. And because of the research capability of that U.S.-backed group, they were able to find out how best to proceed to achieve effective eradication. The development of drug-resistant diseases and drug-resistant bacteria are a new kind of problem. Enhancing the ability of our own CDC to study this problem, and disseminate the information, would add another dimension.

There was one other thing—I just made a note of this as we were going along—which may be appropriate. In the United States major foundations and major universities, both private and public, have very large investments in the drug industry. Ought not those foundations exert influence on the policies of those companies through the stocks

that they own to improve their promotional practices? These institutions are given special tax privilege by the U.S. Government—the tax privileges and might respond, if they learned of the results of Dr. Silverman's study, to undertake appropriate action on the companies. Many of the foundations have policies in the area of social responsibility and do try to influence the policies of the companies that they invest in. I am sure that is not common for all universities. I am sure it is not common for all foundations. But this may be another avenue worth pursuing.

Dr. SILVERMAN. Mr. Chairman, there is another avenue that deserves particular emphasis. When my associates, Dr. Aida LeRoy and Mia Lydecker, and I finished our compilation, we took all our data, some of which I showed to the committee today, and sent it to every one of the drug companies involved, asking them to check for the accuracy of the translations and the fairness of our presentation. Very few changes were requested, and in every instance, we acceded to the company's request. We thought that they were the better judges of accuracy than we were.

During our study, it turned out that not all companies were using the same approaches. In my discussion today, I cited only those cases in which there were glaring differences between the promotional campaign in the United States and the campaign by the same company elsewhere. But there were two companies that were a little different. We found out that they were saying precisely or essentially the same thing in all countries for the products we studied.

We went to the heads of these companies, or their representatives, and said "How come?" One of them said, "We figure that this approach of full disclosure is probably going to cost us sales for the short run, but in the long run we will profit." And officials of the other company explained their attitude by saying, "Well, we sleep better at night that way."

Senator BEALL. Well, I think it would be worthwhile to identify those companies, doctor. We do not want to characterize this as an industry-wide problem. There are companies that recognize their responsibility and I think that since we identify those people whom we criticize, I think we should identify those people whom we applaud, also.

Dr. SILVERMAN. I would be glad to identify them. One of them is Merck and the other is Syntex.

Senator BEALL. Thank you, doctor.

Mr. SOMMER. Dr. Wegman, is PDR translated into Spanish? Is it available in Spanish?

Dr. WEGMAN. I do not know. I do not believe I have seen it in Spanish.

Dr. SILVERMAN. I do not believe so.

As a partial answer to your question, much of the material that is disseminated to physicians in the United States through what is called "The Medical Letter"—this is the publication of a nonprofit organization, which is based here, and sends copies on subscription to tens of thousand physicians of the United States—is now being regularly translated into Spanish and sent to several thousand Latin American physicians in some countries.

Dr. WEGMAN. I might add to that, Milton. You may not know, but the foundation that I am on, the Pan American Health and Education Foundation, is underwriting the reprinting of the Spanish version of The Medical Letter, "Carta Médica," and is distributing it to every country in Latin America which wants it, at no cost to the government. Several countries are distributing "Carta Médica" widely, although, for cost reasons some of the advantage of The Medical Letter is lost. A great beauty of The Medical Letter is that it is a 4-page leaflet that comes every 2 weeks and can be read with speed. For reasons of economy in the Spanish reproduction, most governments distribute six issues at once, every quarter, which makes it less likely to be read and assimilated.

Mr. SOMMER. But is there any discussion in the foundation that you were referring to that are doing the PDR in Spanish? It seems to me that that ought to be a step in the right direction in getting the data distributed throughout Latin America.

Dr. LEE. PDR, you know, is a book of drug advertisements, it is paid advertising.

Mr. SOMMER. But Dr. Silverman, I think, referred to it as meeting the FDA standards.

Dr. LEE. Yes.

It contains a limited number of drugs, and only the drugs that the drug companies want are included in the PDR.

Dr. WEGMAN. Let me point out another problem with translation; it would have to be an adaptation because drug names are different in Latin America. A drug identified by one name here goes under a completely different name in Latin America. For example, in one of the communications that was sent to the countries by WHO some years ago, the list of synonyms for chloramphenicol would knock your eye out. I have it right handy here, I think. There are at least 50 or 60 different synonyms for chloramphenicol sold in different countries.

Dr. LEE. We have been trying for 10 years to get a drug compendium in the United States that would replace the PDR. I think if we could do that or if a similar document could be produced for the Latin American countries, a practical, useful compendium that could essentially replace the PDR in the physician's office, which is where it is found in the United States and where it is used every day by physicians as they write prescriptions, would be an excellent idea.

Senator BEALL. Senator Nelson has a bill in to provide for a compendium.

Dr. LEE. Yes, he does.

And if a comparable action could be taken through, let us say the Pan American Health Organization, with some stimulus from the United States to do that, I think that might be very helpful.

Mr. GORDON. The problem of multiplicity of names, of course, was dramatized by the thalidomide case, if you will recall. We had testimony by Dr. Helen Taussig that even after the alarm went out about thalidomide throughout the world, children were still being born in Brazil and other countries with defective limbs because when they were told about thalidomide they went to their medicine cabinets and saw Kevadon, Contergan, Profamil, Slip, Sedalis, and perhaps more than 80 other names. It was just impossible to take them off the market.

I have one question for Dr. Wegman. I understand that you went to Cuba not too long ago.

Dr. WEGMAN. You have anticipated me. I wanted to bring that in. I had a fascinating visit to Cuba last summer and I was able to contrast it a little bit with China, the other Socialist society that I had visited. My situation in Cuba was quite different from China, as Phil remembers. When we were there, we were deaf, dumb and blind because we could not read or understand Chinese. In Cuba, I am completely fluent with the language and I have been there many times before so that I was able to make comparisons. One thing was very striking. I passed a number of drug stores as I was driving around—I was visiting the Ministry of Health on Pan American Health and Education Foundation and PAHO business—and the drug stores all had almost empty shelves. So I asked what was going on here, and they said well, up to January 1959 our drug stores on a worldwide basis stocked some 40,000 pharmaceutical items. Today, the list is down to 1,400.

I might point out—and I do not necessarily wish to say that there is any causal relation—that health indices in Cuba have improved dramatically since 1959. The infant mortality has dropped to where it is by far the lowest in Latin America. I am ashamed of the fact that for so many years the Cubans were unable to get antibiotics that they needed during the blockade. Now they are getting them in other ways. But I think there is a distinct advantage to the fact that the amount of drugs they have been able to import has been cut down.

Senator BEALL. Thank you, doctors. We appreciate your coming this morning.

And we will recess the subcommittee until tomorrow morning at 9:30.

[Whereupon, at 11:58 a.m., the subcommittee was recessed, to reconvene at 9:30 a.m., Thursday, May 27, 1976.]

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

THURSDAY, MAY 27, 1976

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

The subcommittee convened, pursuant to recess, at 9:35 a.m., in room 318, Russell Senate Office Building, Senator Jacob Javits presiding.

Present: Senator Javits.

Also present: Benjamin Gordon, staff economist; Judah C. Sommer, minority counsel; and Karen Young, research assistant.

Senator JAVITS. The subcommittee will come to order.

This morning we will hear as witnesses Mr. Robert Ledogar, Department of Economic and Social Affairs, United Nations, New York, N.Y., and Mr. George Squibb of North Kingston, R.I.

The Chair wishes to make a brief opening statement before the hearing commences.

Today's hearing continues the Senate Monopoly Subcommittee's examination of pharmaceutical company practices in labeling and promoting prescription drugs sold in Latin America.

I share the concern expressed by the witnesses and by Senator Beall, who chaired yesterday's hearing, respecting the questionable practices of some drug companies in promoting the use of their drugs without adequate or appropriate prescribing information.

However, Senator Beall through his questioning of the witnesses, it must be clearly understood that:

a. Misleading and incomplete information to promote the sale of drugs by some American drug companies or their foreign subsidiaries in Latin America is beyond the jurisdiction of the Food and Drug Administration which regulates drug advertisements and promotion in this country.

b. Improper marketing practices should be subject to the legislative control of the foreign country in which they take place, for what goes on within any country is the responsibility of that country.

Grave questions have been raised that certain drug promotion practices abroad may be legally correct, but are they ethically and morally less than honest?

Now, it is my judgment that the United States may well have means to call domestic pharmaceutical concerns to account in the marketing of pharmaceuticals in foreign countries in order to require them to

follow more ethical procedures in their advertising and labeling requirements and the course which is in accord with and does not violate the laws of the country where the drug is marketed.

The question to be decided is whether the means, which I believe the United States does have, should be invoked or not. Such enlightenment as the witnesses can give us on that subject would be very welcome.

Mr. Ledogar, would you proceed? We hope that you will confine your direct statement to 10 minutes and the total statement will be included in the record, even though you omit some part of it.

Proceed in any way you wish.

STATEMENT OF ROBERT J. LEDOGAR, DEPARTMENT OF ECONOMIC AND SOCIAL AFFAIRS, UNITED NATIONS, NEW YORK, N.Y.

Mr. LEDOGAR. My name is Robert Ledogar, Senator, and I am presenting my statement as a private citizen.

Senator JAVITS. That is, you are not appearing here in any representative capacity for the United Nations?

Mr. LEDOGAR. That is right.

Senator JAVITS. This is just a way of identifying what you do for a living?

Mr. LEDOGAR. That is right. I joined the United Nations after I completed the work in question, and my testimony in no way represents a position of the United Nations.

Senator JAVITS. Proceed.

Mr. LEDOGAR. My statement consists of four parts: First, a brief summary of what I consider to be the main problems with the development, marketing and use of prescription drugs in Latin America; second, the relation of transnational pharmaceutical corporations to these problems; third, the impact of U.S. foreign policy on the situation; and fourth, some recommendations.

As a preface, however, I am obliged to make it clear that I speak only as a private citizen. Although I am currently serving with the staff of the United Nations, my remarks here today are the outcome of investigations carried on before I joined the U.N. in preparation for a book entitled "Hungry for Profits: U.S. Food & Drug Multinationals in Latin America." This book was published by IDOC/North America, but the work was completed prior to my current U.N. affiliation. Consequently, what I have to say does not rest on any information obtained as a U.N. staff member, nor does it reflect the official views of the United Nations.

There are two sets of problems besetting Latin America with respect to pharmaceutical products. The first affects the urban middle and upper classes for the most part, and it is a problem of excessive consumption of pharmaceutical products under unnecessarily hazardous conditions. Those who can afford it may buy almost any non-narcotic drug without prescription (despite a statement on the label which says that the drug is for sale by prescription only), and the labeling and advertising of such products, generally speaking, carry fewer warnings and claim more extensive healing powers than is permitted for the same product in the United States or Western Europe. Exam-

ples of such labeling and advertising are given in my book called "Hungry for Profits, as well as the works of Drs. Silverman and Lee.

The second and more serious problem is that of the low-income majority of Latin Americans who, for the most part, do not consume pharmaceuticals in great quantity because those products which are available are too expensive and/or unsuited to their needs. Seventy-two percent of Brazilians, for example, die before the age of 50; 10 percent of them die before their first birthday. Communicable and endemic diseases aggravated by malnutrition are the main causes of such deaths.

What Brazil, like most other countries of Latin America, needs from the pharmaceutical industry is the development of very inexpensive drugs to combat diseases like tuberculosis, measles, diphtheria, whooping cough, schistosomiasis, Chagas disease, and the myriad of intestinal infections which ravage the low-income populations. This means that research and development must be carried out with these local and low-income concerns primarily in mind. This is, unfortunately, not the kind of R. & D. which receives highest priority in the multinational pharmaceutical business.

Nearly all of the pharmaceutical products on sale throughout the world today are discovered and developed in the United States or Europe. Since multinational firms make their money by selling to the higher income populations of North America, Europe, and Japan, along with the urban middle and upper classes of Asia, Africa, and Latin America, they have very little economic incentive to produce cheap drugs to combat diseases from which their main customers do not suffer.

Now, my purpose is not to make the transnational pharmaceutical industry the scapegoat for all of Latin America's ills. The industry has discovered and developed drugs and vaccines which have saved millions of lives among rich and poor. Even if one believes that such discoveries and more might have taken place if the industry were structured differently than it is, credit should be given where it is due. Latin American governments certainly bear a very large share of the responsibility for the problems I have just described. They invited multinational industry to their shores and, even though this was done frequently with the active encouragement of the U.S. Government, they could have refused; and they remain free to expel, nationalize, or otherwise discipline these firms.

But, I think one can fairly blame the multinational industry for at least two things: For the maintenance of high prices on drugs currently available and for its tendency to favor the political, economic and therapeutic status quo. Multinational industry's role in the maintenance of high prices on the international market has already been investigated by this subcommittee and will perhaps be discussed further by other witnesses at these hearings. I am more concerned with the industry's failure to produce what the people really need and its ability to resist efforts by concerned local interests to develop a low-cost chemotherapy more suited to such needs.

When, for example, 45 percent of a sample of foreign-held patents registered in Argentina from 1957–67 were for products which were neither being manufactured nor imported into Argentina, the effect could only have been to discourage Argentine research and

development. Transnational industry frequently enters Latin America or expands there by buying out already existing local firms. In individual cases, such mergers may have beneficial effects, but the overall impact is again to reduce the incentive and scope for local research and development.

This is especially the case when transnational firms dominate the entire industry, as they do in many Latin American countries where they may be responsible for three-quarters or more of total sales volume. Most of the raw materials for drugs sold in Latin America come from outside Latin America.

Central America, for example, imports 90 percent of its raw materials for drugs. This is hardly the road to self-sufficiency. And the multinationals openly resist efforts by Latin American governments to foster an independent national research and development capability.

An ambitious and well-financed plan mounted in Brazil in 1971 to utilize government, university and other local laboratories to produce 400 basic medicines cheaply and efficiently for nationwide distribution was openly resisted by foreign-owned firms, in the end, the plan was emasculated, resulting in only a very small transfer of secondary R. & D. facilities by a few companies to Brazil.

Mr. GORDON. How did they resist?

What did they do to show their resistance?

Mr. LEDOGAR. Well, we have reported several public statements on the part of Executives of the transnational firms in opposition to the Government's plan in this respect.

No one knows exactly the internal workings of Brazilian politics, except those deeply involved in it, but the public statements, I think, bear witness to their opposition.

Mr. GORDON. Thank you.

Senator JAVITS. Proceed.

Mr. LEDOGAR. Just as they complain about excessive controls by the FDA in this country, the multinational firms are hardly likely to favor an improvement in the generally inadequate government control systems in Latin America for drug labeling and marketing. Since the investigative work for my book was completed, several transnational drug firms from the United States have admitted to giving bribes to officials of foreign governments. None of the countries have been identified. I was able to obtain evidence on bribery in Latin America only in the case of one firm—a Swiss company which had a list of 135 Brazilian regulatory officials to whom it gave small "donations"—but everyone knows that bribery is a frequent occurrence.

The transnationals say they have to engage in it in order to survive. As individual companies, they probably do. The point is that they are able to unite and flex their muscles when their common interests are seriously threatened. Despite the fact that they dominate the drug industry in many countries, the multinationals have done little to change the regulatory status quo. One can only conclude that it suits their purposes just as it is.

Where does U.S. foreign policy come into all of this? First of all, despite some recent changes in legislation, our Government offers substantial encouragement to foreign investment by transnational firms

headquartered in this country through tax incentives, guarantees, loans and the services of our commercial representatives abroad. Drug companies have taken special advantage of these incentives as several examples in my book illustrate.

In a broader way, however, U.S. foreign policy supports the activities of transnational firms overseas by openly encouraging the maintenance of a "favorable business climate" in those countries we consider to be our friends. We support regimes which encourage investment by U.S. firms. Relations are cooler with countries which place heavy restrictions on such investment. Our special relationship with Brazil, for example, is due in part to that nation's heavy reliance on, and strong encouragement of, U.S. private investment as opposed to the more restrictive attitude of the Andean Pact countries.

The crux of the problem is here. For most business a "favorable investment climate" means a minimum of Government interference. Simplified rules and regulations, tax incentives, freedom to compete with (and/or buy out) local industries, a limit to price controls, plenty of cheap labor and little labor militancy—this in itself bespeaks a conservative, if not repressive, type of regime. But with the pharmaceutical industry there are added requirements.

In their case, a "favorable business climate" also means: Weakness of safety controls on labeling and advertising; no efforts to control the proliferation of brand names; freedom to locate research and development facilities wherever these are most profitable for the company; absence of adverse publicity; and freedom to produce and sell not necessarily what is most needed in the country but what is more economically efficient from the standpoint of profits.

This puts the U.S. Government in the position of supporting activities which are contrary to the best interests of the majority of people in Latin America. It makes us the ally of transnational business in its tendency to support the status quo and oppose change.

What can be done to change this situation?

A general review of our Government's whole supportive attitude toward U.S. foreign investments, together with the specific incentives, is certainly in order, but that is a very large issue which transcends this committee's present specific concern with the pharmaceutical industry. Short of such a broad policy review, there is very little that the U.S. Government can do unilaterally to alter the conduct of U.S. firms acting through local subsidiaries overseas. We cannot interfere in the internal affairs of other nations to impose standards of our own. There are serious difficulties, moreover, with the imposition of unilateral controls by the U.S. Government on U.S.-based firms in the absence of similar controls on European and Japanese firms by their Governments.

What our Government can do is to support multilateral efforts toward the greater regulation of transnational investment in less developed countries as well as independent multilateral efforts to assist less developed countries in solving their most serious health problems. I would like to offer the following specific recommendations:

(1) That the U.S. Government take an active role in seeking an international convention on the conditions of trade, sale, marketing, advertising, and labeling of pharmaceutical products. I have in mind a role similar to that taken most recently by our

Government in urging international action on the question of bribery in international business dealings.

(2) That the U.S. Government support the recommendation of the United Nations Group of Eminent Persons (of which you, yourself, Senator, were a member) that the affiliates of transnational corporations should be required to reveal to host governments any sales prohibitions and restrictions in manufacturing imposed by home or other host countries with respect to the health and safety of consumers.

(3) That the U.S. Government, through its representatives to the World Health Organization, support current efforts of that organization to improve its international system of information on drugs and look for ways to restructure the Geneva Research Center for monitoring adverse reactions to drugs so that it may be more suited to the needs of less developed countries.

(4) That the U.S. Government offer, preferably through multilateral channels, financial and technical assistance, independent of any influence from private U.S. firms, for improving the capacity of regulatory agencies in less developed countries to exercise control over the pharmaceutical industry.

(5) Finally, but most important, that the United States redouble the research efforts of its own Government agencies and offer, through multilateral channels, more technical and financial aid to independent, noncommercial research facilities in less developed countries to discover and develop cheaper and better drugs to combat the diseases which afflict and shorten the lives of many millions of our fellow human beings.

Mr. Chairman, these recommendations do not constitute the total solution to the problems I have described earlier, but if they were to be carried out we would have made a good start.

Senator JAVITS. Thank you, Mr. Ledogar. It is very interesting.

Now, it would be simple for me to ask you to identify the Swiss firm to which you refer.

Is there any reason why it should not be identified?

Mr. LEDOGAR. It is identified in my book, Senator.

Senator JAVITS. As what? It is published.

Mr. LEDOGAR. Let me check to be perfectly accurate.

Senator JAVITS. And refer us to the page in your book where it is identified.

Mr. LEDOGAR. It is Ciba-Geigy, on page 17.

Senator JAVITS. Ciba-Geigy?

Mr. LEDOGAR. Yes.

Senator JAVITS. And is there any part of the book you want to put into the record to tell us the story?

Mr. LEDOGAR. I can quote it. It is a single paragraph if you wish. It reads:

> Sources within the Brazilian parliament recently called for an investigation into the compromising relationship between multinational pharmaceutical firms and the nation's drug control agencies.
>
> A parliamentary investigating committee was given an initial document of the Swiss firm Ciba-Geigy containing a list of over 135 public officials in the SNFMF [which is the Brazilian regulatory agency] and other licensing agencies who receive small gifts and donations from the company.

I can give the source for that, which is a newspaper report from Brazil.

Senator JAVITS. What is the newspaper?

Mr. LEDOGAR. I will give you that in a second. It is Diario do Comércio, Belo Horizonte, May 3, 1975.

Senator JAVITS. A local paper?

Mr. LEDOGAR. Yes.

Senator JAVITS. And that was an accusation, of course. You have no other proof than that, have you?

In other words, the newspaper said so and that does not prove it.

Mr. LEDOGAR. The newspaper reported the statement made in Parliament.

Senator JAVITS. A parliamentary flap over it?

Mr. LEDOGAR. That is right.

Senator JAVITS. But that is the total proof, is that right, that you have?

Mr. LEDOGAR. Yes; what I have is the newspaper report about the parliamentary inquiry in Brazil.

Senator JAVITS. Related to the parliamentary inquiry and that is the total evidence that you have that backs up your statement?

Mr. LEDOGAR. That is the evidence I have.

Senator JAVITS. Well, I think it is only fair to make clear what the evidence is so that we do not accept a statement of fact as being a fact because it is, as far as I can see, a newspaper report on the charges.

Mr. LEDOGAR. I know of no evidence that the charges were ever denied.

Senator JAVITS. They never denied them, is that right?

Mr. LEDOGAR. Not to my knowledge.

Senator JAVITS. That does not prove it.

I happen to be a lawyer, and I just want to be fair in anything you say.

I am not in any way challenging you, but I do think it is important to have the basis set forth on the record, that is the basis for your statement.

The other thing that interests me about this is your own statement that any one of these countries could deal with the situation, could it not?

For example, you say in Brazil there is a very promising effort to produce 400 basic medicines and so on which was emasculated, et cetera, and the fact it was openly resisted by foreign-owned firms, again it is nothing wrong with openly resisting if they think it is wrong.

You say in this case they prevailed, but is that not the fault of Brazil?

What do you want the United States to do about that?

Mr. LEDOGAR. Senator, there is a general U.S. foreign policy favoring the interest of the multinational firms.

I cannot prove that the United States exerted pressure in this case, but there is the general climate. Everyone in the Brazilian Government knows that policies restricting business practices and unfavorable to the interest of multinationals are not generally looked upon by the U.S. Government as in the good interest of the mutual relations between our countries.

Senator JAVITS. So it is a climate that you complain of.

Mr. LEDOGAR. Yes.

Senator JAVITS. Does that climate differ in different countries, have you found?

Mr. LEDOGAR. Yes, it does, Senator.

For example, the group of so-called Andean Pact countries have developed a series of fairly strong restrictions on foreign investment.

They do not refuse foreign investment by any means, but they have very special rules under which foreign investment is allowed, restrictions on profit, packaging and so on.

Senator JAVITS. So that the climate which you complain of created by the U.S. Government does not extend to the Andean Pact countries.

In other words, it is not a universal climate created by the United States.

What you say is, it is true in some countries and not in others. You have just given us an example of Brazil as contrasted with the Andean Pact countries, Peru and the others.

Mr. LEDOGAR. That is correct, but I believe our policy generally favors the Brazilian approach rather than that of the Andean Pact countries.

Senator JAVITS. Nonetheless, if the country wants to do it, there is nothing in our policy that stops them.

Mr. LEDOGAR. That is correct.

Senator JAVITS. Colombia is an Andean Pact country. We enjoy excellent relations with Colombia.

Mr. LEDOGAR. Yes.

Senator JAVITS. So it is not necessarily built into the American diplomatic system either.

Mr. LEDOGAR. The reason I raise the issue here, Senator, is I do not believe it is necessarily involved in every aspect of our foreign relations, but I think this climate is generally favored and I think that the United States policy should be more judicious, particularly with regard to these issues which affect the consumers, such as safety regulation and the improvement of the safety regulating mechanisms in these countries.

Senator JAVITS. Well, what you are really arguing, as I see it, is that lax regulations and controls should not be what the pharmaceutical companies themselves seek; that they ought to be more public spirited than that.

Is that not what you are really arguing?

It is a fact that notwithstanding the U.S. climate that you charge, I am not necessarily in agreement, but it is true there are countries which do what they think they ought to do.

Mr. LEDOGAR. Senator, I do not believe a great deal in urging public spiritedness to companies. I do not believe it achieves a great deal.

I recommend multinational action to improve the climate.

Senator JAVITS. The OECD this morning announced a new set of ethical rules for what they call transnational corporations.

Mr. LEDOGAR. Yes.

Senator JAVITS. Have you looked at those?

Mr. LEDOGAR. Yes, I have.

Senator JAVITS. Do you know anything about those?

Mr. LEDOGAR. I know what I have read in the New York Times this morning.

Senator JAVITS. Do you have any opinion on whether that is the kind of thing you want to see happen?

Mr. LEDOGAR. Well, again, going on the newspaper report, it appears the United States adopted a generally conservative position, as opposed to Sweden, with regard to the revealing of information.

For example—apparently because the United States prevailed—the convention, or the agreement, calls for public revealing of the operating results and sales by geographical area rather than by country, and I suspect the case was similar with regard to No. 7, which calls for revealing research and development expenditures for the enterprise as a whole, rather than research and development expenditures by country.

Now, in the case of the OECD countries, this may not be as important as in the case of less developed countries.

What I've urged is that in such negotiations the United States adopt an attitude which is not so defensive of the interest of business and not consistently take the stance that seems to be represented here.

Senator JAVITS. Well, I was with Secretary Kissinger and I believe that a most enlightened and forward-looking setup of proposals was made to the developing countries.

I was also his adviser at the session of the United Nations General Assembly in early September last year where again we observed the advanced proposals.

I did not consider those particularly reactionary or conservative.

Now, all I am raising, Mr. Ledogar, is that these may be your views, but you are not God either, neither am I or anybody else. They are your views and you have opinions, but that does not mean that the United States is wrong. That is all I raise with you.

This happens to be in the business I know something about which is the international practices of transnational corporations.

I am interested in your view about the substance, and I think that is a much stronger argument, if you will allow me to suggest it to you, the ultimate fact is because there is a lot to economics and a lot to business, more than the evidence on which you base it.

For example, I would not indict a company as guilty of giving bribes on a parliamentary speech or the report of a newspaper.

You are saying you are reporting a fact that the paper said so and so and a member of Parliament said the same thing, but that does not necessarily convict an enterprise.

It would take a lot more proof than that as illustrated in the investigation by the subcommittee headed by Frank Church.

I am impressed with the fact that the kinds of medicines, at the kind of price that should be helping the many millions of people, with all kinds of intestinal illnesses in countries like Brazil, are simply not made available because, you say, it is not profitable to do so.

Now, do you recommend that the United States offer aid of that kind?

The United States can give direct aid in tons of aspirin or anything else it wants to, is that not so?

Mr. LEDOGAR. I do recommend U.S. aid of a certain kind.

Very often, in the past, U.S. aid has been tied in with the development of the subsidiaries of the U.S. corporations.

Senator JAVITS. How do they do that?

Mr. LEDOGAR. Well, we had the Cooley loans up until the end of the 1960's where foreign exchange funds were loaned to American companies to develop their enterprises in the aid-receiving countries. U.S. foreign aid is very frequently tied in with the purchase of Ameri-materials, and so on.

This committee has, itself, investigated the purchasing by U.S. AID of pharmaceuticals from American companies and others for delivery to less developed countries.

What I would urge is aid to independent and multilateral research and development, which is not necessarily tied in with the interest of American business abroad.

Senator JAVITS. Well, now, suppose the U.S. Government purchased from pharmaceutical companies vast quantities of some simple remedy for diarrhea.

What objection is there to that as long as it got to the ultimate consumer at low prices?

Why not buy it from U.S. firms? They are probably the cheapest and the best.

I am talking about doing what you want to do.

Why exclude purchase from U.S. firms?

Mr. LEDOGAR. I do not necessarily exclude purchase from U.S. firms, but the key issue is local research and development under conditions of priority for the needs of the people in that country.

Senator JAVITS. But local research and development may not be very good, whereas the international research and development is.

Mr. LEDOGAR. That is the problem. It needs to be improved.

Senator JAVITS. Why scale glass mountains when you have excellent research facilities in Switzerland and the United States, Canada, France, and Germany?

Why not use those?

What is the magic of local research facilities?

Mr. LEDOGAR. As you said, it is not good business to do research and development for diseases of the pepole who cannot pay for drugs.

Senator JAVITS. But we are talking now about the locus of research and development, not the substantive part of it.

Mr. LEDOGAR. That is right.

Senator JAVITS. The United States and the Soviets are now cooperating and trying to do something about many forms of cancer. That will benefit the whole world.

What is wrong with that?

If you tried to locate that activity in some country which has no facilities, no technicians, no experts, maybe not even the climate for it, what is the purpose?

Research is international.

Why does it particularly have to be local? As long as it is done with an eye to the broadest human use, that is all I am saying.

Would you concur with that statement?

Mr. LEDOGAR. I concur in that.

Senator JAVITS. As long as it is done?

Mr. LEDOGAR. That is right.

Senator JAVITS. What about the World Health Organization? Have you looked into what it is doing in these areas?

Mr. LEDOGAR. Yes, I have, Senator. There have been a number of efforts over the years by the World Health Organization to improve the situation with regard to information and regulation of the drug industry, and of course, to improve research and development.

Unfortunately, many of those efforts in the World Health Organization have not succeeded, again due to differences of opinion nad priorities between developed and less developed countries representatives within the World Health Organization.

Senator JAVITS. Well, Mr. Ledogar, thank you very much. I appreciate everything you have said, and mind you, my examination may sound contentious to you but I think you do have a valid thesis, and I was trying to refine it and really get it down to what we can wisely do.

Mr. LEDOGAR. I appreciate that.

Senator JAVITS. Mr. Gordon, any questions?

Mr. GORDON. Mr. Ledogar, do you know the percentage of profits to net worth or to investment derived by multinational drug companies from their foreign operations as compared to those from their domestic operations?

Mr. LEDOGAR. Mr. Gordon, that kind of information is reported in round figures in annual reports by drug companies but the figures themselves are contested.

Mr. GORDON. Actually, they are not reported in annual reports accurately because of the practice of overpricing imports and underpricing exports.

Mr. LEDOGAR. Well, my point is the annual reports state a global figure for foreign income from foreign operation as opposed to income from domestic-type operations in many cases.

However, it is highly questionable whether or not those figures represent actual profit because they do not report the results of underpricing of exports or overpricing of imports in the receiving countries. We're talking about the general practice of transfer pricing. No one has effectively been able to determine the real figures. There have been reports on individual cases showing that real profits are much higher than actually reported.

For example, Global Reach, the book by Barnett and Müller, reported on a study in Colombia which calculated overpricing of imports and overpricing of exports by a group of multinational firms and then divided the total into the declared net worth of their subsidiaries in Colombia. It was found that effective annual rates of return ranged from 92.1 percent to 962.1 percent and the average was 79.1 percent.

The average of declared profits submitted to the Colombia Tax Authorities by these same firms was 6.7 percent.

There are other studies of this same kind, but in general the reporting is simply not there. This is one of the major concerns of people in this field: To improve the international reporting of real rates of return.

Mr. GORDON. Are you aware of the hearings that we had on this particular subject, that is, the overpricing of imports and underpricing of exports?

Mr. LEDOGAR. Yes, I am. I refer to it briefly in my book. There were cases of overpricing reported in Colombia, and when the authori-

ties compared import drug prices with other countries in Latin America, they found very great discrepancies from one country to another. The United States found similar discrepancies of prices when it investigated, in this subcommittee, the prices charged to the U.S. AID in the period from 1968 to 1969.

For example, for tetracyclines, the cost in Pakistan was $370 per kilogram.

In Colombia, the same company charged $100 per kilogram.

Bristol Myers in Colombia charged $250 per kilogram and $190 per kilogram in Pakistan, and so on down the line.

There were these series of differential prices with no apparent reason.

Mr. GORDON. Thank you.

Senator JAVITS. Thank you, Mr. Ledogar. It is very kind of you to come. We appreciate your testimony.

Mr. Ledogar, you do not have to stand by unless you wish to.

Mr. Squibb, you may proceed.

STATEMENT OF GEORGE S. SQUIBB, CONSULTANT TO THE PHARMACEUTICAL INDUSTRY

Mr. SQUIBB. My name is George S. Squibb. I live at 1545 Boston Neck Road in Saunderstown, R.I., and I am here at the request of the committee. I am a consultant to the pharmaceutical industry, with which I have been associated for 40 years in various capacities—30 years with E. R. Squibb & Sons, finally as vice president for marketing, and the last 9 or 10 years with various small manufacturing pharmaceutical companies one of which, Barr Laboratories of Northvale, N.J., I now serve as director.

During my career I have served on board of directors, executive management committees, patent and research committees, and in all kinds of professional and trade groups in nearly every State in the country. I have been active in committee work for the PMA and NPC, the two major industry trade groups, and was elected to two terms as chairman of the National Pharmaceutical Council.

I am a lawyer, member of the New York Bar, with special graduate study at the Food and Drug Law Institute. I know the pharmaceutical business backward and forward, and am vitally concerned with its future both personally and from the conviction that all matters affecting public health must be of vital importance to all of us in the years ahead.

Over 10 years ago I was given an assignment by my company to study the relationships between the pharmaceutical industry and various Government offices and legislatures, Federal and State, because at that time there was a particularly sharp concern on the part of some of the industry's managers that things were changing in the pattern of public awareness of the procedures of medical care and that a little attention to this developing situation might be helpful. That assignment resulted in the production of two papers on the problems and practices of the pharmaceutical industry, both of which are part of the record of these hearings. Into these papers I injected a little gentle advice to the industry which caused all sorts of uproar at the time, but which I now have the satisfaction to note was all good and

has been picked up as their own gospel by many of those who were most horrified at the original expression. As a matter of fact as I review those words of 8 or 9 years ago in the light of current events I am amazed at how close to the mark they were in foretelling what was going to happen in the pharmaceutical field given the attitudes which were then, and still are prevelant. All of which only goes to prove that developments are predictable on the one hand, and on the other that the legend of the unheeded prophet, Cassandra, is still relevant today.

Not having learned any restrictive lesson from this earlier experience, I am here again to discuss some recent controversies involving the pharmaceutical industry, and to express from my experience what might be a way to avoid such unpleasant situations in the future.

I am here today to express from my experience what might be a way to avoid the situation which we are discussing now, the promotional excesses in countries outside the United States by U.S. firms.

Certainly none of us, in the industry or outside it, can take any pride or satisfaction in listening to the recital of the promotional excesses that the committee has heard in the last few days. Essentially, however, this is just the newest example of the fact that pharmaceutical managers live and work in a goldfish bowl which makes all of their actions reviewable by a large and varied audience of critics, most of whom are not inclined to be overly sympathetic.

The root of most of the problems that the industry has with its critics over promotional matters is the feeling that somehow sales pressures, advertising, commercial exploitation and selling in its strict dollar and cents aspects are all foreign to, and incompatible with, the practice by the physician of his profession. Choice of treatment, drug selection, and indeed, the whole physician-patient relationship seem not properly affected by any forces outside the physician's training, abilities and understanding of the patient and his malady.

The idea that anything coming out of such fields as advertising, sampling, sales pressures, price advantage, or third party recommendation of any kind could intrude on this relationship is somehow repugnant to the public who still regard the medical profession as a sort of prefabricated-all-knowing-group of specialists of superior and perhaps even secret powers who need no help or direction from those inspired by motives other than the specific cure of the patient at hand. Commercialism of all kinds, and medicine, have always been uneasy associates. It is difficult to keep this relationship in proper balance, and it is the struggle to do so that leads to hearings of this type, and eventually is the cause of much of the governmental regulation imposed on the industry.

We now have before us examples of how promotional activities vary from country to country on the same drug by the same company. Indeed, it appears that promotional claims for certain drugs which are forbidden in this country are emphatically stated in other countries, and that a fair case can be made for what looks like the exploitation of ignorance of peoples who lack the medical scientific experience which has evolved in the United States in the last 30 years or so. It is difficult to imagine any justification at all for the promotion or sale of a drug for an indication for which is not a specific, or any promotion or sale of a drug without adequate information as

to the side effects, toxic or otherwise, of the dosage recommended. Nowhere is there any voice of industry who would argue for such courses of action, and yet here are examples of just such things happening. How can this be?

In the record of hearings of this committee are two significant explanations offered as to just how these promotional differences between countries are explained or rationalized. One approach is the one set forth by the president of a major pharmaceutical house that whatever standards, indications, or claims for a drug are approved by the in-house scientific staff of his organization as to the "medical positioning" of a product, that is their standard of guidance, everywhere in the world. He stated further and specifically that they would not use the standard of what is approved by FDA for that drug in this country if there should be any difference. The more you think about this approach the more puzzling the ethical implications become. It takes quite a bit of self-confidence, and perhaps even arrogance, to be able to ignore completely any findings by the FDA contrary to your own.

While the track record of the FDA includes some questionable judgments in the past that have not held up to the test of time, certainly the vast body of its findings and its regulations are sound, and probably are the production of the most advanced system of drug review operating in the world today. However, if such a policy were actually used, there would be no variation in promotion among different countries except where regulation required some limitation. It would appear from testimony given here that is practically never the case, and variation exists in the promotional claims for the same product among countries which have virtually no regulations at all. Therefore, it is doubtful even a pharmaceutical house with an internal business-research relationship of extraordinary balance and understanding can or does follow any such policy to the letter today.

The second approach is described by a former medical director of a large pharmaceutical house which maintained two different medical staffs, one apparently with a less rigid approach to promotional procedures which could be used overseas. Somehow, I feel this latter approach, or variations of it is the more common, and probably the more easily rationalized of the two.

It must be recognized that there is such a thing as honest difference of informed medical opinion on the evaluation of individual drugs. It seems that there is always available some medical specialist or some source of information to contradict opinions expressed by others. It has been said time and time again that medicine is not an exact science, and certainly drug utilization appears to be one of its more inexact areas. But for the purposes of public health today, a judgment has to be made and a line drawn somewhere. It is suggested that a little line drawing is now indicated.

There are at least two complicating factors which get in the way of a quick and easy solution to this problem. First, is the obviously different opinions that scientists of good reputations and sincerity have about not only the physical qualities of drugs, but also about the whole philosophy of risk versus anticipated therapeutic benefit.

Government regulatory bodies tend toward policies which take absolute safety as the dominant note, while independent scientists tend to evaluate a drug more on a risk-versus-results basis with the individual

physician determining the applicability of the particular drug to a particular case.

Second, there is the basic doubt as to a universal and automatic competence of the FDA or any other governmental agency in all matters it touches. Rigid acceptance of FDA controls, with appeal or review difficult and very expensive, makes for an unsatisfactory system. Political pressures are significant in drug control regulation when they should not be, and there is sometimes too much shortsighted action taken just to get rid of an immediate problem. This results in an ever-increasing body of industry rules which tend to develop into a rigid formula for establishing black and white, without any regard for the vast grey area which exists in medical procedures.

It would seem that one of the best ways that is now available to evaluate a new product, or a new use of an old one, is to try it in a market where there is some latitude permitted in promotion efforts. This is not to justify in any way exploitation of a product for indications known to be wrong, or without warning of possible side effects that have been established by previous use elsewhere. Full disclosure is always essential. Absence of conscious deception is always essential. Acknowledgment of different opinion is always essential. After that, if there is still room for use of the product with advantage to the patient, it is clear there should be opportunity to do so.

Mr. GORDON. In your prepared statement you said: " * * * that one of the best ways that is now available to evaluate a new product, or a new use of an old one, is to try it in a market with some latitude permitted in the promotional efforts." You are not implying this takes place, are you?

Mr. SQUIBB. Certainly not.

Mr. GORDON. You agree that opinions are not sufficient, but we need "adequate and well-controlled studies."

Mr. SQUIBB. I mean sound medical opinions.

Mr. GORDON. Resulting from adequate and well-controlled studies.

Mr. SQUIBB. Resulting from medical studies. It could be all types of studies, or course, made in different geographic situations and for different conditions of living in different parts of the world.

For honest men of good will, the problem is exquisitely difficult. Such scientists do not accept the automatic infallibility of Government regulators, nor do they accept the limitations placed by arbitrary controls on their own conclusions.

Dishonest men who deliberately exploit ignorance to their own advantage by offering hope of cure without concern for anything except the monetary return to themselves are the object of our efforts here today. Just where and how to separate the two groups should be easy, but in fact gets more and more difficult as medicine increases in its potency and complexity.

As far as the established companies of the American pharmaceutical industry are concerned, and it seems that all too often they are the ones that are concerned with the problem under discussion here, the solution ought to be found right in their own internal operations.

The industry constantly claims for itself high standards of ethics and close attention to its admitted unique high degree of social responsibility, yet all too often it seems to fail in this regard in promotional matters. It would seem that as a matter of policy, if the question

were effectively put, no board of directors of a responsible American pharmaceutical house in this day and age of sensitivity to consumer criticism would ever knowingly permit its companies' products to be marketed under double or deceptive standards, or in any way whatsoever that would result in extraordinary risk to the public in any part of the world.

Mr. GORDON. You recall the opening statement of Senator Beall yesterday. He referred to the annual meeting of the stockholders of the Warner-Lambert Pharmaceutical Co. in 1972 where 97 percent of the stockholders voted "No" on a resolution that the company change its policy by divulging to foreign doctors what U.S. law now demands, that it tells U.S. doctors about the toxicity of its Chloromycetin, a product of its Parke-Davis division.

Mr. SQUIBB. I cannot imagine such a thing could happen if the directors were really aware of what they were saying.

I do not think they were in that case, in my opinion.

To me, it is impossible to conceive that anyone would vote that way if they knew what they were doing.

Mr. GORDON. But they did, 97 percent of them.

Mr. SQUIBB. Sure, the management voted as by proxy.

The shareholders sent in their proxies and they voted for that statement, but I do not think they realized what they were saying.

Mr. GORDON. Yes, they did, because Dr. David Lewis and Dr. Richard Burack explained at the meeting the consequences of the present policy. Nevertheless, they still voted 97 percent.

Mr. SQUIBB. That, of course, is the point I'll make later.

If industry continues to ignore, either willfully or through ignorance, the results are the same and we are going to get for the industry a whole series of regulatory developments which are going to be unfavorable to them. There is no question about that.

I would certainly hope that no board of directors would ever again, or at least after these hearings and perhaps after the publicity given the matter, would come out with anything like a position such as that.

The fact is that such questions are rarely, if ever, put to the Boards. It is customary for the directors to leave all day-to-day operating procedures to its field management, and then simply to inspect the financial results of such procedure.

In the pharmaceutical industry, something a lot more responsible than that is called for on the part of directors. They must question precisely the way their organization is carrying out its social responsibility and to set specific standards and guidelines for the promotion of its products.

If they feel that their own research staff is of such caliber and integrity as to set standards and to control and limit all promotion activities of the company, then this should be their policy and it should be applied everywhere uniformly where regulation permits. If they should wish to follow such a policy without regard for outside opinion except where such opinion is imposed upon them by law, it would be their right to do so. Without making the individual judgments themselves, they would still have to understand exactly how such judgments were arrived at between the sales and scientific departments of their organizations and would accept the infallibility of those decisions with the clear understanding that theirs was the final responsibility. It is

doubtful that any board today, in spite of the Warner-Lambert decision, would take such an extreme position, and we heard yesterday some others who testified recently in this matter, in contradiction to outside opinion, but by following such a procedure of observation and review, a board would establish an ethically consistent approach to all promotional programs for its company's products no matter where the promotion was directed.

The current trend toward the personal responsibility of corporate officers and directors for all actions of their companies, and particularly those which affect the health and welfare of their customers, is one which has to be taken very seriously, indeed, in the pharmaceutical industry and here is a good place to start. It seems clear that most boards would prefer to rely on some combination of their own internal research standard and that of the FDA, or other appropriate regulatory body. But any such combination would have to define and establish, in advance, guidelines for aggressive promotion men for whom sales volume is the overriding issue.

If the pharmaceutical industry cannot find within its own operations the solution to the obvious problem it creates for itself by promotional practices which set different standards for different peoples, then a solution will be forced on it in one way or another from outside. Several possibilities are immediately apparent, the most obvious being expanded governmental regulatory control made possible by enabling legislation. Certainly, the conduct of American industry overseas is receiving all kinds of attention these days, most of it sharply critical, and there will be plenty of precedents for the imposition by the FDA of some kind of sanctions against those who stray from U.S. standards in their conduct of their foreign business ventures. Even if the only practical method to do so is to demand industry to protect its stockholders from the liability claims inevitably arising from damages related to improper drug use by observing defensible standards of product, a way can and will be found to do it.

Control through the World Health Organization is another possible way to insure that only balanced, accurate, and scientifically documented claims are made for medicinal preparations anywhere in the world. This body could certainly assume an advisory position in this area which would be of great value especially to those countries without their own body of scientific knowledge and expertise.

Nine years ago Dr. Helen Taussig has described to the committee in earlier hearings some of the possibilities that could be developed along World Health lines, but clearly a lot more study is necessary to make sure that objective medical standards can be so achieved staying clear of all the varying social and political pressures that all too often seem to become dominant in a global approach to any problem.

Nine years ago before this committee I stated that a pharmaceutical manager must accept the fact that his industry indeed carries a high degree of social responsibility or he can see that social responsibility spelled out for him slowly but surely by legislation prescribing more and more of his operations, and taking over more and more of the functions he now guards so fiercely.

The thrust of those hearings concerned prices in the pharmaceutical industry, but my comment is just as applicable today to promotional practices which seem to the public to ignore any feeling of responsi-

bility toward the patient, and clearly go against the most basic principles of medical ethics. By continuing such practices the industry is making serious long-range trouble for itself, if not here today, then down the line as foreign governments become more alive to public health problems.

It is very stupid, indeed, for a well-established, profitable and progressive industry to endorse or to permit practices in its sales promotion areas which can produce only the short term dollar return, and then will lead to restrictive controls which will overreach the abuses with which we are now concerned and go on to other pharmaceutical affairs now left unregulated. Such is the inevitable result of the abuse of corporate power, and it's about time that corporate management realized it. I would like to see the pharmaceutical industry take the lead in that realization.

Thank you.

Senator JAVITS. Mr. Squibb, I find your presentation very, very interesting, but as a practical matter, do you really think the acceptance by American pharmaceutical concerns of their social responsibility is likely soon enough to be responsive to the goals which have been testified to in the context of these hearings?

Mr. SQUIBB. Sir, it could start tomorrow. I am always optimistic.

It has been my family's philosophy for 125 or 130 years that these things are all possible.

We have seen an increasing development of a social responsibility over a long time, but I would rather see it worked out that way than through Government regulations.

It is hearings like this and the publicity that we saw in the papers this morning that I think force the industry into these improved social responsibilities.

I think there is no question about it that the climate today, changing just in the last 2 years, in the degree of the responsibility of the boards of directors is going to have an effect on some of these things that go on in the pharmaceutical business, particularly because it involves health.

Senator JAVITS. Your family has an enviable reputation and position in this field.

Of course, you yourself by testifying here evidence your own social responsibility.

I understand your own feeling in the matter and it is very laudable.

I must say I, too, wish business would shake itself up, but often Government cannot wait for that but must induce it.

What I am interested in—and your whole testimony supports this—is that many of the charges of excess promotion and lack of disclosure are assumed by your testimony.

You assume that a good deal of what has been charged here is true.

Mr. SQUIBB. I know it is true. I do not assume it. I know it.

Senator JAVITS. Well, your testimony is very important because it describes a most deplorable situation. I have really two questions for you and then I must leave. Perhaps counsel would wish to ask some further questions.

One is this: Do you believe from your experience that it would be practical to apply FDA standards to overseas sales and promotion or

is there a reason why some different set of standards should apply where local law does not call for standards like those of the FDA?

Mr. SQUIBB. I do not believe I follow your question.

Senator JAVITS. In other words, if we assume local law permits standards other than those set by the FDA for domestic sales and promotion, do you think that there should be different standards abroad by pharmaceutical companies from those which the FDA requires them to apply here, or should they be the same everywhere?

Mr. SQUIBB. I do not necessarily accept the fact that the FDA standards for all products are the correct ones, but you do not have to accept that for it is not so much a question of legality as a question of the ethical, the proper, true, fair and complete explanation of the use and nature of the product that is under question. Whether it is law or not, in my opinion, makes no difference; the law will require you to do certain things, but your ethical approach should be the same everywhere.

Senator JAVITS. Well, I think that to me is the key.

If there is no reason why uniform standards cannot be applied everywhere, then I see no reason why you should not strive toward that as an objective. If means are not available, let us say there are no doctors in an area—and that is true in much of the world—then you may have to omit some element of the standards; but as far as they can be applied, let us put it that way, you feel that whatever is done here ought to be done everywhere as far as it can be done?

Mr. SQUIBB. If it is the correct and proper way from what we hear then, it is the correct and proper approach to the individual problem.

Senator JAVITS. Well, Mr. Squibb, thank you very much. It seems to me that is the key point that I wish to bring out under questioning.

Mr. Ledogar, did you have a comment you wish to make on this?

Mr. LEDOGAR. If I may, very briefly.

I do not think the issue is really universal standards.

The Business and Industry Advisory Committee which represents U.S. multinational firms raised that issue when commenting on the report of the United Nations group of eminent persons of which you were a member.

The issue is disclosure. Apparently, there is a resistance within industry to even disclose to host governments the FDA requirements with regard to health and safety on drugs.

I do not believe that there can be universal standards because the needs vary greatly from one country to another, but we can at least let everyone know around the world what the FDA requires and that will go a long way toward enabling governments to judge for themselves what the specific dangers of a drug are and to apply that information to the conditions in their country.

Senator JAVITS. Well, Mr. Ledogar, I see nothing inconsistent between what you have said and what Mr. Squibb and I have been saying because the FDA requires the very publicity and information which you have just mentioned. It is an element. I see no difference.

What is the difference?

Mr. LEDOGAR. But the FDA cannot require it overseas.

Senator JAVITS. I understand that but what we are trying to find out is if there is any way we can. That is what we are here for.

Mr. LEDOGAR. Yes, and I believe it should be done.

Senator JAVITS. In other words, are you against our applying of FDA standards to the extent possible overseas as well as domestically?

Mr. LEDOGAR. Yes, I think in some cases it can be an interference in the internal affairs of another government.

Senator JAVITS. And that is your reason for being against?

Mr. LEDOGAR. Also because standards cannot be the same all around the world.

Senator JAVITS. No one said they are to be the same.

All we said is insofar as it is possible, but you do not accept that? You say we would be interfering in the internal affairs of another government?

Mr. LEDOGAR. I do not believe we can unilaterally impose them.

Senator JAVITS. No one is trying to impose them, sir.

All we are saying is if we can find a way to do it that we should make FDA standards universal insofar as they can be applied in each given country.

Mr. LEDOGAR. I am simply saying a first step is disclosure.

Senator JAVITS. All right, Mr. Ledogar, thank you.

Do you have questions, Mr. Gordon?

Mr. GORDON. Mr. Squibb, on the top of page 6, you stated that: "Government regulatory bodies tend toward policies which take absolute safety and so on and so forth, and then you say while the independent scientists tend to evaluate a drug on a risk-benefit basis."

Is that not what the FDA uses as a basis for approving or rejecting a drug?

Mr. SQUIBB. I would think, for example, of the Delaney amendment.

Mr. GORDON. That does not deal with drugs. That deals with food additives.

Mr. SQUIBB. But I say Government regulatory bodies tend to look toward absolute safety, and they have to because of the publicity attendant to any accident or any fatal or harmful results of the drug.

I think that is a well-established fact and it is inevitable that they do so.

We heard some testimony yesterday from Dr. Lee that the individual physician can determine whether the illness or the condition for which he is using the drug is such as to warrant risking the chance of serious side effects from the drug.

There is no question about that possibility, whereas the regulation may say specifically it cannot be used for that indication for the reason there are a lot of serious side effects.

The risk factor that an individual physician can determine is often a major consideration as to whether that drug is properly used.

Mr. GORDON. In your prepared statement you also say: "There is the basic doubt as to a universal and automatic competence of FDA or any other governmental agency in all matters it touches."

I merely want to emphasize that at least the FDA does not have a financial interest in getting a drug on the market, whereas a company generally does.

Mr. SQUIBB. That is right. This is again the problem I point out, the difficulty and conflict between commercialism and medicine.

It is a very difficult problem, and of course, all these companies that make these remarkable drugs are commercial operations which require a profit for their stockholders on the one hand, then on the other

there are these principles of social responsibility and medical ethics which are difficult often to correlate. This is why we are struggling here today.

Senator JAVITS. Thank you very much, Mr. Squibb and Mr. Ledogar.

The subcommittee will stand in recess, subject to the call of the Chair.

[Whereupon, at 10:45 a.m., the subcommittee recessed to reconvene at the call of the Chair.]

APPENDIX

STATEMENT BY

ROBERT J. LEDOGAR

AUTHOR AND PRIVATE CITIZEN

BEFORE SUBCOMMITTEE ON MONOPOLY

SENATE SMALL BUSINESS COMMITTEE

May 27, 1976

My statement, Mr. Chairman, will consist of four parts: first, a brief summary of what I consider to be the main problems with the development, marketing and use of prescription drugs in Latin America; second, the relation of transnational pharmaceutical corporations to these problems; third, the impact of United States foreign policy on the situation; and fourth, some recommendations.

As a preface, however, I am obliged to make it clear that I speak only as a private citizen. Although I am currently serving with the staff of the United Nations, my remarks here today are the outcome of investigations carried on before I joined the U.N. in preparation for a book entitled Hungry For Profits: U.S. Food & Drug Multinationals in Latin America. This book was published by IDOC/North America, but the work was completed prior to my current U.N. affiliation. Consequently, what I have

to say does not rest on any information obtained as a U.N. staff member, nor does it reflect the official views of the United Nations.

There are two sets of problems besetting Latin America with respect to pharmaceutical products. The first affects the urban middle and upper classes for the most part, and it is a problem of excessive consumption of pharmaceutical products under unnecessarily hazardous conditions. Those who can afford it may buy almost any non-narcotic drug without prescription (despite a statement on the label which says that the drug is for sale by prescription only), and the labelling and advertising of such products, generally speaking, carry fewer warnings and claim more extensive healing powers than is permitted for the same product in the United States or Western Europe. Examples of such labelling and advertising are given in my book, as well as in the works of Drs. Silverman and Lee.

The second and more serious problem is that of the low-income majority of Latin Americans who, for the most part, do not consume pharmaceuticals in great quantity because those products which are available are too expensive and/or unsuited to their needs. 72% of Brazilians, for example, die before the age of 50; 10% of them die before their first birthday. Communicable and endemic diseases aggravated by malnutrition are the main causes of such deaths. What Brazil, like most other countries of Latin

America, needs from the pharmaceutical industry is the development of very inexpensive drugs to combat diseases like tuberculosis, measles, diptheria, whooping cough, schistosomiasis, Chagas disease, and the myriad of intestinal infections which ravage the low-income populations. This means that research and development must be carried out with these local and low-income concerns primarily in mind. This is not the kind of R&D which receives highest priority in the multinational pharmaceutical business. Nearly all of the pharmaceutical products on sale throughout the world today are discovered and developed in the United States or Europe. Since multinational firms make their money by selling to the higher income populations of North America, Europe, and Japan, along with the urban middle and upper classes of Asia, Africa and Latin America, they have very little economic incentive to produce cheap drugs to combat diseases from which their main customers do not suffer.

My purpose is not to make the transnational pharmaceutical industry the scapegoat for all of Latin America's ills. The industry has discovered and developed drugs and vaccines which have saved millions of lives among rich and poor. Even if one believes that such discoveries and more might have taken place if the industry were structured differently than it is, credit should be given where it is due. Latin American govern-

ments certainly bear a very large share of the responsibility for the problems I have just described. They invited multinational industry to their shores and, even though this was done frequently with the active encouragement of the U.S. government, they could have refused; and they remain free to expel, nationalize, or otherwise discipline these firms.

But one can fairly blame the multinational industry for at least two things: for the maintenance of high prices on drugs currently available and for its tendency to favor the political, economic and therapeutic status quo. Multinational industry's role in the maintenance of high prices on the international market has already been investigated by this subcommittee and will perhaps be discussed further by other witnesses at these hearings. I am more concerned with the industry's failure to produce what the people really need and its ability to resist efforts by concerned local interests to develop a low cost chemotherapy more suited to such needs. When, for example, 45% of a sample of foreign-held patents registered in Argentina from 1957-67 were for products which were neither being manufactured nor imported into Argentina, the effect could only have been to discourage Argentine research and development. Transnational industry frequently enters Latin America or expands there by buying out already existing local firms. In individual cases

such mergers may have beneficial effects, but the overall impact is again to reduce the incentive and scope for local research and development. This is especially the case when transnational firms dominate the entire industry, as they do in many Latin American countries where they may be responsible for three-quarters or more of total sales volume. Most of the raw materials for drugs sold in Latin America come from outside Latin America. Central America imports 90% of its raw materials for drugs. This is hardly the road to self-sufficiency. And the multinationals openly resist efforts by Latin American governments to foster an independent national research and development capability. An ambitious and well-financed plan mounted in Brazil in 1971 to utilize government, university and other local laboratories to produce 400 basic medicines cheaply and efficiently for nation-wide distribution was openly resisted by the foreign-owned firms. In the end the plan was emasculated, resulting in only a very small transfer of secondary R&D facilities by a few companies to Brazil.

Just as they complain about excessive controls by the FDA in this country, the multinational firms are hardly likely to favor an improvement in the generally inadequate government control systems in Latin America for drug labelling and marketing. Since the investigative work for my book was completed, several transnation-

al drug firms from the United States have admitted to giving bribes to officials of foreign governments. None of the countries have been identified. I was able to obtain evidence on bribery in Latin America only in the case of one firm—a Swiss company which had a list of 135 Brazilian regulatory officials to whom it gave small "donations"—but everyone knows that bribery is a frequent occurrence. The transnationals say they have to engage in it in order to survive. As individual companies they probably do. The point is that they are able to unite and flex their muscles when their common interests are seriously threatened. Despite the fact that they dominate the drug industry in many countries, the multinationals have done little to change the regulatory status quo. One can only conclude that it suits their purposes just as it is.

Where does United States foreign policy come into all of this? First of all, despite some recent changes in legislation, our government offers substantial encouragement to foreign investment by transnational firms headquartered in this country through tax incentives, guarantees, loans and the services of our commercial representatives abroad. Drug companies have taken special advantage of these incentives as several examples in my book illustrate.

In a broader way, however, U.S. foreign policy sup-

ports the activities of transnational firms overseas by openly encouraging the maintenance of a "favorable business climate" in those countries we consider to be our friends. We support regimes which encourage investment by U.S. firms. Relations are cooler with countries which place heavy restrictions on such investment. Our special relationship with Brazil, for example, is due in part to that nation's heavy reliance on, and strong encouragement of, U.S. private investment as opposed to the more restrictive attitude of the Andean Pact countries.

The crux of the problem is here. For most business a "favorable investment climate" means a minimum of government interference. Simplified rules and regulations, tax incentives, freedom to compete with (and/or buy out) local industries, a limit to price controls, plenty of cheap labor and little labor militancy—this in itself bespeaks a conservative, if not repressive, type of regime. But with the pharmaceutical industry there are added requirements. In their case, a "favorable business climate" also means: weakness of safety controls on labelling and advertising; no efforts to control the proliferation of brand names; freedom to locate research and development facilities wherever these are most profitable for the company; absence of adverse publicity; and freedom to produce and sell not necessarily what is most needed in the country but what is more economically efficient from

the standpoint of profits.

This puts the United States government in the position of supporting activities which are contrary to the best interests of the majority of people in Latin America. It makes us the ally of transnational business in its tendency to support the status quo and oppose change.

What can be done to change this situation? A general review of our government's whole supportive attitude toward U.S. foreign investments, together with the specific incentives, is certainly in order, but that is a very large issue which transcends this committee's present specific concern with the pharmaceutical industry. Short of such a broad policy review, there is very little that the U.S. government can do unilaterally to alter the conduct of U.S. firms acting through local subsidiaries overseas. We cannot interfere in the internal affairs of other nations to impose standards of our own. There are serious difficulties, moreover, with the imposition of unilateral controls by the U.S. government on U.S.-based firms in the absence of similar controls on European and Japanese firms by their governments.

What our government can do is to support multilateral efforts toward the greater regulation of transnational investment in less developed countries as well as independent multilateral efforts to assist less developed countries in solving their most serious health problems. I would like to offer the following specific recommendations:

1) That the United States government take an active role in seeking an international convention on the conditions of trade, sale, marketing, advertising and labelling of pharmaceutical products. I have in mind a role similar to that taken most recently by our government in urging international action on the question of bribery in international business dealings.

2) That the United States government support the recommendation of the United Nations Group of Emminent Persons that the affiliates of transnational corporations should be required to reveal to host governments any sales prohibitions and restrictions in manufacturing imposed by home or other host countries with respect to the health and safety of consumers.

3) That the United States government, through its representatives to the World Health Organization, support current efforts of that organization to improve its International System of Information on Drugs and look for ways to restructure the Geneva Research Center for Monitoring Adverse Reactions to Drugs so that it may be more suited to the needs of less developed countries.

4) That the United States government offer, preferably through multilateral channels, financial and technical assistance, independent of any influence from private U.S. firms, for improving the capacity of

of regulatory agencies in less developed countries to exercise control over the pharmaceutical industry.

5) Finally, but most important, that the United States redouble the research efforts of its own government agencies and offer, through multilateral channels, more technical and financial aid to independent, non-commercial research facilities in less developed countries to discover and develop cheaper and better drugs to combat the diseases which afflict and shorten the lives of many millions of our fellow human beings.

Mr. Chairman, these recommendations do not constitute the total solution to the problems I have described earlier, but if they were to be carried out we would have made a good start.

STATEMENT BY

Philip R. Lee, M.D.*

BEFORE THE

SUBCOMMITTEE ON MONOPOLY

SMALL BUSINESS COMMITTEE

UNITED STATES SENATE

May 26, 1976

Mr. Chairman and members of the Subcommittee:

I am pleased to have this opportunity to appear before the Subcommittee on Monopoly, Small Business Committee to respond to your request to discuss the results of Dr. Silverman's studies on drug product promotion in Latin America. Like Dr. Silverman, the views I express are my own and do not necessarily represent those of my colleagues at the University of California.

Although I have had the opportunity of reviewing the results of Dr. Silverman's studies in detail, I want to focus my remarks today on the problem of drug resistant pathogenic bacteria and the relationship of this problem to drug promotion, physician and pharmacist prescribing, and pharmacist dispensing in Latin America.

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* Professor of Social Medicine; Director, Health Policy Program, School of Medicine, University of California, San Francisco.

Specifically, I will discuss in some detail the problems that arose in Central America because of an epidemic of Shiga dysentary due to Shigella dysenteriae strains resistant to chloramphenicol, tetracycline, streptomycin and sulfonamides, and the problems that arose in Mexico because of an epidemic of typhoid fever caused by chloramphenicol resistant Salmonella typhi. Until the epidemic of typhoid fever in Mexico in 1972, chloramphenicol was the drug of choice for this disease throughout the world. In Mexico it proved ineffective because of drug resistance.

The epidemic of Shiga dysentery was due to chloramphenicol resistant organisms, but because the treatment of choice is ampicillin this was not a matter of prime importance. That epidemic was important because it spread rapidly among susceptible populations and it had a high fatality rate. The patient with Shiga dysentery suffers from explosive diarrhea, with up to 40 bowel movements per day, blood and mucus in the stools, severe cramps and dehydration. The preferred treatment of choice is ampicillin when the organisms are susceptible, which is usually the case. In other forms of Shigellosis the frequency of resistance of the pathogens to ampicillin and other antimicrobial agents has restricted drug therapy to only those patients with serious illness.

Why do I choose to focus my remarks on the problem of drug resistant enteric pathogens in Mexico and Central America, when Dr. Silverman's study included a wide range of drugs from antibiotics to tranquilizers? I do so because I believe the problem is related to the promotional practices of the drug companies, it is serious and it can affect not only the residents of the countries involved and all those who visit there as well, but people who have never traveled to Latin America.

The development of pathogenic bacterial resistance to antimicrobial drugs has been a serious problem in the United States since the development of penicillin resistant staphylococci in the 1950's. In the 1960's resistant strains of meningocoocci appeared, causing meningitis in members of the Armed Forces. Patients with bacillary dysentery in various parts of the world were found to harbor strains of Shigella resistant to several antimicrobial drugs. In the late 1960's the epidemic of Shiga dysentery in Central America was caused by Shigella resistant to chloramphenicol and other antimicrobial drugs. In the 1970's a typhoid fever epidemic in Mexico was found to be due to Salmonella typhi strains resistant to chloramphenicol. Recently, in the United States and Egypt cases of meningitis due to Hemophilus Influenza strains resistant to ampicillin and penicillin have been reported. In 1975, physicians at the U.S. Naval Medical Research Unit No. 3 in Cairo, Egypt, reported for the first time isolating chloramphenicol resistant Salmonella paratyphi-A from a patient admitted with chronic entenic fever.

The increasing prevalence of drug resistant strains of bacteria is, in part, apparently related to the widespread use of antibiotics and other antimicrobial agents. This use is due to a considerable extent to irrational prescribing by physicians, irrational dispensing by pharmacists where they are permitted to dispense antibiotics without a physician's consent and to the underlying promotional practices by the drug companies that encourage irrational prescribing and dispensing.

It is within the context of the worldwide problem of increasing drug resistance that I want to discuss the recent Shiga dysentery epidemic in Central America and the typhoid fever epidemic in Mexico. In both cases the causative organisms were resistant to chloramphenicol, a fact of great importance, particularly in the Mexican epidemic.

Chloramphenicol is an antibiotic which is well known to this Committee because of the Committee hearings on the subject in 1967 and 1968, and the subsequent hearings on antibiotics, particularly in 1972.

Chloramphenicol marketed in the United States since 1949, is unquestionably a potent antibiotic. But because its use may result in serious adverse effects, including fatal blood dyscrasias (aplastic anemia, thrombocytopenia and granulocytopenia) it must not be used when less dangerous drugs will be effective.

In the United States the Food and Drug Administration (FDA) limits approval of the conditions for which it may be promoted by manufacturers to infections caused by Salmonella typhi sensitive to chloramphenicol, and the following serious infections caused by susceptible strains:

-- Salmonella species;

-- Hemophilus Influenzae, specifically meningococcal infections;

-- Rickettsia strains;

-- Lymphgranuloma-psittacosis group;

-- Various gram negative bacteria causing bacteremia, meningitis or other serious gram negative infections; and

-- Other susceptible organisms that have been demonstrated to be resistant to all other appropriate antimicrobial agents.

In spite of these clear indications and the fact that chloramphenicol can be dispensed in the United States only on a physician's prescription, there is still significant misuse and overuse. In a recent study in Tennessee, for example, it was found that half the chloramphenicol prescriptions for Medicaid patients were

for upper respiratory infection. Fortunately only 204 of the 3,409 physicians participating in that program prescribed chloramphenicol. The problem was primarily with the 20 physicians who wrote 55 percent of the chloramphenicol prescriptions. For most of the patients who received a chloramphenicol prescription it was prescribed unwisely.(1)

It is unfortuante that the prescribing patterns of some physicians, such as those found in the Tennessee study, still persist. The trend with respect to chloramphenicol in the United States has improved significantly in the past decade. In the late 1960's, prior to important hearings by this Committee which brought the hazards of chloramphenicol use to the public's attention, the FDA certified more than 40 million grams of chloramphenicol annually. After the hearings, in the early 1970's, the figures were between 6-8 million grams annually. This is still far more than is needed for the patients for when chloramphenicol is indicated, but it does show that change is possible. Part of the improvement was due, in my opinion, to improved public understanding stemming from your Committee's hearings.

The situation that Dr. Silverman found in his study of drug promotion in Latin America is far different and far more serious and one that poses a greater hazard for the public. In his testimony today he noted:

> In Mexico and Colombia, the Parke-Davis brand marketed as Chloromycetin is promoted for use not only for life-threatening conditions but also for tonsillitis, pharynsitis, bronchitis, urinary tract infections, ulcerative colitis, pneumonia, staphylococcus infections, streptococcus infections, eye infections, yaws, and gonorrhea.

In Central America, a competitive brand marketed by McKesson is recommended for whooping cough.

In the United States, the Parke-Davis product carries a long list of contraindications, warnings, and adverse reactions. Perhaps the most alarming of these include aplastic anemia and other serious or fatal diseases of the blood-forming system.

In Mexico, the Parke-Davis product carries only a limited list of warnings. In Central America, no contraindications or warnings are given, and no adverse reactions are disclosed.

The McKesson product statement discloses a few hazards in Central America but none in Colombia and Ecuador.

What are the consequences of this type of promotion? What are the possible hazards? First, physicians and pharmacists will be more likely to prescribe and dispense chloramphenicol either when it is not needed, when it is contraindicated, or when other drugs would be more appropriate. Patients will be more likely to take chloramphenicol without particular concern for the possible hazards, or they may be totally unaware of the hazards and some will undoubtedly suffer serious, indeed fatal, side effects. Dr. Silverman has already noted that Mexico has an unusually high rate of fatal aplastic anemia, related, at least in part, to the widespread, irrational use of chloramphenicol. This is reason enough to markedly restrict the promotion, prescribing and dispensing of chloramphenicol in those countries in which it is used.

The regulation of the manufacture, promotion and marketing of drugs is the responsibility of the government in each country where drugs are made, sold and promoted. Drug companies may, and indeed do, adopt standards that exceed the requirements in many countries. The regulation of the drug industry in Mexico, Guatemala or any other country should, however, be a matter of concern for the United States because inadequate regulation poses a hazard both for the citizens of the countries involved, for visitors to those countries and potentially for those who may never travel. In short, inadequate regulation poses a potential threat to world health.

The emergence and widespread prevalence of drug resistant enteric pathogens in two recent Latin American epidemics illustrate these problems. These epidemics were a menace not only to the people of Central America and Mexico, but they were also a potential hazard to all those who visited there.

In order to explain why I believe the development of drug resistant enteric pathogens respresents a serious problem, I must review a little history, a little pharmacology and some microbiology.

In the early 1960's, it was found that patients with bacillary dysentery harbored strains of Shigella that were resistant to several antimicrobial drugs. When these resistant strains were cultured in vitro with sensitive strains of Shigella or even other gram negative bacteria, the genes for multiple drug resistance were transferred to the drug senstive strains without simultaneous transfer of any other genetic marker from the donor strain. The resistance (R) factors have been identified, and resistant strains have been found not only in hospital populations but also in domestic livestock, especially when antibiotics

were routinely present in the animal feed. They have also been found in the enteric (intestinal) bacteria of a human population never exposed to antibiotics for therapeutic purposes.[2] In discussing this phenomena, Goldstein, Aronson and Kalman observed:

> Thus, the transfer factors evidently occur widely; the extensive use of antibiotics merely favoring their proliferation by a selection mechanism. They constitute a significant problem in hospital patients, as evidenced by a study in which stool cultures from 100 apparently normal hospitalized infants revealed multiple drug resistant bacteria in 81 of them.[3]

Why is drug resistance important? Why is it important that the resistance (R) factor can be transferred to other enteric organisms? What does all this have to do with the promotion of drugs in Latin America?

The problem is important to the millions of people who live in Latin America, it is important for the 2.5 million residents of the United States who travel to Mexico annually, it is important to the millions of residents of the United States, Europe, Asia and Africa who travel to Mexico and the other Latin American countries every year. At least one-third of the travelers to Mexico and many other Latin American countries are likely to suffer an episode of gastroenteritis during or following their trip.[4] Although many of these are minor, many are serious and some have proved lethal.

There are three enteric infections that pose significant potential risks to Americans or others traveling in Mexico and other Latin American countries:

typhoid fever (Salmonella typhi), Shiga dysentery (Shigella dysenteriae type one) and amebiasis (Centamoeba histolytica).

In 1969, Shiga dystentery appeared in Central America in epidemic forms after an absence of several decades. The epidemic began in Guatemala in late 1968 or early 1969. The epidemic spread through Guatemala, British Honduras, El Salvador, Honduras and Nicaragua; the following year it appeared in Costa Rica and Mexico. In Guatemala alone there were an estimated 12,500 deaths and in El Salvador an additional 2,000 deaths occurred. The death rate from Shiga dysentery in Guatemala in 1969 was five times that of 1968 and sevenfold greater than in 1967. In a report on this epidemic from the United States Center for Disease Control in Atlanta, Georgia, it was noted:

> The Central American strain displayed unusual virulence, with a case-fatality ratio for untreated patients of 8.4 percent; the ratio was 10-15 percent for those whose illnesses were severe enough to require hospitalization, although appropriate therapy reduced fatalities to one percent. The epidemic strain was resistant to tetracycline, streptomycin, chloramphenicol and sulfonamides. (5)

Fortunately the organisms were not resistant to ampicillin, which is the treatment of choice in cases of Shiga dysentery.

The cases were not limited to Central America and Mexico. Shortly after Shiga dysentery appeared in Mexico, increasing numbers of cases were noted in the United States. In 20 cases reported in California, 18 of the 20

patients had visited Mexico or Central America. In addition, cases have been reported in the United States among individuals who had not traveled to Mexico or Central America, indicating that there had been transmission within the United States.

Since the 1969 epidemic of Shiga dysentery in Guatemala, there has been a steady increase in the cases of Shiga bacillus dysentery reported in the United States. The cases reported by the Center for Disease Control between 1965 and 1972 were as follows:(6)

Year	Border States*	Other States	Total
1965	0	1	1
1966	2	0	2
1967	0	3	3
1968	4	1	5
1969	3	11	14
1970	13	15	28
1971	38	4	42
1972	58	12	70

* California, Arizona, Texas, New Mexico.

The greatest increase in cases has been in the border states of California, Arizona, Texas and New Mexico where the total rose from three in 1969 to 58 in 1972. Nationwide the total number of cases of Shiga dysentery rose from 14 in 1969 to 70 in 1972.

The Shiga dysentery epidemic subsided almost as quickly as it developed. The hazard of a possible future epidemic is not only the severity of the disease, but the fact that strains may develop which are resistant not only to chloramphenicol and the sulfonamides, but also to ampicillin, which is the drug of choice in patients with Shiga dysentery.

The epidemic of typhoid fever in Mexico in 1972 illustrates the problems that arise when the organisms causing the disease are resistant to the drug of choice, in this case chloramphenicol. In May 1972, Mexican authorities announced the existence of a widespread outbreak of typhoid fever. A total of 6,342 cases was reported in 1972, a 100 percent increase over the 1971 total. The epidemic in Mexico subsided in mid-1973. Isolates of Salmonella typhi from the epidemic demonstrated R-factor-mediated resistance to chloramphenicol, streptomycin, tetracycline and sulfonamides; a phenomena similar to that previously found in other Latin American enteric (intestinal) pathogens. In a report from the United States Center for Disease Control it was noted:

> At the outset of the epidemic the case-fatality rate was greatly elevated, averaging 13.5 percent for March and April of 1972. Ninety-six percent of all Salmonella typhi strains isolated at the time were later determined to be resistant to chloramphenicol. The fact that this drug was then still considered the treatment of choice for typhoid fever probably accounted for the initially high fatality rate. However, where

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> antibiotic resistance to the epidemic strain (phage type degraded Vi approaching A) was recognized, the change to ampicillin as standard therapy resulted in a rapid decline in mortality.(7)

The experience of the LaRaza Infectious Disease Hospital in Mexico City, the source of most of the bacteriologically confirmed cases, illustrated the magnitude and seriousness of the epidemic. In 1970, the hospital reported 179 cases of typhoid fever. In 1971, the number of cases in the hospital rose to 197. In 1972, 1,676 cases of typhoid fever were treated with 60 deaths. This is a case fatality rate of 3.6 percent. In 1973, the number of cases dropped to 681 with 13 deaths (a case fatality rate of 1.9 percent). By 1974, the number of cases had dropped to the pre-epidemic level, with 191 cases and no deaths.(8)

Although the use of ampicillin was effective in many of the cases treated in the Mexican epidemic, this fact can hardly be a cause for optimism, as noted by Anderson and Smith:

> The poor response to chloramphenicol is hardly surprising, but ampicillin, to which the Mexican strain is sensitive in vitro, has proved a disappointment in general for the treatment of typhoid fever, and it would be an error to regard it as anything better than a second-line drug in this respect.(9)

In addition to the thousands of cases of chloramphenicol resistant typhoid fever reported in Mexico during the epidemic, cases due to the Mexican epidemic strain of Salmonella typhi (S. typhi) were also reported in the United States and Great Britain.

Chloramphenicol resistance has been reported in individual strains of Salmonella typhi since 1950, but prior to the Mexican epidemic in 1972 no epidemic caused by a resistant strain had been reported. According to Anderson and Smith[12] chloramphenicol resistance in Salmonella typhi was apparently first reported in England in 1950. It was subsequently reported in India, West Africa, Greece, Israel, Chile, Kuwait and Spain. In the cases from Kuwait, each case was suspected of being infected in a different place-- one in Aden, one in Cario, and one in Pakistan. The resistance in the Greek and Israeli strains was caused by a transferable extrachromosomal element known as a resistance (R) factor. In the strains isolated for the three cases in Kuwait the organisms were resistant to ampicillin, chloramphenicol and tetracyclines. This resistance factor (ACT) was also transferable en bloc at high frequency to escherichia coli. It was Anderson's and Smith's view that the S. typhi acquired the ACT resistance (R) factor in Kuwait, although it is possible that it is widespread throughout the Middle East. The Salmonella typhi isolated from a case in London that apparently originated in Spain was resistant to chloramphenicol, streptomycin and sulfonamides. The resistance was transferred en bloc at low frequency to escherichia coli.

The problems are not limited to Europe, the Middle East and the Americas. In April 1975, drug resistant bacterial pathogens were found in stool cultures of Vietnamese children evacuated to the United States. The following bacterial pathogens were isolated from 49 percent of 367 stool specimens:

-- Shigella	16	(4.3%)
-- Salmonella	15	(4.1%)
-- Enteropathic E. coli	161	(44%)
-- Edwardsiella	7	(1.9%)
-- Yersinia pseudotuberculosis	2	(0.5%)
-- Arizerra	1	(0.3%)

Among the Shigella isolates, the most common antibiotic sensitivity pattern was resistance to ampicillin, tetracycline and chloramphenicol with susceptibility retained to colistin, gentamicin and sulfamethoxazole-trimethoprim. Antibiotic sensitivity among the Salmonella and enteropatheric E coli was more variable. None of the bacterial pathogens isolated among the Vietnamese children were Salmonella typhi, but they were nonetheless the cause of serious disease in a number of children.(11)

Although the isolation of antibiotic resistant Shigella and Salmonella appear to have been isolated incidents, the Mexican epidemic of typhoid fever demonstrated that the threat of epidemics due to chloramphenicol resistant Salmonella exists. The risk is greatest in countries with high levels of poverty, poor sanitation, crowded living conditions, the presence of Salmonella typhi and the widespread use of antibiotics.

Cases of typhoid fever due to the chloramphenicol resistant strain of Salmonella typhi that caused the Mexican epidemic have been reported in the United States and Great Britain. Eighty cases, in 17 states, have been reported in the United States since the Mexican epidemic. Although this does not pose

an immediate threat in the United States or Great Britain the problem is potentially serious on a worldwide basis. In discussing the problem, Anderson and Smith observed:

> The ultimate appearance of epidemic strains of S. typhi carrying R factors coding for chloramphenicol resistance is most likely in countries where two conditions are satisfied. The first is that typhoid fever must be common, so that the organism is frequently present in the human intestine. The second condition is that chloramphenicol should be used indiscriminately, so that its widespread selective pressure will promote the emergence of stable R factors coding for the respective resistance. Both these conditions are satisfied in Mexico: it is a country with a relatively high incidence of typhoid fever; and not only is chloramphenicol used on a large scale by doctors but it can be bought by the general public. (12)

Why do I dwell on this problem at such length and ignore the other problems that may arise in Latin America because of the promotion of prescription drugs by multinational corporations that Dr. Silverman has described?

I do so, Mr. Chairman, because I believe the indiscriminate use of chloramphenicol in Latin America, specifically in Mexico, is related to the way this drug is promoted and it is also related to the prevalence of chloramphenicol resistant enteric pathogens, such as Salmonella typhi.

In my opinion the regulatory policies related to the promotion and dispensing of chloramphenicol in Mexico and other Latin American countries are seriously inadequate and pose a threat to world health. Not only must the regulations relating to the drug industry be changed, but those relating to prescribing and dispensing must also be changed.

In discussing the occurrence of chloramphenicol resistant strains of Salmonella typhi in England, Anderson and Smith of the Enteric Reference Laboratory, Public Health Laboratory Service, pointed the way to what must be done:

> The British cases of typhoid infected in Mexico, and the epidemic which caused them, are a warning of this, and are a reminder that if antibiotics such as chloramphenicol are to retain their efficacy for important diseases, their use should be largely if not entirely restricted to those diseases throughout the world. (13)

In concluding, Mr. Chairman, I would like to propose a five step course of action to begin to deal with the promotional practices of multinational drug companies in Latin America.

First, all major United States pharmaceutical firms that market drugs in Latin America should be asked to review their present promotional practices and adopt a standard of promotion and marketing throughout the world that is fully consistent with, if not identical to, the practices required in the United States.

Second, the American public should be made aware of the hazards posed by the misuse of antibiotics, particularly the problems posed for travelers to

countries where antibiotics may be dispensed without a prescription and the individual receiving the drug need not be informed about its potential hazards. Perhaps the United States Public Health Service could develop an informational document for international travelers on the problems posed by the misuse of antimicrobial agents.

Third, the Center for Disease Control (CDC) should be given the resources needed to carry out the clinical, epidemiologic and laboratory studies necessary to determine the nature and extent of the health hazard posed by the emergence of drug resistant pathogenic organisms. The CDC should have the staff, facilities and equipment to monitor the emergence of resistant strains, to work with local health departments and others to study problems as they arise. The director of CDC should be asked to report annually on the problems of drug resistant pathogenic organisms, the hazards posed and what actions are appropriate to reduce or eliminate the hazards.

Fourth, the Department of State and the Department of Health, Education and Welfare should be fully apprised of Dr. Silverman's findings and requested to propose policies to deal with the problem to the World Health Organization, particularly the office for the Western Hemisphere Region, the Pan American Sanitary Bureau.

Fifth, the FDA should be asked to review its authorities and report to Congress what measures, including new legislative authority, might be taken to restrict the use of critically important antibiotics, such as chloramphenicol, to those patients where its use is essential.

Finally, Mr. Chairman, let me commend you, the members of this Committee and the Committee staff, particularly Mr. Ben Gordon, for again bringing to the attention of Congress and the American people a serious problem related to the promotion, marketing, prescribing, dispensing and use of drugs that poses a very real hazard to our health.

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Statement

by

Milton Silverman, Ph.D.

Lecturer in Pharmacology, Schools of Pharmacy and Medicine, and Senior Faculty Member, Health Policy Program, University of California, San Francisco

before

Subcommittee on Monopoly, U.S. Senate Small Business Committee

May 26, 1976

Mr. Chairman:

I am pleased to respond to your invitation and meet with you and your fellow committee members to report on how the multinational drug companies promote their prescription drug products in the United States, and how they or their affiliates or subsidiaries promote the identical products in Latin America.

I must note at the outset that I am not a physician or a pharmacist. I am a pharmacologist. I must further note that any views I may express here today are my own, and do not necessarily represent those of my university.

And, as a final prefatory statement, let me acknowledge that without the dedicated and courageous pioneering investigations conducted by you and your committee, and especially by Mr. Benjamin Gordon, much of the work that my colleagues and I have been able to accomplish over the past years in our own investigations would have been far more difficult if not impossible.

The research on which I am prepared to report today will be published tomorrow by the University of California Press under the title of The Drugging of the Americas. It involves an in-depth study of the promotion to the medical profession of 26 drugs marketed in the form of 40 products by 23 global drug companies.

Most of these firms are American. Others are based in Switzerland, France, and West Germany.

The drugs we selected for investigation are, beyond doubt, valuable and in some cases life-saving--but only when they are

used appropriately. Although each is demonstrably effective in one or more conditions, each has equally demonstrable hazards. Some of the side-effects may be only annoying. Others may be serious or fatal.

Only with a knowledge of both the advantages and the potential hazards can a physician select the right drug to prescribe for each patient--to get the maximum benefit with the least possible risk.

In the United States, physicians are given such information--the good and the bad--in what is known as the package insert. In many instances, the essential elements of the package insert are published--if the manufacturer so elects--in PDR, Physicians' Desk Reference. This book, sometimes called the "bible for prescribers," is distributed annually at no cost to every practicing physician.

Although the statements are prepared--and paid for--by the drug industry, no firm is free to make any statements it may desire. Claims for efficacy or usefulness are restricted to those for which the company has submitted convincing scientific evidence to the Food and Drug Administration. All potential hazards must be fully and openly disclosed. In some cases, the company is required to include a special warning, such as "Do not use for trivial conditions."

It is important to emphasize that such information, required by law, is intended only to inform the physician. If he wants, the physician may use the drug for an unapproved indication. He

may ignore the warnings partially or totally.

For many years, it has been known that the situation in some other countries is somewhat different. As you yourself disclosed a decade ago in your hearings on Chloromycetin--the Parke-Davis brand of chloramphenicol--the warnings published for the product in the United States were far more strict than those included in promotion in Great Britain. You will recall, Mr. Chairman, that when you called this discrepancy to the attention of a company official, he offered the defense that full disclosure of hazards was not required by British law.

That revelation before your committee was a brief but important prelude to what we can report today.

In our own studies, we investigated the 26 drugs as they were promoted in the United States, Mexico, the six Central American countries--Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, and Panama--and in Colombia, Ecuador, Brazil, and Argentina.

Essentially, we conducted a comparison of what each company said about its product to physicians in the United States through PDR, and what it said about the identical product to Latin American physicians in somewhat comparable Latin American reference volumes.

Here, two points are important.

First, I am in no position either to support or to condemn the policies and decisions of FDA as reflected in PDR. But PDR

may be viewed as a useful standard for comparison, since it has the virtual blessings of an important government agency, it is based in large part on the advice of distinguished nongovernmental experts, it is widely distributed to physicians and frequently used by them, and the drug industry--although it may dispute certain FDA decisions--has learned to live with them, and to live with them without substantial financial trauma.

Second, it must be clearly understood that PDR and the Latin American reference books are not the same. In PDR, the statements presumably have governmental approval. The promotional statements in the Latin American books, however, do not have official approval from any governmental agency; they say what the company wants to say.

There is still one other exception. In Argentina, the statements are written not by the companies but by the editors. Accordingly, the companies bear no responsibility for this promotional material.

Comparison of the drug promotion shows two facts beyond dispute:

1. In the United States, the promotional claims for efficacy--the indications for use--are generally brief. In most cases, they conform to the views expressed in standard textbooks of pharmacology and in such authoritative and internationally-recognized works as Goodman and Gilman's The Pharmacological Basis of Therapeutics and the AMA's AMA Drug Evaluations. In contrast, in the

Latin American books, the claims for efficacy are long, numerous, and often--at least in my mind--grossly exaggerated.

2. In the United States, the list of the contraindications, warnings, and potential adverse reactions is lengthy and detailed. Virtually every unhappy, serious, or possibly lethal side-effect to which a physician should be alert is included.

But in striking contrast, the potential hazards published in the Latin American volumes are usually minimized, glossed over, or totally ignored. In some cases, not a single danger is disclosed.

Let me cite some examples--

Antibiotics

Consider first the antibiotic chloramphenicol, which has figured so prominently in the hearings of this committee. It is unquestionably a potent and useful drug, but its known dangers are such that it is promoted in the United States for only such serious infections as typhoid fever and a few other life-threatening but relatively infrequent infections in which the causative organism is shown to be susceptible to the drug.

Physicians in this country are advised not to use it in trivial infections, or when other effective but less dangerous drugs are available.

In Mexico and Colombia, the Parke-Davis brand marketed as Chloromycetin is promoted for use not only for life-threatening conditions but also for tonsillitis, pharyngitis, bronchitis,

urinary tract infections, ulcerative colitis, pneumonia, staphylococcus infections, streptococcus infections, eye infections, yaws, and gonorrhea.

In Central America, a competitive brand marketed by McKesson is recommended for whooping cough.

In the United States, the Parke-Davis product carries a long list of contraindications, warnings, and adverse reactions. Perhaps the most alarming of these include aplastic anemia and other serious or fatal diseases of the blood-forming system.

In Mexico, the Parke-Davis product carries only a limited list of warnings. In Central America, no contraindications or warnings are given, and no adverse reactions are disclosed.

The McKesson product statement discloses a few hazards in Central America but none in Colombia and Ecuador.

In the case of tetracycline, marketed by Lederle under the name of Achromycin, numerous adverse reactions are given in the United States, a few in Mexico and Brazil, and none in the Central American countries.

For Squibb's amphotericin B, marketed as Fungizone, physicians in this country are told that this valuable but potentially toxic antibiotic should be used primarily for the treatment of progressive and potentially fatal forms of fungal infections. No such warning is listed in the Latin American promotion.

Schering's Garamycin carries roughly the same indications in the United States and Latin America, but the warnings are minimized

in the Latin American promotion.

Oral Contraceptives

A similar situation was discovered in the case of a number of oral contraceptives--Ovulen marketed by Searle, Norlestrin or Prolestrin marketed by Parke-Davis, Ortho Novum marketed by Otho, Novulon marketed by Johnson, Norinyl marketed by Syntex, and Ovral or Anfertil marketed by Wyeth.

In PDR, all of these are described as indicated for only one use--contraception. In the Latin American countries, they are openly recommended for contraception, and also for the control of premenstrual tension, menstrual pain, problems of the menopause, and a host of other conditions.

In the United States, physicians are warned of the possibility of many side-effects, especially thromboembolic changes that can lead to serious or fatal blood clots.

In Latin America, for all the products studied here, the risk of thromboembolic changes is ignored. No adverse reactions of any kind are given for the Searle product in Ecuador, Colombia, or Brazil, for the Parke-Davis product in Central America, and for the Wyeth product in Ecuador, Colombia, or Brazil.

Anti-Arthritics

For Ciba-Geigy's anti-arthritis drugs Butazolidin and Tandearil, only a few indications for use are approved in the United States but many in Mexico, Central America, Colombia, and Ecuador. In contrast, the warnings are numerous in this country but few in Latin America.

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No adverse reactions of any kind are disclosed for McKesson's competitive brands in Central America, Colombia, or Ecuador.

U.S. physicians are cautioned against the use of such drugs for prolonged periods. The result may be serious or fatal adverse reactions. A somewhat similar warning is given in Mexico, but the matter is not mentioned in the other countries.

In the United States, Merck's Indocin is approved for use in four serious forms of arthritic disease. In Latin America, many other indications are recommended.

In the case of this product, it seems noteworthy that the hazards listed in the Latin American countries are approximately the same as those given in this country.

Corticosteroids

Four widely-used corticosteroid hormones were included in our investigation--Schering's Meticorten and Celestone, Lederle's Aristocort or Ledercort, and Upjohn's Medrol. All can be of great value in the control of arthritis, asthma, and a variety of other conditions. But all of them, especially if used for excessive periods, may cause unpleasant or deadly side-effects--a flare-up of latent tuberculosis, bone-softening and fractures of the vertebral bones, peptic ulcer with perforation and hemorrhage, psychic changes, and many others.

Few of these hazards are disclosed for Meticorten in Latin America, and none for Celestone in Central America Colombia, Ecuador, and Brazil. For both Aristocort and Medrol, the major hazards are glossed over or given in nonspecific terms.

The promotion of another steroid hormone, Winthrop's Winstrol, offers even more striking inconsistencies. It is described to Latin American physicians as useful to increase weight, appetite, and strength. Such indications are not listed in PDR.

What is disclosed in PDR is the risk of such adverse reactions as stunting the growth of children, jaundice, interference with normal sexual development in children, and undesirable sexual changes in adults. Few of these are disclosed in Mexico and Brazil, still fewer in Central America, and none in Colombia and Ecuador.

Tranquilizers

Among the so-called major or antipsychotic tranquilizers included in our study were Sandoz's Mellaril and SKF's Stelazine. As with other drug classes, the approved indications for use are few in the United States and numerous in Latin America. Among the indications not approved in this country but listed for the Sandoz product in Central America is use of the drug for the treatment of children with behavioral disorders, hostility reactions, inability to adapt in school, insomnia, sleep walking, bed wetting, and nail biting. Many adverse reactions for Mellaril are disclosed in the United States, a few in Mexico, but none in Central America, Colombia, or Ecuador.

In the case of Stelazine, physicians in the United States are warned of the risk of the development of tardive dyskinesia--a disorder marked by involuntary movements of the lips, tongue,

hands, fingers, and feet. Speech may be seriously affected, the face distorted, and maintenance of body position impossible. In some patients, the condition may become irreversible. No effective treatment is known.

In the promotion of Stelazine, the danger of this development is disclosed to physicians in the United States. It is not listed in the reference works in Mexico, Central America, or Brazil. In fact, no adverse reactions are listed for Stelazine in the Central American countries or Brazil.

Antidepressants

With the antidepressants, the story is the same--rigorously limited indications for use in the United States, with full disclosure of hazards. The reverse is obvious in Latin America--many recommendations, but few hazards disclosed. This holds for Ciba-Geigy's Tofranil and Lakeside's Norpramin. In the case of Lilly's Aventyl, however, indications for use are limited in both the United States and Mexico, and the disclosure of hazards is similar in the two countries.

With Warner-Chilcott's Nardil, a member of the particularly dangerous group of MAO-inhibitor antidepressants, a long list of contraindications, warnings, and adverse reactions is disclosed to physicians in the United States, only relatively minor dangers are noted in Mexico, and none is disclosed in the Central American countries.

Anticonvulsants

Our last group includes three anticonvulsants widely used for the control of epilepsy. One is diphenylhydantoin, or phenytoin, marketed by Parke-Davis as Dilantin and by McKesson as Kessodantin. The promotion of the Parke-Davis product discloses only a few hazards in Mexico, fewer still in Colombia and Ecuador, and none in Central America. Only one warning is presented for the McKesson product in Central America, Colombia, and Ecuador, and no adverse reactions are disclosed.

A similar situation was found for Sandoz's Mesantoin, with only one warning presented to physicians in the Central American countries, and no adverse reactions disclosed.

With Ciba-Geigy's Tegretol, numerous adverse reactions are disclosed to physicians in the United States, a few to their colleagues in Mexico, Colombia and Ecuador, but none to physicians in Central America or Brazil.

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It is difficult to estimate with any precision the prices that patients are forced to pay for this kind of promotion--pay not in terms of pesos or quetzals or colones, but in needless injury and needless death.

Information on the frequency of adverse drug reactions in Latin America is far from adequate, just as it is far from adequate in the United States and Europe. Nevertheless, in every country in which we have worked, medical experts--especially hematologists, pathologists, and microbiologists --have expressed

to us their dismay, their frustration, their anger at what one described as "this whole sickening business."

--They have described to us the rise of resistant strains of bacteria, due almost certainly to the excessive and irrational use of antibiotics. Physicians and pharmacists are distributing these potent drugs as if they were popcorn.

--They have described the rate of fatal aplastic anemia in Mexico, now one of the highest in the world, related in substantial part to the use of chloramphenicol. One leading microbiologist in Guatemala told us, "When a child is given chloramphenicol for typhoid fever, and it dies from aplastic anemia, this is a tragedy but perhaps an unavoidable tragedy. But where it happens when the drug is used to treat a case of virus pneumonia, or an undiagnosed respiratory infection, or a sore throat, this is unconscionable."

--Others have told us of serious reactions to amphotericin B, given to treat minor fungus infections without any of the precautions made known to U.S. physicians.

--They have told us of serious or fatal blood disorders--including agranulocytosis and aplastic anemia--following prolonged use of anti-arthritis drugs.

--They have told us of the excessive use of steroids resulting in perforated peptic ulcer or explosive flare-ups of tuberculosis or candidiasis.

--They have told us of the cases of permanent brain damage caused by excessive use of antipsychotic tranquilizers--and some-

times by tranquilizers given to control bed wetting or nail-biting in children, or an inability to get along in school.

We do not know how often such tragedies occur. In most cases, it seems, neither the patient nor his family, nor even the physician, is aware that the irrational use of a drug was responsible.

One fact that may possibly be related is that, generally throughout the Latin American countries, there is no such thing as medical malpractice. Malpractice suits are unknown.

Another related factor may be the influence and the numbers of detail men, or visitadores. In the United States, there is one detail men for about 10 physicians. In Ecuador, there is one for every 8 physicians. In Colombia, there is one for every 5. And in Guatemala, Mexico, and Brazil, there is one for every 3. There are some physicians in Latin America who take advice from none of these visitadores, whom they call "visiting professors of therapeutics." There are other physicians who take advice only from these company representatives.

In many of these countries, the average detail man makes a bigger income, part salary and part commission, than does the average physician.

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The inconsistencies we have found are glaring. I suspect that similar differences could be found in the case of many other products marketed by many other global drug firms.

When these inconsistencies became apparent to us, we showed them to heads of some of the American and European companies involved, and asked how these could be explained.

In no instance did the company spokesman deny the differences. Their responses usually included these defenses:

1. "Latin American physicians don't need any warnings. They're already aware of any hazards." (Such a claim, we learned, totally infuriates Latin American medical specialists--medical school professors, clinical pharmacologists, and particularly hematologists and pathologists who, by the nature of their specialties, are most aware of the damage done and where the bodies are buried.)

2. "We make more full disclosure in our package inserts." But, we have found, there are also discrepancies in these inserts, which are not always full or complete. Further, many physicians do not see the package inserts, and usually they are quickly discarded.)

3. "It is our detail men who give each physician full information on hazards." (This is a defense we have long heard in this country. But in Latin America, as in the United States, it is generally held that "you don't knock your own product"--certainly not if you're working on commission.

4. "Physicians know that, if they write to us, we will be glad to send them more complete information." (This defense does not deserve the dignity of a comment.)

5. It is said that "no drug manufacturer would engage in such shoddy practices--would tamper with the truth, or cover up dangers--because in the long run, this would cost him the confidence of the medical profession." (I don't know the answer to this one so far as Latin American physicians are concerned. I don't know that much about the Latin American medical profession. I do know, however, that where the profession in the United States in concerned, such a defense is nonsense. Over the years, we have witnessed the record of the so-called "Dear Doctor letters," through which many major drug companies were required by FDA to notify every physician in the country that they had, in fact, tampered with the truth, or made claims that could not be supported, or failed to disclose hazards. We have seen the remarkable cases of Chloromycetin and MER/29, and all the civil suits for damages. And what happened to the good name of the companies--to their reputation with the medical profession--to their annual sales and their annual profits? The answer is distressingly clear--by and large, essentially nothing happened.)

There are two additional defenses that are more noteworthy--

6. "The differences in promotion represent honest differences in opinion. That is, we're honestly convinced that we're right and FDA is wrong." (Such an attitude might be more palatable if a company said one thing to physicians in the United States, where FDA is constantly looking over its shoulder, and another thing to all physicians everywhere in Latin America. It is more difficult to accept, however, when it is obvious that

what a company says about its product in Mexico City is not the same as what it says in Guatemala City or San Jose de Costa Rica, which is different from what it says in Bogota, Colombia, or Quito, Ecuador, or Rio de Janeiro.

7. And finally, there's the statement: "Each of our foreign subsidiaries is managed by a citizen of the country. He knows the laws and regulations, and abides by them. We're not breaking any laws."

This defense has apparently been impenetrable. In your own hearings, Mr. Chairman, it was effective in blocking further investigations. The reason is clear: copies of up-to-date Latin American drug laws are not easily available in this country. Fortunately, it became possible for us to work on the spot in Latin America, to acquire copies of the laws, and to analyze them with the aid of Latin American attorneys and drug specialists, both governmental and private.

The legal situation may be summarized as follows:

--In a number of countries, the companies are telling the truth. They are not breaking any drug laws because there are no laws requiring disclosure of hazards. Each company can follow its own conscience and its own ethical standards

--In a few countries, the picture is not clear. Governmental officials believe they have the legal authority to require full disclosure, but the authority has not been spelled out

in adequate detail.

--But in some countries--notably Colombia--there is no lack of clarity. The laws are on the books. They require full disclosure of all hazards to all physicians. And these laws are being flaunted. If companies say they are not breaking the laws in Colombia, they are lying.

One internationally-famed health educator, Dr. José Félix Patino, the former Minister of Health in Colombia, put it this way to us: "U.S. manufacturers would be put to shame if the U.S. public knew how they are promoting their products in Latin America."

Even within some of the multinational companies, top medical scientists are beginning to discover the situation for themselves. They are appalled to find what their own firms have been doing. I believe that when this record is disclosed to company boards of directors and to company stockholders, they, too, will be appalled.

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In any consideration of this whole unappetizing business, full recognition must naturally be given to the fact that what constitutes good medical practice--or rational drug use--may often be influenced by many factors: the extent of poverty, literacy, purchasing power, standards of living, access to health care, the prevalence of particular diseases; the particular population groups at risk, social and cultural standards, and religious attitudes.

Thus, what may be unacceptable medical care in the cities may be acceptable in the jungle. What may be unacceptable to a wealthy patient, who can afford to obtain first-class medical care, may be tolerated by a peasant or an inhabitant of the barrios, who exists on an average per capita income of $200 a year.

It must also be recognized that many Latin American patients--for whatever the reason--do not have ready access to a physician. If they or their children are stricken, they seek help from the pharmacist. In many communities, there is no physician, and the pharmacist is the only health professional available. Accordingly, even though this may be in violation of the law, the pharmacist has no other recourse: he must diagnose, he must prescribe, and he must dispense. Tragically, the drug information available to the pharmacist is usually no better than that supplied to physicians, and he may be dangerously uninformed or misinformed.

Here, then, is the crux of the problem: it is not whether a physician or a pharmacist will be influenced in his prescribing decisions by such factors as poverty, cultural attitudes, and the like. It is whether or not he is given ready access to the scientific facts on which he can base the appropriate prescribing decision. It is whether or not the drug companies tell the truth--and all the truth.

The problem is not simply a matter of violating laws in the developing nations, as important as that may be. It is that what should be the objective presentation of knowledge is being

twisted by the morals of the marketplace. It is that medical science is being prostituted.

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There are, Mr. Chairman, many related aspects on which others far more competent than I may wish to comment.

There are the matters of drug prices and the handsome profits that global drug companies have been extracting by means of their promotional practices in Latin America. This may be blood money, indeed.

There are the matters of ethics and morality, and how drug companies view their social responsibilities--to their corporate officers, their stockholders, and to patients here and abroad.

There is the matter of telling the truth--all the truth--and of deciding whether the truth depends on international borders, whether what is truth in one country may be untruth in another. Thus, I find great difficulty in comprehending how a company can describe one of its products as dangerous in San Diego but safe a few miles across the border in Tijuana. Or how it can promote the product as effective in only four conditions in Washington, D.C., in ten in Mexico, and in seventeen in Central America.

Finally, Mr. Chairman, there is one additional aspect that I am sure has not escaped your attention. Over the years, you

and I have heard American drug companies bitterly complain in public that the present FDA laws are excessively harsh and, in fact, are actually unnecessary. The companies insist they would live up to their moral and social responsibilities, laws or no laws.

The record of their performance in Latin America, where the laws have been safely bent, broken, or ignored, or where there are no legal restrictions on drug promotion, might--to coin an expression--make a person wonder.

STATEMENT BY

GEORGE S. SQUIBB, CONSULTANT TO PHARMACEUTICAL INDUSTRY

BEFORE SUBCOMMITTEE ON MONOPOLY

SENATE SMALL BUSINESS COMMITTEE

MAY 27, 1976

Over ten years ago I was given an assignment by my company to study the relationships between the pharmaceutical industry and various government offices and legislatures, federal and state, because at that time there was a particularly sharp concern on the part of some of the industry's managers that things were changing in the pattern of public awareness of the procedures of medical care and that a little attention to this developing situation might be helpful. That assignment resulted in the production of two papers on the problems and practices of the pharmaceutical industry, both of which are part of the record of these hearings. Into these papers I injected a little gentle advice to the industry which caused all sorts of uproar at the time, but which I now have the satisfaction to note was all good and has been picked up as their own gospel by many of those who were most horrified at the original expression. As a matter of fact as I review those words of eight or nine years ago in the light of current events I am amazed at how close to the mark they were in foretelling what was going to happen in the pharmaceutical field given the attitudes which were then, and still are prevelant. All of which only goes to prove that developments are predictable on the one hand, and on the other that the legend of the unheeded prophet, Cassandra, is still relevant today.

Not having learned any restrictive lesson from this earlier experience, I am here again to discuss some recent controversies involving the pharmaceutical industry, and to express from my experience what might be a way to avoid such unpleasant situations in the future.

Certainly none of us, in the industry or outside it, can take any pride or satisfaction in listening to the recital of the promotional excesses that the Committee has heard in the last few days. Essentially however, this is just the newest example of the fact that pharmaceutical managers live and work in a goldfish bowl which makes all of their actions reviewable by a large and varied audience of critics, most of whom are not inclined to be overly sympathetic.

The root of most of the problems that the industry has with its critics over promotional matters is the feeling that somehow sales pressures, advertising, commercial exploitation, and selling in its strict dollar and cents aspects are all foreign to, and incompatible with, the practice by the physician of his profession. Choice of treatment, drug selection, and indeed, the whole physician-patient relationship seem not properly affected by any forces outside the physician's training, abilities and understanding of the patient and his malady. The idea that anything coming out of such fields as advertising, sampling, sales pressures, price advantage, or third party recommendation of any kind could intrude on this relationship is somehow repugnant to the public

who still regard the medical profession as a sort of pre-fabricated-all-knowing-group of specialists of superior and perhaps even secret powers who need no help or direction from those inspired by motives other than the specific cure of the patient at hand. Commercialism of all kinds, and medicine, have always been uneasy associates. It is difficult to keep this relationship in proper balance, and it is the struggle to do so that leads to hearings of this type, and eventually is the cause of much of the governmental regulation imposed on the industry.

We now have before us examples of how promotional activities vary from country to country on the same drug by the same company. Indeed it appears that promotional claims for certain drugs which are forbidden in this country are emphatically stated in other countries, and that a fair case can be made for what looks like the exploitation of ignorance of peoples who lack the medical scientific experience which has evolved in the United States in the last thirty years or so. It is difficult to imagine any justification at all for the promotion or sale of a drug for an indication for which is not a specific, or any promotion or sale of a drug without adequate information as to the side effects, toxic or otherwise, of the dosage recommended. Nowhere is there any voice of industry who would argue for such courses of action, and yet here are examples of just such things happening. How can this be?

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In the record of hearings of this Committee are two significant explanations offered as to just how these promotional differences between countries are explained or rationalized. One approach is the one set forth by the president of a major pharmaceutical house that whatever standards, indications, or claims for a drug are approved by the in-house scientific staff of his organization as to the "medical positioning" of a product, that is their standard of guidance, everywhere in the world. He stated further and specifically that they would not use the standard of what is approved by FDA for that drug in this country if there should be any difference. The more you think about this approach the more puzzling the ethical implications become. It takes quite a bit of self-confidence, and perhaps even arrogance, to be able to ignore completely any findings by the FDA contrary to your own. While the track record of the FDA includes some questionable judgments in the past that have not held up to the test of time, certainly the vast body of its findings and its regulation are sound, and probably are the production of the most advanced system of drug review operating in the world today. However, if such a policy were actually used there would be no variation in promotion among different countries except where regulation required some limitation. It would appear from testimony given here that is never the case, and variation exists in the promotional claims for the same product among countries which have no virtually regulations at all. Therefore it is

doubtful even a pharmaceutical house with an internal business-research relationships of extraordinary balance and understanding can or does follow any such policy to the letter today.

The second approach is described by a former medical director of a large pharmaceutical house which maintained two different medical staffs, one apparently with a less rigid approach to promotional procedures which could be used overseas. Somehow I feel this latter approach, or variations of it is the more common, and probably the more easily rationalized of the two.

It must be recognized that there is such a thing as honest difference of informed medical opinion on the evaluation of individual drugs. It seems that there is always available some medical specialist or some source of information to contradict opinions expressed by others. It has been said time and time again that medicine is not an exact science, and certainly drug utilization appears to be one of its more inexact areas. But for the purposes of public health today, a judgment has to be made and a line drawn somewhere. It is suggested that a little line drawing is now indicated.

There are at least two complicating factors which get in the way of a quick and easy solution to this problem. First, is the obviously different opinions that scientists of good reputations and sincerity have about not only the physical qualities of drugs, but also about the whole philosophy of risk versus anticipated

therapeutic benefit. Government regulatory bodies tend towards policies which take absolute safety as the dominant note, while independent scientists tend to evaluate a drug more on a risk-versus-results basis with the individual physician determining the applicability of the particular drug to a particular case. Second, there is the basic doubt as to a universal and automatic competence of the FDA or any other governmental agency in all matters it touches. Rigid acceptance of FDA controls, with appeal or review difficult and very expensive, makes for a unsatisfactory system. Political pressures are significant in drug control regulation when they should not be, and there is sometimes too much short-sighted action taken just to get rid of an immediate problem. This results in an ever increasing body of industry rules which tend to develop into a rigid formula for establishing black and white, without any regard for the vast gray area which exists in medical procedures.

It would seem that one of the best ways that is now available to evaluate a new product, or a new use of an old one, is to try it in a market where there is some latitude permitted in promotion efforts. This is not to justify in any way exploitation of a product for indications known to be wrong, or without warning of possible side effects that have been established by previous use elsewhere. Full disclosure is <u>always</u> essential. Absence of conscious deception is <u>always</u> essential. Acknowledgement of

different opinion is always essential. After that, if there is still room for use of the product with advantage to the patient, it is clear there should be opportunity to do so.

For honest men of good will the problem is exquisitely difficult. Such scientists do not accept the automatic infallibility of government regulators, nor do they accept the limitations placed by arbitrary controls on their own conclusions.

Dishomest men who deliberately exploit ignorance to their own advantage by offering hope of cure without concern for anything except the monetary return to themselves are the object of our efforts here today. Just where and how to separate the two groups should be easy, but in fact gets more and more difficult as medicine increases in its potency and complexity.

As far as the established companies of the American Pharmaceutical industry are concerned, and it seems that all too often they are the ones that are concerned with the problem under discussion here, the solution ought to be found right in their own internal operations. The industry constantly claims for itself high standards of ethics and close attention to its admitted unique high degree of social responsibility, yet all too often it seems to fail in this regard in promotional matters. It would seem that as a matter of policy, if the question were effectively put, no Board of Directors of a responsible American Pharmaceutical house in this day and age of sensitivity to

to consumer criticism would ever knowingly permit its companies' products to be marketed under double or deceptive standards, or in any way whatsoever that would result in extraordinary risk to the public an any part of the world. The fact is that such question is rarely, if ever, put to the Boards. It is customary for the Directors to leave all day-to-day operating procedures to its field management, and then simply to inspect the financial results of such procedure. In the pharmaceutical industry something a lot more responsible than that is called for on the part of Directors. They must question precisely the way their organization is carrying out its social responsibility and to set specific standards and guidelines for the promotion of its products. If they feel that their own research staff is of such caliber and integrity as to set standards and to control and limit all promotion activities of the company, then this should be their policy and it should be applied everywhere uniformly where regulation permits. If they should wish to follow such a policy without regard for outside opinion except where such opinion is imposed upon them by law, it would be their right to do so. Without making the individual judgments themselves, they would still have to understand exactly how such judgments were arrived at between the sales and scientific departments of their organizations and would accept the infallibility of those decisions with the clear understanding that theirs was the final responsibility. It is doubtful that any Board today would take such an

extreme position in contradiction to outside opinion, but by following such a procedure of observation and review a Board would establish an ethically consistent approach to all promotional programs for its company's products no matter where the promotion was directed.

The current trend towards the personal responsibility of corporate officers and directors for all actions of their companies, and particularly those which affect the health and welfare of their customers, is one which has to be taken very seriously in the pharmaceutical industry and here is a good place to start. It seems clear that most Boards would prefer to rely on some combination of their own internal research standard and that of the FDA, or other appropriate regulatory body. But any such combination would define and establish, in advance, guidelines for aggressive promotion men for whom sales volume is the overriding issue.

If the pharmaceutical industry can not find within its own operations the solution to the obvious problem it creates for itself by promotional practices which set different standards for different peoples, then a solution will be forced on it in one way or another from outside. Several possibilities are immediately apparent, the most obvious being expanded governmental regulatory control made possible by enabling legislation. Certainly the conduct of American industry overseas is receiving all kinds of attention these days, most of it sharply critical, and there will be plenty of precedents for the imposition by the FDA of

some kind of sanctions against those who stray from U.S. standards in their conduct of their foreign business ventures. Even if the only practical method to do so is to demand industry protect its stockholders from the liability claims arising from damages related to improper drug use by observing defensible standards of product, a way can and will be found to do it.

Control through the World Health Organization is another possible way to ensure that only balanced, accurate, and scientifically documented claims are made for medicinal preparations anywhere in the world. This body could certainly assume an advisory position in this area which would be of great value especially to those countries without their own body of scientific knowledge and expertise. Dr. Helen Taussig has described to the Committee in earlier hearings some of the possibilities that could be developed along World Health lines, but clearly a lot more study is necessary to make sure that objective medical standards can be so achieved staying clear of all the varying social and political pressures that all too often seem to become dominant in a global approach to any problem.

Nine years ago before this Committee I stated that a pharmaceutical manager must accept the fact that his industry indeed carries a high degree of social responsibility or he can see that social responsibility spelled out for him slowly but surely by legislation prescribing more and more of his operations, and

taking over more and more of the functions he now guards so fiercely. The thrust of those hearings concerned prices in the pharmaceutical industry, but my comment is just as applicable today to promotional practices which seem to the public to ignore any feeling of responsibility towards the patient, and clearly go against the most basic principles of medical ethics. By continuing such practices the industry is making serious long range trouble for itself, if not here today, then down the line as foreign governments become more alive to public health problems. It is very stupid, indeed, for a well established, profitable, and progressive industry to endorse or to permit practices in its sales promotion areas which can produce only the short-term dollar return, and then will lead to restrictive controls which will overreach the abuses with which we are now concerned and go on to other pharmaceutical affairs now left unregulated. Such is the inevitable result of the abuse of corporate power, and it's about time that corporate management realized it. I would like to see the pharmaceutical industry take the lead in that realization.

Testimony, May 26, 1976, before Subcommittee on Monopoly, U.S. Senate Committee on Small Business.

I am Myron E. Wegman, John G. Searle Professor of Public Health at the University of Michigan*and Dean Emeritus of the School of Public Health.

My presence here today has two bases: my long concern with health in Latin America and my present position as chairman of an ad hoc seminar on achieving rational use of medicines. My contacts with Latin America date back twenty-five years, from early consultation work and then almost nine years of full-time employment with the Pan American Sanitary Bureau, Secretariat of the Pan American Health Organization and Regional Office of the World Health Organization, the last four years as Secretary-General. I have traveled extensively in the Americas and still serve as consultant to the Bureau in a variety of ways. I am also a member of the WHO Expert Advisory Panel on Health Manpower.

Our seminar in Ann Arbor was stimulated by Professor and Mrs. Alvin Zander, who brought together a group of us, including professors from a variety of fields, including medicine, dentistry, law, nursing, pharmacy, psychology, and ethics, to examine various aspects of the problem of achieving rational use of medicines. The Zanders have faced personal tragedy in the loss of a daughter under circumstances overwhelmingly suggestive of the fact that medicine she had received while on foreign travel was not rationally prescribed for the illness she was suffering. She died of the type of blood dyscrasia described over and over again before this committee.

As we got into the problem we could hardly believe the frightfully misleading and incomplete promotion of drugs in many countries of the world, including Spain and Latin America. We learned early that many drug companies

*mailing address Ann Arbor, Michigan 48109.

had no compunction about saying one thing at home and another abroad. I should note, to be sure, that U.S. centered companies are no different in this respect from companies with headquarters in other parts of the world.

Our seminar early decided to broaden its interests to consider the ethical values involved, utilizing a small grant from a program called University Values Year, to bring in guest speakers. We have tried to look at commercial aspects, professional educational aspects, private practice aspects, legislative aspects, and patient behavior and health education aspects.

I should note that in my presence here I am speaking as an individual since our seminar group has not yet formulated its conclusions or reached consensus on recommendations; these we expect to have ready this fall.

Latin America is a particularly sensitive area of the world in regard to drug promotion and utilization. The people of Latin America have the same kind of fascination with drugs and specific medication that is found in every part of the world. They are, however, more vulnerable to imported drugs since the national pharmaceutical industry in the various countries is much less developed than in the U.S.A. or Western Europe. This situation is changing and the government of Peru, for instance, has recently taken the lead, on behalf of the Andean Pact countries, in developing national resources for producing generic drugs. In another respect, that of local quality control, a national equivalent of our Food and Drug Administration is either essentially absent in many Latin American countries or has seriously limited powers and resources. The problem is further complicated because in any developing economy there is a general tendency to give market-place considerations precedence over regulatory or consumer protective activities.

Finally, one important way to get at irrational use of drugs is through better education of the physicians who prescribe the drugs and the pharmacists who dispense them without prescription, legally or illegally. Yet most Latin American countries have major problems with education of professional health personnel. The oldest medical school in the hemisphere is that of the University of San Marcos, in Lima, Peru, but it, along with the great majority of the medical schools in the various countries, suffers from shortage of equipment and teaching resources. Improving health professions education has been a long-standing concern of PAHO and WHO. The Pan American Health and Education Foundation, of which I am a Trustee, is engaged in an important program to help get textbooks to medical and nursing students in every country of Latin America at reduced rates. The problem of limited educational resources makes it more difficult to compete with the educational efforts of the pharmaceutical companies, each of which, naturally, is intent upon promoting its own product and has easy access to sophisticated advertising and informational techniques. Thus the question of partisan promotion of drugs is significant at all levels of medical education.

Mr. Chairman, to my knowledge, your own interest in the problem of drug distribution in this area goes back many years. I am aware of the hearings you held some years ago at which testimony was received on the efforts of the Pan American Health Organization and the World Health Organization to provide help and guidance to the member countries and to foster a spirit of international cooperation in this field. Nevertheless, I thought it might be useful to mention some of the PAHO/WHO activities in this field. During my own period as a full-time staff member of the

Pan American Health Organization I recall a number of Latin American countries asking for help in controlling the quality and advertising of drugs distributed in those countries.

Among the most significant of the many World Health Assembly resolutions in this field was WHA 16.36, adopted in May 1963, asking member states to inform the Organization immediately of problems with drugs and asking the Director-General to transmit information received in this way to member states. One specific example of action under this resolution came from a report to WHO by our Food and Drug Administration that, because of the incidence of reactions, FDA was requiring even stricter labeling of chloramphenicol. The Director-General sent a circular to all countries on 25 June 1971, giving full details, but, sad to say, little action resulted. Incidentally, this was not the first time WHO had warned governments about blood dyscrasia with chloramphenicol.

In May, 1968, the Twenty-first World Health Assembly adopted a statement of fundamental principles for the advertising of pharmaceutical products, specifying ethical and scientific criteria, and called these to the attention of every member government. The text of WHA 21.41 follows;

WHA21.41 The Twenty-first World Health Assembly,

Having considered the Director-General's report on pharmaceutical advertising;

Having noted resolution EB41.R24 of the Executive Board on the matter;

Considering that, if it is not objective, pharmaceutical advertising in whatever form is detrimental to the health of the public; and

Holding that the adherence to certain fundamental principles for the advertising of pharmaceutical products is essential,

URGES Member States to enforce the application of the ethical and scientific criteria for pharmaceutical advertising as annexed to this resolution.

ANNEX

ETHICAL AND SCIENTIFIC CRITERIA
FOR PHARMACEUTICAL ADVERTISING

All advertising on a drug should be truthful and reliable. It must not contain incorrect statements, half-truths or unverifiable assertions about the contents, effects (therapeutic as well as toxic) or indications of the drug or pharmaceutical speciality concerned.

Advertising to the Medical and Related Professions

In describing the properties of a drug and its use, stress should be laid on rendering facts and data, whereas general statements should be avoided. Statements should be supported by adequate and acceptable scientific evidence. Ambiguity must be avoided. Promotional material should not be exaggerated or misleading.

A full description, based on current scientific knowledge, should include information on the producer and sponsor of the product advertised; full designation (using generic or non-proprietary names) of the nature and content of active ingredient(s) per dose; action and uses; dosage, form of administration, and mode of application; side-effects and adverse reactions; precautions and contra-indications; treatment in case of poisoning; and references to the scientific or professional literature.

A fair balance should be maintained in presenting information on effectiveness on the one hand and adverse reactions and contra-indications on the other.

Advertising to the Public

Advertisements to the public should not be permitted for prescription drugs, for the treatment of certain diseases and conditions which can be treated only by a doctor and of which certain countries have established lists, or in a form which brings about fear or distress, or which declares specific remedies to be infallible, or suggests that they are recommended by members of the medical profession.

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Even more recently the Organization strengthened its long-time activity in monitoring adverse reactions by setting up a central unit in Geneva. As of November 1, 1975, only a small fraction of WHO's 150 member countries were reporting systematically, yet 101,000 reports were received about 12,000 drugs.

In another attempt to help regulate production of drugs resolution WHA 28.65 was adopted in May of 1975 on revised requirements for "good practices in the manufacture and quality control of drugs," calling on the member countries to adopt measures for quality control not only in manufacture but also in imported drugs.

All of these efforts, sadly, have accomplished precious little. There are a number of reasons for this paucity of action. WHO can pass noble and high sounding resolutions, distribute information, give advice, outline better procedures, but in the end, unfortunately, most ministries of health, even when the authority exists, simply do not have the clout to compete with other parts of government or with the commercial interests involved.

Another difficulty is that most of the countries of the world simply do not have the resources either for control of drugs manufactured internally or for those imported. The WHO Expert Committees have done yeoman service in setting up standards that can be followed by all countries but until conditions change most of the people of the world are not going to have the benefit of these standards.

Fundamentally, responsibility for what goes on within any country is the responsibility of that country. In the strictest sense the manufacturer who says "It is not illegal for me to make exaggerated claims in a country

that has no laws against exaggerated claims." is legally correct. This is where the problem of ethical and moral values come in. It appears to me, as a professional person, absolutely unconscionable for a manufacturer to hide behind such a defense when human lives are involved. It is simply not true that, because a particular antibiotic may need to be prescribed more often in a developing country, where the diseases for which it is useful are more prevalent, it is therefore justifiable to exaggerate the indications and minimize the contraindications. This is arrant and dangerous nonsense, as is the argument that reactions are less frequent in these countries, where, in fact, there is inadequate reporting. It is one thing to say that in a country with a high incidence of typhoid fever one may be justified in treating a typical clinical picture without awaiting laboratory confirmation. It is another to imply that because typhoid is prevalent the drug should be promoted for every case of diarrhea.

In 1947 I wrote a short paper on what I called Noxicity of Antibiotics. At that time most people were concerned with toxic reactions but I argued that there were at least three other "noxa" involved--encouragement of the development of resistant strains, interference with bacterial balance, which leads to overgrowth of other organisms, and a "masking" phenomenon, where overdependence on the antibiotic closes the physician's eyes to the need for other diagnostic and therapeutic efforts. These difficulties have not disappeared and are perhaps even more important in developing countries with insufficient health manpower.

In our seminar in Ann Arbor we have discussed the ethical and moral values involved. There is no doubt but that in a free-market society it is the ethical responsibility of a company management to earn profits

for its stockholders. But, equally, it has ethical responsibility to present to all physicians and pharmacists objective and complete information on the utility and the dangers of its products. Every physician knows that, on occasion, a dangerous drug must be used because the potential benefits outweigh the risks, but that is no excuse at all for downplaying those risks or exaggerating the benefits. Human considerations must come before profit considerations, yet the record developed at your own earlier hearings, Mr. Chairman, carries overwhelming evidence of the callous way such distortions have been carried out, and the situation has not changed.

What can the U.S. Government do? I am told by my colleagues in the Pan American Health Organization and World Health Organization that our Food and Drug Administration has cooperated with the international health organizations in supplying information and providing technical advice and consultation. FDA should be supported in these efforts and we should look for means to obtain more cooperation in relation to health considerations from other branches of government, including those branches dealing with commerce and industry.

I understand that there is no way to compel U.S. companies to change procedures of subsidiaries in other countries, that carry out all of their operations within other countries. Furthermore, the situation that we are discussing here is by no means unique to U.S. companies. Swiss, German, French, and other manufacturers are no different in their operations. It is a shameful posture, however, for a nation that prides itself on leadership, to say that, because one's competitors engage in reprehensible practices, one is justified in following suit (or in showing the way!). Is there not some way to approach U.S.-based, multi-national corporations,

which depend so much on maneuvering tax liabilities among their operations, through controlling write-offs of taxes in other countries?

Other steps, small as they are, might also be taken. The U.S. delegation could sponsor a resolution at the next World Health Assembly calling on all manufacturers everywhere to make their promotional materials similar among all countries or else to inform the various ministries of health how promotional materials differ, and why. The International Federation of Pharmaceutical Manufacturers Associations and the International Pharmaceutical Federation are non-governmental organizations in official relations with WHO and thus have the privilege of taking part in the discussion of such a resolution. In turn it is to be hoped that these federations would exercise more pressure on their own members for higher standards.

Further attention might be given to education of the health professions in more rational use of drugs through greater support by the U.S. Government for international assistance, both our own AID program and that of PAHO/WHO.

Mr. Chairman, may I commend you again for studying this important problem. The very fact that you are bringing the actual situation to light is of benefit in itself. What you report and what you recommend can, I believe, benefit the health of all people.

ANN ARBOR, MICH., *May 31, 1976.*

Senator GAYLORD NELSON,
Chairman, Senate Subcommittee on Monopoly, Select Committee on Small Business, U.S. Senate, Washington, D.C.

DEAR SENATOR NELSON: In the May 26–27 hearing on Promotion and Labeling of Drugs in Latin America, the Warner-Lambert Company's Annual Meeting of May 1972 was frequently mentioned. Among other references to the meeting, Mr. George Squibb testified that "It would seem that as a matter of policy, if the question were effectively put, no Board of Directors of a responsible American pharmaceutical house in this day and age of sensitivity to consumer criticism would ever knowingly permit its companies' products to be marketed under double or deceptive standards or in anyway whatsoever that would involve extraordinary risk to the public in any part of the world." He was then asked how he would explain the Warner-Lambert Company's 97 percent "No" vote in the annual meeting even after Dr. Lewis and Dr. Burach had informed them of the medical realities of the issue, particularly the case of the Parke Davis Company's Chloromycetin labeling in many countries abroad which contrasted so strikingly with the United States label. As I recall, Mr. Squibb replied that he could not imagine that such a thing could happen, that it could only have happened if the Directors were not really aware of the issue and thus did not understand the problem.

Since I had attended the Annual Meeting of Warner-Lambert, spoken with Mr. Weiringa and Dr. Hodges, President and Vice President for Research for Parke Davis which is part of the Warner-Lambert Company, after the meeting, and had knowledge of the aftermath of the meeting in relation to Chloromycetin labeling abroad, I thought I could clarify the issue of what went on from the viewpoint of my own experience at least and that my account would serve as an example of United States drug company labeling and promotion abroad and of efforts to change labeling of one drug as well as shed light on some of the testimony given in this hearing.

Mr. Judah Sommer, minority counsel of the Subcommittee, suggested that I write a letter to the Subcommittee to be entered into the record of the testimony of the 27th. Dr. Myron Wegman, who testified on the 26th, had already entered into the record our—my husband's and mine—documentation of Parke-Davis Chloromycetin labeling in Spain. Attached is the list of that documentation that Dr Wegman entered into the testimony on May 26th and that also documents this account. It would be more meaningful if the documentation could immediately follow this account at the end of the May 27th testimony.

Mr. Benjamin Gordon originally asked my husband or me to testify but we decided that Dr. Wegman's testimony would be more valuable.

Sincerely yours,

MRS. ALVIN F. ZANDER.

c. to Mr. Ben Gordon.

Address until June 19: % Mr. Ed Bordin, Rte. 3 Idlewood Beach, Holland, Mich. 1–616–335–9872.

STATEMENT OF MRS. ALVIN F. ZANDER

Our daughter died of aplastic anemia in January 1972 after having been given a medicine by a physician in Spain for a minor ailment, which medicine we believe, was the most likely cause of her death.

Shortly after her death it was called to our attention that Parke Davis Chloromycetin labels in Spain and other countries did not carry warnings that possibly fatal aplastic anemia might follow its use and listed many more indications for use, some trivial than the United States label. A letter we wrote to the Parke Davis Company inquiring if this were a fact and, if so, what were the reasons justifying it, elicited no reply. When we learned that Warner-Lambert's Annual Meeting had on the agenda a proposal by the Project on Corporate Responsibility and forced onto the agenda by the Federal Trade Commission, that labels abroad should be the same as the FDA-approved labels in the United States, we decided that I should attend the meeting.

Dr. Lewis and Dr. Burach and others did speak at the meeting attended by the Board of Directors about what inadequate labeling abroad actually meant in terms of death and suffering. I recall one of these doctors stating that a recent study on incidence of fatal aplastic anemia after taking chloramphenicol

(generic name for Parke Davis's brand Chloromycetin) was similar to that of the thalidomide victims, the only difference being that the victims of aplastic anemia were dead and their plight could not speak for them. The vote was a little more than 97 percent against the proposal. It was a vote of the stockholders and the proposal was specifically that the labeling should be the same abroad as in the United States which brought in other issues than the fundamental one of pharmaceutical companies providing objective, scientific, and complete information on proper use of their products in whatever country they are sold so that, as Mr. Squibb speculated, perhaps the question was not well put. Nevertheless, information on the fundamental issue of what inadequate misleading labeling can mean at least of one drug, Chloromycetin, in terms of human life has been brought to the attention of the company.

As a consumer whose daughter had recently died of aplastic anemia and whose letters to the Parke Davis Company were unanswered, I spoke after the end of the business meeting during the question and answer period and was only allowed to read from a one-page statement but was not allowed to read the Spanish label for Chloromycetin that I had brought with me which contradicted the chairman's, Warner-Lambert's chief executive officer's, statement that warnings of possible fatal aplastic anemia were indeed included.

After the meeting Mr. Weiringa, then President of Parke Davis and now, I believe, president of Warner-Lambert, said that he had not seen the letter addressed to him and that he would arrange an interview for me with him or preferably the medical director, Dr. Robert Hodges, Vice President for Research, as being more knowledgeable of medical aspects. At my request, he also said I could bring a physician with me and that he would give me the Chloromycetin labels for the countries abroad in which Parke Davis sold its products which, it seemed to me, were just elementary basic information needed to consider the issue intelligently by anyone—me, the President, the Board, the stockholders. Shortly thereafter, however, Mr. Weiringa rescinded his offer, saying supplying such information was "against the policy of the company".

This meant that we had to go through the time-consuming process of trying to collect Chloromycetin labels from abroad on our own travels and those of our friends for in many countries, since Chloromycetin is sold over-the-counter, to anyone and without a prescription, the labels are readily available. These labels varied greatly from those more similar to ours in the United States, such as in England, to many with no warnings at all and as many as 45 listed indications for use, many of them trivial. The Parke Davis Chloromycetin United States label has very strong, repeated, and explained warnings of possible fatal aplastic anemia and other warnings and states that it must not be used for minor illnesses, only for very serious illnesses susceptible to its action that cannot be treated with any less hazardous medicine.

Dr. Ronald Bishop and I met with Dr. Hodges for a long and cordial interview. Dr. Hodges described his own personal views of the product and explained the company's position regarding why labels were different abroad. (I have a file of notes of all my conversations and copies of letters and other statements of Parke Davis officials giving their views and will send them to include in the testimony if the Subcommittee so desires.) Dr. Hodges asked to see the Spanish label and when I inquired who was responsible for the labeling of Parke Davis products abroad, he replied that he was not but did not say who was responsible. It seemed strange to me that someone in his position would have to ask me to see the label when the Chloromycetin foreign labels were almost sure to be brought up at the annual meeting.

We then sent the Spanish label first, then later Chloromycetin labels from other countries to Mr. Weiringa, the President. Within a few months Mr. Weiringa called to say that the company had revised its Chloromycetin Monograph which is the company's basic information on the drug, is sent to all their international locations, and is used as the basis—along with each country's regulatory system's input—for labels in that country. Mr. Weiringa said that the new Monograph was essentially the same as the United States label but would not give us a copy since it was again "against company policy". Nor could an American physician obtain a copy, only a practicing physician in a foreign country in which Chloromycetin was sold. Upon inquiry, Dr. Hodges said the Monograph was basically the same as the United States label except that indications would vary in different countries and he was very definite that the company would not give us a copy or any information of this type. So again many months—about eight, I think—were spent in our finally successful efforts to obtain the Monograph from abroad.

The Monograph was a great improvement over the information in the labels we had previously collected, warning of the possibility of fatal aplastic anemia and stressing that Chloromycetin must not be used for trivial illnesses. The prescription against use for trivial illnesses came many years after—I think about twenty—it had been required by the FDA on the United States label! However, the new Monograph omitted some important points such as that the recommended blood studies which could detect blood dycrasias, such as aplastic anemia related to dosage and prolonged use, so that the drug could be stopped and the blood-manufacturing bone marrow could reverse itself back to normal, these blood studies could not be relied upon to detect the fatal irreversible type of aplastic anemia which did not appear for weeks or months after use of choramphenicol. This means that a physician prescribing chloramphenicol has no way of knowing whether the next patient to whom he gives chloramphenicol may be the rare individual who will die of aplastic anemia, a disease affecting the blood-manufacturing ability of the bone marrow so that the victim has insufficient red cells to fight off anemia, insufficient white cells to fight off infection, and not enough platelets to stop the flow of blood anywhere, so he must live off the blood of others as long as possible, perhaps a few months, while undergoing steroid therapy with its many devastating effects. Letters from physicians in medical journals are blaming lack of this information abroad for overuse of chloramphenicol because the conscientious physician believes he can catch and reverse aplastic anemia if he takes blood studies. Also the new Monograph still encourages much unnecessary use. We obtained the opinions of seven physicians all of whom were critical of the new Monograph. We have included in our documentation a copy of the opinions of Dr. Harry Dowling, former head of the AMA Council of Drugs, on the inadequacies of even this new improved Chloromycetin Monograph for other countries. (We will ask permission to provide the opinions of the other physicians if it would be useful to include them.)

Again it took some time before we were able to obtain abroad any new labels based on the new Monograph. These new labels were a real improvement but had faults similar to the new Monograph. Such faults and omissions may seem slight but they can cause unnecessary death to someone so in fact they are very important.

We have a few samples of Parke-Davis Chloromycetin 1972 advertising in Spain sent to us by some Spanish doctors which carry no warnings, only that one could write to the company for information. Also the Parke-Davis entries for Chloromycetin in the Vademecum Daimon, Spain's PDR (Physician's Desk Reference in U.S.) are also inadequate. A Spanish physician has painstakingly analyzed the devastating inadequacies of this publication of the pharmaceutical companies giving information on use of their products and his findings have appeared in medical journals here as well as abroad. Enclosed is a letter-to-the-editor in the British medical journal Lancet, June 22, 1974, p. 1281 clearly showing the extent of improper over-the-counter use of chloramphenicol in Spain.

We also received an example of promotion to the public in Spain of Chlorostrep, a Parke-Davis product which is a combination of chloramphenicol and streptomycin, promoted to use for common summer diarrheas, again with no warnings and also a letter sent to physicians in Spain by the Parke-Davis Company reminding them in the coming summer travel season with increased "common and infectious entercholitis" to use this product of "well proven efficacy and therapeutic safety" which will "produce a fast remission of the symptoms in your patients, *avoiding at the same time any complication.*" (My emphasis.) To make this gross distortion of information on possible effects of Chloromycetin even more reprehensible, these letters were sent after the new Monograph was written which stated clearly the risk of fatal aplastic anemia and that Chloromyctin was not to be used for trivial illnesses. We did write to Parke-Davis about this particular item since our only grandchild was unexpectedly traveling in Spain and this Parke-Davis promotion was directed at a common complaint of travelers there—but we received no reply.

In the fall of 1973 we went to Spain and had conversations with two Spanish physicians who vividly described the inadequacies of information on use of medicines by pharmaceutical companies and with the Chief of the Antibiotics Division and the Director of the Division of Chemical Analysis of the Centro Nacional de farmacobiologia (Control of Medicines) who described the present, perhaps more hopeful situation, (Notes of these conversations are included in

the documents submitted.) with improved chloramphenicol labels and the beginning of an adverse reaction reporting system.

Our experience, beginning with the Warner-Lambert Annual Meeting, suggests that perhaps basic information on just exactly what kind of labeling abroad, at least for Chloromycetin, the Parke Davis Company was producing was not known to top officers, stockholders, and most likely Board Members. When this was brought rather forcibly to their attention, even though the vote against the proposal was 97%, steps were taken in the case of Chloromycetin to rectify the inadequate label. I do not know what other response was made by the company.

Mr. Squibb's conjecture that the vote could only have happened if the Directors were not really aware of the issue, that they did not realize fully the problem, in essence may be right in terms of the deeper issue involved, that of a pharmaceutical company providing objective, scientific, and complete information on its products whether at home in the United States or abroad.

We heartily endorse Mr. Squibb's recommendations that Boards of Directors must act more responsibly, "must question precisely the way their organization is carrying out its social responsibility and set specific standards and guidelines for the promotion of its products" and that "corporate officers and directors should be held personally responsible for all the actions of their companies and particularly those which affect the health and welfare of their customers" and that such responsibility should be strictly enforced.

The information given or not given by a pharmaceutical company about its product can and does always very directly mean life or death, health or sickness to its consumers and whether it is one or the other depends basically on the integrity and vigilance of the Board of Directors, the officers, and the personnel of the company. Otherwise, as Mr. Squibb said, "If the pharmaceutical industry cannot find within its own operations the solution to the obvious problem it creates for itself by promotional practices which set different standards for different peoples, then a solution will be forced on it in one way or another from outside."

Also the failure, from our point of view, of the Parke Davis Company to produce a Chloromycetin Monograph for its international locations comparable to the one worked out with the FDA for United States makes one seriously question whether even with the best of intentions a pharmaceutical company can give objectives, scientific, and complete information on its products when it must also serve its other commercial responsibility to its stockholders.

Will there continue to be unnecessary deaths such as the one of a young woman, a Mrs. Anderson, who followed almost exactly in our Judy's footsteps the following summer and died the same way—slowly, painfully, and unnecessarily—but in her case the coroner has the bottle containing chloramphenicol which she bought over the counter in Spain for a minor "smokers" cough? Or will these hearings spur action to bring about necessary change?

An Example of United States Drug Company Labeling & Promotion Abroad
Samples of information on Chloromycetin (chloramphenicol) provided by the Parke Davis Company in Spain 1969-1974 acquired by Mr. and Mrs. Alvin Zander.

Labeling

1. Parke Davis Chloromycetin label in U.S.

2. Parke Davis Chloromycetin labels in Spain acquired in 1969-1973.

3. Parke Davis new Chloromycetin Monograph sent to all international locations as basis for new labeling.

4. Dr. Harry Dowling's "opinions, not proven facts" on the new Monograph.

5. Zanders' comparison of new Monograph with U.S. label.

6. New Parke-Davis Chloromycetin Spanish label based on new Monograph, July 1973.

7. Zanders' comparison of new Spanish label with U.S. label.

Promotion

8. Parke Davis Chloromycetin entries in Vademecum Daimon, Nov. 1972. Spanish physicians' desk reference published by pharmaceutical companies.

9. Parke Davis Chloromycetin advertising samples, Nov. 1972.

10. Parke Davis Chlorostrep advertisements directed to public, mid 1973.

11. Letter to physicians in Spain promoting Chlorostrep by Parke Davis, April 25, 1973.

12. Parke-Davis Chlorostrep label, older one acquired September 1973.

13. Parke Davis Chlorostrep label, new one based on 1973 Chloromycetin Monograph.

Control of Medicines in Spain

14. Control of medicines in Spain asperceived by Mr. and Mrs. Zander after personal interviews in Spain with two physicians and two officials.

15. Notes on conversations with two Spanish physicians, September 1973.

16. Notes on interview with Chief of Antibiotic Division and Director of Division of Chemical Analysis of the Centro Nacional de Farmacobiologia (Control of Medicines), Madrid, September 1973.

17. Centra Nacional de Farmacobiologia (CNDF('s new statements on chloramphenicol used as a basis for new labeling of chloramphenicol products of Parke-Davis and other companies in Spain.

Labeling

1. Parke Davis Chloromycetin label in U.S.

[illegible], Parke Davis, Detroit, Mich., U.S.A.

The bottle and box have the following information which is not on the Spanish box or bottle:

CAUTION - Federal law prohibits dispensing without prescription.

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.

WARNING - Keep out of the reach of children (also USUAL ADULT DOSE is given.)

(The Physicians Desk Reference to Pharmaceutical Specialties & Biologicals gives the same information.)

KAPSEALS • CAPSULES

CHLOROMYCETIN®

(CHLORAMPHENICOL)

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 rickettsiae, 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

HJ

CHLOROMYCETIN
(CHLORAMPHENICOL)

48-hour period. Total urinary excretion of chloramphenicol in thes
studies ranged from a low of 65% to a high of 99% over a three-d
period. From 8 to 12% of the antibiotic excreted is in the form of fre
chloramphenicol; the remainder consists of microbiologically inacti
metabolites, principally the conjugate with glucuronic acid. Since t
glucuronide is excreted rapidly, most chloramphenicol detected in t
blood is in the microbiologically active free form. Despite the s
proportion of unchanged drug excreted in the urine, the concentratio
of free chloramphenicol is relatively high, amounting to several hundr
mcg./ml. in patients receiving divided doses of 50 mg./kg./day. Sm
amounts of active drug are found in bile and feces. Chloramphenic
diffuses rapidly, but its distribution is not uniform. Highest concent
tions are found in liver and kidney, and lowest concentrations are fou
in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospi
fluid even in the absence of meningeal inflammation, appearing in c
centrations about half of those found in the blood. Measurable lev
are also detected in pleural and in ascitic fluids, saliva, milk and in t
aqueous and vitreous humors. Transport across the placental barri
occurs with somewhat lower concentration in cord blood of newbo
infants than in maternal blood.

INDICATIONS

IN ACCORD WITH THE CONCEPTS IN THE "WARNING BOX" AB
THIS INDICATIONS SECTION, CHLORAMPHENICOL MUST BE USE
ONLY IN THOSE SERIOUS INFECTIONS FOR WHICH LESS POTE
TIALLY DANGEROUS DRUGS ARE INEFFECTIVE OR CONTRAI
DICATED. HOWEVER, CHLORAMPHENICOL MAY BE CHOSEN T
INITIATE ANTIBIOTIC THERAPY ON THE CLINICAL IMPRESSI
THAT ONE OF THE CONDITIONS BELOW IS BELIEVED TO BE PRE
ENT; *IN VITRO* SENSITIVITY TESTS SHOULD BE PERFORMED CO
CURRENTLY SO THAT THE DRUG MAY BE DISCONTINUED AS SO
AS POSSIBLE IF LESS POTENTIALLY DANGEROUS AGENTS AR
INDICATED BY SUCH TESTS. THE DECISION TO CONTINUE USE O
CHLORAMPHENICOL RATHER THAN ANOTHER ANTIBIOTIC WH
BOTH ARE SUGGESTED BY *IN VITRO* STUDIES TO BE EFFECT
AGAINST A SPECIFIC PATHOGEN SHOULD BE BASED UPON SEV
ITY OF THE INFECTION, SUSCEPTIBILITY OF THE PATHOGEN
THE VARIOUS ANTIMICROBIAL DRUGS, EFFICACY OF THE VARIOU
DRUGS IN THE INFECTION, AND THE IMPORTANT ADDITIONA
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 t
routine treatment of the typhoid "carrier state."

**2. Serious infections caused by susceptible strains in accor
ance with the concepts expressed above:**

a. Salmonella species

*In the treatment of typhoid fever some authorities recommend that chloramphenicol
administered at therapeutic levels for 5-10 days after the patient has become afebrile
lessen the possibility of relapse.

Insert in Chloromycetin package circulated in Latin America - May 1972

The bottle and box have the following information which is not on the Spanish box.
CAUTION - Federal law prohibits dispensing without prescription.
WARNING - Blood dyscrasias may be associated with the use of chloramphenicol.
It is essential that adequate blood studies be made. See enclosed warnings and regulations.
WARNING - Keep out of the reach of children. (also USUAL ADULT DOSE is given.)
(The Physicians Desk Reference to Pharmaceutical Specialties & Biologicals give the same information.)

CHLOROMYCETIN
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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 at proximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytocenia, 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.

CHLOROMYCETIN
(CHLORAMPHENICOL)

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)

(1) In most cases therapy with chloramphenicol had been instituted wi
the first 48 hours of life.
(2) Symptoms first appeared after 3 to 4 days of continued treatment v
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 respirati
(d) death within a few hours of onset of these symptoms.
(4) The progression of symptoms from onset to exitus was accelerated v
higher dose schedules.
(5) Preliminary blood serum level studies revealed unusually high concen
tions of chloramphenicol (over 50 mcg./ml. after repeated doses).
(6) Termination of therapy upon early evidence of the associated symp
matology frequently reversed the process with complete recovery.

DOSAGE AND ADMINISTRATION

DOSAGE RECOMMENDATIONS FOR ORAL CHLORAMPHENICOL PREPARATIONS

The majority of microorganisms susceptible to chloramphenicol will respo
to a concentration between 5 and 20 mcg./ml. The desired concentration
active drug in blood should fall within this range over most of the treatm
period. Dosage of 50 mg./kg./day divided into 4 doses at intervals of 6 ho
will usually achieve and sustain levels of this magnitude.

Except in certain circumstances (e.g., premature and newborn infants a
individuals with impairment of hepatic or renal function) lower doses may
achieve these concentrations. Chloramphenicol, like other potent drugs, sh
be prescribed at recommended doses known to have therapeutic activity. Cl
observation of the patient should be maintained and in the event of any adve
reactions, dosage should be reduced or the drug discontinued, if other fact
in the clinical situation permit.

Adults

Adults should receive 50 mg./kg./day (approximately one 250 mg. capsule
each 10 lbs. body weight) in divided doses at 6-hour intervals. In exceptio
cases patients with infections due to moderately resistant organisms may
quire increased dosage up to 100 mg./kg./day to achieve blood levels inhibit
the pathogen, but these high doses should be decreased as soon as possi
Adults with impairment of hepatic or renal function or both may have reduc
ability to metabolize and excrete the drug. In instances of impaired metab
processes, dosages should be adjusted accordingly. (See discussion un
Newborn Infants.) Precise control of concentration of the drug in the bl
should be carefully followed in patients with impaired metabolic processes
the available microtechniques (information available on request).

Children

Dosage of 50 mg./kg./day divided into 4 doses at 6-hour intervals yields bl
levels in the range effective against most susceptible organisms. Severe inf
tions (e.g., bacteremia or meningitis), especially when adequate cerebrosp
fluid concentrations are desired, may require dosage up to 100 mg./kg./d
however, it is recommended that dosage be reduced to 50 mg./kg./day as s

CHLOROMYCETIN
(CHLORAMPHENICOL)

as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants
(See section titled "Grey 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.

CHLOROMYCETIN, brand of chloramphenicol, Reg. U.S. Pat. Off.

*Trademark for dispensing package

PARKE, DAVIS & COMPANY
121 852800
DETROIT, MICHIGAN, U. S. A.
HJ
Dec. 1968

1973 PDR the same

(1) U.S. Chloromycetin Parke Davis label, received May 1972 ...

2. Parke Davis Chloromycetin labels in Spain acquired in 1969-1973.

Purchased in Madrid, Spain
On October 29, 1969 (same inserts May, August & November 1972)
To the Medical Profession:

CHLOROMYCETIN (*)

(*) Registered trademark.

Chloromycetin (chloramphenicol, P. D. and Co.) is a crystallized antibiotic with specific therapeutic activity against a great variety of pathogenic micro-organisms.

Chloromycetin is absorbed very well when administered orally and quickly gives effective concentrations in the fluids and tissues of the organism.

Dosage and Administration

In general, clinical experience with Chloromycetin in acute and chronic infections of adults indicates that the majority respond rapidly to an oral dose of 50 mg per kilo weight per day, administered fractionally over several days or until the signs and symptoms of the infection have been brought under control. When the temperature becomes normal, a dose of 25 mg per kilo weight per day, administered fractionally, is generally sufficient. On the basis of an analysis of the dosage used in adults, it has been established that a total dose of Chloromycetin ranging between 10 and 15 g is sufficient in the majority of acute infections. It may be necessary to give 15 g or more in chronic infections. The interval between doses should never be greater than 6 hours, in order that the concentration of Chloromycetin in the blood may never drop below the minimal effective concentration.

In the majority of infections, the dosage of Chloromycetin for infants an children at the beginning of therapy is calculated at between 50 and 100 mg per kilo weight per day, administered fractionally at 4-to-6-hour intervals. In a severe infection, 75 to 100 mg per kilo weight per day may be given at the beginning of the therapy. A dosage of 30 to 50 mg per kilo weight is

generally adequate afterward.

Warning. Apparently because of physiological immaturity, premature infants and infants born at term who are less than 1 month of age require a special dosage. These children often have difficulties with doses that are tolerated well by older children.

A dose of not more than 25 mg per kilogram weight per day, administered fractionally at intervals of 6 to 8 hours, is suggested for prematures. For infants born at term but less than 1 month old, a dose of not more than 50 mg per kilogram weight per day is suggested, given at intervals of 6 to 8 hours. The dosage should be adjusted according to the blood levels of the antibiotic in cases of prolonged administration or the use of doses greater than those recommended.

Clinical Indications

Chloromycetin is effective in many clinical conditions, including typhoid fever and other salmonelloses; bacillary dysentery (shigellosis) and other enteric infections; pertussis, infections of the urinary tract; respiratory infections (bacterial and viral pneumonia), peritonitis, brucellosis; ocular and otic infections, meningitis, rickettsial diseases (Rocky Mountain spotted fever, typhus, scrub typhus), and venereal infections.

Tolerance

Chloromycetin is generally well tolerated, and changes in the blood follow its use. It is desirable, nevertheless, to make periodic examinatic of the blood in cases of prolonged or intermittent administration.

The use of elevated doses of Chloromycetin in prematures and infant born at term but less than 1 month old has been associated with abdominal distension with or without emesis, progressive pallid cyanosis, or vasomot collapse, in some cases with fatal results. These adverse effects have not been reported in children with a dose of 50 mg per kilogram weight per day or less. Interruption of the therapy has corrected the adverse effects in many cases, and the patient's recovery has been complete.

A la Profesión Médica:

CHLOROMYCETIN*

El Chloromycetin (cloranfenicol, P. D. y Cía.) es un antibiótico cristalizado con actividad terapéutica específica contra una gran variedad de microorganismos patógenos.

El Chloromycetin se absorbe muy bien por vía oral y da rápidamente concentraciones eficaces en los líquidos y tejidos del organismo.

DOSIFICACION Y ADMINISTRACION

En general, la experiencia clínica con el Chloromycetin en las infecciones agudas y crónicas de los adultos indica que la mayoría responde rápidamente a una dosificación oral de 50 mg. por kilo de peso y por día, administrada en forma fraccionada durante varios días o hasta que los signos y síntomas de la infección hayan sido dominados. Cuando se normaliza la temperatura, generalmente es suficiente una dosificación de 25 mg. por kilo de peso y por día, administrada en forma fraccionada. En base a un análisis de la dosificación empleada en adultos se ha establecido que en la mayoría de las infecciones agudas es suficiente una dosis total de Chloromycetin que oscile entre 10 y 15 g. En las infecciones crónicas pueden ser necesarios 15 g. o más. Los intervalos entre la dosis nunca deben ser mayores de seis horas, a fin de evitar una disminución de la concentración de Chloromycetin en la sangre por debajo de la concentración eficaz mínima.

La dosificación del Chloromycetin para lactantes y niños al comienzo de la terapéutica, en la mayoría de las infecciones, se calcula entre 50 y 100 mg. por kilo de peso y por día, administrados en forma fraccionada a intervalos de cuatro a seis horas. Al comienzo de la terapéutica en una infección severa se pueden administrar de 75 a 100 mg. por kilo de peso y por día. Después, una dosificación de 30 a 50 mg. por kilo de peso es generalmente adecuada.

ADVERTENCIA.—Los niños prematuros y los nacidos a término de menos de un mes de edad, aparentemente debido a inmadurez fisiológica, requieren una dosificación especial. Estos niños a menudo tienen dificultades con dosis bien toleradas por niños de más edad.

Se sugiere para los niños prematuros una dosificación de no más de 25 mg. por kilogramo de peso por día, fraccionadamente, a intervalos de seis a ocho horas. Para los nacidos a término de menos de un mes de edad se sugiere una dosificación de no más de 50 mg. por kilogramo de peso por día, fraccionadamente, a intervalos de seis a ocho horas. En los casos de administración prolongada o cuando se utilicen dosis mayores que las recomendadas, las concentraciones sanguíneas de antibiótico deben servir como guía para graduar la dosificación.

INDICACIONES CLINICAS

El Chloromycetin es eficaz en muchos estados clínicos, inclusive: fiebre tifoidea y otras salmonelosis; disentería bacilar (shigelosis) y otras infecciones entéricas, tos ferina, infecciones de las vías urinarias; infecciones del aparato respiratorio (neumonías bacterianas y por virus psitacosis); infecciones oculares y otitis, meningitis, rickettsiosis (fiebre de las Montañas Rocosas, tifus, fiebre fluvial japonesa) infecciones venéreas.

TOLERANCIA

Por lo general, el Chloromycetin es bien tolerado, y las alteraciones de la sangre consecutivas a su empleo son raras. Sin embargo, conviene efectuar exámenes periódicos de sangre en los casos de administración prolongada o intermitente.

En los prematuros y los nacidos a término de menos de un mes el uso de dosis elevadas de Chloromycetin ha sido asociado con distensión abdominal, con o sin emesis, cianosis pálida progresiva, o colapso vasomotor, en algunos casos con resultados fatales. No se han comunicado estos efectos adversos en niños con una dosificación de 50 mg. por kilogramo de peso por día, o menos. La interrupción de la terapéutica ha corregido los efectos adversos en muchos casos con restablecimiento completo de los pacientes.

ENVASE

El Chloromycetin se suministra en cápsulas de 250 mg. (N.° 379), frascos de 12 y 24.

PARKE, DAVIS & COMPAÑI

Laboratorios Principales, Detroit, Michigan, E. U. A.
Laboratorios Parke Davis, S. A. E.
Madrid

79

* Marca registrada.

Spain 5

Spain 10/29/69

3. Parke Davis new Chloromycetin Monograph sent to all international locations as basis for new labeling.

Spain, Barcelona - Recd
New Chloromycetin Monograph 5-18-93
(See attached Monograph in English)

CHLOROMYCETIN

(cloranfenicol, Parke-Davis)

PARKE-DAVIS

MADRID - ESPAÑA

Monografía de Cloranfenicol

La experiencia clínica ha demostrado que el cloranfenicol (Chloromycetin, Parke-Davis) es un antibiótico eficaz en una gran variedad de procesos infecciosos bacterianos y rickettsiales. Su actividad antimicrobiana es marcada, atraviesa fácilmente las barreras orgánicas y se difunde rápidamente en casi todos los tejidos y líquidos del organismo.

ACTIVIDAD Y FARMACOLOGIA

El cloranfenicol ejerce principalmente una acción bacteriostática sobre un amplio espectro de bacterias gramnegativas y grampositivas, y es también activo contra las rickettsias y los microorganismos del grupo linfogranuloma-psitacosis. Es particularmente activo contra la **Salmonella typhi** y el **Haemofilus influenzae.** Su mecanismo de acción consiste en el entorpecimiento o la inhibición de la síntesis proteica, que se verifica tanto en células intactas como en sistemas enzimáticos acelulares. En contraste con lo que ocurre con otros antibióticos, el desarrollo de resistencia al cloranfenicol, tanto experimentalmente como en el humano, parece ser reducido.

Administrado por vía oral, el cloranfenicol es rápidamente absorbido en el tubo digestivo y alcanza concentraciones determinables en sangre media hora después de su administración.

La concentración máxima de cloranfenicol libre después de la administración de la primera dosis ocurre generalmente en el transcurso de una hora.

El cloranfenicol es excretado principalmente por el riñón, eliminándose en la orina entre el 68 % y más del 90 % de la dosis; en la bilis y en las heces se encuentran pequeñas cantidades de cloranfenicol activo. El cloranfenicol se difunde rápidamente en casi todos los tejidos y líquidos del organismo; pasa al líquido cefalorraquídeo, aun en ausencia de inflamación meníngea. También alcanza concentraciones determinables en los líquidos pleurítico y ascítico, y en la saliva y la secreción láctea. Se difunde rápidamente en los medios del ojo. En la sangre del cordón umbilical del recién nacido alcanza concentraciones algo más bajas que en la sangre materna.

El palmitato de cloranfenicol es hidrolizado en el intestino y libera cloranfenicol, y siempre que contenga el polimorfo eficaz da concentraciones sanguíneas del antibiótico similares a las obtenidas con otras formas de cloranfenicol para administración oral.

El succinato sódico de cloranfenicol, administrado por vía intravenosa o intramuscular, también es hidrolizado en el organismo y da cloranfenicol libre. Como el cuccinato sódico de cloranfenicol administrado parentéricamente es en parte excretado como tal por el riñón antes de que se verifique su hidrólisis, da concentraciones séricas de cloranfenicol libre más bajas que las que se obtienen con dosis equivalentes de cloranfenicol por vía oral, pero clínicamente eficaces.

INDICACIONES

El cloranfenicol, un agente terapéutico muy activo, no debe ser empleado en procesos infecciosos leves y debe ser administrado según indicación e instrucciones médicas. El cloranfenicol está indicado en:

Meningitis bacteriana.

Fiebre tifoidea.

Rickettsiosis.

Infecciones intraoculares.

Infecciones causadas por microorganismos del género bacteroides, septicemias causadas por bacterias gramnegativas.

Otras infecciones graves en las que los estudios bacteriológicos o el criterio clínico indican que el cloranfenicol es un antibiótico adecuado.

También es clínicamente eficaz en:

Disentería bacilar.

Infecciones causadas por el bacilo de Friedländer.

Infecciones estafilocócicas.

Neumonías bacterianas.

Gastroenteritis infantil.

Laringotraqueobronquitis.

Brucelosis (fiebre de Malta).

Psitacosis.

Tracoma.

Cólera.

La experiencia clínica ha demostrado la eficacia del cloranfenicol en la terapéutica de procesos infecciosos en oftalmología, otorrinolaringología y dermatología.

CONTRAINDICACIONES

El cloranfenicol está contraindicado en caso de antecedentes de hipersensibilidad al mismo y/o de reacciones tóxicas provocadas por él.

ADVERTENCIAS Y PRECAUCIONES

La administración del cloranfenicol puede acompañarse del desarrollo de discrasias sanguíneas, inclusive anemia aplásica. Siempre que sea posible, es conveniente efectuar hemogramas antes de instituir la terapéutica con el cloranfenicol y repetirlos a intervalos adecuados durante la misma, especialmente en caso de terapéutica prolongada o intermitente. Se debe considerar la posibilidad de interrumpir la administración de cloranfenicol si hay disminución de cualquiera de los elementos figurados de la sangre imputable al mismo, contrapesando este efecto con la gravedad y la evolución del proceso infeccioso. Se deben evitar tratamientos repetidos con el cloranfenicol, así como su administración concurrente con otros fármacos que se sabe causan depresión de la médula ósea y aun anemia aplásica.

Se debe administrar el cloranfenicol según indicación e instrucciones médicas, y no se debe emplear en procesos infecciosos leves.

Como otros antibióticos, el cloranfenicol puede alcanzar concentraciones sanguíneas excesivas aun con las dosis convencionales cuando se le administra a pacientes con insuficiencia hepática o renal, inclusive la debida inmadurez fisiológica en el prematuro y el recién nacido a término. No se debe administrar el cloranfenicol durante el parto.

El médico debe recordar también que, durante la lactancia, el cloranfenicol es excretado en la secreción láctea.

Como la de otros antibióticos, la administración de cloranfenicol puede acompañarse de superinfección por microorganismos no susceptibles, inclusive hongos.

El cloranfenicol no es una excepción con respecto a la interacción de fármacos; en consecuencia, en los casos en que se le administra concurrentemente con anticoagulantes o anticonvulsivos, puede ser necesario ajustar la dosificación de estos agentes terapéuticos en conformidad.

REACCIONES ADVERSAS

REACCIONES HEMATOLOGICAS:

Se ha atribuido el desarrollo de discrasias sanguíneas, inclusive anemia aplásica, a la administración de cloranfenicol. Se han observado dos tipos de depresión de la médula ósea. Uno de los tipos ocurre durante la terapéutica, es reversible con la interrupción de la misma y está relacionado con la dosificación.

El otro tipo, irreversible en más de la mitad de los casos, ocurre raramente, puede presentarse semanas o meses después de terminada la terapéutica, no está relacionado con la dosificación pero posiblemente con una predisposición hereditaria y puede evolucionar hacia una anemia aplásica que puede ser letal. La incidencia comunicada de anemia aplásica varía en todo el mundo.

También se ha comunicado la observación en casos de anemia hipoplásica, de trombocitopenia y de granulocitopenia consecuentemente a la administración del cloranfenicol.

REACCIONES GASTROINTESTINALES:

Pueden presentarse náuseas, vómitos, glositis y estomatitis, diarrea y enterocolitis; la incidencia es baja.

REACCIONES NEUROLOGICAS:

Se ha informado acerca de casos de neuritis óptica y de neuritis periférica coincidentes, por lo general, con un tratamiento prolongado.

REACCIONES DE HIPERSENSIBILIDAD:

A veces ocurren reacciones de hipersensibilidad.

SINDROME GRIS:

En prematuros y recién nacidos a término han ocurrido reacciones tóxicas y hasta letales; los signos y síntomas que acompañan a estas reacciones constituyen lo que se conoce como "síndrome gris". Se ha comunicado un solo caso de síndrome gris en un niño de tres meses, y otro caso único en un recién nacido a cuya madre se le había administrado cloranfenicol por vía intravenosa durante el parto. Los puntos siguientes resumen las características del "síndrome gris":

1. En la mayoría de los casos se había instituido la terapéutica dentro de las primeras 48 horas de vida.
2. Las manifestaciones clínicas aparecieron después de tres o cuatro días de tratamiento continuo con cloranfenicol, administrado según la dosificación convencional para adultos, impropia para niños de esa edad y no tolerada por ellos.
3. El orden de aparición de los síntomas fue el siguiente:
   a) Distensión abdominal con o sin vómitos.
   b) Cianosis pálida progresiva.
   c) Colapso vasomotor, frecuentemente acompañado de respiración irregular.
   d) Muerte pocas horas después de la aparición de las manifestaciones clínicas.
4. La evolución del proceso desde la aparición de las manifestaciones clínicas hasta el **exitus letalis** fue tanto más rápida cuanto más elevada la dosificación de cloranfenicol.
5. Con frecuencia, en los casos en que se interrumpió la terapéutica inmediatamente después de la aparición de las manifestaciones clínicas, el proceso se invirtió, con restablecimiento completo del niño.

DOSIFICACION Y ADMINISTRACION

Por lo general se recomienda una dosificación de 50 mg/kg/día, fraccionada en cuatro dosis administradas a intervalos de seis horas. En casos excepcionales, como los de infección causada por microorganismos moderadamente resistentes o de infección grave, como septicemia o meningitis, se puede aumentar la dosificación a 100 mg/kg/día. Sin embargo, esta dosificación más elevada debe reducirse, tan pronto como sea posible, a criterio del médico.

En casos muy graves o en los que la administración oral de cloranfenicol no es factible, se puede administrar inicialmente el cloranfenicol por vía intravenosa o intramuscular en forma de succinato. En tales casos se recomienda pasar a administrar el cloranfenicol por vía oral tan pronto como sea posible, a criterio del médico.

En casos de insuficiencia hepática o renal, la capacidad de metabolizar o excretar el cloranfenicol puede estar reducida, por lo que el médico deberá ajustar la dosificación en conformidad.

PREMATUROS, RECIEN NACIDOS A TERMINO Y OTROS NIÑOS CON INMADUREZ FISIOLOGICA. (Véase "Síndrome Gris" bajo REACCIONES ADVERSAS.)

Por lo general, una dosificación de 25 mg/kg/día, fraccionada en cuatro dosis administradas a intervalos de seis horas, produce y mantiene concentraciones sanguíneas e histicas de cloranfenicol adecuadas para dominar la mayoría de las infecciones en prematuros, recién nacidos a término y otros niños con inmadurez fisiológica. Generalmente, después de las dos primeras semanas de vida, los nacidos a término pueden tolerar una dosificación máxima de 50 mg/kg/día, fraccionada en cuatro dosis administradas a intervalos de seis horas. En caso de duda se puede verificar la concentración sérica de cloranfenicol mediante métodos analíticos.

COMENTARIO CLINICO

INFECCIONES MENINGEAS:

Muchos microorganismos capaces de causar meningitis, especialmente el **Haemophilus influenzae,** el neumococo, el meningococo, el estreptococo y el estafilococo son susceptibles al cloranfenicol, el cual pasa al líquido cefalorraquídeo aun en ausencia de inflamación meningea. No se puede demorar la institución de la terapéutica hasta conocer los resultados de las pruebas de laboratorio. Muchos clínicos consideran el cloranfenicol como el medicamento de elección en casos de meningitis causada por **H. influenzae,** puesto que casi todas las cepas de este microorganismo son susceptibles a dicho antibiótico. Se recomienda la administración parentérica de cloranfenicol hasta que el paciente sea capaz de tomar las formas orales del antibiótico.

RICKETTSIOSIS:

La respuesta al claronfenicol de los pacientes con una rickettsiosis, inclusive el tifus exantemático, el tifus murino, la enfermedad de Brill-Zinsser, la fiebre fluvial japonesa (enfermedad de Tsutsugamushi), la fiebre de las Montañas Rocosas, la fiebre Q y la viruela rickettsial, ha sido espectacular, con eliminación virtual de la mortalidad y acortamiento marcado de la evolución de la enfermedad. El promedio de duración del período febril después de la institución de la terapéutica con cloranfenicol es de dos días en los pacientes con tifus exantemático, y de tres a cuatro días en los pacientes con otras rickettsiosis. Se debe prolongar el tratamiento durante cuatro días después de la normalización de la temperatura y durante no menos de seis días en total. Los pacientes que recaen responden tan bien al tratamiento como los pacientes con una infección primaria.

En los pacientes con fiebre de las Montañas Rocosas, la temperatura se normaliza alrededor del cuarto día después de instituida la terapéutica. Se debe continuar el tratamiento durante 24 horas después de la normalización de la temperatura.

FIEBRE TIFOIDEA:

Muchas autoridades consideran el cloranfenicol como el medicamento de elección de la terapéutica de la fiebre tifoidea. Por lo general, la temperatura se normaliza tres o cuatro días después de instituida la terapéutica, independientemente de la edad del paciente y de la gravedad o del período de evolución del proceso infeccioso. A fin de disminuir la posibilidad de recaída, es importante continuar la terapéutica durante ocho o diez días después de la normalización de la temperatura. No se recomienda el cloranfenicol para el tratamiento de los portadores de bacilos de la tifoidea.

OTRAS INFECCIONES GRAVES:

Cuando el médico cuenta con los medios de laboratorio necesarios para la ejecución correcta de pruebas de susceptibilidad **in vitro** del microorganismo infectante a los antibacterianos de que dispone, puede decidir basar su uso del cloranfenicol sobre los resultados de tales pruebas. Sin embargo, debe tener presente que se deben considerar los resultados de dichas pruebas solamente como una guía para la selección del antibacteriano apropiado, ya que en ciertas circunstancias pueden no ser fidedignos, como ocurre en el caso de la **S. typhi.**

OTRAS SALMONELOSIS:

En tanto que el cloranfenicol ha demostrado ser un agente terapéutico útil para mejorar y acortar la evolución clínica de las salmonelosis distintas de la fiebre tifoidea, los resultados no son tan uniformes como en ésta. La duración recomendada del tratamiento es la misma que para la fiebre tifoidea.

DISENTERIA BACILAR (SHIGELOSIS) Y OTRAS INFECCIONES ENTERICAS:

Si bien las medidas de sostén, como la reposición de electrólitos y la hidratación, son muy importantes, el cloranfenicol puede contribuir a la erradicación de los microorganismos y al dominio de la infección.

ENFERMEDADES VENEREAS:

El cloranfenicol es eficaz en algunas enfermedades venéreas, como el granuloma inguinal, el linfogranuloma venéreo y la blenorragia resistente a otros antibióticos.

SEPTICEMIAS:

El cloranfenicol ha demostrado ser útil en casos de septicemia causada por microorganismos susceptibles al mismo. Es particularmente valioso en casos de septicemia debida a bacterias gram negativas.

INFECCIONES DE LAS VIAS RESPIRATORIAS:

Debido a su amplio espectro bacteriano y a su capacidad de difusión en el foco infeccioso, el cloranfenicol puede ser valioso en el tratamiento de casos de infección grave de las vías respiratorias causadas por microorganismos susceptibles al mismo.

INFECCIONES QUIRURGICAS:

Las infecciones quirúrgicas, como infección de la herida operatoria, peritonitis o abscesos intraabdominales secundarios a perforación intestinal, diverticular o apendicular, generalmente son causadas por microorganismos susceptibles al cloranfenicol. Debido a su amplio espectro bacteriano, que abarca particularmente todas las cepas de microorganismos de los géneros Clostridium y Bacteroides, y a su capacidad de difusión en el foco infeccioso, el cloranfenicol puede ser valioso en dichas complicaciones. En tales circunstancias se debe administrarlo, en la dosificación recomendada, sólo como coadyuvante de la cirugía.

OTRAS INFECCIONES:

Se ha observado asimismo que el cloranfenicol es eficaz en la terapéutica de varias otras infecciones, como la brucelosis, bartonelosis, fiebre recurrente, peste bubónica, psitacosis, tracoma e infecciones causadas por microorganismos de los géneros Bacteroides y Clostridium.

TALLERES GRAFICOS J U - S A
☎ 246 16 85 - 246 43 09.—Virgen de la Fuencisla, 23.—Madrid - 27

England - April - May, 1973
(same for each country)

CHLOROMYCETIN

(chloramphenicol, Parke-Davis)

PARKE-DAVIS

Clinical use has established chloramphenicol (Chloromycetin*, Parke-Davis) as an effective antibiotic in a wide variety of bacterial and rickettsial infections. It possesses high antimicrobial activity, crosses tissue barriers readily, and diffuses widely and rapidly through nearly all body tissues and fluids.

ACTION AND PHARMACOLOGY

Chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is also active against rickettsial organisms and the lymphogranuloma-psittacosis group. It is particularly active against *Salmonella typhi* and *Hemophilus influenzae*. The mode of action is through interference with or inhibition of protein synthesis in intact cells and in cell-free systems. Development of resistance to chloramphenicol, both experimentally and in man, appears to be low in contrast to other antibiotics.

Chloramphenicol administered orally is absorbed rapidly from the gastrointestinal tract, producing detectable concentrations in the blood within one-half hour after administration. Average peak serum levels of free chloramphenicol after the first dose generally occur within one hour.

The principal route of excretion of chloramphenicol is through the urine, total urinary excretion ranging from 68 to over 90 percent. Small amounts of active drug are found in the bile and feces. Chloramphenicol diffuses rapidly throughout tissues and body fluids. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation. Measurable levels are also detectable in pleural and ascitic fluids, saliva, and in milk. It diffuses readily into the aqueous and vitreous humors of the eye. Transport across the placental barrier occurs with somewhat lower concentration in cord blood than in maternal blood.

Chloramphenicol Palmitate which contains the effective polymorph is hydrolized to free chloramphenicol before absorption. Resulting blood concentrations are similar to those produced by the administration of other oral forms of chloramphenicol.

Chloramphenicol sodium succinate when administered intravenously or intramuscularly is also hydrolyzed to free chloramphenicol within the body. Part of the parenterally

*Trademark of Parke-Davis

administered chloramphenicol sodium succinate is excreted by the kidneys prior to hydrolysis and, although serum levels of free chloramphenicol are lower than when a comparable dose of chloramphenicol is given orally, they are clinically effective.

INDICATIONS

Chloramphenicol is a potent therapeutic agent and should not be used for trivial infections. It should be administered according to the instructions of a medical practitioner. Chloramphenicol is specifically indicated for:

- bacterial meningitis
- typhoid fever
- rickettsial infections
- intraocular infections
- bacteroides infections
- septicemias due to gram-negative organisms
- other serious infections where bacteriological evidence or clinical judgment indicates that chloramphenicol is an appropriate antibiotic.

It is also clinically effective in:

- bacillary dysentery
- infections due to Friedländer's bacillus
- staphylococcal infections
- bacterial pneumonias
- infantile gastroenteritis
- laryngotracheal bronchitis
- undulant fever (Brucellosis)
- psittacosis
- trachoma
- cholera

Clinical eperience has demonstrated the value of chloramphenicol in the treatment of infective conditions in ophthalmology, otology, and dermatology.

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to the drug.

PRECAUTIONS AND WARNING

Blood dyscrasias including aplastic anemia may be associated with the administration of chloramphenicol. If facilities are available, it is well to determine the routine blood profile before therapy, and blood studies should be repeated at appropriate intervals especially during prolonged or intermittent therapy. Consideration should be given to discontinuing the drug if evidence of depression of any of the blood elements appears attributable to chloramphenicol, weighing these effects against the seriousness and course of the disease under treatment. Repeated courses of chloramphenicol and concurrent therapy with other drugs known to cause bone marrow depression or even aplastic anemia should be avoided.

Chloramphenicol should be administered according to the direction of a medical practitioner, and it should not be used for the treatment of trivial infections.

Excessive blood levels, as with other antibiotics, may result from administration of the recommended dose to patients with impaired liver or kidney function, including those due to immature metabolic processes in the premature and full-term infant. Chloramphenicol should not be administered during labor.

The medical practitioner should also remember that chloramphenicol is excreted in the milk of the lactating mother.

As with other antibiotics, the use of chloramphenicol may result in an overgrowth of non-susceptible organisms including fungi.

Chloramphenicol is not alone in the phenomenon of drug interaction and when patients are concurrently receiving anticoagulants or anticonvulsants, dosage adjustment of these agents may be necessary.

ADVERSE REACTIONS

HEMATOLOGICAL REACTIONS:

Blood dyscrasias including aplastic anemia have been attributed to the administration of chloramphenicol. Two types of bone marrow depression have been observed. One type may occur during therapy, is reversible on cessation of treatment, and is dose related.

The second type which may occur weeks to months after therapy is rare; it may be genetically related, and is not dose

related. In more than half of the cases, it is irreversible. It may lead to aplastic anemia which may be fatal. The reported incidence of aplastic anemia varies throughout the world.

Hypoplastic anemia, thrombocytopenia, and granulocytopenia have also been described following administration of chloramphenicol.

GASTROINTESTINAL REACTIONS:

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur; incidence is low.

NEUROLOGICAL REACTIONS:

Optic and peripheral neuritis have been reported usually following long-term dosage.

HYPERSENSITIVITY REACTIONS:

Sensitivity reactions are sometimes encountered.

GRAY SYNDROME:

Toxic reactions including fatalities have occurred in the premature and newborn infant; the signs and symptoms associated with these reactions are known as the "gray syndrome". Single reports have appeared in an infant as old as three months, and in an infant born of a mother receiving chloramphenicol intravenously during labor. The following points summarize the studies of the "gray syndrome".

1. In most instances therapy has been instituted within the first 48 hours of life.
2. Symptoms first appeared after 3 to 4 days of continued treatment with conventional adult dosage of chloramphenicol not tolerated by and incorrect for this age group.
3. The symptoms appeared in the following order:
   a. Abdominal distention with or without vomiting.
   b. Progressive pallid cyanosis.
   c. Vasomotor collapse, frequently accompanied by irregular respiration.
   d. Death within a few hours of onset of symptoms.
4. Progression of symptoms from onset to exitus was accelerated with higher dosage schedules.
5. In some cases upon early recognition of the associated symptomatology, termination of therapy frequently reversed the process with complete recovery.

DOSAGE AND ADMINISTRATION

Dosage of 50 mg./kg./day in divided doses at six-hour intervals is recommended for the average patient. In exceptional cases, such as with patients having infections due to moderately resistant organisms or suffering from infections such as septicemia or meningitis, dosage schedules up to 100 mg./kg./day may be prescribed. However, these high doses should be decreased as soon as clinically indicated.

Chloramphenicol in the form of chloramphenicol succinate may be administered intravenously or intramuscularly in seriously ill patients or under conditions in which the patient is not able to take the drug by mouth. In such instances, it is highly desirable that the physician change over to orally administered cloramphenicol as soon as is practicable.

In instances of impaired hepatic or renal function, the ability to metabolize or excrete chloramphenicol may be reduced and the medical practitioner should adjust the dose accordingly.

PREMATURE AND NEWBORN INFANTS AND CHILDREN WITH IMMATURE METABOLIC PROCESSES
(see gray syndrome under ADVERSE REACTIONS)

A total of 25 mg./kg./day divided into four doses at six-hour intervals usually produces and maintains a concentration of chloramphenicol in blood and tissues adequate to control most infections in premature and newborn infants and children with immature metabolic processes. 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 four doses at six-hour intervals. Precise control of serum blood levels, when in doubt, may be achieved through analytical methods.

CLINICAL DISCUSSION

MENINGEAL INFECTIONS:

Many microorganisms causing meningitis, especially *Hemophilus influenzae*, pneumococci and meningococci as well as streptococci and staphylococci, are susceptible to chloramphenicol. The drug enters the cerebrospinal fluid even in the absence of meningeal inflammation. Institution of therapy cannot be delayed until results of laboratory tests are known. Many clinicians consider chloramphenicol the drug of choice for meningitis caused by *Hemophilus influenzae*, as virtually all strains are sensitive to this antibiotic. Parenteral dosage is recommended until the patient is able to take oral medication.

RICKETTSIAL DISEASES:

The response of patients with rickettsial infections, including epidemic and murine typhus, Brill-Zinsser's disease, scrub typhus, Rocky Mountain Spotted Fever [spotted fever, tick fever, tick typhus (England), Fiebre Petequial (Colombia), Febere Maculosa (Brazil)], Q fever, and rickettsial pox has been dramatic with virtual elimination of mortality and marked shortening of the course of illness. Average length of febrile period after administration of chloramphenicol is 2 days in patients with epidemic typhus fever and 3 to 4 days in those with other rickettsial fevers. Treatment should be carried out for a minimum of 6 days or 4 days after the temperature returns to normal. Patients in relapse respond as readily to treatment as do those with primary infection.

In patients with Rocky Mountain Spotted Fever, defervescence of fever occurs about the fourth day after therapy is started. Treatment should be continued for 24 hours after normal temperature is attained.

TYPHOID FEVER:

Chloramphenicol is considered by many authorities as the drug of choice for this disease. After therapy is started, fever generally subsides in 3 or 4 days regardless of age, severity of illness or stage of disease. To lessen possibility of relapse, it is important that therapy be continued for from 8 to 10 days after reaching the afebrile period. Chloramphenicol is not recommended for routine treatment of the typhoid "carrier state".

OTHER SERIOUS INFECTIONS:

When facilities are available for the accurate performance of *in vitro* bacterial sensitivity tests against the infecting organism, the medical practitioner may wish to be guided in his use of chloramphenicol by the results of such testing. He should remember, however, that the disc and other sensitivity methods are to be regarded only as a guide to appropriate therapy since *in vitro* tests may, under certain circumstances, be unreliable such as with *S. typhi*.

OTHER SALMONELLOSES:

While chloramphenicol has proved to be a useful therapeutic agent in ameliorating and shortening the clinical course of salmonella infections other than typhoid, results are not as uniform. Recommended duration of treatment is the same as for typhoid fever.

DYSENTERY DUE TO SHIGELLA OR OTHER ENTERIC PATHOGENS:

While supportive measures such as electrolyte and fluid replacement are most important, chloramphenicol has served to eradicate the infectious agent and to control the infection.

VENEREAL INFECTIONS:

Chloramphenicol is effective in some venereal infections such as granuloma inguinale, lymphogranuloma venereum, and cases of gonorrhea resistant to other antibiotics.

SEPTICEMIAS:

Chloramphenicol has proved useful in septicemias due to microorganisms susceptible to its action. It is particularly valuable in gram-negative bacterial septicemias.

RESPIRATORY TRACT INFECTIONS:

Because of its wide antibacterial spectrum and its ability to diffuse into infective foci, chloramphenicol may be of value in the treatment of severe respiratory tract infections due to susceptible microorganisms.

SURGICAL INFECTIONS:

Surgical infections such as severe post-operative wound infections, peritonitis, or intraabdominal abscess from ruptured intestine, diverticula, or appendix, usually are due to microorganisms sensitive to chloramphenicol. Again, because of its wide antibacterial spectrum, including particularly all strains of clostridia and bacteroides, and ability to diffuse into infective foci, chloramphenicol may be of value in such complications.

Administration in the recommended dosage should be adjunctive to surgical intervention.

MISCELLANEOUS INFECTIONS:

Chloramphenicol has also been found effective in the treatment of brucellosis, bartonellosis, relapsing fever, plague, psittacosis, trachoma, bacteroides, and clostridial infections.

4. Dr. Harry Dowling's "opinions, not proven facts" on the new Monograph.

Note: These are Dr. Dowling's opinions and not what he considers proven fact in every case.

HARRY F. DOWLING, M. D.
208 BLISS LANE
GREAT FALLS, VIRGINIA 22066
TELEPHONE 759-3120

November 25, 1973

Prof. and Mrs. Alvin Zander
3 Harvard Place
Ann Arbor, Michigan 48104

Dear Mr. and Mrs. Zander:

I apologize for taking so long to answer your letter, but I have been on an extended vacation since it came andhave just gotten to it.

In general, pharmaceutical firms are not likely to restrict their claims in labels and advertisements unless they are specifically required to do so. Pressure from the medical profession and the public has some effect, but usually not as much as that which results from the requirements of a regulating agency. As I have shown on page 252 of my book, "Medicines for Man" (Knopf, 1970) advertisements in the leading journals in England were not as completely informative and balanced as advertisements for the same drugs in this country. Although professional ethics and social consciousness are at as high a level in England, their regulatory agencies do not have control of advertising. In the southern European countries, such as Spain, one has the impression that almost anything goes with respect to advertising of drugs. Public opinion and professional attitudes lag well behind those of Great Britain, Holland, the Scandinavian countries, Canada and the United States. This is reflected, as you have indicated, in the advertisement for chloramphenicol which you sent me.

The opening statement that chloromycetin has therapeutic activity against a great variety of pathogenic micro-organisms would probably not be allowed in an advertisement by the FDA because, leading off as it does, it immediately gives the impression that the antibiotic should be used in many infections.

The information about the gray syndrome (paragraphs 5, page 1,and 6, page 2) is not adequately explained. It results from the fact that the kidneys of infants do not have the capacity to metabolize chloramphenicol, thus allowing it to build up in the blood to dangerous concentrations. Full disclosure requires that doctors be warned not to use it in this age group unless absolutely necessary and then only if the concentration in the blood can be monitored. (In this respect, the American version is probably deficient). The symptoms of the condition should be given in detail.

The rarity of the blood dyscrasias is stressed in the Spanish labelling, without a parallel explanation of the fact that aplastic anemia following the use of chloramphenicol is almost always fatal, and, as you indicate, usually continues even if administration of the antibiotic is stopped.

The aplastic anemias and other fatal blood dyscrasias should be separated out from the depression in the number of lucocytes which can be detected by blood counts and which disappears when the chloramphicol is discontinued. Many people believe that these are separate entities. At any rate, it is questionable whether frequent blood counts will ever alert the physician to the appearance of aplastic anemia in time to prevent death from occurring. If the drug is to be allowed on the market at all, there should be a conspicuous warning about these serious blood cyscrasias as in the American labelling.

In my opinion, no clinical diagnosis (including typhoid fever) should lead the physician to select chloramphenicol as the drug of choice today (since some other safer drug is available for for every condition in which it could be used, and the other drug is just as good or better than chloramphenicol. This includes ampicillin for typhoid fever and tetracycline for H. influenzae meningitis). Accordingly, chloramphenicol should be a secondary drug, to be used only when bacteriologic evidence shows that chloramphenicol is effective against the pathogenic micro-organism causing the disease while other safer antibiotics are not effective, or in cases where the patient is hypersensitive to the other antibiotic. The American labelling takes this into consideration.

In summary, I believe that the Spanish labelling is not comprehensive enough with respect to indications and adverse reactions, that it should contain a specific warning regarding severe blood dyscrasias in a conspicuous place, and that, as it stands, it suggests that the drug should be used for many infections for which I do not believe it is indicated, and that the present labelling will encourage overuse of the antibiotic.

I sympathize with you in the deep sorrow which follows the tragic death of your daughter and admire the way you are responding so constructively instead of giving way to despair. I hope that your efforts will bring much-needed reforms.

Sincerely,

Harry F. Dowling

HARRY F. DOWLING, M. D.
208 BLISS LANE
GREAT FALLS, VIRGINIA 22066

TELEPHONE 759-3120

December 19, 1973

Prof. and Mrs. Alvin Zander
3 Harvard Place
Ann Arbor, Michigan 48104

Dear Mr. and Mrs. Zander:

I have no objection to your quoting what I wrote, so long as you make it clear that it is my opinion and not what I consider to be proved fact in every case. For instance, most pediatricians believe that chloramphenicol is the drug of choice for H. inluenzae meningitis, because many articles have been written about its use and they consider tetracycline more toxic for infants than chloramphenicol. Also, everyone does not agree that blood counts may not predict the onset of aplastic anemia in time to keep the full-blown disease of aplastic anemia from developing.

In answer to your question, I do not believe that working for a stricter U. S. label would be very valuable in controlling labelling abroad. Rather, since the U. S. label now contains statements that should be on labels abroad, the best thing to do is to push for them.

With regard to the longer monograph, I have the following criticisms:

(1) The second paragraph on page 1 does not distinguish between in vitro susceptibility and clinical effectiveness. It starts off talking about bacteriostatic effect and ends with a clinical judgment, that it is particularly effective against Salmonella typhi and Hemophilus influenzae. This gives the impression that the drug should be used for any of the conditions in the total list.

(2) On page 2, under indications, the statement is made that "chloramphenicol is specifically indicated for" and this is followed by some specific indications, such as typhoid and rickettsial infections and some very general categories, such as bacterial meningitis. It is of course not specifically indicated in all types of bacterial meningitis. The same criticism applies to intraocular infections and septicemias due to gram negative organisms. The next list of infections should be headed, "It is sometimes clinically effective in:..... The last paragraph about infective conditions in ophthalmology, otology and dermatology is so loose as to be almost ludicrous.

In other words, I do not think this monograph as it stands is the proper basis for good labelling.

Sincerely,

Harry F. Dowling

Harry F. Dowling

5. Zanders' comparison of new Monograph with U.S. label.

* Comparison of the Parke-Davis Newly-Revised Chloromycetin Monograph Sent to All International Locations and the Parke-Davis U.S. Chloromycetin Label (and Physicians' Comments).

A great improvement warning of fatal aplastic anemia and against trivial use. However, the United States label begins with a very strong, boxed, and at times underlined WARNING that serious and fatal blood dyscrasias, including aplastic anemia are known to occur after administration of chloramphenicol, that it must not be used in trivial illnesses or when not indicated or as a prophylactic to prevent bacterial infection, and that blood studies during treatment are essential. In contrast, the Parke-Davis Monograph begins with a very positive descriptive statement on the drug: "Clinical use has established chloramphenicol (Chloromycetin, Parke-Davis) as an effective antibiotic in a wide variety of bacterial and rickettsial infections." The U.S. descriptive statement which follows the WARNING box, on the contrary, is in essentially restrictive terms, stating that it is an antibiotic that " 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 "Indication" section)."

Parke-Davis does discuss adverse hematological reactions from use of Chloromycetin including aplastic anemia but in general the Monograph downplays both the incidence and mortality rate of irreversible aplastic anemia and gives less detailed information than the U.S. label so that the importance of this adverse reaction is diminished. The one good important principle of use that Parke-Davis states clearly, but without the U.S. examples and emphasis, is that Chloromycetin should not be used for trivial illnesses. However, this is not enough.

As we understand it, the basic concept of the U.S. label is that because of the possible adverse reactions, especially the serious and fatal hematological reactions, use of Chloromycetin should be restricted even in treatment of serious diseases to those which cannot be treated by any less potentially hazardous drug and that this need for Chloromycetin must be determined by prior sensitivity testing of the microorganism involved (except for a few very serious conditions where initial treatment with Chloromycetin may be instituted concurrently with sensitivity testing in order to change to another less hazardous therapeutic agent as soon as possible) and its use must be accompanied by blood studies, preferably while the patient is in a hospital. In contrast, the Parke-Davis Monograph, instead of severely restricting use (except for trivial illnesses) in the manner in which it is now restricted in the U.S., still seems to us to encourage unnecessary use. The major point of the U.S. label is to restrict unnecessary use as much as possible in order to limit the number of unnecessary aplastic anemia deaths. The Parke-Davis Monograph pays lip-service to the U.S. basic principle by listing the adverse reactions (without the extremely

* We have a very detailed comparative analysis to back up this summary statement.

strong U.S. warnings) but rejecting the U.S. method and principle of restricting unnecessary use and, in fact, in many subtle and some not-so-subtle ways encouraging such use in the Indications and Clinical Discussion sections, their initial description of the drug, and throughout the Monograph. The Monograph ~~both~~ implies many more Indications for use 1) in listing and discussing diseases in which Chlorr-mycetin is "effective", " of value", and "useful", 2) by using much broader disease terms such as "intraocular infections", "infective conditions in opthalmology, otology, and dermatology", "respiratory tract infections" and "surgical infections", and 3) sometimes by more specifically naming a disease that would not be included in theU.S. Indications such as "laryngotracheal bronchitis". Another way in which the Monograph encourages greater use is by omitting other important negative facts in the U.S. label which would restrict use, such as : 1) that blood studies do not preclude the later appearance of irreversible aplastic anemia, 2) that blood dyscrasias have occurred after both short-term and prolonged therapy, and 3) that there are reports of aplastic anemia attributable to chloramphenicol which later terminated in leukemia, and by omitting U.S. instructions: 1) that repeated courses of the drug should be avoided whenever possible, 2) that chloramphenicol must not be used as a prophylactic agent to prevent bacterial infection, and 3) that treatment should not be continued longer than required to produce a cure with little or no risk of relapse.

Important!

We have also solicited the views of members of the medical profession to confirm or correct our judgment. The ~~two~~ doctors that have already responded have the same basic reaction to the Monograph as ours. A hematologist friend strongly criticized the Monograph mostly for its style, saying it is written more to sell Chloromycetin than to educate the physician in its proper use. He said if the company had wanted to educate thephysician, they would have started the Monograph with a strong Warning and given more prominence to statements that it should not be used for trivial illnesses. The section on Indications is often only indicating where Chloromycetin is effective; for many of the conditions it should indicate use of other drugs if they had taken into account the risk/benefit ratio, in his opinion. He feels Parke-Davis misused the word Indications, often indicating conditions where it "may be useful" when other medicines should be used first. He calls attention to the fact that the U.S. label begins the Indications section with a capitalized statement of the very restrictive principles governing use of Chloromycetin, which is totally lacking in the Parke-Davis Monograph.

A physiologist friend also thinks the Monograph and the U.S. label are very different, saying that they not only differ factually on some important points but in particular and most important, they differ in tone; the Monograph essentially saying that there are lots of places to use Chloromycetin, it's a great drug and the U.S. label saying to be very careful, only use it under very special circumstances. He also says that many of the Indications (or implications for Indica-

cations under both Indications and Clinical Discussion) are either not included in the list of U.S. Indications or could only possibly be included under the U.S. general indication of serious infections which, however, the U.S. qualifies with the phrase " for which less potentially dangerous drugs are ineffective or contraindicated", a very important restrictive general qualification Parke-Davis does not mention.

Another doctor friend described the Monograph as "loosely written" and suggested checking the Monograph's Indications and, I assume, implications for use with a specialist in infectious diseases. Until we obtain this expert opinion, our comments and comparison should be considered the personal reaction of laymen not well-informed on classification of diseases, for instance.

Another hematologist commenting on the hematological warnings in the Monograph said that what the Monograph states is true but it is so soft pedalled it will be relatively ineffective in restricting use compared to the U.S. label. Again the comment was made that it is not what is said but how it is said. so that there is not enough emphasis on adverse effects.

Still another doctor, who did not comment on the whole Monograph, seemed to agree with sections in the Clinical Discussion dealing with the very serious diseases specifically listed in the U.S. label (in infectious diseases) which warranted initial use of chloramphenicol with concurrent testing) even though for some he stated that there were equally effective drugs. He criticized the Septicemia section as warranting more information and concluded that in some instances the information is general and disappointingly brief and would like to see the Company emphasize more strongly that chloramphenicol is not an agent that should be used for the treatment of colds or for fevers.

Another doctor in communicable diseases felt that the warnings and descriptions of adverse effects are clearly presented in the Monograph but agreed that a statement of warning on the containers sold overseas "would be humane".

Another difference between the Parke-Davis Monograph for other countries and the Parke-Davis U.S. label is in the manner of administration of Chloromycetin Succinate. The Monograph describes intramuscular use of Chloromycetin Succinate as "clinically effective although serum levels of free chloramphenicol are lower than when a comparable dose of chloramphenicol is given orally." In contrast, the U.S. banned intramuscular administration as ineffective, approving only intravenous parenteral administration.

A gastroenterologist who believes that Chloromycetin should be used for the treatment of immediately life threatening infections such as typhoid fever and for no other infectious conditions unless the responsible organism is clearly identified, has been demonstrated as being sensitive only to chlorom henicol, and if the clinical situation is such that the risk of withholding treatment is greater than the risk of its administration yet realizes that there are conditions notably in Southeast Asia where there is a grave shortage of physicians and where different criteria may apply (though he hesitates to comment on t ese without local knowledge) but who does not see why restrictions on the use of chloramphenicol in U.S. law should be loosened when it comes to countries such as Germany, England or Spain where the problem of physician density and physician coverage is not strikingly different than it is in this country, makes the following comments on the ne Parke-Davis materials: 1)As far as the new Monograph is concerned, in his judgment it is not sufficient to confine theindications to conditions which are "not trivial". Not trivial is one thing and life threatening is another. Moreover, in my judgment the Monograph is deficient in that it fails to make clear that in many instances alternative modalities of treatment may be available which are equally effective and safer. Since this is an area in which he is not an expert, he suggests our consulting an expert in infectious diseases. He is particularly concerned about bacteriocics and pneumococcal infections. 2) As far as the new Spanish label based on the new Monograph is concerned, he says it contains a warning but it is neither loud nor clear. It's phrasing isnot as cautionary as that of the U.S. product and he sees no reason why it should not be. He also criticizes the closing statement "For complete instructions on prescribin consult the product Monograph available at the request of a physician.", say ng that he feels that it is not the reponcibility of the physician to have to write to the company at any time concerning adverse reactions. since this places the responsibility on the shoulderso the physician which is clearly that of the manufacturer. 3) He goes on to comment on the promotional material, in particular that of Chlorostrep, which appears to be a continued promotional campaign in which Chloromycetin is in fact combined with another antibiotic. A further concern of his is that the promotional material does not mention adverse reactions. He feels that if these adverse reactions are anything other than trivial it should, both in this and other instances. He pointed out that it seems useful to make a clear distinction between promotional literature suchasthat with and warnings inserted in the package however strong these warnings may be. In other words an aggressive promotional campaign cannot be offset by prom nently displayed warnin s once the package is purchased. The promotional material is seen by many, the warnings are seen by few. He found it difficult to understand why thepromotional material should be allowed to to continue in the manner in which it is done with Chlorostrep, for instance, in Spain. Package inserts may or may not meet the letter of the law, they rarely meet the spirit of the law. The experience with cigarette advertising may be used to illustrate the point. He considered the Spanish Chlorostrep poster particularly offensive and would warmly support that its publication over the name of Parke-Davis be brought to the attention of appropria e legislativ authorities.

6. New Parke-Davis Chloromycetin Spanish label based on new Monograph, July 1973.

Spain, Malaga
July 1973 #13
(new label based on new Parke-Davis Chloromycetin Monograph)

A la Profesión Médica:

CLOROMYCETIN®

El Chloromycetin (cloranfenicol Parke-Davis) es un antibiótico cristalizado con actividad terapéutica contra una gran variedad de microorganismos patógenos.

El Chloromycetin se absorbe muy bien por vía oral y da rápidamente concentraciones eficaces en los líquidos y tejidos del organismo.

DOSIFICACION Y ADMINISTRACION

Por lo general se recomienda una dosificación de 50 mg/kg/día, fraccionada en cuatro dosis administradas a intervalos de seis horas. En casos excepcionales, como los de infección causada por microorganismos moderadamente resistentes o de infección grave, como septicemia o meningitis, se puede aumentar la dosificación a 100 mg/kg/día. Sin embargo, esta dosificación más elevada debe reducirse tan pronto como sea posible, a criterio del médico.

En casos de insuficiencia hepática o renal, la capacidad de metabolizar o excretar el cloranfenicol puede estar reducida, por lo que el médico deberá ajustar la dosificación en conformidad. En caso de duda y si se dispone de los medios laboratorio, se puede verificar la concentración sérica de cloranfenicol mediante métodos analíticos.

Prematuros, recién nacidos a término y otros niños con inmadurez fisiológica. (Véase «Síndrome Gris» bajo reacciones adversas.)

Por lo general, una dosificación de 25 mg/kg/día, fraccionada en cuatro dosis administradas a intervalos de seis horas produce y mantiene concentraciones sanguíneas e hísticas de cloranfenicol adecuadas para dominar la mayoría de las infecciones en prematuros, recién nacidos a término y otros niños con inmadurez fisiológica. Generalmente, después de las dos primeras semanas de vida los nacidos a término pueden tolerar una dosificación máxima de 50 mg/kg/día, fraccionada en cuatro dosis administradas a intervalos de seis horas. En caso de duda, se puede verificar concentración sérica de cloranfenicol mediante métodos analíticos.

Por razones mencionadas posteriormente (ver síndrome gris) estas dosis no deberán ser normalmente excedidas.

INDICACIONES CLINICAS

El uso clínico ha establecido el cloranfenicol (Chloromycetin Parke-Davis) como un antibiótico de gran eficacia para una extensa variedad de grupos de infecciones bacterianas, por rickettsias y por linfogranuloma-psitacosis.

Posee una gran actividad antimicrobiana, atraviesa las barreras de los tejidos, se difunde ampliamente y con rapidez por casi todos los tejidos y líquidos del cuerpo incluso por el líquido cefalorraquídeo. El cloranfenicol es un agente terapéutico muy potente, no debe ser utilizado para infecciones triviales. Debe ser administrado bajo las instrucciones del médico.

El cloranfenicol deberá ser considerado por el médico para el tratamiento de grupos de infecciones bacteroides, infecciones por rickettsias y por linfogranuloma-psitacosis. La decisión será tomada basándose en el espectro antibiótico, en la condición general clínica y el posible riesgo que envuelva.

El Chloromycetin está específicamente indicado para la meningitis bacteriana, fiebres tifoideas, septicemia por organismos gram-negativos y otras infecciones serias donde la evidencia bacteriológica o el juicio clínico indiquen que Chloromycetin es el antibiótico apropiado.

La experiencia ha demostrado el valor de el cloranfenicol en el tratamiento de condiciones infecciosas en oftalmología, otología y dermatología.

ADVERTENCIAS

El cloranfenicol debe tomarse bajo la dirección de un médico.

No debe ser utilizado en infecciones triviales.

Discrasia sanguínea e incluso anemia aplástica pueden estar asociadas a la administración de cloranfenicol. Análisis de sangre a intervalos apropiados deben ser realizados, donde sea posible, en el caso de que se piense prolongar o repetir la administración.

El cloranfenicol no está alineado en el fenómeno de interacción de droga y cuando los pacientes están recibiendo concurrentemente anticoagulantes o anticonvulsivos, una adaptación de la dosificación de estos últimos podría ser necesaria.

REACCIONES ADVERSAS

Discrasia sanguínea e incluso aplástica con exitus letalis han sido, en raras ocasiones, asociadas a la administración de cloranfenicol. Sequedad de boca y con menos frecuencia náuseas, ocasionalmente también se presenta diarrea o vómitos pero estos síntomas son raras veces tan severos como para justificar la suspensión del antibiótico. A veces se encuentran casos de reacciones de sensibilidad.

Durante una administración oral prolongada se ha registrado neuritis óptica y periférica. Los niños prematuros y los recién nacidos, debido a su inmadurez fisiológica requieren una dosificación reducida. En este grupo de edad se han dado casos de reacciones tóxicas e incluso exitus letalis.

Las muestras y síntomas que deben servir de aviso son distensión abdominal, letargo, trastornos respiratorios que conducen a una cianosis gris. Designado el «síndrome gris» es sabido que está asociado a unos planes de dosificación excesiva, no apropiada para este grupo. Su progresión puede ser interrumpida y revertida la condición si se suspende la terapia rápidamente al conocer a tiempo la sintomatología asociada.

ENVASE

El Chloromycetin se suministra en cápsulas de 250 mg. N.º (379), frascos de 12 y 24.

PARA INSTRUCCIONES COMPLETAS SOBRE LA PRESCRIPCION, PUEDEN CONSULTAR LA MONOGRAFIA DEL PRODUCTO A LA DISPOSICION DE LOS MEDICOS QUE LA SOLICITEN.

Laboratorios Parke Davis, S. A. E.

Madrid

Acquired in Malaga, Spain
in July 1973

CHLOROMYCETIN

Chloromycetin (chloramphenicol Parke-Davis) is a crystalized antibiotic with therapeutic activity against a great variety of pathogenic micro-organisms.

Chloromycetin is absorbed very well when administered orally and quickly gives effective concentrations in the fluids and tissues of the organism.

DOSAGE AND ADMINISTRATION

Generally a dose of 50 mg/kg/day is recommended, divided in four doses administered at intervals of 6 hours. In exceptional cases, such as infections caused by moderately resistent micro-organisms, or in serious infections like septicemia andmeningitis, the dose can be increased to 100/mg/kg/day. However, this higher dose should be reduced as soon as it is possible and by the physician's criterion.

In cases of hepatic or renal insufficiency, when the capacity to metabolize or to excrete the chloramphenicol can be reduced, the physician should adjust the dose accordingly. In case of doubt and if laboratories are available for tests, the serum concentration of chloramphenicol can be verified by analytic methods.

Premature infants, newborn infants and other children with physiological immaturity. (See "Gray Syndrome" under Adverse Reactions).

In general, a dose of 25 mg/kg/day divided in four doses administered at intervals of 6 hours produces and maintains chloramphenicol concentrations in blood and tissues adequate to control the majority of infections in premature infants, newborn infants and others with physiological immaturity. Generally after the first two weeks of life full-term infants can tolerate a maximum dose of 50mg/kg/day, divided in 4 doses administered at intervals of 6 hours. In case of doubt, serum chloramphenicol concentrations should be verified by analytical methods.

Because of reasons mentioned hereinafter (see "Gray syndrome") these doses should not be normally exceeded.

CLINICAL INDICATIONS

Clinical use has established that chloramphenicol (Chloromycetin Parke-Davis) is an antibiotic of great efficacy against an extensive variety of bacterial infections by rickettsial and lymphogranuloma-psitacosis micro-organisms.

It has a great anti-microbial activity and diffuses rapidly throughout tissues and body fluids, including the cephalo-spinal fluid. Chloramphenicol is a potent therapuetic agent which should not be used for trivial infections. It should be administered according to the instructions of a physician.

Chloramphenicol should be considered by the physician for the treatment of bacteroides infections, infections by rickettsias and lymphogranuloma-psitacosis. His decision should be based on the antibiotic spectrum, on the general clinical condition and the possible risk which is involved.

Chloromycetin is indicated specifically for bacterial meningitis, typhoid fever, septicemia due to gram-negative organisms and other serious infections where the bacteriological evidence or the clinical judgment indicate that Chloromycetin is the appropriate antibiotic.

Experience has demonstrated the value of chloramphenicol in the treatment of infectious conditions in ophthalmology, otology and dermatology.

WARNING

Chloramphenicol should be administered under the direction of a physician.

It should not be used for trivial infections.

Blood dyscrasias including aplastic anemia may be associated with the administration of chloramphenicol. Blood studies should be repeated at appropriate intervals when possible, especially during prolonged or intermittent therapy.

Chloramphenicol is not alone in the phenomenon of drug interaction and when patients are concurrently receiving anticoagulants or anticonvulsants, dosage adjustments of these agents may be necessary.

ADVERSE REACTIONS

Blood dyscrasias including aplastic anemia with fatalities have been, on rare occasions, associated with the administration of chloramphenicol. Dryness of the mouth and less frequently nausea are occasionally present, as well as diahrrea and vomiting but these symptoms are rarely severe enough to warrant discontinuing the drug. Sensitivity reactions are sometimes encountered.

During prolonged oral administration some optical and peripheral neuritis have been reported. Premature infants and recently new-born infants, due to their physiological immaturity, require a lower dosage. In this age group there have been cases of toxic reactions, including fatalities.

The symptoms that should serve as warning are abdominal distention, lethargy respiratory problems conducive to cyanosis. Designated as the "Gray Syndrome", it is known to be associated with excessive dosage, not appropriate for this age. Its progression can be interrupted or reversed by discontinuation of the therapy as soon as the symptomology is observed.

PRESENTATION

It is administered in capsules of 250 mg. No. (379), in containers of 12 and 24 units.

FOR COMPLETE INSTRUCTIONS ON PRESCRIBING CONSULT THE PRODUCT MONOGRAPH AVAILABLE AT THE REQUEST OF A PHYSICIAN.

PARKE-DAVIS

Laboratories Parke Davis, S.A.E.

Madrid

7. Zanders' comparison of new Spanish label with U.S. label.

The new Spanish label is a considerable improvement over the old Spanish label both in its indications for use and in its warnings of adverse effects. The new label states clearly - twice- that Chloromycetin should not be used for trivial infections and should be used under the instructions of a physician, the most important new statement which, coupled with the warning - twice- of blood dyscrasias including fatal aplastic anemia instead of the bland "changes in the blood following its use are rare" of the old label, should have a salutory effect in cutting down unnecessary use.

The new label also states that the decision to use Chloromycetin should be based on the antibiotic spectrum, the general clinical condition, and the possible risk involved. This is much better than no general guidelines at all as in the old label but it is still weak compared to the U.S. label. The new label's indications for use are usually based on the micro-organisms or groups of micro-organisms involved instead of on sites of infections such as urinary tract infections and respiratory infections of the old label although it still includes infections in otology, opthalmology, and dermatology. More importantly the specific indications for use are more similar to the more restricted U.S. label list. However, the Spanish label gives the physician the choice of basing his decision to use chloramphenicol on bacteriological evidence or clinical judgment while the U.S. label says sensitivity testing is essential.

The new label, after repeating that Chloromycetin should not be used for trivial infections and under the direction of a physician, warns that blood dyscrasias including aplastic anemia may be associated with administration of chloramphenicol and that blood studies should be repeated at appropriate intervals when possible especially during prolonged or intermittent treatment. The old label had only 'Gray Syndrome' under Warning and under Tolerance just that "Chloromycetin is well tolerated and changes in the blood are rare" plus a similar blood study statement. The new label repeats both statements under Adverse Reactions, including there, however "aplatic anemia with fatalities". Again a distinct improvement over the old but lacking the strength and fullness of the U.S. warning and explanation.

The new label also includes other adverse effects: dryness of mouth, nausea, vomiting, sensitivity reactions, optical and peripheral neuritis, and warns to use lower dosage when given concurrently with anticoagulants and anticonvulsants and in cases of hepatic or renal insufficiency which the old label does not mention. Both labels treat the possibly fatal "Gray Syndrom" for premature and recently new born infants quite fully, far more so than the blood dyscrasias, in contrast to the U.S. label.

For more comments comparing the new Spanish label with the U.S. label, see "Comparison of the new German label with the old German label and the U.S. label." The new Spanish label and the new German label are very much alike being based on the same Monograph. However, the new Spanish label is perhaps a little better than the new German label in that it states that Chloromycetin should not be used for trivial infections and should be used under the direction of a physician in Indications as well as under Warning. The Spanish label also divides the diseases in which should be used into those in which its use should be considered mmd by the physician and those in which it is specifically indicated.

The old German label was even worse than the Spanish old label in the tremendous number of indications for use and the comparison is stronger and in more detail but much of it applies to the Spanish labels.

Promotion

8. Parke Davis Chloromycetin entries in Vademecum Daimon, Nov. 1972.
Spanish physicians' desk reference published by pharmaceutical companies.

Spain Barcelona November 1972 13
Parke-Davis entries in Vademecum Daimon (Spain PDR)
(physicians desk reference published by pharmaceutical companies)

CHLOROMYCETIN

Composition: Chloramphenicol Parke Davis.

ACTION: Antibiotic of ample spectrum, which covers a large number of bacteria--gram negative and gram-positive-- all the microorganisms of the rickettsia, linphogranuloma and inguinal as well as psitacosis granuloma.

Indications: Typhoid fever and other salmonellas, bacillar dysintery rickettsiosis, infections of the urinary tract caused by a variety of gram negative and gram positive bacteria, serious surgical infections, including peritonitis, some respiratory infections, meningitis, veneral diseases such as phlenorhagia resistant to othe antibotics, inguinal granuloma and veneral linphogranuloma. Septicemias, bruccelosis, psitacosis, etc.

Administration: 50 mg/kg/day, in 4 fraccionated doses every 6 hours. For premature and newly born babies and others with physiological immaturity, 25/mg/kg/day.

CAUTION: If it is possible, it is convenient to have hemograms before establishing the Chloromicetin therapy and they should be repeated if a prolonged or intermittent administration is necessary, or in cases when the dose given is higher than usual, in order to prevent a possible depression of the bone marrow. Although rarely, some irreversible discracias have been observed. The "gray syndrome" has been described in premature and newly born babies.

As it concerns to hypersensitive reactions, some febril reactions, cutaneous eruptions and allergic reactions can be observed.

For more information on adverse reactions and indications please write write to the laboratory for a monograph of Chloromicetin.
*Presentation:

CLOROSTREP (capsuls and liquid)

Composition: Each capsule or tea spoon contains 125 mg Of Chloromycetin and 125 mg of dihydrostreptomycin.

Indications: Salmonella and shigella infections, ulcerous colitis, gastroenteritis, pre and post operatory intestinal tract, etc.

Dose; Children: 1 or 2 tea spoons every 6 hr, adults 2-4 capsules every 6 hours.

Presentation: 8 Capsules in a container. Liquid in a 60 cc bottle.

*Presentation: Capsules of 250 mg,12 in a container; 122,60 pts with 24; 228.90 pts. Cream at 1%, tube with 30 g, 79.20 pts. Topical at 10%, 5 cc container, 96.40 pts. Intramuscular:vials with 1 g, 96.40 pts; with 2 g. 166 pts. Succinate: vial 1 g, 86.30 pts.

Chloromycetin

Dose:

In general a dose of 50 mg/kg/day is recommended, in 4 doses given with intervals of 6 hours. In serious cases like septicemia and meningitis the dose could be increased to 100 mg/kg/day.

For premature babies and babies up to a month old it is recommended not to give over 25 mg/kg/day due to their physiological immaturity.

Chloromycetin - flask with 12 capsules P.V.P. 122.60 (pesetas
" " " 24 " 228.90 "
Palmitato of Chloromycetin: flask with 60 cc 129.90 "
Topical chloromycetin: Flask with 5 cc 76.10 pesetas

For more information about prescribing the product, request the monograph which will be available to you and which describes indications and adverse reactions of the product.

Spain, Barcelona November 1972 Dr.
Parke-Davis leaflet in Vademecum Darimon, Spain's PDR

Parkelase with Chloromicetin lytic

Composition: Combination of two enzymes, fibrinolisin and desoxirrribonucleose with chloramphenicol, in ointment.

Action: Enzymatic and antibiotic debridement.

Indications: The same as for Parkelase when an infection -a complication- is suspected or exists. Burns, wounds, cervicits, vaginitis, ulcers etc.

Dose: 1 to 3 daily applications.

Presentation: Ointment -tubes with 10 and 30 grams.

1-Dosification - "See attached prospect (literature)"

2."Algunas" some respiratory infections

3. "Comoblennoragia"

usually have dificulties with doses well tolerated by older children.

For prematures it is suggested no more than 25 mg of Ch. per kilogram of weight per day, divided and at 6 to 8 hours interval. Por babies less than a month old it is suggested no more than 60 mg per kilogram of weight and daily, divided in doses at 6 or 8 hours interval. When a prolonged administration or larger doses are required, the concentrations of antibiotic in the blood sbould be the guide to graduate the dose.

Tolerance:

Generally Ch. is well tolerated and blood alterations consecutive to its use are rare. However, it is convenient to have periodical blood tests when its administration is prolonged or intermitent.

In prematures and babies less than a month old the high doses of Ch. has been associated with abdominal distension, with or without emesis, cyanosis, pale or progressive, or vasomotor collapse, in some cases with fatal results. These effects have not been reported on children treated with 50 mg of Ch. per kg. per day, or less. The interruption of the therapy has corrected in many cases the adverse effects, with complete recovery.

Packing: In containers with 8 capsules and flasks with 60 cc.

PARKE DAVIS, MADRID.

Spanish "PDR" November 1972 Vademecum Daimon

Parke Davis, S. A. E., Laboratorios

Emilio Vargas, 6. Madrid (17)

BENADRYL
COMPOSICION: Clorh. de difenhidramina.
ACCION: Antihistamínico, antiespasmódico y sedante.
ADMINISTRACION: Según cuadro clínico.
PRESENTACION: *Ampollas* de 1 cc (50 mg), caja con 2. *Cápsulas* de 25 y 50 mg, frascos con 25. *Crema* al 2%, tubo con 30. *Líquido*, frasco con 120 cc.

BENADRYL EXPECTORANTE
COMPOSICION: Cada 100 cc: Benadryl, 280 mg; Cloruro amónico, 2,70 g; Citrato sódico, 1,14 g; Cloroformo, 0,45 g; Mentol, 22 mg.
ACCION: Antitusivo y expectorante, con potente acción antihistamínica.
POSOLOGIA: Adultos, 1 a 2 cuchtas. varias veces al día; *niños,* ½ a 1 cuchta. 2 veces al día, según edad.
PRESENTACION: Frasco con 120 cc.

CALADRYL, crema y loción
COMPOSICION: Benadryl al 1 % con calamina, alcanfor y excipiente.
ACCION: Antihistamínico y antipruritico de aplicación local.
INDICACIONES: Contra el prurito producido por urticaria, herpes zoster, sarampión, etc. En reacciones alérgicas cutáneas. Picaduras de insectos, quemaduras e irritaciones solares. Dermatitis por dentición en niños, erupciones por pañales húmedos.
PRESENTACION: Crema, tubo con 42 g. *Loción,* frasco con 120 cc.

CLOROMICETIN
COMPOSICION: Cloranfenicol *Parke-Davis.*
ACCION: Antibiótico de amplio espectro, el cual comprende un gran número de bacterias gram-negativas y gram-positivas, todos los microorganismos del género rickettsia, linfogranuloma venéreo, del granuloma inguinal y de la psitacosis.
INDICACIONES: Fiebre tifoidea y otras salmonelosis, disentería bacilar, rickettsiosis, infecciones de las vías urinarias causadas por una variedad de bacterias gram-negativas y gram-positivas, infecciones quirúrgicas graves, inclusive peritonitis, algunas infecciones respiratorias graves, meningitis, enfermedades venéreas, como blenorragia resistente a otros antibióticos, granuloma inguinal y linfogranuloma venéreo. Septicemias, brucelosis, psitacosis, etc.
POSOLOGIA: 50 mg/kg/día, fraccionada en 4 dosis administradas a intervalos de 6 horas. En prematuros, recién nacidos a término y otros niños con inmadurez fisiológica, 25 mg/kg/día.
ADVERTENCIAS: Siempre que sea posible, es conveniente efectuar hemogramas antes de instituir la terapéutica con el CLOROMICETIN y repetirlos durante la misma si es prolongada o intermitente o cuando la dosificación sea muy elevada, en previsión de una posible depresión reversible de la medula ósea. Se han observado, aunque raramente, discrasias sanguíneas irreversibles. El «síndrome gris» se ha descrito en prematuros y recien nacidos a término.
Por lo que se refiere a reacciones de hipersensibilidad, pueden presentarse reacciones febriles, erupciones cutáneas y reacciones alérgicas.
Para más información sobre reacciones adversas e indicaciones, solicitar al Laboratorio monografía de Cloromicetin.
PRESENTACION Y P.V.P.: Cápsulas de 250 mg, frascos con 12, 122,60 pts.; con 24, 228,90 pts. *Crema* al 1 %, tubo 30 g, 79,20 pts. *Tópico* al 10 %, frasco 5 cc, 76,10 pts. *Intramuscular,* viales con 1 g, 96,40 pts.; con 2 g, 166 pts. *Succinato,* vial 1 g, 86,30 pts.

CLOROSTREP, cápsulas y líquido
COMPOSICION: Cada cáps. o *cuchta.* contiene: Cloromicetin, 125 mg; Dihidroestreptomicina, 125 mg.
INDICACIONES: Infecciones por salmonella y shigella, colitis ulcerosa, gastroenteritis, pre y postoperatorio intestinal, etc.
POSOLOGIA: Niños, 1 a 2 cuchtas. cada 6 horas; *adultos,* 2 a 4 cáps. cada 6 horas.
PRESENTACION: Cápsulas, frasco con 8. *Líquido,* frasco con 60 cc.

COMBEX
COMPOSICION: Cada cc: Vit. B_1, 10 mg; Vit. B_2, 0,33 mg; Nicotinamida, 10 mg; Acido pantoténico, 4 mg; Vitamina B_{12}, 10 mcg.
INDICACIONES: Anemias perniciosa, alimenticia y del esprue; astenia, neuritis, polineuritis, anorexia, debilidad, pelagra, hiponutrición, hepatitis y cirrosis hepática.
POSOLOGIA: Adultos, 2 cc al día o alternos; *niños,* de 0,5 a 1 cc en días alternos.
PRESENTACION: Vial de 10 cc.

COSLAN
COMPOSICION: Por cápsula: 250 mg de Acido mefenámico. *Supositorios* de 125, 250 y 500 mg de Acido mefenámico.
ACCION: Analgésico, antipirético y antiinflamatorio.
INDICACIONES: Cefaleas, dolores crónicos y del postoperatorio, dolor muscular, dolor traumático, odontalgias, gripe y estados afines.
POSOLOGIA: Adultos, 2 cáps. o 1 suposit. 500 mg 3 veces al día; *niños* de 6 meses a 3 años, 1 suposit. 125 mg 3 veces al día; de 4 a 8 años, 1 suposit. 250 mg 3 veces al día; de menos de 10 kg de peso, 12 mg/kg, 3 veces al día.
PRESENTACION Y P.V.P.: Cápsulas, frascos con 10, 40,70 pts.; con 25, 97,40 pts. *Supositorios,* cajas con 12, de 125 mg, 51,40 pts.; de 250 mg, 65,40 pts.; de 500 mg, 86,79 pts.

ELDEC, cápsulas
COMPOSICION: Asociación de vitaminas, minerales, hormonas, aminoácidos y fermentos digestivos.
ACCION: Suplemento fisiológico integral. Para contrarrestar precozmente los procesos seniles.
POSOLOGIA: 1 cáps. 3 veces al día con las comidas. En las mujeres, interrumpir el tratamiento durante los días que dure la regla.
PRESENTACION: Cápsulas precintadas, frasco con 25.

EPANUTIN, cápsulas
COMPOSICION: Cada cápsula contiene: 0,10 g de Difenilhidantoinato sódico.
INDICACIONES: Epilepsia (gran mal y psicomotora).
POSOLOGIA: Niños mayores de 6 años y *adultos,* 1 cáps. 2 a 4 veces al día, hasta 6 cáps.
PRESENTACION: Cápsulas, frasco con 100.

EPANUTIN CON FENOBARBITONA, cápsulas
COMPOSICION: Cada cáps. contiene: Epanutin (difenilhidantoinato sódico), 0,10 g, y Fenobarbitona, 0,05 g.
INDICACIONES: Tratam. de la epilepsia cuando se desee un efecto sedante complementario.
POSOLOGIA: Hasta 3 cáps. diarias, a criterio médico.
PRESENTACION: Cápsulas, frasco con 50.

GAMMA GLOBULINA PARKE DAVIS
COMPOSICION: Gamma globulina humana en solución al 16 %.
INDICACIONES: Profilaxis y modificación del sarampión, hepatitis, rubéola y otras enfermedades víricas. Terapéutica de la agammaglobulinemia e hipogammaglobulinemia.
POSOLOGIA: Solamente por vía intram. La dosis profiláctica es 0,22 cc por kg de peso (2 cc por cada 10 kg de peso) y la dosis de modificación es 0,04 cc (0,5 cc por cada 10 kg de peso).
PRESENTACION Y P.V.P.: Inyectable, vial de 1 cc, 165 mg, 178,60 pts.; vial de 2 cc, 330 mg, 334,60 pts.

GERIPLEX, cápsulas
COMPOSICION: Asociación integral de vitaminas y minerales, reforzada con 25 fermentos digestivos (Taka-Diastasa).
INDICACIONES: Deficiencias vitamínicas y minerales. Anorexia, convalecencia, astenia, embarazo.
POSOLOGIA: 1 ó 2 cápsulas diarias.
PRESENTACION: Cápsulas, frascos con 25 y con 50.

HUMACORT, ungüento
COMPOSICION: 1 % de Cloranfenicol; 0,5 % de Paromomicina y 1 % de Acetato de hidrocortisona en una base especial de petrolato líquido y polietileno.
INDICACIONES: Dermatosis piógenas inflamatorias y pruríticas.
POSOLOGIA: De 2 a 4 aplicaciones al día.
CONTRAINDICACIONES: Quemaduras extensas.
PRESENTACION: Ungüento, tubos con 30 g.

HUMATIN, cápsulas y líquido
COMPOSICION: Sulfato de paromomicina.
ACCION: Nuevo antibiótico de amplio espectro de acción antibacteriana y amebicida.
INDICACIONES: Infecciones entéricas por gérmenes gram-negativos y gram-positivos, tratamiento del coma hepático, supresión o reducción preoperatoria de la flora intestinal y en amebiasis, lambliasis, teniasis y otras parasitosis intestinales.
POSOLOGIA: Adultos, en el coma hepático, 75 mg/kg/día, o más, durante 4-6 días, según grado de insuficiencia hepática y respuesta del paciente; en el resto de las indicaciones, de 25 a 50 mg/kg/día, en tratamientos de 6-7 días. *Niños,* dosis proporcional.
PRESENTACION: Cápsulas de 250 mg, frasco con 8. *Líquido,* frasco con 60 cc, equiv. cuchta. a 125 mg de sulfato de paromomicina.

KETOLAR
COMPOSICION: Clorhidrato de ketamina Parke Davis.
INDICACIONES: Nuevo y diferente anestésico general disociativo, intravenoso o intramuscular, para inducción, como único anestésico o para suplementar anestésicos de baja potencia.
POSOLOGIA: Dosis medias iniciales, vía i.v. 2 mg/kg de peso; vía intram., 10 mg/kg de peso. Para mantenimiento de anestesia repetir con dosis iguales o mitad de las antes señaladas.
PRESENTACION: Vial de 10 cc a concentración de 50 mg por cc; de 20 cc a concentración de 10 mg por cc. Envases clínicos de 25.

MATPASEC, cápsulas
COMPOSICION: Por cáps.: Carbonato de calcio, 600 mg; Sulfato ferroso, 150 mg; Vit. B_{12} cristalizada (Cianocobalamina), 5 mcg; Acido fólico, 0,25 mg. Vit. A (1,2 mg), 4000 U.; Vit. D (10 mcg), 400 U.; Mononitrato de tiamina, 3 mg; Vit. B_2 (Riboflavina), 2 mg; Nicotinamida (Niacinamida), 10 mg; Vit. B_6 (Clorhidrato de piridoxina), 3 mg, Vit. C (Acido ascórbico), [illegible] miligramos.
INDICACIONES: Suplemento dietético que cubre las necesidades de minerales y vitaminas de la madre durante el embarazo y la lactancia, así como las del niño.
POSOLOGIA: Durante la gestación y la lactancia, 1 cáps. al día o más, a criterio médico.
PRESENTACION: Cápsulas, frascos con [illegible] y con 50.

MIDIKEL, tabletas y líquido
COMPOSICION: Por tableta: 0,50 g de metoxipiridazina. *Por cucharadita* (5 cc) equivalente a 0,250 g.
INDICACIONES: Infecciones urinarias, respiratorias, quirúrgicas y de tejidos blandos, disenterías bacilares. Infecciones de la boca [illegible]
POSOLOGIA: Adultos, dosis inicial, 2 tabletas o [illegible] cuchtas. (1 g); días sucesivos, 1 tab. o 2 cuchtas. (0,5); *niños,* dosis inicial, ½ tab. o una cuchta. (0,250 g) por cada 8 kg de peso el primer día; sucesivos, mitad dosis anterior.
PRESENTACION: Tabletas, envases con [illegible] 400. *Líquido,* frasco con 60 cc.

NEO-BENADRYL
COMPOSICION: Por cáps.: 25 mg de clorhidrato de bromodifenhidramina.

Continúa en la pág. [illegible]

Parke Davis — Cont.

ACCION: Antihistamínico potenciado con reducción de efectos sedantes.
INDICACIONES: De manera especial, en pacientes en que se quiera evitar la acción sedativa de los antihistamínicos.
POSOLOGIA: 1 cáps. 3 veces al día.
PRESENTACION: Cápsulas, frasco con 25.

NORLESTRIN

COMPOSICION: Por tableta: 2,5 mg de Acetato de noretindrona y 0,05 mg de Etinilestradiol.
INDICACIONES: Control de la ovulación, amenorrea, dismenorrea, esterilidad endocrina, hemorragia uterina funcional, menopausia.
POSOLOGIA: Comenzar la terapéutica al 5.º día de iniciado el ciclo menstrual, tanto si el período ha terminado o no. Interrumpir el tratamiento a los 21 días de iniciado y volver a comenzar 7 días más tarde, aunque el período no se presente.
PRESENTACION: Tabletas, envase con 21.

PALADAC, gotas

COMPOSICION: Por cc: Vitam. A, 6667 U.I.; Vit. D, 667 U.I.; Vit. E, 8,34 mg; Vit. B_1, 1,67 mg; Vit. B_2, 2 mg; Vit. B_6, 1,67 mg; Vit. B_{12}, 3,33 mcg; Nicotinamida, 16,66 mg; Acido pantoténico, 10 mg; Vit. C, 83,33 mg; Yoduro de potasio, 0,11 mg.
INDICACIONES: Suplemento polivitamínico-mineral para cualquier edad, pero de preferencia para lactantes y niños pequeños.
POSOLOGIA: Dosis medias diarias, 0,3 cc para lactantes hasta 1 año; niños mayores de esta edad, 0,6 cc. Puede mezclarse con leche, jugo de frutas, sopas, cereales y otros alimentos.
PRESENTACION: Gotas, frasco con 30 cc, acompañado de un cgr. graduado a 0,3 y 0,6 cc.

PALADAC, líquido

COMPOSICION: Por 5 cc: Vit. A, 5000 U.; Vit. D, 1000 U.; Vit. B_1, 3 mg; Vit. B_2, 3 mg; Vit. B_6, 1 mg; Vit. B_{12}, 5 mcg; Nicotinamida, 20 mg; Acido pantoténico, 5 mg; Vit. C, 50 mg.
INDICACIONES: Deficiencias vitamínicas, anorexia, astenia, convalecencia, desnutrición, estimulante del crecimiento y trofismo normal en los primeros años.
POSOLOGIA: Lactantes, ½ cucharadita al día; *niños y adultos,* 1 o más cucharaditas.
PRESENTACION: Líquido, frasco con 60 cc.

PALADAC CON MINERALES

COMPOSICION: Por tableta: Vitamina A, 5000 U.I.; Vit. D, 400 U.I.; Vit. C, 50 mg; Vit. E, 10 U.I.; Vit. B_1, 3 mg; Vit. B_2, 3 mg; Vit. B_6, 1 mg; Vit. B_{12}, 5 mcg; Nicotinamida, 20 mg; Acido pantoténico, 5 mg; Calcio, 23 mg; Fósforo, 17 mg; Yodo, 0,05 mg; Potasio, 2,5 mg; Hierro, 5 mg; Magnesio, 1 mg.
INDICACIONES: Suplemento polivitamínico-mineral para todas las edades.
POSOLOGIA: Una tableta al día o más, a criterio médico. De sabor agradable, debe ser masticada.
PRESENTACION: Tabletas, frasco con 30.

Parke Davis — Cont.

PARKELANIA, comprimidos

COMPOSICION: Cada comp. contiene: Hidróxido de magnesio, 200 mg; Hidróxido de aluminio (Gel desecado), 200 mg; Simeticona (Metilpolisiloxano activado), 20 mg; Exc., c.s.
INDICACIONES: Para el alivio de la hiperacidez y el malestar gástrico debido a flatulencias, frecuentemente causadas por deglución de aire o por comidas que sientan mal.
POSOLOGIA: 1 ó 2 comp. según se requiera, preferentemente entre comidas o a la hora de acostarse. Pueden masticarse o dejar que se disuelvan en la boca.
PRESENTACION: Comprimidos, caja con 60.

PARKELASE, ungüento para aplicación tópica

COMPOSICION: Combinación de dos enzimas líticas, fibrinolisina y desoxirribonucleasa.
ACCION: Desbridamiento enzimático.
INDICACIONES: Heridas, quemaduras, cervicitis, vaginitis, úlceras, etc.
POSOLOGIA: De 1 a 3 aplicaciones diarias.
PRESENTACION: Ungüento, tubos con 10 y 30 g (el de 30 g con 6 aplicadores vaginales).

PARKELASE CON CLOROMICETIN

COMPOSICION: Combinación de dos enzimas líticas, fibrinolisina y desoxirribonucleasa, con cloranfenicol, en forma de ungüento.
ACCION: Desbridamiento enzimático y antibiótico.
INDICACIONES: Las mismas del PARKELASE, cuando exista o se sospeche infección sobreañadida. Heridas, quemaduras, cervicitis, vaginitis, úlceras, etc.
POSOLOGIA: De 1 a 3 aplicaciones diarias.
PRESENTACION: Ungüento, tubos con 10 g y 30 gramos.

PARKELASE VIAL

COMPOSICION: Combinación de dos enzimas líticas, fibrinolisina y desoxirribonucleasa.
ACCION: Desbridamiento enzimático.
INDICACIONES: Fístulas, tractos sinuosos, cavidades de abscesos, úlceras varicosas, supuraciones de oído, cervicitis, vaginitis, quemaduras, escaras.
POSOLOGIA: De 1 a 3 aplicaciones diarias. Para más detalles consultar el folleto que acompaña cada envase.
PRESENTACION: Tópico, caja con frasco vial con polvo liofilizado y amp. de cloruro sódico para disolución.

PARLIF, cápsulas

COMPOSICION: Cada cápsula contiene: 100 mg de Acido flufenámico, nuevo producto del grupo de los fenamatos, sin relación alguna con los esteroides.
INDICACIONES: Procesos inflamatorios de cualquier localización, como otitis, sinusitis, bronquitis, neumonía, neumonitis, gripe, odontalgias, afecciones traumáticas, etc. En los procesos reumáticos tales como artritis, artrosis, etc.
POSOLOGIA: 2 cápsulas después del desayuno y la cena.

Parke Davis — Cont.

CONTRAINDICACIONES: La excelente tolerancia del Pectri permite emplearlo en enfermos diabéticos, hepáticos, renales, etc. Está contraindicado en los procesos del tracto gastrointestinal en actividad. El uso seguro de este medicamento, durante el embarazo y lactancia, no ha sido establecido.
PRESENTACION: Cápsulas, frasco con 60.

PITOCIN, ampollas

COMPOSICION: Hormona oxitócica sintética exenta de factor vasopresor (10 U./cc).
INDICACIONES: Inercia uterina, inducción del parto, operación cesárea, etc.
PRESENTACION: Ampolla de 1 cc, envases con 2 y 100; de ½ cc, envase con 100.

PITOCIN BUCAL

COMPOSICION: Hormona oxitócica sintética exenta de factor vasopresor (200 U./tab.).
INDICACIONES: Inducción del parto, inercia uterina, etc.
POSOLOGIA: Se colocarán las tabletas en los espacios parabucales; el intervalo entre las dosis será siempre de ½ hora y el número de tabletas que se aplicarán en cada una de ellas seguirá este esquema: 1-1-2-2-3-3-3.
PRESENTACION: Tabletas de 200 U., frasco con 15.

PITRESSIN TANATO EN ACEITE

COMPOSICION: Hormona vasopresora y antidiurética en suspensión oleosa. Cada cc contiene 5 U. vasopresoras.
INDICACIONES: Diabetes insípida.
POSOLOGIA: De 3 a 5 U. cada 36 ó 48 horas, según respuesta, siempre por vía intramuscular.
PRESENTACION: Ampollas de 1 cc, caja con 6.

POLYQUIL, líquido y grageas

COMPOSICION: Cada cucharadita (5 cc), lo mismo que cada *gragea,* contienen 50 mg de Pamoato de piriviniO.
ACCION: Oxiuricida.
INDICACIONES: Tratamiento de la oxiuriasis con una sola dosis.
POSOLOGIA: Niños, 1 cuchta. de 5 cc por cada 10 kg de peso en dosis única; *adultos,* 1 grge. por cada 10 kg de peso en dosis única.
PRESENTACION: Líquido, frasco con 60 cc acompañado de una cucharita de 5 cc. *Grageas,* frasco con 15.

POLYQUIL COMPUESTO

COMPOSICION: Cada cucharadita (5 cc) contiene 25 mg de Pirvinio básico y el equivalente a 750 mg de Hexahidrato de piperazina.
INDICACIONES: Ascaridiasis y oxiuriasis.
POSOLOGIA: Debe hacerse el tratamiento en dos días sucesivos. En cada uno de ellos se administrará por vía oral una cucharadita (5 cc) por cada 10 kg de peso. La dosis diaria no debe exceder de 5 cucharaditas.
PRESENTACION: Líquido, frasco con 150 cc acompañado de una cucharita de 5 cc.

Parke Davis — Cont.

QUADRIGEN (TOXOIDES DIFTERICO Y TETANICO Y VACUNAS CONTRA LA POLIOMIELITIS Y LA TOS FERINA)

COMPOSICION: Vacuna contra la poliomielitis y la tos ferina, y Toxoides diftérico y tetánico, concentrados, purificados y adsorbidos en fosfato de aluminio.
INDICACIONES: Profilaxis de poliomielitis, difteria, tétanos y tos ferina.
POSOLOGIA: Hasta 6 meses de edad, 4 inyecciones a intervalos de 1 mes; entre cada 6 meses hasta 5 años, 3 inyecciones a intervalos de 1 mes. En todos los casos, una dosis de refuerzo a los 6 ó 12 meses de la inmunización primaria.
CONTRAINDICACIONES: No deberá usarse en niños mayores de 6 años.
PRESENTACION: Vacuna, caja conteniendo 1 ampolla de 1 cc, jeringuilla y aguja para una sola vez, esterilizadas por radiaciones gamma.

TAKA-DIASTASA, comprimidos y líquido

COMPOSICION: Enzimas del Aspergillus oryzae (asociación de 25 fermentantes).
INDICACIONES: Insuficiencia digestiva de hidratos de carbono.
POSOLOGIA: Adultos, 1-2 comp. durante o después de las comidas; *niños* mayores de 2 cuchtas.; *niños* pequeños, 20-30 gotas.
PRESENTACION: Comprimidos, frasco de 25. *Líquido,* frasco con 120 cc.

TAKA-DIASTASA con Pepsina y Pancreatina

COMPOSICION: Taka-Diastasa, 0,13 g; Pepsina, 0,05 g; Pancreatina, 0,13 g por gragea.
INDICACIONES: Insuficiencias digestivas de hidratos de carbono, grasas y proteínas.
POSOLOGIA: 1-2 grageas durante o después de las comidas.
PRESENTACION: Grageas, frasco con 50.

VACUNA ANTICATARRAL

COMPOSICION: Por cc: M. Catarrhalis 1 millones; K. Pneumoniae, 50 millones; Neisserias, 250 millones; H. Influenzae, 250 millones; Streptococos, 25 millones.
INDICACIONES: Profilaxis de las complicaciones secundarias al catarro común.
POSOLOGIA: Adultos y niños mayores, 0,50 y 1 cc a intervalos de 7 días. Las personas muy susceptibles al catarro pueden recibir una serie de 6 dosis: 0,1 cc; 0,25 cc; 0,35 cc; 0,50 cc, 0,75 cc, 1 cc a intervalos de 7 días. Las dos de 1 cc en cada mes de invierno. Las dosis para niños son de 10 a 16 años, ⅔ dosis adultos; de 7 a 10 años, ½; 2 a 7, ⅓.
PRESENTACION: Vacuna, vial con 5 cc.

VACUNA ANTICATARRAL ORAL PARKE-DVIS

COMPOSICION: Una gragea contiene: micrococos, 30 mil millones; Estreptococos, 1 mill.; Estafilococos (albus, aureus), 1 mill.; M. Catarrhalis, 2,5 mil mill.; H. influenzae (Pfeiffer), 2,5 mil mills.; Klebsiella Neumoniae mil mill.; Corynebacterium Diphteriae, 1 mill. Como inmunogen: 2 mil mill. de cada

Continúa en la s.g.

DESCRIPCION de ESPECIALIDADES

Parke Davis — Cont.

de los anteriores microorganismos, excepto de los dos últimos.
ACCION: Profilaxis de las complicaciones secundarias del catarro común.
POSOLOGIA: Adultos, 1.ª semana, 2 grag. diarias; semanas sucesivas, 2 grag. 2 veces a la semana; *niños*, mitad dosis.
PRESENTACION Y P.V.P.: Grageas, envase con 20, 100 pts.

ZARONTIN, líquido
COMPOSICION: Por 5 cc: 250 mg de Ethosuximida (alfa-metil-alfa-etilsuccinamida).
INDICACIONES: Antiepiléptico para tratamiento específico del pequeño mal.
POSOLOGIA: Hasta 6 años, 1 cuchta. (250 mg) al día; *mayores de 6 años*, 2 cuchtas. al día. Más adelante, ajustar dosis a la respuesta clínica.
PRESENTACION: Líquido, frasco con 120 cc.

NOTAS

Pelletier, S. R. C., Laboratorios

Isabel Serrano, 8, dupl. Madrid (20)

TOCOFEROL-CAROTEN
COMPOSICION: Por cc: Ext. de germen de trigo, 600 mg; Caroteno, 50 000 gammas.
INDICACIONES: Esterilidad, impotencia, astenias, abortos, amenorreas, lactancia, anemias. Acción normalizante del ciclo menstrual.
POSOLOGIA: 1 amp. al día intramusc. *Gotas*, 15-20 al día.
PRESENTACION Y P.V.P.: Inyectables de 2 cc, caja con 8 amp., 43,85 pts. *Gotas*, frasco con 22 cc. 30,75 pts.

VITACAROTENE A + D MASIVO OLEOSO
COMPOSICION: Por cc: Vit. A, 400 000 U.I.; Vit. D (calciferol), 600 000 U.I.
POSOLOGIA: 1 amp. por vía bucal por las mañanas, disuelta en caldo, sopa o leche. La cantidad de amp., a criterio médico.
PRESENTACION Y P.V.P.: Ampolla de 2 cc, caja con 1, 22,55 pts.

VITACAROTENE COMPLEJO GOTAS
COMPOSICION: Por cc: Provitamina A Caroteno, 10 000 U.I.; Vit. D, 5000 U.I.; Aceite de germen de trigo Vit. E, 10 mg.
INDICACIONES: Las del VITACAROTENE PURO.
POSOLOGIA: Igual.
PRESENTACION Y P.V.P.: Gotas, frasco con 22 cc, 30,45 pts.

VITACAROTENE COMPLEJO FORTISIMO OLEOSO
COMPOSICION: Por amp.: Vit. D, 500 000 U.I.; Provitamina A Caroteno, 300 000 U.I.; Aceite de germen de trigo Vit. E, 100 mg.
INDICACIONES: Las del VITACAROTENE PURO.
POSOLOGIA: Igual.
PRESENTACION Y P.V.P.: Ampolla de 3 cc, caja con 1, 31,80 pts.

VITACAROTENE PURO FORTISIMO OLEOSO
COMPOSICION: Por comp.: 500 000 U.I. de Provitamina A Caroteno.
INDICACIONES: Hemeralopias y afecciones oculares, raquitismo, osteopatías, osteoporosis, osteomalacia, calcioterapia, desmineralización intensiva, anemias, grandes infecciones, sinusitis, otitis.
POSOLOGIA: 1.ª semana, 1 amp. (vía bucal); 2.ª semana, otra amp. de VITACAROTENE COMPLEJO MASIVO durante el tiempo que el médico crea oportuno.
PRESENTACION Y P.V.P.: Ampolla de 3 cc, caja con 1, 38,60 pts.

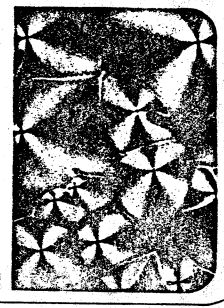
VITACAROTENE PURO GOTAS OLEOSO
COMPOSICION: 10 000 U.I. de Provitamina A Caroteno por cc.
INDICACIONES: Ver VITACAROTENE PURO.
POSOLOGIA: Lactantes, 1-5 gotas día; *niños* de 1-5 años, 5-10 gotas al día; de 6-15 años, 15-25 gotas día. *Adultos*; 25-50 gotas día.
PRESENTACION Y P.V.P.: Gotas, frasco con 22 cc, 30,45 pts.

9. Parke Davis Chloromycetin advertising samples, Nov. 1972.

Palmitato de cloranfenicol.

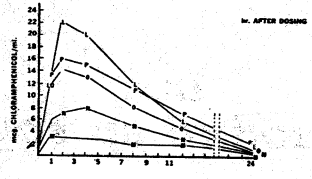
¿Por qué elegir el

Cristales del polimorfo A de Palmitato de cloranfenicol.



Porque con el PALMITATO DE CLOROMICETIN Ud. tiene la seguridad de que su paciente recibe un producto de eficacia reconocida, ya que de su morfología cristalina controlada (más del 90% de polimorfos no-A) resulta una absorción óptima y unos niveles sanguíneos eficaces.

Los estudios de Aguiar demuestran que se obtuvieron niveles sanguíneos más altos con el polimorfo no-A de cloranfenicol.



Comparación de los niveles en sangre obtenidos con la suspensión de palmitato de cloranfenicol, conteniendo varias proporciones de polimorfos A y no-A, siguiendo la dosis oral simple, equivalente a 1,5 gr. de cloranfenicol (% de polimorfo no-A en la suspensión: M: 0 por 100; N: 25 por 100; O 50 por 100; P: 75 por 100; L: 100 por 100).

DOSIFICACION:

Por lo general, se recomienda una dosificación de 50 mg/kg/dia, fraccionada en cuatro dosis administradas a intervalos de seis horas. En casos graves, como septicemia y meningitis, se puede aumentar a 100 mg/kg/dia.

En niños prematuros y nacidos a término de menos de un mes de edad, se recomienda no pasar de 25 mg/kg/dia, debido a la inmadurez fisiológica de los mismos.

CLOROMICETIN. Frasco 12 cápsulas. P. V. P. 122,60 pts.
CLOROMICETIN. Frasco 24 cápsulas. P. V. P. 228,90 pts.
PALMITATO DE CLOROMICETIN. Frasco 60 c. c. P. V. P. 129,90 pts.

SUCCINATO DE CLOROMICETIN. Vial de 1 gr. P. V. P. 86,30 pts.

CLOROMICETIN TOPICO. Frasco de 5 c. c. P. V. P. 76,10 pts.

PARA MAS INFORMACION DE PRESCRIPCION DEL PRODUCTO, SOLICITE MONOGRAFIA QUE TENEMOS A SU DISPOSICION DESCRIBIENDO INDICACIONES Y REACCIONES ADVERSAS DEL PRODUCTO.

PARKE-DAVIS

5 Spain, Barcelona November, 1972
(Advertising)
[illegible]

A CHESS PROBLEM: Whites play and give "check mate" in 3 moves.

More than 20 years of clinical experience with Chloromycetin:

Therapeutic efficacy:

Ample spectrum: gram positive and gram negative bacteria. Microorganisms of venereal linphogranuloma, psitacosis, etc.

Constant efficacy:

Minimal development of resistent bodies and frequently effective against bodies resistent to other antibiotics.

Fast intestinal absorption:

The maxim concentration of Ch. in the blood after its first ingestion, is obtained generally in an hour.

Ample organic diffusion:

Penetrates the tissues (including the L.C.R.) ? and effective concentrations are obtained in the place of infection.

More than 20 years of experience in the fabrication of Ch. guarantee the product.
Investigation of Ch. is a permanent task of Parke Davis - Rigorous control of quality.

Why to choose the Palmitato of Chloromycetin?

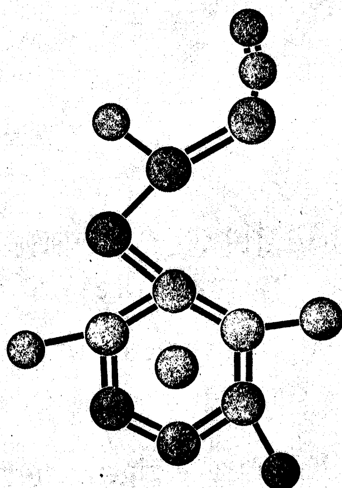
Because you have the security that your patient receives a product of recognized effectivity, because its morphology controlled (more than 90 of polimoprhs no-A) results in optimal absorption and effective blood levels.

The studies by Aguilar show that higher sanguine levels were obtained with the polimorph no-A of Ch.

(Graph)

Shows a comparison of the blood levels obtained with the suspension of palmitato of Ch. containing different amounts of polimorphs A and no-A. Simple dose equivalent to 1.6 g. (% of polimorph no-A in the suspension: M: 0 for 100; N: 25 for 100, 0 60 for 100; P: 75 for 100, L: 100 for 100)

Spain, Barcelona November 1973
Agency colored ad
(translation last 2pp.)
9



CLOROMICETIN

"Dentro del 'Screening Program de PARKE-DAVIS' que comprendió unas 6.000 pruebas con tierra y con más de 20.000 clases de hongos, Burkholder, en 1947, encontró una cepa de hongos, el Streptomyces Venezuelae, en una tierra procedente de Caracas, que producía el CLOROMICETIN activo tanto frente a los gérmenes gram positivos como negativos[1]"

Posteriormente, también en PARKE-DAVIS se logró la síntesis del CLOROMICETIN.

Secretos de su mayor eficacia:

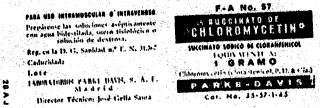
1. Menor número de resistencias.
2. Más amplio espectro.
3. Rápidas absorción y difusibilidad.
4. Niveles sanguíneos elevados y proporcionales con las dosis administradas.
5. Dosificarlo correctamente.

Adultos: 50 mg. por kilo de peso y día.
Niños: 50 a 100 mg. por kilo de peso y día. En niños prematuros se recomienda no pasar de 25 mg. por kilo de peso y día.

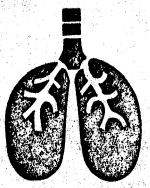
La investigación del CLOROMICETIN sigue siendo una tarea permanente en PARKE-DAVIS.

La eficacia del CLOROMICETIN responde al más preciso y riguroso control de calidad.

PARKE-DAVIS, cuyo rigor científico está bien probado, seguirá en su línea de no combinar el CLOROMICETIN con otros antibióticos.



APARATO RESPIRATORIO



Infecciones broncopulmonares bacterianas y víricas, especialmente indicado en la neumonía primaria atípica y en la tos ferina.
"...hoy por hoy, de acuerdo con la mayoría de autores, la cloromicetina es el antibiótico que menos resistencia ofrece a los gérmenes más habituales de las vías respiratorias..." [1]

INTERVENCIONES QUIRURGICAS

Infecciones piógenas estafilocócicas.
Peritonitis por perforaciones digestivas, cuya flora mixta cae dentro del espectro del CLOROMICETIN.
Infecciones biliares (colecistitis, abscesos hepáticos, etc.).
Infecciones aparato genitourinario (pielonefritis, cistitis, prostatitis, metritis y flemones perirrenales).

EL CLOROMICETIN SUCCINATO

puede utilizarse en:

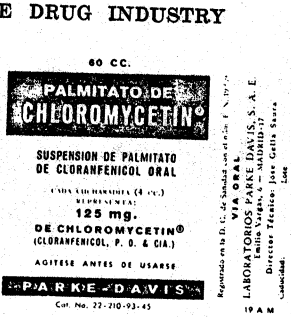
Venoclisis: En el post-operatorio y post-partum inmediatos, así como para los que requieren medidas de rehidratación y antibioterapia conjunta.

Vía intramuscular.

Localmente, pues no irrita los tejidos.

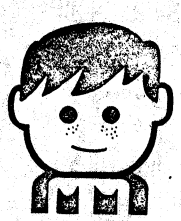
Aerosoles.

1. "Experimentación clínica de la cloromicetina en procesos broncopulmonares crónicos". 1968. Profesor A. Damiano.



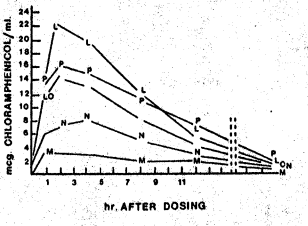
PEDIATRIA

EL PALMITATO DE CLOROMICETIN PARKE-DAVIS CONTIENE MAS DEL 90 POR 100 DEL *POLIMORFO NO-A*, FORMA CRISTALINA QUE ASEGURA UNA ABSORCION OPTIMA Y UNOS NIVELES SANGUINEOS MAS EFICACES AL HIDROLIZARSE MEJOR QUE LAS OTRAS FORMAS CRISTALINAS DE PALMITATO DE CLORANFENICOL.



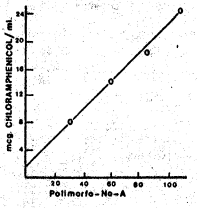
EL PALMITATO DE CLOROMICETIN presenta un sabor muy agradable. Especialmente indicado en infecciones, tales como:

Neumonías.
Tos ferina.
Infecciones entéricas.
Infecciones vías urinarias.
Meningitis. Salmonelosis.



Los estudios de Aguilar demuestran que se obtuvieron niveles sanguíneos más altos con el polimorfo no-A de cloranfenicol.

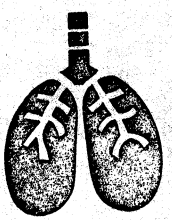
Comparación de los niveles en sangre obtenidos con la suspensión de palmitato de cloranfenicol, conteniendo varias proporciones de polimorfos A y no-A, siguiendo la dosis oral simple, equivalente a 1,5 gr. de cloranfenicol (% de polimorfo no-A en la suspensión: M: 0 por 100; N: 25 por 100; O: 50 por 100; P: 75 por 100; L: 100 por 100).



Este gráfico muestra que a medida que aumenta el porcentaje de polimorfo no-A en la suspensión, el nivel en sangre también se incrementa. Esto es, prácticamente, una línea recta de afinidad.

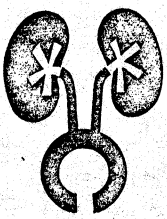
POLIMORFO NO-A
Microfotografía
con microscopio polarizante.

APARATO RESPIRATORIO



APARATO DIGESTIVO

APARATO URINARIO



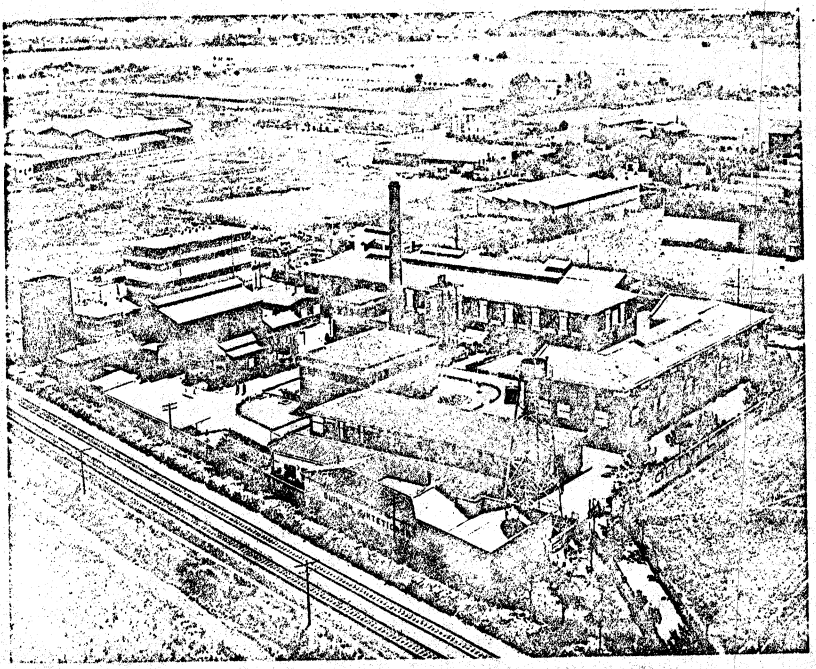
El CLOROMICETIN, por la pequeñez de su molécula, su gran estabilidad y el hecho de que se presente en cápsulas, garantiza una absorción óptima y rápida en la parte proximal del tubo digestivo.

Dada su excelente absorción, la vía parenteral debe de reservarse sólo para casos excepcionales.

Frente a las tetraciclinas, el CLOROMICETIN tiene la ventaja de que altera escasamente la flora normal del intestino grueso.

INFECCIONES LOCALES

El Cloromicetin Tópico es una solución de cloranfenicol al 10 por ciento en propilenglicol, para su uso en infecciones del oído (otorrea crónica, otitis media supurativa, infecciones quirúrgicas, etc.) y en el tratamiento tópico de infecciones locales, tales como quemaduras infectadas, úlceras varicosas, abscesos, etc.



VISTA GENERAL DE LA FABRICA
DE CLOROMICETIN, DE PARKE-DAVIS,
EN ALCALA DE HENARES

EN ESPAÑA, PARKE-DAVIS UTILIZA
PARA LA SINTESIS DEL CLOROMICETIN
LAS MAS MODERNAS
TECNICAS DE FABRICACION

LABORATORIOS PARKE-DAVIS, S.A.E.
MADRID - BARCELONA

cloramic - 1-70-30

Spain Barcelona
Late autumn, 1972,
Large, glossy, colored
advertising brochure

Parke Davis LABORATORY, MADRID—Barcelona, Spain

CHLOROMYCETIN

"The PARKE DAVIS "Screening Program" covered 6,000 tests with earth and more than 20,000 kinds of mushrooms. Burkholder in 1947 found the Streptomyces Venezuelae, a layer of mushrooms, in earth from Caracas, Venezuela, which produced ChloromYcetin active against the gram positive and gram-negative germs." 1.

Afterwards, also Parke Davis accomplished the syntesis of Chloromycetin. Its greatest efficacy is:

1. Minor number of resistent bodies
2. More ample spectrum
3. Rapid absorption and diffusibility
4. Higher sanguineous levels and proportionate to the administered dose.
5. Correct doses.

Adults: 50 mg/kg. weight per day.
Children: 50-100 mg/kg weight per day. For Premature infants no more than 25 mg/kg per day
1. Manual de Terapeutica Darmon, Professor W. Hadorn

The investigation of Chloromycetin continues to be a permanent task at Parke Davis. The efficacy of ChloromYcetin responds to the most precise and rigorous control of its quality.

Parke Davis, whose scientific responsibility is well proven, will continue in its policy of not combining the Chloromycetin with other antibiotics.

SUCCINATO OF CHLOROMYCETIN
Sodic Succinate of Chloramphenicol
Equiv. 1 Gram - Parke Davis

-For intramuscular or intravenous use: Prepare the solutions aseptically with distilled water, physiologic serum or dextrose.

Registered in the Dept. of Health No. 31367.
Parke Davis Laboratories, Madrid

SURGERY: Pyogenus staphiloccocus infections, peritonitis (perforation in the digestive tract). Its mixed bacterial flora which falls within the spectrum of chloromycetin.
Infections like colecistitis, hepatitis, etc.
Infections of the genito-urinary apparatus: pielonephritis, cistitis, prostatis, metritis and peri-renal phlemon.

Respiratory apparatus: Broncopulmonary infections caused by bacteria and virus. Specially indicated in the atypical primary pneumonia and whopping cough. "As of today and according to the majority of authors, chloromycetin is the antibiotic that offers less resistance to the most habitual germs of the respiratory tract. *

*Clinical experimentation of chloromycetin in chronic bronchial-pulmonary process" 1968, Prof. A.Damiano.

Succinato of Ch. (cont.)

Venoclisis: In the post-operative and post-partum as well as for the cases requiring re-hydration and anti-biotherapy.

Intramuscular. Locally, because it does not irritate the tissues.
Aerosols.

PALMITATO OF CHLOROMYCETIN - Suspension of Palmitato of Ch.Oral
Each teaspoonful (4 cc) represents
125 mg of Ch. Parke Davis
(Shake well before using)

IN PEDIATRICS: Palmitato of Ch. contains more than 90% of the polimorph No-A in crystalline form, which insures optimal absorption and the most efficient sanguine levels because it hydrolizes better than the other crystalline forms of Palmitato of Ch.

It has a pleasant flavor. It is especially indicated in infections such as: pneumonias, whooping cough, enteric and urinary infections, meningitis, salmonellosis.

(Graphs)
Legend:
Studies made by Aguilar show that higher sanguine levels were obtained with the Chl. polimorph no-A.

A comparison of the levels obtained by the suspension of Palm. of Ch. containing several amounts of polimorph A and No-A -following the oral simple dose- of 1.5 gr. of Ch. (% of polimorph no-A in the suspension: M: 0 per 100; N: 25 per 100; 0: 50 per 100; P:75 per 100, L:100 per 100).

Second graph: shows that along with the increase of percentage of polimorph no-A in the suspension, the blood level is also increased. This represents practically a straight line of affinity.

CHLOROMYCETIN:
Chloramphenicol U.S.P. (Parke Davis) 250 mg.

Because of its small molecule, its great stability and the fact that it is offered in capsules, guarantees optimal and fast absorption in the proximal part of the digestive tube.

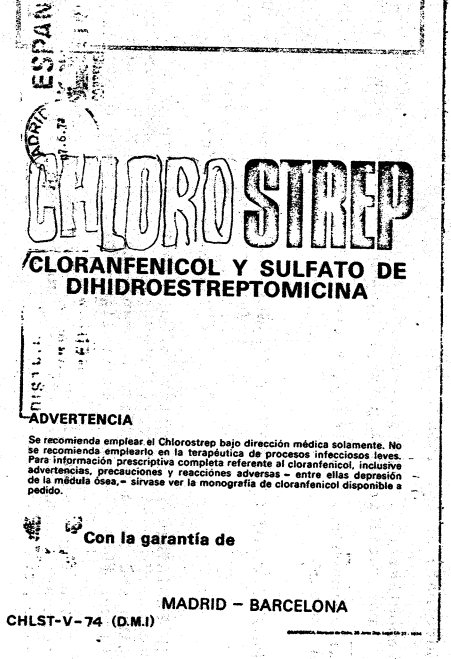
Because of its excellent absorption the parenteral way should be used only in exceptional cases.

Ch. has the advantage over the tetracyclines that it scarcely alters the intestinal flora.

FOR LOCAL INFECTIONS: Topical Chloromycetin is a solution of Ch. at 10% in propilenglycol, for use in ear infections (chronic othorrea, otitys, post operative infections, etc.) and for the treatment of local infections as infected wounds (burns), varicose ulcers, abscesses, etc.

10. Parke Davis Chlorostrep advertisements directed to public, mid 1973.

Acquired in Barcelona, Spain 1974 (June)
4 glossy colored advertisements



STREP

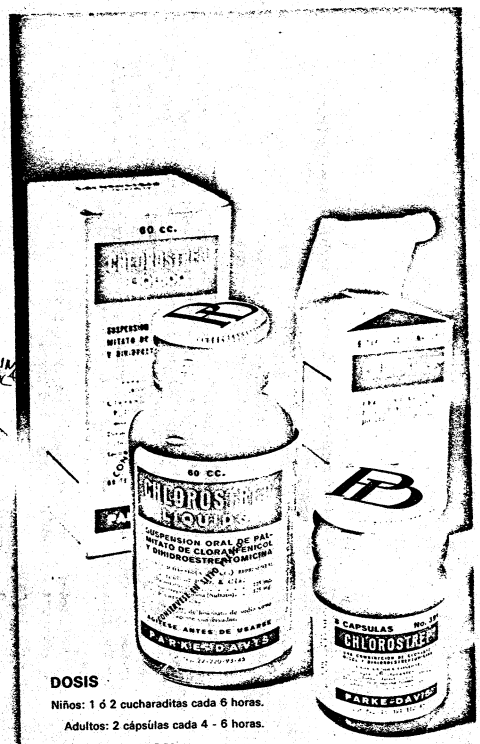
(Cloranfenicol y Sulfato de Dihidroestreptomicina)

ATACA POR DOS FRENTES

GENERAL
CLORAMFENICOL

LOCAL
DIHIDROESTREPTOMICINA
Y CLORAMFENICOL

Cuando se administra el cloranfenicol por via oral, la mayor parte de la dosis es absorbida en el intestino, se distribuye en los tejidos y líquidos del organismo y ejerce una acción antibiótica general; la cantidad no absorbida, sin embargo, es suficiente para dar una concentración de cloranfenicol terapéuticamente eficaz en el intestino. Cuando se administra la estreptomicina por via oral, prácticamente no es absorbida en el intestino y alcanza en él una concentración elevada.



DOSIS

Niños: 1 ó 2 cucharaditas cada 6 horas.

Adultos: 2 cápsulas cada 4 - 6 horas.

PRESENTACION:

Frascos de 8 cápsulas P. V. P. 119,80

Frascos de 60 cc. P. V. P. 160,40

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY 15541

Acquired in Spain, Barcelona June 1974
(translation of glossy colored pictured ad)

CHLOROSTREP - Chloramphenicol and Sulfate of Dihydrostreptomicine

IT ATTACKS BY TWO FRONTS

GENERAL	LOCAL
Chloramphenicol	Dihydrostreptomicine and chloramphenicol

When chloramphenicol is administered by the oral route, the major part is absorbed in the intestime, it distributes itself among the tissues and liquids in the organism and exercieses an antibiotic action in general; the amount not absorbed, however, is enough to give a concentration therapeutically acceptable in the intestine. When streptomycine is administered by the oral route, practically it is not absorbed in the intestine and reaches it in a very high concentration.

DOSE

Children: 1 to 2 teaspoonfuls every 6 hours
Adults: 2 capsules every 4 - 6 hours

PRESENTATION:

Bottle of 8 capsules	P V. P. 119.80
Bottle of 60 cc.	P.V.D. 160/40

(Back page)

CHLOROSTREP - Chloramphenicol and Sulfate of Dihydrostreptomicine

WARNING

It is recommended to use Chlorostrep only under the direction of a physician. It is not recommended to use it in therapy of trivial (minor) infectious processes. For complete prescribing information regarding chloramphenicol, including warnings, precautions and adverse reactions - amongst them depression of the bone marrow - please see the monograph on chloramphenicol available on request.

WITH THE GURANTEE OF

PARKE-DAVIS
MADRID- BARCELONA

CHLST-V-74 (D.M.I) Grafiberica Marques de Cadiz 25 Feres Dep Legal 27- 1974

(10) Spain
Barcelona
May
1973
glossy, colored advert

DIARREAS ESTIVALES E INFECCIOSAS

LAS VACACIONES MAS COMPLETAS CON...

CHLOROSTREP

ATACA POR DOS FRENTES

Spain, Barcelona May, 1973
Translation of Spanish, glossy, colored, publicidad.

CHLOROSTREP - Chloramphenicol and Sulfate of Dihydroestrtomicine.

Capsules P.V.P. 119,80 LOCAL DIHYDROESTRPTOMYCINE

Liquid P.V.P. 159,60 GENERAL Chloromycetin

It Broadens the Bacteria Spectrum for a Greater Clinic Efficacy

The association of chloramphenicol and streptomycine has a broader bacteria spectrum than any other antibacterian agent clinically used alone. This spectrum extremely broad, attacks the microorganisms that commonly cause the infectious diarrhea, enteric and mix infections that can occur in the postoperatory surgery

It attacks by two fronts:

When chloramphenicol is administered by the oral route, the majority is absorbed in the intestine, it distributes itself among the tissues and liquids in the organism and exercises an antibiotic action in general; the amount not absorbed, however, is enough to give a concentration therapeutically accepted in the intestine. When (strept is administered by the oral route, practically is not abosrbed in the intestine and reaches in it a very high concentration.

For complete information on prescriptions including indications and adverse reactions, write for the monograph.

MADRID, BARCELONA

Advertising page: Summer and Infectious Diarrheas:

Your vacation can be more complete with
CHLOROSTREP

It atacks by two fronts. PARKE DAVIS

11. Letter to physicians in Spain promoting Chlorostrep by Parke Davis, April 25, 1973.

Spain, Barcelona May, 1973
(sent to physicians in Spain)

PARKE-DAVIS

LABORATORIOS PARKE-DAVIS, S. A. E.
MADRID

Madrid, 25 de abril de 1973

Distinguido Colega:

Con la llegada del período primavera-verano y los cambios higiénico-dietéticos, viajes, etc. que suele implicar, se produce un visible aumento de incidencia de enterocolitis banales e infecciosas.

Solamente queremos recordarle una vez más, la comprobada eficacia y seguridad terapéutica especificamente en estos procesos del CHLOROSTREP, cápsulas y líquido, que actuando simultáneamente en dos frentes, local-intestinal y general, producirá una rápida remisión de los síntomas en sus pacientes, evitando las complicaciones. Le recordamos especialmente la forma líquida en los niños y su muy útil empleo en los ancianos.

Esperando quede satisfecho con los resultados de nuestro preparado y poniéndome a su entera disposición para cualquier asunto relacionado con nuestros productos,

Atentamente le saluda,

R. Picatoste

Dr. Ricardo Picatoste Merino
PARKE-DAVIS, DEPARTAMENTO MEDICO

Spain, Barcelona
May 1973
(sent to physicians in Spain)

PARKE DAVIS LABORATORIES, S.A.E.

Madrid

Madrid, April 25 1973

Dear Colleague:

The arrival of the spring-summer season and the dietetic-hygienic changes, travelling,etc. associated with it, there is a significant rise in the incidence of enterocholitis,common and infectious.

Once more we would like to remind you that CHLOROSTREP offers a well proven efficacy and therapeutic safety to attack these processes. It is manufactured in capsules and liquid, which attacking by two fronts -local-intestinal and general, will produce a fast remission of the symptoms in your patients, avoiding at the same time any complication. We especially remind you that the liquid form is very useful for administration to children and old people.

We hope you will be very pleased with the results of our product. We are at your disposal for any matter related with our products.

Sincerely yours,

Dr. Ricardo Picatoste Merino
PARKE DAVIS, Medical Department.

12. Parke-Davis Chlorostrep label, older one acquired September 1973.

"Old" label — pre 1973 new P-D Chloromycetin Monograph

Acquired: Port Bou, Spain
Sept. 22, 1973

A la Profesión Médica:

CHLOROSTREP®

El Chlorostrep es una combinación de Chloromycetin (cloranfenicol, P. D. & Cia.) y dihidroestreptomicina, en cápsulas y líquido. Cada cápsula o cucharadita contiene 125 mg. de cada uno de estos antibióticos. Cuando estos dos agentes antibióticos están combinados, ejercen una acción sinérgica que parece ampliar el espectro bacteriano susceptible.

Esta preparación es de valor en el tratamiento de infecciones entéricas de tipo disentérico y de las muchas infecciones mixtas que se encuentran en la cirugía del intestino. Se ha empleado el Chlorostrep con éxito en el tratamiento de la tuberculosis anorrectal y en la fístula anal, postoperatoriamente, consecutivamente a la extirpación de un quiste pilonidal infectado; y preparatoriamente, en cirugía rectal y del intestino.

DOSIFICACION Y ADMINISTRACION

Se puede administrar el Chlorostrep en una dosificación de 2 a 4 cápsulas o cucharaditas cada seis horas en casos de diarrea o en la enteritis disentérica. La dosis tolerada se calcula sobre el contenido de Chloromycetin, pues la dihidroestreptomicina no producirá efectos generales debido a que no se absorbe en el intestino. En el preoperatorio, se puede administrar esa dosificación diariamente durante tres o cuatro días antes de la operación. Esta combinación es particularmente útil en el postoperatorio, conjuntamente con la administración de líquidos por vía oral. En los pacientes con infecciones causadas por patógenos comunes, este tratamiento debe administrarse durante cinco o seis días. Cuando se emplea en estados como fístula anal tuberculosa el Chlorostrep debe ser administrado en una dosificación mayor, aumentando la dosis diaria o siguiendo un esquema de administración más prolongado.

PRECAUCIONES: Las precauciones ordinarias relativas a los antibióticos de amplio espectro, como el Chloromycetin, deben ser observadas como se indica más adelante. Además, se debe tener presente que aun cuando se hayan eliminado los microorganismos intestinales comunes del cuadro bacteriano, los microorganismos no susceptibles, tales como monilia, pueden reemplazar la flora patógena o normal. Es esencial mantener una vigilancia constante del paciente. Si aparecen nuevas infecciones debidas a microorganismos no susceptibles deben tomarse las medidas apropiadas.

La administración oral de antihistamínicos generalmente aliviará las reacciones alérgicas que ocasionalmente pueden seguir al empleo de cualquier

preparación antibiótica. Debe interrumpirse la terapéutica si no se pueden dominar las reacciones de sensibilidad.

ADVERTENCIA.—Los niños prematuros y los nacidos a término de menos de un mes de edad, aparentemente debido a inmadurez fisiológica, requieren una dosificación especial. Estos niños a menudo tienen dificultades con dosis bien toleradas por niños de más edad.

Se sugiere para los niños prematuros una dosificación calculada a base de no más de 25 mg. de Chloromycetin por kilogramo de peso por día, fraccionadamente, a intervalos de seis a ocho horas. Para los nacidos a término de menos de un mes de edad se sugiere una dosificación de no más de 50 mg. de Chloromycetin por kilogramo de peso por día, fraccionadamente, a intervalos de seis a ocho horas. En los casos de administración prolongada o cuando se utilicen dosis mayores que las recomendadas, las concentraciones sanguíneas del antibiótico deben servir como guía para graduar la dosificación.

TOLERANCIA

Por lo general, el Chlorostrep es bien tolerado, y las alteraciones de la sangre consecutivas a su empleo son raras. Sin embargo, conviene efectuar exámenes periódicos de sangre en los casos de administración prolongada o intermitente.

En los prematuros y los nacidos a término de menos de un mes, el uso de dosis elevadas de Chloromycetin ha sido asociado con distensión abdominal, con o sin emesis, cianosis pálida progresiva, o colapso vasomotor, en algunos casos con resultados fatales. No se han comunicado estos efectos adversos en niños con una dosificación de 50 mg. de Chloromycetin por kilogramo de peso por día, o menos. La interrupción de la terapéutica ha corregido los efectos adversos en muchos casos, con restablecimiento completo de los pacientes.

ENVASE

El Chlorostrep se suministra en frascos de 8 cápsulas y en forma de líquido en frascos de 60 cc. (N.º 391).

PARKE-DAVIS

Laboratorios Principales, Detroit, Michigan, E. U. A.
Laboratorios Parke Davis, S. A. E.
Madrid

FROM: [redacted], SPAIN
Sept. 22, 1973

CHLOROSTREP

Chlorostrep is a combination of chloromycetin and dihydroestreptomycin in capsules and liquid. Each capsule or spoonful contains 125 mg of each antibiotic. When they are combined they exercise a synergic action which seems to broaden the suceptible bacterian spectrum.

It is very valuable in the treatment of enteric infections of the type diarrheic and of the many mixed infections found in the surgery of the intestines. It has been used successfully in the treatment of anorectal tuberculosis and the annal fistula; also in post operatory cases, after the extirpation of an infected cyst, and pre-operatory cases of rectal surgery and intestinal surgery.

Dosification:

It can be administered in doses of 2 or 4 capsules or in spoonfuls each every 6 hours in cases of dyarrhea or dysinteric enteritis. The tolerance is calculated on the chloromycetin content because the dihydrostreptomycine will not produce general effects due to the fact that it not absorbed by the intestine. In preoperatory cases this dose can be used 3 or 4 days before the operation. This combination is particularly useful in the post-operatory patients together with the administration of liquids orally. In the patients with infections caused by pathogens the treatment should be continued during 5 or 6 days. When used for fistula annal and tuberculosis the Ch. should be given in larger doses, increasing the daily dose or following a scheme of longer period of administration.

Precautions:

The ordinary precautions used for antibiotics of ample spectrum should be observed. Besides, it should be noted that when the common intestinal microorganisms are eliminated, the non suceptible microorganisms such as monilia can replace the pathogen or normal flora. It is important to keep contant vigilance of the patient. If new infections appear due to microorganisms non susceptible, due measures should be applied.

Oral administration of antihistaminics should alleviate the allergic reactions that occasionally can follow the use of the antibiotic. It should be interrupted if sensitivity reactions cannot be controlled

Warning:

Premature babies and up to one month old, apparently due to physiological immaturity, require special dose. Those children

usually have difficulties with doses well tolerated by older children.

For prematures it is suggested no more than 25 mg of Ch. per kilogram of weight per day, divided and at 6 to 8 hours interval. For babies less than a month old it is suggested no more than 60 mg per kilogram of weight and daily, divided in doses at 6 or 8 hours interval. When a prolonged administration or larger doses are required, the concentrations of antibiotic in the blood should be the guide to graduate the dose.

Tolerance:

Generally Ch. is well tolerated and blood alterations consecutive to its use are rare. However, it is convenient of have periodical blood tests when its administration is prolonged or intermitent.

In prematures and babies less than a month old the high doses of Ch. has been associated with abdominal distension, with or witnout emesis, cyanosis, pale or progressive, or vasomotor collapse, in some cases with fatal results. These effects have not been reported on children treated with 50 mg of Ch. per kg. per day, or less. The interruption of the therapy has corrected in many cases the adverse effects, with complete recovery.

Packing: In containers with 8 capsules and flasks with 60 cc.

PARKE DAVIS, MADRID.

13. Parke Davis Chlorostrep label, new one based on 1973 Chloromycetin Monograph.

"New" label based on 1973 "new" Parke Davis Chloromycetin Monograph

Acquired: Madrid Spain
Aznar Pharmacy
Sep. 26, 1973

A la Profesión Médica:

CHLOROSTREP®

El uso clínico ha establecido el cloranfenicol (Chloromycetin® Parke-Davis) como un antibiótico efectivo de un amplio espectro bacteriano en el grupo de infecciones por rickettsias y en el linfogranuloma psitacosis.

Posee una gran actividad antimicrobiana, atraviesa las barreras de los tejidos y se difunde ampliamente con rapidez por casi todos los tejidos y líquidos del cuerpo incluso por el líquido cerebroespinal.

La estreptomicina es un antibiótico clínicamente indicado en infecciones causadas por organismos susceptibles. Administrada por vía oral su absorción es mínima aunque hayan pasado cantidades relativamente grandes a través del tramo intestinal en altas concentraciones.

Chlorostrep cápsulas es una combinación de cloranfenicol y estreptomicina: cada cápsula contiene 125 mg. de Chloromycetin (cloranfenicol Parke-Davis) y 125 mg. de estreptomicina como Sulfato.

INDICACIONES

El cloranfenicol es un potente agente terapéutico. Debe tomarse bajo la dirección de un médico y no debe ser utilizado en infecciones triviales. El cloranfenicol está específicamente indicado en la meningitis bacteriana, fiebre tifoidea, infecciones por rickettsias, infecciones bacteroides, infecciones intraoculares, septicemia debido a organismos gramnegativos y otras infecciones serias donde la evidencia bacteriológica o clínica dictaminan el cloranfenicol como el antibiótico apropiado.

La estreptomicina por vía oral no es absorbida sistemáticamente y pasa a través del intestino en altas concentraciones, muchas bacterias patógenas intestinales, incluyendo shigellas y el grupo coli, son susceptibles a su acción bactericida.

El Chlorostrep se usa con éxito en el período pre-operatorio en operaciones de colon o recto, infecciones mixtas encontradas en la cirugía del intestino, tuberculosis ano-rectal, fístula anal, excisiones de quistes y senos pilonidales infectados y en infecciones entéricas o de tipo diarreico.

PRECAUCIONES

El Cloranfenicol debe tomarse bajo la dirección de un médico.

No debe usarse en infecciones triviales.

Discrasias sanguíneas e incluso anemia aplástica ha sido en raras ocasiones asociados a la administración de cloranfenicol. En los casos de administración prolongada o repetición de dosis deben hacerse análisis de sangre a intervalos regulares.

El cloranfenicol no está alineado en el fenómeno de interacción de droga y cuando los pacientes reciben concurrentemente anticoagulantes o anticonvulsivos, podría ser necesaria una adaptación de la dosificación de éstos.

REACCIONES ADVERSAS

Discrasias sanguineas e incluso anemia aplástica con exitus letalis, han sido, en raras ocasiones, asociadas a la administración de cloranfenicol. Sequedad de boca y con menos frecuencia náuseas, ocasionalmente también se presenta diarrea o vómito pero estos síntomas son raras veces tan severos como para justificar la suspensión del antibiótico. A veces se encuentran casos de reacciones de sensibilidad.

DOSIFICACION

La dosis para adultos y niños está calculada ampliamente sobre la base de 50 mg. de cloranfenicol por cada kg. de peso/día, dividida en dosis con intervalos de 6 horas, equivalente a 2 ó 4 cápsulas o cucharaditas de suspensión.

La dosis para niños prematuros y recién nacidos, de menos de dos semanas de vida debe ser reducida a 25 mg. de cloranfenicol por cada Kg. de peso día. La causa de esta reducción es la inmadurez fisiológica presente en estos niños. Más información acerca de este asunto es proporcionada en la monografía del producto bajo el título de síndrome gris.

En el período pre-operatorio puede darse la dosis indicada durante 3 ó 4 días antes de la operación intestinal. El Chlorostrep es particularmente útil en el período post-operatorio, conjuntamente con la administración de líquidos por vía oral. En los pacientes con infecciones causadas por gérmenes patógenos comunes este tratamiento debe continuarse durante 5 ó 6 días, cuando se emplea en casos como fístula anal tuberculosa, el Chlorostrep debe ser administrado en una dosificación mayor, aumentando la dosis diaria o siguiendo un esquema de administración más prolongado. En casos de insuficiencia hepática o renal la capacidad de metabolizar o excretar el cloranfenicol puede estar reducida por lo que el médico debe ajustar la dosis consiguientemente.

ENVASE

El Chlorostrep se suministra en frascos de 8 cápsulas y en forma de líquido en frascos de 60 cc.

PARA INSTRUCCIONES COMPLETAS SOBRE LA PRESCRIPCION, CONSULTAR LA MONOGRAFIA DEL PRODUCTO A LA DISPOSICION DE LOS MEDICOS QUE LA SOLICITEN.

PARKE-DAVIS

Laboratorios Parke Davis, S. A. E.
Madrid

Acquired: Madrid, Spain
Azucar Pharmacy
Sep. 28, 1973

CHLOROSTREP

The clinical use has established Cholramphenicol as an effective antibiotic of ample bacterial spectrum in the group of infections caused by richetsia and psitacosis limphogranuloma.

Its large antimicrobial activity penetrates the tissue barrier and expands thru them very quickly, as well as in the body fluids and the spinal fluid.

Streptomycine is clinically indicated in infections caused by susceptible organisms. Orally administrated its absorption is minimal even though large amounts go through the intestinal tract in high concentrations.

Chlorostrep capsules is a combination of chloramphenicol and streptomycin; each capsule contains 125 mg. of Ch. and 125 mg. of streptomycine as sulfate.

Indications:

Ch. is a potent therapeutic agent. It should be used under a physician's directions and should not be used for trivial infections. It is specially indicated for bacterial meningitis, typhoid fever, ricketsia, bacteroid infections and intraocular infections; septicemia due to gram negative organisms and other serious infections where bacteriologic or clinic evidence determine the ch. as the appropriate antibiotic.

The streptomycine used orally is not systematically absorbed and passes thru the intestine in high concentrations, many pathogen bacteria including shigellas and the coli group, are susceptible to its bactericide action.

Ch. is used successfully in the pre-operatory stage of rectal or colon surgery, mixed infections found in intestinal surgery, anal-rectal tuberculosis, anal fistulas, cysts and pilonidal infections as well as enteric or dyarrhea infections.

Precautions:

Ch. should be used under physician's instructions. It should not be used for trivial infections.

Blood including dyscracias and aplastic anaemia have been associated in rare ocassions to the use of ch. When a long or repeated treatment is necessary, blood tests should be done at regular intervals.