other drug firms I came to the belief that Squibb was, if anything, more ethical than most.

In the enclosed mimeographed copy of my 1960 statement I have bracketed an excerpt beginning on page 7 and concluding on page 8. I request that this excerpt be quoted in my statement as a partial answer to your questions regarding testimonials.

There were proof mills that would deliver data at so much per head and in extreme cases we used them. There were drugs that were declared useless after clinical trial by experts that subsequently became marketable using the testimonials of less experienced physicians to prepare a New Drug Application. I have adequate reason to believe that other firms were less fastidious than we were and purchased favorable reports. I always felt that a bribe was degrading not only to the one who accepted the bribe but also to the one who offered it. The testimony regarding Henry Welch in the "Kefauver Hearings" is an extreme example of the lengths to which some companies went. My 1960 statement made an oblique reference to the Welch affairs since it was made before the investigation exposed his activities. In retrospect the language is quite clear.

As I recall, there were at least two journals that subsisted on purchases of reprints used for advertising and promotion. They may still exist.

Drug studies are almost invariably included under research expense and I pointed out the absurdity of the practice in my 1960 statement.

Question. Dr. Frederick Wolff estimated before this committee that out of $10 spent on drugs, $6 are spent unnecessarily. Dr. George Baehr of New York said that the $6 figure was too low—that more than 60% of the drugs prescribed are not needed. Would you be willing to make an estimate?

Answer. I know of no way to make an accurate estimate of the percentage of drugs that patients pay for unnecessarily. In so far as prescription drugs are concerned I would keep my estimate consistent with the answer I have already given, namely about 50%. I should not be surprised if an actual study yielded a higher percentage of unnecessary drug expense. Naturally if we include over-the-counter drugs the unnecessary medication expense would be much higher.

I should like to amplify the comment that the antibiotic-cold preparation episode I described is being repeated by Upjohn and Squibb regarding Panalba and Mysteclin-F. I gave a reasonably detailed account of the 1963 episode because I feared that the present confrontation would follow the same pattern and that the final outcome might be the same. Recently Morton Mintz reported that Upjohn sent out 22,000 letters and that Squibb had put its detail staff to work on the problem.

Just as I was intrigued by the report that Lederle sent out 7,500 letters in 1963, I find 22,000 equally intriguing. Why 22,000 out of more than 300,000 physicians? Obviously a process of selection was used in 1963 and a process of selection is being used now.

We would have to be naive, indeed, if we concluded that these figures represent a random sampling of physicians and, it would constitute an incredible indictment of the medical profession as a whole if it were a random and representative sample. If I were a drug company executive faced with this problem and had to decide how to get the most mileage out of the letters I would use a simple logical process.

I have already said that a detailman is an expensive piece of property. Since his time is limted, it cannot be squandered and so drug companies try to develop a set of rules that will make it possible to use the detailmen's time most profitably. One of the indices used is a rating scale of the physician's prescribing habits. Squibb used a scale of four categories, and I doubt that other companies use a substantially different method. At one end of the scale is the non-prescriber or occasional prescriber. I would probably fall into this category since I write between 100 and 150 prescriptions per year. The infrequent attempts of detailmen to try to see me tends to confirm my position on the scale. At the other end of the scale is the "heavy prescriber". For our purposes we can accept the definition given in the AMA's Fond du Lac study that appeared in the record of the "Kefauver Hearings". A heavy prescriber is a physician who writes over 100 prescriptions per week! This is the prime target of the detailman and in this group we probably have the least discriminating physicians in the country. I find it difficult to believe that anyone can write that number of prescriptions and still take time to discriminate. In this group we also have the physicians most likely to raise a howl of protest over the prospect of taking away one of their toys. This is the group to whom I would send the letter and I feel reasonably certain that this was the group selected. The letters of protest come, not

from a representative group, but from the least discriminataing physicians and from the physicans least qualified to give an intelligent scientific appraisal of the problem.

Again, if I were a drug company executive, and I had an adequate detail staff, I would choose Squibb's method over that of Upjohn. The detailman is best acquainted with the prescribing habits and the different ways the physicians in his territory think. He is best able to determine which is the most fertile ground in which the seed of discontent and protest can be planted. As I said in 1963, "the real need is for data not protest". I hope Commissioner Ley will pay some attention to this.

One of the differences between the 1963 episode and the present confrontation is the lack of publicity given to the present confrontation in the throw-away news media. This is probably only a lull before the storm. I enclose with my statement Exhibit #6 which is quite typical of letters of protest and is the first pertinent article that has come to my attention. I clipped it from the "Letters to Tribune" section of the March 24, 1969 issue of *Medical Tribune*. As usual the letter to the FDA does not contain a scrap of scientific data and is a tirade full of illogical irrelevancies. In his letter Dr. Johnson says, "The FDA was created as an agency to prevent the movement in channels of interstate commerce of adulterated and/or *misbranded* food, drugs, and cosmetics" (my emphasis). Apparently Dr. Johnson is not aware of the efficacy provisions of the 1962 legislation. The FDA's proposal to take Panalba and Mysteclin-F off the market, as I interpret the law, falls within the statutory authority given to the FDA. The interference with Dr. Johnson's concept of the practice of medicine is an unfortunate side effect of regulatory action.

This is only one of some 3,000 letters the FDA is reported to have received. I expect we will see more of them. Actually I believe that the FDA could do a valuable public service by publishing a large random sample of the letters it has received. I feel that if the protesters are given enough rope they will hang themselves.

Question. Isn't it strange that although the AMA's Council on Drugs has always been against the use of combinations, the AMA still accepts advertising for them!? How do you account for this?

Answer. The answer to the question of the discrepancies that exist between the AMA's Council on Drugs, the AMA's advertising staff, and the AMA's editorial policy can be found in the record of the Kefauver Hearings. Following the Ben Gaffin Survey, which is reported in the record, the AMA apparently came to the realization that there is gold in drug advertising and that it was giving up a significant source of income. The AMA Seal of Acceptance was dropped and as I recall the Council on Drugs no longer had any voice in advertising policy.

The record of the Kefauver Hearings covers some 13,000 pages and while I have a reasonable knowledge of all of it, I cannot keep all of it always at my finger-tips. If my memory serves me, one of the members of the Council on Drugs who disagreed with the official position of the AMA in the Kefauver Hearings stated that the Council was not consulted even though the main issue was drugs.

You probably are acquainted with the disparity Dr. Charles May exposed regarding the editorial and advertising policies of the AMA. Although the AMA carried a scientific article indicating that Norlutin produced masculization in female fetuses with sufficient frequency to consider its use unsafe, the advertising pages blithely continued to carry advertisements for Norlutin which made no mention of this danger. The schizophrenic policies of the AMA are strange and are not amenable to the laws of logic and reason. Miss Yuncker's term "delirium" understates the diagnosis and prognosis. Delirium implies an acute transient disorder. The AMA's disease is chronic and probably incurable.

Question. What is the role of the Medical Director in allocating research funds? Does he determine what field is to be looked into? What criteria are used? Sales needs or medical needs? Can you tell us something about the quantity and quality of the research undertaken?

Answer. During the time I served as a member of the Fellowship and Grants Committee, the committee was composed of 4 members; the Vice-President for Research and Development, the Director of Laboratories, the Medical Director, and the Vice-President in charge of Promotion (sic). As I recall the budget available for clinical research done by my staff was between $250,000 and $350,000. While I had virtually complete command of the funds allocated for clinical studies of drugs, I had little or no authority in the selection of the drugs to be studied. If I recommended a clinical study it was almost invariably approved unanimously.

I believe that the total Squibb Research and Development budget was in the order of $6,000,000 throughout my tenure. Most decisions regarding the overall

Research budget were made by the Executive Management Committee of which I was a member. I had one of six to eight votes. Many research programs were instituted not because they promised a worthwhile drug, but because they promised profit. Molecular manipulation came into its own during my time in the industry. In my opinion about 20 to 25% of the total Research and Development budget was spent on worthwhile projects.

The actual dollar figures given by drug companies for "Research and Development" are probably accurate, but the term Research and Development covers a multitude of sins.

Question. What kind of doctors did you get to perform your clinical investigations? Did you have any experiences with so-called "proof" mills? (Can you name any?)

Answer. As I indicated in my prepared statement the drug industry doctor must rub shoulders not only with the giants of medicine, but also with its dregs. I doubt that by experience was different from that of others who serve or served the same function. Since the uninspired concoctions outnumber the worthwhile drugs by at least 10 to 1 most of the contact is with a rather shabby lot. I would prefer to name no names. I did work with proof mills, but again I would prefer not to name them.

When one views the scene from inside the drug industry he witnesses strange occurrences. I remember clearly an occasion when we were making preliminary studies of a drug that was being produced in very small quantities by a laboratory operation. We sent a highly placed authority enough of the drug to treat two patients and were somewhat puzzled by the fact that he sent us favorable data on three patients. When, shortly thereafter, he sent us laboratory data containing an item dated one day after the post mark on the letter, we black-listed him. To put the incident in its proper context I must confess that black-listing him consisted of taking his name out of the file of reliable investigators who could serve as adequate guides to important decisions. His card was transferred to another file that indicated that he could be used as a proof-mill when and if we should have need for one. It was one of the most obvious illustrations of what the FDA has called "graphite data" (i.e. data derived from a pencil rather than from laboratory studies) that came to my attention. We did not report it to the FDA and the secret was kept "within the family". To the best of my knowledge, it still is.

Question. Precisely what functions does a drug firm's medical director perform in determining what should or should not be said in advertising? (If the medical director doesn't have this responsibility, then who does?)

Answer. About four years ago I prepared an essay entitled *The Good Life of a Drug Company Doctor.* It was intended for publication in a lay magazine and in it I tried to give a distillate of my experience, in non-technical language, giving an account of both the advantages and disadvantages of such a career. In it I pointed out the doctor's function in the "review" and "approval" of advertising copy as one of the disadvantages.

"Drug companies boast that *all* advertising copy is reviewed or approved by the medical staff. Most require approval since review is pointless if the doctor has no voice in determining what is and what is not acceptable. This poses problems for the doctor. In the first place *all* advertising copy makes a mountain of paper, some of which is difficult to digest. Over-all the task is dull and boring. In addition, the doctor who does not approve the majority of copy that reaches his desk is not likely to keep his job. Yet over and again he is faced with advertising that is obviously misleading and which he cannot approve in good conscience. The dilemma is best resolved by a bizarre process of reasoning.

"Drug advertisements are never simple expositary statements; they are works of art. The artist who puts a house in his landscape does not have to draw in every brick of the wall or every shingle on the roof. A line here and there, proper shading and texture, and the mere suggestion of totality usually suffice. The eye and the mind of the viewer fill in the gaps in a manner that is predictable and therefore can be manipulated. A drug advertisement is a total composition subject to the same rules. It allows considerable latitude in creating ambiguities. This, too, constitutes an obvious objection to a compendium since it would not permit this latitude.

"The doctor who reviews advertising copy must learn to ask himself not whether the advertisement is misleading, but rather whether it can pass. An over-simplified illustration of what can and what cannot pass is furnished by a well known optical illusion. Two lines, exactly equal in length, can be made to

appear unequal by placing arrow-heads that converge at the ends of one line and diverge at the ends of the other line. The misleading nature of this device and the predictable response are not important. If one line is labeled 'effect of Drug A' and the other 'effect of Drug B' it can pass provided that the advertisement does not specifically state that the lines are unequal. Under these conditions the advertisement can be defended against any attempt to prove it false or misleading. Obviously that which cannot be proved false must be true and the truth cannot be misleading. The doctor who wishes to keep his job in the drug industry will find it mandatory to use this kind of reasoning.

"In desperate situations what can pass can be stretched to almost infinite limits. The determining factors are the mental and verbal facility of the doctor or lawyer who must defend it. One can always escape under a smoke-screen of words and if worse comes to worse, he can admit to an 'honest error' and challenge anyone to prove that there was any *intent* to mislead. Typical examples of these techniques are documented in the record of the Kefauver Hearings."

As Dr. Goddard said in his article in Esquire: "High-priced lawyers will spend hours in conference with FDA officials, haggling over the wording of promotional material, engaging in semantic arguments as to whether a certain section of government regulations does or does not give FDA the right to limit the company's 'freedom' in a certain area". About three and one half years after I deplored the type of advertising that leads to the chain reaction: fever equals infection equals a prescription for an antibiotic, I clipped the advertisement I have marked Exhibit #1 from the J.A.M.A. I believe it speaks for itself.

To demonstrate the kind of advertising that apparently meets the new FDA requirements I have clipped two advertisements from the March 1969 issues of *Medical Tribune*. These are marked Exhibits #2 and #3. The difference between Exhibit #1 and #2 is only in the degree of sophistication used and that the FDA requirement for full disclosure and "*balance*" have been met. Nevertheless the basic technique of creating a short circuit between a sign, and symptom, a complaint, a catch-all syndrome, or a catch-all diagnosis and the name of a drug that can be written on a prescription pad is followed to the letter. Exhibit #2 is in extremely poor taste not only because the woman depicted in the photograph can be suffering from anything from simple exhaustion, to anemia, through chronic schizophrenia, and on to any chronic debilitating disease, but also because it is only slightly, if at all, removed from the crass television commercials that say she has "tired blood" and needs Geritol, or those that say she has the "blahs" and needs AlkaSeltzer. She needs careful diagnostic work-up and not a prescription for Valium t.i.d. or q.i.d. The advertisement is a total composition deliberately intended to convey the impression that the "always weary" (a diagnositic category unknown to me) can be treated by writing a prescription for Valium.

Exhibit #3 is even worse and probably represents the best in advertising and the very worst in drug advertising. Advertising becomes more effective as it makes a stronger appeal to the irrational unconscious needs of the reader. To imply that the extremely variable and complex psychodynamics that may lead to symptom formation or psychopathology in this critical period of many men's lives can conveniently be dropped into a wastebasket labeled "Torschlusspanik" and treated with Librium approaches criminal neglect. I know of no scientific evidence that supports this oversimplified diagnosis and recommendation for therapy.

At the time when Dr. Fritz Freyhan (in the March issue of the American Journal of Psychiatry) is deploring the deficiencies in the training that even psychiatric residents get in psychopharmacology, and states that drug therapy cannot be divorced from an understanding of the basic principles of psychiatry, we have drug companies educating physicians about "Torschlusspanik." Significantly these advertisements appear in the *Medical Tribune* and not in the *Psychiatric News* or the *American Journal of Psychiatry* of the same period. It seems that they are directed at the more unwary average practitioner. It gives him another name he can write on a prescription pad thereby increasing his concept of his own omnipotence and fostering the delusion that every human problem can be solved with a prescription pad.

A question that is frequently asked, and it is invaribly asked in a tone that conveys amazement and total disbelief is: "Do doctors actually prescribe on the basis of advertising?" This device was used frequently in the Kefauver Hearings and most witnesses avoided the question since an affirmative answer left one open to the accusation that he was questioning the intelligence and integrity of his colleagues.

I note that Dr. Annis, the AMA's official representative, conceded that the chloramphenicol-bronchoscope advertisement was a "Madison Avenue Trick." According to the New York Times Dr. Annis said you were calling doctors dolts by suggesting that they would prescribe a drug on the basis of what they had read in an advertisement. It is important to note that *dolts* is Dr. Annis' term and not yours. The same peculiar reversal was true throughout the Kefauver Hearings. The mere suggestion that doctors are indeed influenced by advertising became an accusation that they were incompetent bunglers, dolts, or both.

I am not prepared to characterize the majority of my colleagues as dolts because I do not believe it is true, nor could I support such an accusation. I am willing, however, to state categorically that my colleagues are human and as human the majority of them are influenced by advertising when they write a prescription. Most medical experts and advertising experts who have examined the question agree that advertising takes the form that is most effective. Ultimately advertising—and it does not matter whether it is drug advertising or advertising for any other product—takes a form that is determined both by the rule of the survival of the fittest and a variation of Gresham's law. I have never found evidence that drug companies waste money on profitless gestures. To imply that the multi-millions spent on drug advertising is spent only because an occasional doctor will be influenced into writing a prescription is not only unrealistic; it is totally illogical.

The common practice of distributing desk accessories (calendars, letter openers, appointment books, etc.) boldly imprinted with the name of one or more drugs is not motivated by the company's wish to waste money on useless gimmicks and gadgets. The mere fact that one of these accessories is on his desk influences the prescription the doctor writes even if the stimulus is sub-liminal.

The notion that doctors study drug advertisements is absurd, and so I question the effectiveness of the "full disclosure" regulation. One "reads" advertisements by turning pages and Exhibits #1, #2, and #3 are examples of my total work of art description. If exhibits #2 and #3 are examples of "balance" then I have no notion of the definition of the word balance. The total effect of the imbalance in these ads is to negate completely any effect that full disclosure might have.

Accepting the Task Force's penchant for understatement I still find it difficult to understand why, on one hand, the Task Force feels that rational prescribing cannot be achieved by rules and regulations, but seems to feel that good drug advertising can be achieved by these methods. It says, "The frequency of biased, inaccurate drug advertising has apparently been reduced since the enforcement of new advertising regulations by the FDA began in 1967."

I find the concept of unbiased advertising untenable since it is a contradiction. The concept of degrees of bias in drug advertising holds, for me, the same connotation as the standard joke about being "slightly pregnant." If Exhibits #2 and #3 are examples of the improvement in drug advertising, may heaven help us! The notion that "training and experience" imbue the physician with God-like qualities that make him immune to the effects of advertising is nonsense. Such a concept betrays a remarkable ignorance of the fact that (contrary to the average patient's belief) the physician is neither omniscient nor omnipotent. It also betrays an incredible ignorance of the psychology of advertising. Just as advertising affects the personal purchases a doctor makes, it also influence the purchase orders he writes for his patients.

It was the AMA that said that drug advertisements are "reminders." Reminders of what?

Question. We have seen, with respect to chloramphenicol, important differences in the advertising and promotion of identical products by the same company in the domestic and foreign markets. In other words, the efficacy and safety of the drug seems to vary with the person's nationality.

(a) Do you know of any other products to which this applies?

(b) What do you think about it?

(c) When you were in the industry, who reviewed overseas advertising?

(d) What criteria were used for domestic and overseas advertising?

Answer. About four years ago I attended a professional meeting in Mexico. Because I was still entertaining the notion that I would write a book about the drug industry I decided to gather some ammunition. Marsalid had been taken off the U.S. market some two years before because its danger outweighted its utility. Accompanied by an interpreter I went to a drug store and after some difficulty in giving Marsalid the proper Spanish inflection I was offered a bottle of the drug over the counter (a common practice in Mexico). Until about

1955 Squibb had only one Medical Director and his authority extended to the overseas market as well as the domestic market. This resulted in a constant source of friction between the Medical Division and the advertising and promotion department of the Overseas Division. The Overseas Division held not only the notion that the safety and efficacy of a drug varied with the patient's nationality, but also that the advertising and promotion of drugs depended on the nationality of the physician. Physicians in any of the countries south of the border were considered less sophisticated than U.S. physicians and a "simpler" approach had to be used. This simpler approach resulted in some rather remarkable distortions. There were many products that were sold south of the border that had become obsolete in the domestic market but I recall only one, an Elixir of Glycerophosphates that had magical tonic qualities south of the Rio Grande and was useless in the States. More frequently, the difference was in the claims made for the same drug.

The real eruption occurred in about 1955 when, as I understood it, Parke-Davis had offered Squibb a license to market chloramphenicol in some of Squibb's South American markets. (Parke-Davis apparently felt that Squibb had a firmer position in these markets and that they could realize more profit from royalties on Squibb's sales than on their own sales.) I was presented with the prospect of marketing chloramphenicol under the Squibb label making all the excessive claims for the drug and excluding a warning statement since it was not required in the countries in which sale is proposed. I refused to approve the tentative copy and made it clear that I would tender my resignation before I would approve the copy. Apparently my colleagues thought I was sufficiently valuable and instead of making a confrontation out of the issue they decided to use an end play. The Overseas Division appointed its own Medical Director who was in no way responsible to me. Curiously Squibb never did market chloramphenicol, at least not to my knowledge. I do not know the reasons why.

As I think back I recall one absurd proposal intended for the South American markets. It was proposed that we add to our injectible penicillin a substance that would produce the taste of garlic when it was absorbed. This, it was said, would impress the patient and would lead him to believe that he had, indeed, been given effective medication. The Medical Division did not approve it. Let me add that to anyone who believes in placebo medication and the mumbo-jumbo of the art of medicine the proposal has merit. It has no place in modern concepts of a science of therapeutics.

To get the full flavor of the kind of jockeying that went on you must understand that during my tenure as Medical Director I used a philosophy of giving in on the smaller issues and reserving veto power on large issues backed up by a letter of resignation I carried in my pocket for almost two years. I still have it in my files and it shows obvious signs of wear.

Question. Why did you leave Squibb?

Answer. Since it is almost 12 years since I resigned I have had sufficient time to reconsider the decision. I cannot count the number of times the question has been asked nor the number of answers I have given. I believe that the best answer can be found in my unfinished essay on *The Good Life of a Drug Company Doctor.* Toward the end I said: "These are only some of the things a drug company doctor must learn if he is to be happy in the industry. After all, *it is a business,* and there are many more things he must learn to rationalize. He must learn the many ways to receive the FDA and, failing in this, how to seduce, manipulate, or threaten the physician assigned to the New Drug Application into approving it even if it is incomplete. He must learn that anything that helps to sell a drug is valid even if it is supported by the crudest testimonial, while anything that decreases sales must be suppressed, distorted and rejected because it is not absolutely conclusive proof. He must learn to word a warning statement so it will appear to be an inducement to use the drug rather than a warning of the dangers inherent in its use. He must learn, when a drug has been found too dangerous for use in this country, he can approve its use in other countries where the laws are less stringent and people have less protection. He must learn, when a drug has been found useless on one side of the Rio Grande, it can be sold as a panacea on the other side and that he is expected to approve the claims made for it. He will find himself squeezed between businessmen who will sell anything and justify it on the basis that doctors ask for it and doctors who demand products they have been taught to want through the advertising and promotion schemes contrived by businessmen. If he can absorb all this, and more, and still maintain any sensibilities he will learn the true meaning of loneliness and alienation."

During my tenure as Medical Director I learned the meaning of loneliness and

alienation. I reached a point where I could no longer live with myself. I had compromised to the point where my back was against a wall and I had to choose between resigning myself to total capitulation or resigning as Medical Director. I chose the latter course.

Actually I have never understood, completely, the reasons that Squibb did not fire me long before I resigned. While I had a magical touch with detailmen and came to be known as "Mr. Raudixin" because I engineered most of the investigation as well as the advertising, promotion and detailing of rauwolfia serpentina (which for many years was Squibb's biggest money maker) I was nonetheless a thorn in the side of most of my business colleagues. Part of my durability can be attributed to the fact that Squibb went through three different sets of management during the time I was with them. Nevertheless, at some time, the honeymoon would have ended and I certainly would have been fired. My successor has long since left Squibb and is in another drug company. For a time, I considered other drug companies but I rapidly learned that no one else would have me and that, even if they did, I would be jumping from the frying pan into the fire. One company made it clear that the president made all final decisions including medical decisions. I could not envision myself as a yes man approving medical decisions made by a layman.

Question. What do you recommend be done about irrational prescribing?

Answer. This question stimulates a rush of many diverse thoughts. First, since I am neither a lawyer nor a legislator I cannot claim any competency in the drafting of legislation. Since I served as one of the many consultants used by Kefauver and his staff during the drafting of S. 1552 I am influenced by the philosophy they adopted.

Next, it has been many years since I became disenchanted (and from the tenor of Dr. Goddard's Esquire article I assume that, one of the reasons he left his position as Commissioner of the FDA, is that he, too, became disenchanted) with the notion that the drug industry can be restrained by legislation. To quote Dr. Goddard, "Operating on an undisclosed, multimillion dollar budget in dues paid by the companies * * * the PMA is able to present a united front to protect the Establishment's business interests against forays by the public, Congress, or any of the federal regulatory agencies * * *. The Drug Establishment functions with all the smoothness of an intricate Swiss watch."

Although I have studied drug industry practices for 18 years and have become inured to the point where nothing surprises me, I am still awed by the amazing versatility the drug industry demonstrates. It seems impossible to write legislation that does not contain loopholes through which the drug industry lawyers can slip. Although the 1962 legislation has resulted in some improvement in some areas, the brave new world it promised has not materalized. If the slightest chink is left in the armor, the drug industry will widen it until a barge can be passed through it. The drug industry's manner of dealing with the full disclosure and balance requirements in drug advertising is an excellent example.

It took 32 years to add to the primitive concepts of drug regulation, enacted in 1906, the concept of safety. At the time the opponents of the legislation claimed that a juridical definition of safety was impossible. The Elixir of Sulfanilimide tragedy salvaged the safety requirement. It took another 24 years to introduce the concept of efficacy and again the opponents claimed that a juridical definition of efficacy was an impossibility. Had it not been for the thalidomide scandal the PMA and AMA lobbies might have won the point. A bill that had been butchered to death was partially resurrected and won unanimous approval. I do not believe that it should be necessary to wait another quarter of a century, or for another tragedy to add to the concepts of safety and efficacy, the concept of rationality. We have reached a point where drugs, and especially combinations, must be proved not only safe and effective but, also, rational. The opponents will claim that this too, is juridically impossible.

My disenchantment with the effectiveness of legislation alone has not led me to the conclusions that attempts to enact legislation with teeth is futile. On the contrary I believe that there is greater need for carefully considered and extremely carefully worded restrictive legislation. Since this is not my province I can only offer guide lines based on scientific concepts and my limited knowledge of the draftng of legislation. I have had enough experience (or perhaps insufficient experience) to comment that if we are not prepared to engage in a Gargantuan struggle, the proposal of effective legislation is a hollow gesture. We can and should try.

In the patent provisions of the original S. 1552, Kefauver proposed that a patent application for "any molecular modification of any patented or unpatented drug or for any combination of two or more drugs" would not be granted a patent unless "the Commissioner (of patents) * * * determined that the change from the prior art made by the modification or combination would not have been obvious to a person having ordinary skill in the art, and (B) the Secretary (of HEW) has determined that the therapeutic effect of such a modification is significantly greater than that of the drug so modified or that *the therapeutic effect of such drugs taken in combination is significantly greater than the therapeutic effect of such drugs when taken separately*". [My emphasis.]

The legislation I have in mind would simply substitute for patent application a new drug application and in place of granting a patent, granting a license to market. Like the efficacy provisions of the 1962 legislation I would make the legislation retroactive. In determining the definition of significantly greater therapeutic effect I would again be guided by the definition of efficacy that appears in the Kefauver-Harris Amendments of the Drug Act, "substantial evidence means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and responsibly concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof".

In brief, the legislation I have in mind has already been written. Making it applicable to drug combinations requires changing a few words. I am not unrealistic enough to believe that such legislation could get past the PMA and AMA lobbies without a Gargantuan struggle. Nonetheless it is required if we are going to put teeth into the drug act.

A valid objection that would be raised is that prescriptions for two or more drugs would cost more. This is a moot point and we must weigh it against the fact that a combination such as Achrocidin is prescribed for at least 10 patients who do not need it, for one who may need it and all patients pay for the antibiotic they may or may not need. The antibiotic constitutes the major part of the cost of the combination. The argument that rational prescribing would cost more than irrational prescribing is, in my opinion, inane and I do not believe that it could survive in any fair debate over the issue

Raising the question of the cost of drugs, I am reminded that I intended to clarify the question of whether licensing, inspection, and strict quality control would raise or lower the cost of drugs. The Task Force Report states: "Any company, large or small, brand name or generic name producer, can institute and maintain an effective quality control program, and most companies have apparently done so. The cost of such a program has been estimated to be about 2.4% of sales for a large company, but may be somewhat more for a smaller firm".

The term "somewhat more" is vague but I believe we can satisfy it if we multiply 2.4% by more than four times and assume that strict quality control for a generic drug would raise its price by 10%. The Committee is aware that the spread between brand name and generic drugs can be in the order of ten times or more, but these are extreme examples. Let us take an average example with which I am well acquainted. Generic Sodium Pentobarbital sells for approximately $4 per thousands. In the catalogues sent to me (a copy of which is enclosed) by wholesale houses the price has varied from $3.85 to $4.40. This is an umbrella price at which I can buy the drug in quantities of 1,000. The pharmacist probably pays less; he certainly does not pay more. In the same catalogue the price of Nembutal (Abbott's brand name for the same drug) remains fixed at $17.00 per thousand. If we assume that the generic brand is not quality controlled and that the institution of quality control would raise the price by 10% we still have a figure of $4.40, or at most, $5.00 per thousand. Even an idiot can conclude that in a competitive market the $17.00 brand would have to lower its price to meet the competition or be forced off the market. It is conceivable that it could be reserved for the carriage trade since there are those people who automatically conclude that anything that costs more must be better. The physician who writes prescriptions for patients cannot and should not indulge in this luxury.

While the relative wholesale price of brand name drugs as compared with generic drugs is just as available to other physicians as it is to me, any attempt to translate these prices into the price the patient pays for his prescription

requires the application of an infinitely variable constant. I almost invariably write generically (I must confess that about 50% of the time I am able to convince myself that writing Trifluoperazine instead of Stellazine is a pedantic exercise that accomplishes nothing since only the patented version of the drug is available). Since I write relatively few prescriptions, I can take time in the 50 minutes I see each patient to have him bring in the filled prescription and determine whether it has been filled by a brand name or a generic drug when I have prescribed generically and a generic brand is available, and inquire who filled it, and how much it cost. The pharmacists cost for 30 capsules of Sodium Pentobarbital is in the order of 12 cents whereas his cost for 30 capsules of Nembutal is about 52 cents. The most frequent practice is to fill a generic prescription for Sodium Pentobarbital with the brand name and to charge accordingly. Some pharmacists who fill it with the generic brand charge $1.15 indicating that they can meet the cost of overhead and make a profit by charging slightly over $1.00 to fill the prescription. When the prescription is filled with the brand name the price varies from $1.85 to $2.25 and he charges between $1.30 and $1.75 to fill the same prescription for the same drug with the brand name version of the drug.

To take another more extreme example, we can use imipramine (Tofranil). This is a commonly prescribed antidepressant which is patented and no generic equivalent exists. I frequently write a prescription for 100 fifty milligram tablets. The umbrella price for me is $105/thousand. The pharmacist probably pays $100/1,000 ($10/100) or less. Yet the patient's cost for a prescription for 100 tablets ranges from $15 to $20. These are figures given to me by my patients. Curiously the drug comes prepackaged in quantities of 100 tablets (which is part of the reason I prescribe that quantity). The pharmacist needs only to affix a prescription label to the bottle; yet he charges from $5 to $10 for this service.

I was pleased when I read the testimony of Dr. William S. Apple, Executive Director of the American Pharmaceutical Association, and found he among others, questioned the equity of the present mark-up system and recommended a fixed fee system. Until such a system becomes the standard practice of pharmacists, the physician is completely in the dark and the actual price the patient will pay for his prescription is unknown. I strongly urge that a fixed fee system replace the variable and unpredictable system of a mark-up which is subject to the whims of the individual pharmacists and is based on the concept of what the traffic will bear. A fixed fee system would bring order and sense into the price that patients pay for a prescription. It seems that the practices of pharmacists are fully as subject to investigation as the practices of the drug industry and the medical profession. All of the causes of the high price of prescription drugs cannot be laid at the doorstep of the drug industry.

Question. Do you have any other suggestions besides legislation to solve the problem of irrational prescribing?

Answer. Like Dr. Goddard I, too, am at my wits end in trying to come up with a reasonable solution to the problem of irrational prescribing. As I have indicated, I believe new legislation regarding irrational combinations can serve as the first step.

Beyond that I would tend to combine suggestions made by others at different times. Dr. Goddard spoke of Therapeutic Committees but was extremely fastidious over the matter of interfering with the practice of medicine. I can understand his reluctance since he was in a very sensitive position. The antagonism of the average practitioner toward the FDA hardly needed fanning by Dr. Goddard.

I do not know if some hospitals call their Formulary Committees Therapeutic Committees. Dr. Goddard's suggestion, as I understand it would model Therapeutic Committees along the lines of Tissue Committees which, I believe, are essential if a hospital is to get accreditation.

There was a time (and to a much lesser extent there still is) when some surgeons made a practice of removing organs from the body, not because the organ was diseased and required removal but, rather, because the surgeon needed a fee. I do not remember the exact chronology but there was a time when unnecessary operations became a *cause celebre* which received much publicity. Whether the formation of Tissue Committees preceded or followed this I am not sure. In any case, the function of a Tissue Committee is to examine the pathological reports on organs removed in surgery. The surgeon who makes more than his share of honest errors soon comes to the attention of the Tissue Committee and he may be censured or even lose his hospital privileges if he continues to indulge in the practice.

Again, as I understand Dr. Goddard's suggestions, Therapeutic Committees would review the doctor's prescribing habits just as Tissue Committees review his surgical habits. The task will be much more difficult than reviewing pathological reports on organs but just as the uterus and the appendix are prime targets for Tissue Committees certain prescribing habits would similarly become prime targets of Therapeutic Committees.

There is another suggestion made first (I believe) by Dr. Barbara Moulton who was formerly with the FDA. Dr. Moulton suggested a special category for drugs that were hazardous and tended to be over-prescribed. She suggested that a prescription for such a drug would not be permitted without the approval of a consultant. I believe the idea has merit and should be given further consideration.

The FDA should be given authority to form a category of "Dangerous Drugs". Supplies and prescriptions for these drugs would be handled in the manner that now holds for narcotics. These would be target areas for Therapeutic Committees but could also be spot checked by FDA inspectors. Since it is impossible to anticipate every contingency I would not insist on a consultation and allow emergency prescription when approval by a consultant or by a Therapeutic Committee would, because of time involved, not be in the best interests of the patient. The doctor should know, however, that when he prescribes such a drug in an emergency and without approval, he may, if he cannot justify its emergency use, expose himself to censure, loss of hospital privileges, or in cases of repeated offenses, suspension of his license.

Offhand I think of only two drugs I would place in that category, chloramphenicol and tranylcypromine (Parnate). There probably are others and there certainly will be others in the future. I am dubious about the possibility that the medical profession would adopt this method of self regulation voluntarily and it is possible that irrational prescribing will have to become a *cause celebre* and that publicity might force its adoption. If Congress gave the FDA authority to form a category of "Dangerous Drugs" the remaining steps would almost certainly have to follow.

In summary, irrational prescribing can be reduced by legislation requiring that a drug combination be rational as well as safe and effective; by steps that would lead to the formation of Therapeutic Committees, by the creation of a class of "Dangerous Drugs", and by publicity, publicity, and more publicity.

Question. What are your feelings regarding a Compendium?

Answer. I know that the Committee and the FDA are enthusiastic about a compendium. I wish I could share the enthusiasm. The tenor of my prepared statement makes it clear that I would favor anything that leads to more scientific practice of therapeutics and takes the black magic out of medical practice. A compendium would be a step in the right direction. The task of preparing it would be monumental, and it would have to be encyclopedic in scope.

My doubts are raised not by its scientific value but by the reception it would get from the average practitioner who needs it most. Like the Medical Letter it would be used by those who are already skeptical and have less need for it.

I enclose a clipping from *Medical World News* dated January 31, 1969 and which I have marked as Exhibit #7. When the President of the American Academy of General Practice was asked about the compendium his reply (according to MWN) was he "* * * would not want a new drug compendium to be put out by the government because it would be 'garbaged up' by all the material the FDA requires". It is difficult to determine how one should respond to this statement of principle. We can hope that it expresses the views of an individual rather than the official views of the Academy over which he presides. The hope is probably a vain one since a negative response to a compendium is essentially the party line handed down by the PMA and the AMA, and is the response one should expect if he has any knowledge of the thinking of the average practitioner.

Probably the greatest fault of the average practitioner is his inability to understand and to admit the limits of his own competence. The secure physician who is confident about the knowledge he does have is much more ready to admit that he does not know everything, and that there are areas where he needs help. Such physicians would probably welcome a compendium that would help them to find their way through the drug jungle.

As the average practitioner becomes more hurried, more harried, and more confused, the gap between what he does know and what he does not know widens and his inability to admit the existence of such a gap increases. An admission that he does need a drug compendium becomes a tacit admission that up to this time he has been groping in the dark.

In addition, it is important to be aware of the exalted position the physician has in the lives of his patients. While many patients have become disenchanted with the AMA, organized medicine, etc., most still cling to the impression that their personal physicians are both omnipotent and omniscient. This is understandable since it insures that the doctor will be better able to help the patient in the time of his need.

Unfortunately many physicians enter into the fantasy entertained by their patients and fulfill their own infantile wishes to be omnipotent and omniscient. The average physician is not about to step off the throne that makes him God.

A compendium will still be a legitimate educational tool and it will have to compete with Madison Avenue tricks. It would be more likely to be successful if we could fill it with free gifts, gimmicks, and gadgets, and in the long run, we may have to learn Madison Avenue tricks which will give us some chance of beating the drug industry at its own game.

STATEMENT OF DR. DALE CONSOLE AT THE KEFAUVER HEARINGS, 1960

I wish to introduce this statement by making my position clear. I am here by invitation and assume that invitation was extended to me because it was felt that my experience as a former Medical Director in the pharmaceutical industry would enable me to assist this committee in its work. I am not here as a witness against the firm with which I was associated. Since I destroyed the records in my private file when I resigned from the industry, I can offer nothing which can be construed as proof. I can offer a distillate of my experience and the opinions I have formed as a result of that experience. These are opinions and are intended to serve only as guides.

There is a simple maxim, I learned from detailmen, which is known to most if not all in the pharmaceutical industry. "If you can't convince them, confuse them." This is a valuable tool in the industry and I have seen it in operation as a guide to detailing as well as to other forms of advertising and promotion of drugs. It operates in what Dr. Lasagna has so aptly called the "numbers racket" with its never-ending barrage of new products, confusing names, conflicting dosage schedules and indications, claims and counter claims. I have seen it in operation here in statements made by industry spokesmen.

Part of that confusion arises from the unqualified use of the term "drugs". Not all drugs are the same and unless we understand this we cannot understand each other. For our purposes I would classify drugs roughly in four categories:

1. Effective drugs prescribed only for patients who need them.
2. Effective drugs prescribed for patients who do not need them.
3. Drugs from which all patients derive either no benefit or no more benefit than would be derived from an inexpensive substitute.
4. Drugs which have a greater potential for harm than for good.

These are all products of the pharmaceutical industry and it should be clear that the cost of drugs cannot be measured by price alone. When a patient pays for a drug which he does not need or for one from which he derives no benefit the cost is excessive regardless of price. To assume that all drugs fall into the first category and to concentrate on lowering the price of a broad spectrum antibiotic pill from sixty cents to fifty or even to forty cents is to miss the point. If we include everything from research cost to the salary of the detailman the total cost of creating, producing and selling drugs in the last three categories exceeds that of effective drugs properly prescribed.

Unfortunately drugs are not always prescribed wisely, and while the physician and patient, among others, must share the responsibility for this with the pharmaceutical industry it is the industry which carefully nurtures and encourages the practice. The incidence of disease cannot be manipulated and so increased sales volume must depend at least in part on the use of drugs unrelated to their utility or need, or in other words, improperly prescribed. Human frailty can be manipulated and exploited and this is fertile ground for anyone who wishes to increase profit. The enormous sales of so-called tranquilizers are only a small part of the crop reaped from this ground. The pharmaceutical industry is unique in that it can make exploitation appear a noble purpose. It is the organized, carefully planned, and skillful execution of this exploitation which constitutes one of the costs of drugs which must be measured not only in dollars but in terms of the inroads the industry has made into the entire structure of medicine and medical care. With the enormous resources at its

command it has usurped the place of the medical educator and has effectively substituted propaganda for education. It is generally accepted that after the average practitioner leaves medical school the drug industry represents the most potent influence determining many aspects of how he practices.

In its desire to create a favorable image the industry confirms this when it justifies the enormous expense of advertising and promotion by claiming that it serves the purpose of postgraduate medical education. Now some of the effects of propaganda and education are identical, but to conclude that drug advertising and promotion in education is one of the many fallacies introduced into these discussions.

Perhaps the committee will get a better understanding of this euphemism if we examine some aspects of it. Since I wish to describe practices which apply to many products and most if not all companies, I shall make my examples general and slightly hypothetical. Since I cannot name them all it would be unfair to brand the one named in the example. I can assure you, however, that the disguise is so thin and the practices so widespread that there will be no difficulty in finding adequate promotional material to document them.

First an extremely simple example. While in medical school the physician is taught; when the patient has a fever, determine its cause, and then treat it accordingly. The drug brochure teaches: when the patient has a fever think of—and here the name of a company's antibiotic follows. (See Exhibit 1 re a thermometer and erythromicin.) There are many variations on this theme and often the symptom and name of the drug appear in bold colored type to eliminate the effect of any intervening words. One need only change the symptom [or sign] and the drug to multiply the examples. To help drive this valuable lesson home in one promotional program a free clinical thermometer was sent to physicians. The invitation is delightfully tempting. Too many physicians, pressed for time, would like to believe that medicine can be practiced with a thermometer and a bottle of pills. The authority of the written word driven home by repetition is often enough to tip the balance. The exercise of judgment takes far more time and uses less drug. If this is education then we should also include lessons on how to smoke an opium pipe.

This approach is used only by the more naive since it does antagonize some physicians. It hardly does justice to the ingenuity of the more experienced drug house.

A better approach is one which is used frequently in the promotion of so-called tranquilizers, but with minor variations spreads to many other drugs. Either in the course of legitimate investigation or in the search for a new promotion device it is found that a drug which is claimed to be effective in relieving anxiety, produces, in rats, specific objectively mensurable changes in a particular area of the brain. Now this is an interesting truly scientific finding but in the present state of our knowledge its significance is unknown. To the promotion people this lack of significance is unimportant since it is both intriguing and impressive. It is presented in an advertisement or a brochure complete with accurate anatomical illustrations of the brain beautifully executed in vivid colors. This is coupled with the claim that the drug relieves anxiety. The usual response of the average practitioner who is not, and is not expected to be, an expert in neuro-physiology is to associate the two and to assume that they support each other. To the expert, however, any attempt to relate the claim and the finding is absurd since there is no known relationship between human anxiety and this finding. It is no more absurd to relate the claim to this finding than to the finding that the drug, when given to cats, makes their tails curl up and form a square knot. The latter is obvious, the former is not. Because it is not, the impressive but irrelevant fact is carefully presented in vivid form. The clarifying facts are equally carefully omitted. The desired effect is achieved by encouraging false associations and the frequency with which this approach is used is adequate evidence of its success. This, too, is called education.

Another example makes good use of the confusion technique. When the novelty of more potent vitamin pills began to wear thin, someone conceived of adding minerals and trace elements. Among these is zinc and since I am not an expert on zinc it may not be significant that I know of no evidence of zinc deficiency in man. If, however, one searches the literature long enough he will find that when chickens are deprived of zinc they cannot form a hard shell on the eggs they lay. When this curious fact is added to others similarly curious and mixed with some which are significant one ends up with an impressive array of "evidence" for the rationale of the product being advertised and apparent reasons

why the doctor should prescribe this mixture of vital ingredients. Now let us look at only one of the facts which are carefully omitted. No mention is made of the fact that the zinc deficiency can only be produced by extremely careful and expensive purification of the diet. Every trace of zinc must be eliminated and if the chickens get only an occasional meal by random pecking in the barnyard they obtain enough zinc to destroy the effect. In short, the deficiency is a laboratory artifact and has no counterpart outside the laboratory. Or stated differently, if one is to draw logical conclusions the zinc makes the vitamin pills invaluable for laboratory chickens provided, of course, that one is willing to go to the expense of purifying their diet.

Here the physician is bludgeoned with a barrage of irrelevant facts he has neither the time, the inclination, nor frequently the expert knowledge to examine critically. Multiply this by a dozen detailmen each selling a dozen products and backed by a dozen wizards in the home office who hold a dozen conferences trying to determine the best way to make nothing appear like a pot of gold. This, too, is called post graduate medical education.

But let me turn to the practice which forms the backbone of all advertising and promotion of drugs. This is the use of the testimonial as scientific evidence of the efficacy of drugs.

It was a practice in the Middle Ages for some people to wear suspended from the neck a cloth bag filled with asafoetida. The foul smell was believed to ward off plague. Apparently someone had observed that some people who used this medicinal fetish did not contract plague. Either it was not observed or not considered important that some who did not use it also did not contract plague. Since it is considered unscientific the practice has long since been abandoned. But it flourished a long time simply because it gave some people a greater sense of security and made them feel better, at least until they contracted plague. While the practice has been abandoned the principle which determined it remains with us essentially unchanged. Since the beginning of time men have stumbled over the meaning of the simple fact that when something is done for or to a person, especially if that something has magical or emotional significance, that person frequently feels better. At the present time it is better recognized but still poorly understood. It has been given the unfortunate title placebo effect. Similarly since the dawn of time men have stumbled over the error of attributing to various agents the ability to ward off or to cure disease without taking into account what happens to those who do not get he benefit of the agent. This practice was not abandoned in the Middle Ages and one need only examine any current medical journal to find examples of it masquerading as science.

Since the committee has had adequate exposure to the controlled study, the double blind, and the placebo, I shall not take the time to expand on this. Let me emphasize that no drug study is fool proof, but that the scientific validity of any study can be immeasurably increased by proper experimental design. [A drug trial which makes no allowance for placebo effect, and which fails to make accurate comparison with an untreated group is suspect, and the vast majority of reports on such studies are simply testimonials, not scientific evidence. A testimonial written by a doctor, even when it is given the additional cloak of respectability afforded by publication in a scientific journal, is still a testimonial. It has no more scientific validity than the opinion expressed by the woman who caught the largest tuna on record, that a certain brand of cigarettes are kind to the throat even when it appears in color on the back cover of a magazine. Yet the claims for the efficacy of an amazing number of modern drug products are based exclusively on this type of evidence.

Testimonials are used not only to give apparent substance to the advertising and promotion of relatively worthless products, but also to extend the indications of effective drugs beyond the range of their real utility. They appear either as complete reprints or as priceless quotations in advertisements or brochures. They convince too many physicians that they should prescribe these drugs.

Now the true nature of these testimonials is well known to the industry and its own contempt for them is shown by its vernacular for sources from which they are easily obtained. These are called "stables". Still it is an important function, usually of the medical division, to send representatives with generous expense accounts to all parts of the country searching out these sources. The burlesque is compounded by calling the drug trials "scientific studies" and by supporting them with grants which are charged to research cost.]

[These are some of the techniques used in this travesty of medical education. While not all drug advertising and promotion is of this type, too much of it is. Some is educational but there is ample evidence to indicate that the industry is only too ready to depart from its self-professed role of the Knight in Shining Armor totally dedicated to Science and the Healing Arts. These practices and others more vicious such as the subtle persuasion to use indiscriminately drugs (such a chloramphenicol) which are dangerously toxic and indicated only in selected desperately sick patients suggest that dedication is primarily to profit, even at the expense of good medical care.]

While the industry's practices and policies in advertising and promotion are necessarily exposed for examination, this is not true in most other areas. Here the camouflage of euphemisms and self-proclaimed virtue is not so easy to penetrate. Research is a good example.

While the industry spokesmen would have us believe that all research is on wonder drugs or better medicinal products this is no more true than the euphemism of post-graduate medical education. They stress that there are many failures for each successful drug. This is true since it is the very essence of research. The problem arises out of the fact that they market so many of their failures. Between these failures which are presented as new drugs and the useless modifications of old drugs (the addition of zinc to vitamins is a good example) most of the research results in a treadmill which moves at a rapid pace but goes nowhere. Since so much depends on novelty, drugs change like women's hemlines and rapid obsolescence is simply a sign of motion, not progress as the apologists would have us believe.

There is an interesting relationship between research and advertising and promotion. In many companies there is considerable antagonism since the advertising people feel, with justification, that they are expected to do what research cannot. The perennial cry is "if research would give us a good drug we could turn out a really good promotion program". Actually they do remarkably well with what they get. Lacking facts which are convincing they invent fictions which are confusing.

I am only slightly amused by the breast beating, statistics juggling, and comparisons with the research costs of other industries. Even the statistics are suspect since I wonder how many cigarette companies charge the cost of paid testimonials to research rather than advertising. I doubt that there are many other industries in which research is so free of risks. Most must depend on selling only their successes. If an automobile does not have a motor no amount of advertising can make it appear to have one. On the other hand, with a little luck, proper timing, and a good promotion program a bag of asafoetida with a unique chemical side-chain can be made to look like a wonder drug. The illusion may not last, but it frequently lasts long enough. By the time the doctor learns what the company knew at the beginning it has two new products to take the place of the old one. This, too, is well recognized and in some companies calls for casuistry of a high order. In others it is simply called a "business decision". While I doubt that it actually does, with this advantage, the pharmaceutical industry can well afford to spend more on "research".

For those who are interested in comparisons I would suggest examination, not of prices, but of the advertising and promotion of identical products by the same company in its domestic and foreign markets. This will probably reveal the rather remarkable fact that the efficacy of some drugs varies according to the position of the Rio Grande.

Now I am more aware than most of the worthwhile contributions of the industry, especially since it was my privilege to play a small part in some of them. I have no wish to minimize them, nor to deny the apologists their right to exaggerate them. To imply, however, that these contributions make up the total, or even the major effort in research, or in other endeavors, is gross distortion.

At this point let me remind you of an old French proverb which states "There are more buyers than sellers". The victim of exploitation is a victim only because in being exploited he serves some purpose of his own. A brief examination of the other side of the coin gives a better understanding of the nature and scope of the problem.

The physician is human and his medical degree does not change this. Since he likes to believe that he helps his patients the wish fulfilling phantasy of the

pill affects him as well as his patient. One need only observe the reactions of many physicians or being exposed to valid evidence debunking a pill they have been using with the delusion of confidence. These vary from mild denial and disbelief to irate protest and one is reminded of the varied reactions of children on being told that there is no Santa Claus or of adults on learning that TV quizzes are frauds.

Keeping up with the voluminous medical literature is an enormous task, and the busy practitioner is forced to neglect it to an increasing degree as his practice increases. Many feel guilty about this. They can read the condensed and pre-digested pap of drug advertising and promotion in the same time it takes to throw it in the waste basket or get a five minute education in the latest advances in medicine from the detailman. It is not surprising that they enter into a *folie a deux* and foster the delusion of advertising and promotion as postgraduate medical education.

The patients contribute their share. Too many are unable to accept that the physician in spite of his limitations is still best able to determine the proper treatment. The best doctor is not necessarily the one who gives a shot for every complaint, and the more conservative physician who does not prescribe the latest drug reported in *Coronet* may be far more competent than the one who does. But fear of disease did not end with the plagues and patients still seek their bag of asafoetida. It is this anxiety which leads some to avoid black cats, and most to seek newer, stronger and more impressive magic from the doctor. Too many physicians respond to this pressure not by dealing with it directly but by trying to produce a tangible symbol of the magic. To the pharmaceutical industry this is an open invitation to exploit both the patient and the doctor, and so it claims to have the magic all wrapped up in pretty packages and with a price tag which makes the magic all the more impressive.

The simple fact that anxiety is virtually impossible to evaluate objectively and that it responds to almost any bag of asafoetida accounts for the market in the so-called tranquilizers. In modern times the anxiety is stirred up not by an epidemic of plague but by advertising and promotion, and the meteoric rise of one of these drugs was not deterred by the early appearance of two lengthy testimonials, back to back, in the *Journal of the American Medical Association.*

This leads one to wonder what motivates editors to accept these articles which do not merit publication. Since they do not accept every paper which they receive they cannot hide behind their usual protest against censorship. Perhaps they are unaware of the damage which can be done by the cloak of respectability they lend and how well they serve the interests of the pharmaceutical industry to whom these atrocities are like manna from Heaven. I do not know if paid advertising influences this.

I have a better notion why public platforms ostensibly dedicated to the dissemination of scientific information are turned over to drug companies to launch programs of obviously biased drug promotion under the guise of scientific symposia. Even the platform of a government agency has been perverted to introduce, on the flimsiest evidence, a new drug which later came under the fire of the Federal Trade Commission. In this case the abuse was so flagrant that it aroused effective protest from a small group of indignant merical educators.

This latter phenomenon is so rare that one must wonder about the responsibility of the leaders and educators in medicine. Most face the problem with denial, complacency, or a sense of futility. Perhaps this is understandable in the light of the fact that the industry alone commands the resources necessary to make propaganda effective. How can legitimate education compete with the philosophy of the opium pipe and the carefully contrived distortions driven home by the trip-hammer effect of weekly mailings, the regular visits of the detailman, the two-page spreads, and the ads which appear six times in the same journal, not to mention the added inducement of the free cocktail party and the golf outing complete with three golf balls stamped with the name of the doctor and the company in contrasting colors.

While I feel that restrictive legislation is necessary to curb the excesses this is a partial answer at best. In all areas relating to the healing arts vulnerability and the facility and temptation to exploit it are so great that self-imposed restraint has always been considered a necessary prerequisite. If the industry could practice this instead of proclaiming virtue we would have the ideal solution. I am unaware of any tendency in this direction and the internal problems in the industry

are such that I see little hope for it. Rules of conduct are laid down but they are intended only as public relations gestures and their force is apparent rather than real. The older, well established, conservative houses once did resist many of the abuses. However, the entry of newer, solely profit-oriented competitors has encouraged an ever-increasing substitution of the more profitable practice for the ethical, and all firms have found themselves under increasing pressure to adopt the practices in order to survive. One can no longer think of pharmaceutical houses as black or white. All are shades of gray and while some are almost black none to my knowledge is white. In this setting it is difficult to conceive of enforcement of rules of conduct from within since one hesitates to throw stones when his own house is made of glass. Participation in intra-industry meetings will convince anyone of this. It is my conviction that unless sweeping reforms are instituted a truly ethical house cannot survive in the present competitive wrangle. The pressure for those reforms will almost certainly have to come from without.

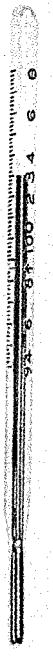
An intelligent program of education should help but it is well to remember that it generally takes several years of intensive analytic treatment to significantly alter one's belief in and need for magic. The abdication of leaders and educators in medicine is disturbing. Post graduate medical education is their province, not the pharmaceutical industry's. Unfortunately, I can contribute far more to a definition of the problem than to its solution, and I am not unappreciative of the potential of the adversary they face. There have, however, been encouraging moves by courageous medical educators to ascertain and disseminate unbiased information on drugs. Unfortunately, the principal audience for this information consists of those who are already skeptical. There are far too many physicians who must still be taught the difference between a free golf ball, the magnetic personality of a detailman, and a scientific fact as criteria for the evaluation of a drug. It is of interest that the industry generally shrugs off these moves since experience has taught that they do not affect its best customers.

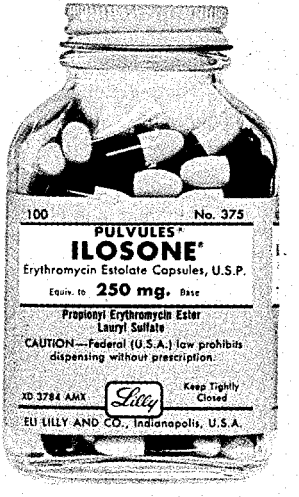
Finally, I suggest with hesitation the consideration of a central agency empowered to approve or to disapprove the sale of drugs on the basis of objective evidence of efficacy and to ban misleading and ambiguous advertising and promotion. I recognize that it will be virtually impossible to set up proper criteria but there are some areas where it is better to be guided by the dictates of good common sense rather than tortured legal constructions. It is a curious fact that as things stand now proof of the efficacy of a drug, to which some scientific rules can be applied, is governed essentially by the rule that anything goes if it cannot be shown that it probably will kill too many people who take it. On the other hand, a drug claim which is obviously misleading must be proved so by a process requiring the mental gymnastics of an insane philosopher. Surely a panel of experts, who can distinguish between privilege and license, charged with the responsibility for protecting medical care can make these decisions better than someone who has something to sell, and who simply makes "business decisions".

I cannot believe that a distraught mother whose infant lies desperately ill faces the same problem and emotions that she does in selecting a cereal from the Super Market shelves. While the physician is interposed between the patient and the drug industry there is a chain of responsibility and each member must accept his share. Drugs are a part of medical care and medical care has unique requirements. If the industry cannot exercise the necessary restraint it should not be free to exploit the privileges. It is this the industry fears most since so much of its sales volume is dependent on exploiting the privilege and since it recognizes the danger of being hoist by its own petard. I know of nothing more likely to generate the pressure necessary to persuade the industry to clean its own house.

EXHIBIT 1

[From the Journal of the American Medical Association, Sept. 21, 1963]





sign of infection?

symbol of therapy!

Ilosone is better absorbed—It provides high, long-lasting levels of antibacterial activity—two to four times those of other erythromycin preparations—even on a full stomach. **Ilosone is bactericidal**—It provides bactericidal action against streptococci, pneumococci, and some strains of staphylococci. **Ilosone activity is concentrated**—It exerts its greatest activity against the gram-positive organisms—the offending pathogens in most common bacterial infections of the respiratory tract and soft tissues. Usual adult dosage: 250 mg. every six hours.

In summary: Ilosone is an antibiotic indicated in infections caused by micro-organisms sensitive to erythromycin, especially streptococci, staphylococci, and pneumococci. Even though Ilosone is the most active oral form of erythromycin, the incidence of side-effects is very low. Infrequent cases of drug idiosyncrasy, manifested by a form of intrahepatic cholestatic jaundice, have been reported. There have been no fatal or definite residual effects. Gastro-intestinal disturbances not associated with hepatic effects are observed in a small proportion of individuals as a result of a local stimulating action of the medication on the alimentary tract. Cutaneous manifestations of hypersensitivity may be observed occasionally; maculopapular skin eruption or urticaria has been noted in less than 0.5 percent of patients. In extremely rare instances, anaphylaxis has occurred with erythromycin therapy.

Ilosone® works to speed recovery

Erythromycin Estolate

Additional information available upon request. Eli Lilly and Company, Indianapolis 6, Indiana. 300381

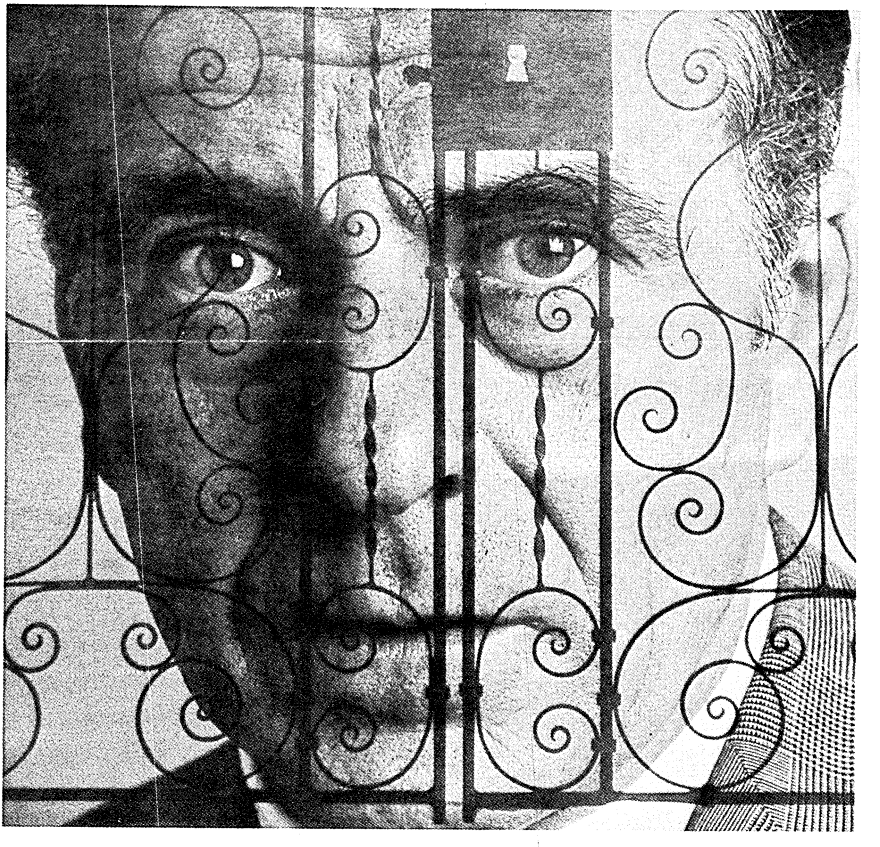
Lilly

EXHIBIT 2

[From the Medical Tribune, Mar. 6, 1969]

EXHIBIT 3
[From the Medical Tribune, Mar. 10, 1969]

a victim of
Torschlusspanik...



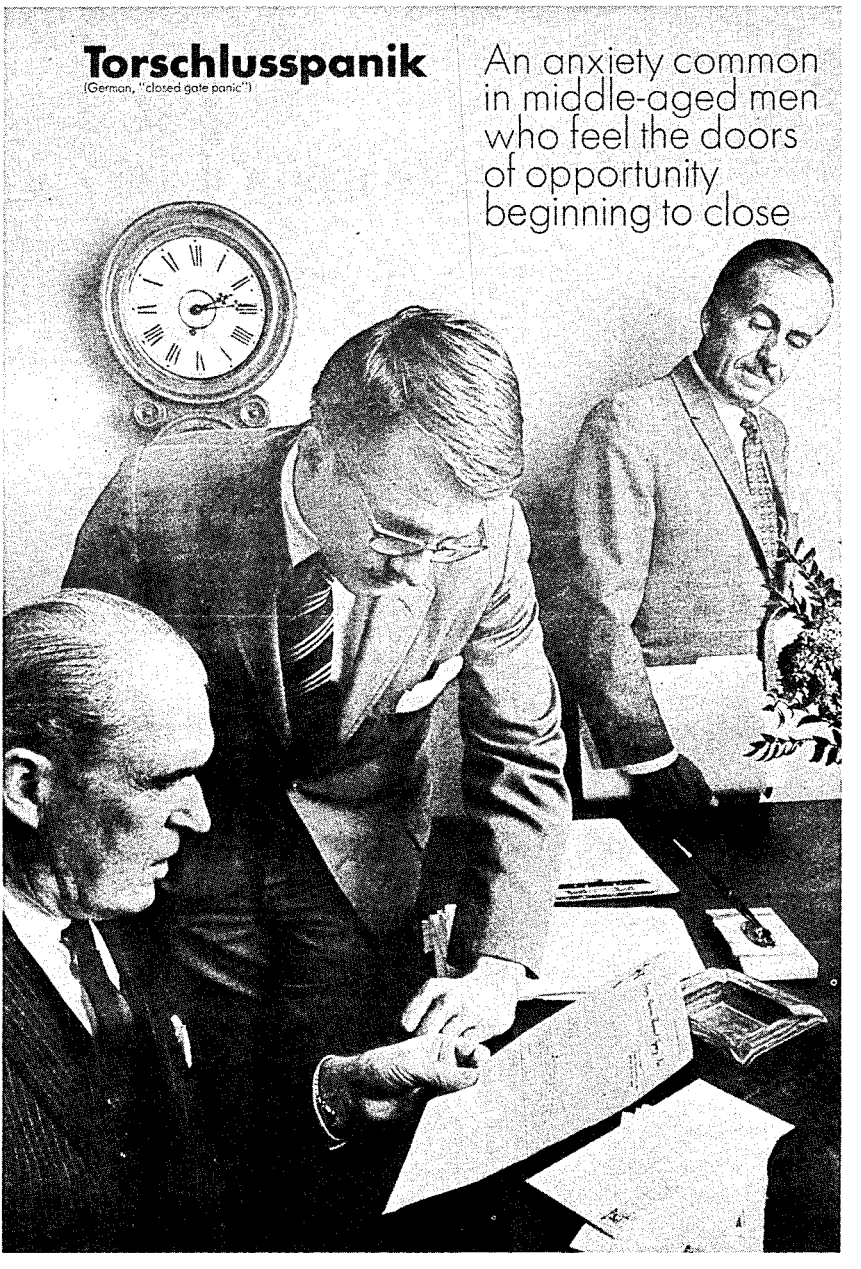

Torschlusspanik
(German, "closed gate panic")
An anxiety common in middle-aged men who feel the doors of opportunity beginning to close

EXHIBIT 4

[From the New York Times, Feb. 2, 1969]

STUDENTS SEND BACK DRUG MAKER'S GIFTS

One-third of the first-year medical students at Columbia University's College of Physicians and Surgeons said yesterday that their "dissatisfaction with the exploitative pricing and promotional practices of the American drug industry" had compelled them to return gift stethoscopes to Eli Lilly & Co.

This follows a similar move announced Friday by 45 second-year students at Harvard Medical School. The Harvard students, returned to the Lilly company a black bag and kit of diagnostic instruments—including a stethoscope.

Robert S. Pynoos, spokesman for the protesting Columbia students, said his group had written a letter to Lilly in which they had expressed disapproval with "the motivation behind these gifts."

The letter said in part: "Promotional programs of this sort are obviously intended to initiate the establishment of close ties between physician and pharmaceutical house, for mutual benefit."

"Such a relationship" the letter continued, "relegates the needs of the patient to a role of secondary importance."

Henry F. DeBoest, vice president of corporate affairs for Lilly, said yesterday that the medical instruments "have been offered with the prior approval of the medical schools." The gifts were "a mark of appreciation for their [the students] willingness to undertake the long, difficult road of an education as a physician."

EXHIBIT 5

[From the New York Post, July 10, 1961]

AMA DELIRIUM

Speaking of the real and the unreal, we wish that we could get rid of the feeling that the American Medical Association is out of this world.

We know better. But the miasma floating from the Senate Caucus Room as the mighty medics battle the Kefauver drug bill did little to clear our heads.

Dr. Hugh H. Hussey, there to speak his piece as chairman of the AMA's Board of Trustees, is dean of a medical college and by all accounts a literate, gracious gentleman. Yet there he sat, through three long sessions, pursuing an argument which went roughly like this:

It is better that a worthless drug be marketed than run the risk of a worthwhile drug being lost so therefore the Food and Drug Administration shouldn't be given power to rule on drug usefulness because the AMA is doing it better in a program that will be working by 1963 and is the only wholly objective agency able to handle the chore since more than half its income comes from the drug industry, the job being one that cannot and should not be done because no company tries to market a worthless drug and FDA already has power to stop them and is making adequate and effective judgments now inasmuch as FDA is incompetent to evaluate at all because drug evaluation is a highly complex and technical matter requiring skilled teams of test designers, pharmacologists, clinicians and statisticians and therefore has to be left to the individual family doctor treating you and me.

Is everything clear?

EXHIBIT 6

[From the Medical Tribune, Mar. 24, 1969]

CHALLENGE TO FDA

Editor, Medical Tribune:

Below is a copy of a letter sent to Herbert L. Ley, Jr., M.D., Commissioner of Food and Drugs, Washington, D.C.:

"1. The editorial from the MEDICAL TRIBUNE, January 30, 1969, is self-explanatory. Mycolog is produced by Squibb.

[The editorial dealt with the inability of a dermatologist to obtain the separate ingredients of Mycolog for patch testing because this would require the formalities of a new-drug investigation.]

"2. Mysteclin F is produced by Squibb and the FDA has requested Mysteclin F no longer be made available as a drug to be prescribed by physicians.

"3. I need a license to practice medicine. The practice of medicine is many things to many people.

"4. Congress never authorized the FDA to assume control of the medical profession nor to direct physicians how to practice medicine.

"5. As a practicing physician, there are many patients in whom I believe Mysteclin F is the drug of choice. I assume the responsibility for each decision I make. I do not believe the reason given for removing Mysteclin F from the market is a legitimate one . . . 'indiscriminate use of antifungal agents is to be avoided.'

"6. The FDA was created as an agency to prevent the movement in channels of interstate commerce of adulterated and/or misbranded foods, drugs, and cosmetics. Your agency has no authority in the areas concerned with the practice of medicine. It only has supervisory control over the pharmaceutical industries, not the medical profession.

"7. There is a big difference between pharmacology, pharmacological efficacy, and the practice of medicine and the medical uses of drugs. Drugs are used in the practice of medicine. Each patient is genetically different from every other patient. Physicians are taught to think and act using the tools of medicine. Pharmacology is but one subject of many taught to physicians. There has been no Congressional authority granted to the FDA to make comments about the medical profession and its actions. Your continued usurpation of granted powers must be recognized and stopped. Your continued intimidation of physicians and drug houses must be challenged and stopped. It must be recognized that your primary concern is not the patient but your own self-preservation according to the best legal minds under the tutelage of Mr. Goodrich. Anonymity of responsibility is your biggest and most powerful weapon since the Supreme Court refuses to pass judgment on any specialized agency such as yours. Knowledge of this isolaton and freedom from legal recourse has made your department wicked and unscrupulous. But who can do anything about it?

"8. Not only am I and my patients to be your victims but you and your family too. By what authority do you presume to have the right to tell physicians how to use drugs medically and when—except by usurping powers not granted you?"

JAMES H. JOHNSON, M.D.,
Chicago, Ill.

EXHIBIT 7

[From Medical World News, Jan. 31, 1969]

SOME PRACTICING PHYSICIANS REPLY

Senator Nelson's subcommittee hasn't invited, and therefore hasn't heard, testimony from the practicing doctors whose drug-prescribing competence has been so severely questioned by pharmacologists and other academicians. To get the other side, MWN has solicited reactions from the president of the American Academy of General Practice, the chairman of the AMA Council on Drugs, and an Oregon internist who says he has repeatedly, but vainly, tried to testify.

The AAGP president, Dr. Maynard I. Shapiro of Chicago, expects to appear before the subcommittee on a yet unspecified date. "I can't agree with the contention that doctors are unable to prescribe drugs accurately on the basis of the information available to them," he says. "I'm confident I have knowledge of the drugs I prescribe. If some question is not answered by the material at hand—the package inserts, ads, and such—I make it my business to find out." He says his additional sources are journal club discussions, curbstone consultations with colleagues, and the companies. "If there is something specific I want to know, I go to the professional services department of a drug company."

Dr. Shapiro feels the doctor may already get too much information. "FDA requires every adverse reaction to be listed—like, for example, one skin lesion in 10,000 cases. This looks a little foolish to some of us in practice. Already the circulars are getting so long and detailed and the type is so tiny I'm afraid a lot of men are not reading them."

Dr. Shapiro would not want a new drug compendium to be put out by the government because it would be "garbaged up" by all the material the FDA requires. He expects the AMA's forthcoming compendium to be more useful. "It will not be a *PDR*. It will be a scientifically composed book with therapeutic and symptom information the government does not provide." Dr. Shapiro says it would be handy if the AMA volume would include cost information. "But I have solved that problem. I keep a copy of the pharmacists' *Red Book*, which gives all costs, in my office desk drawer."

The chairman of the AMA council, Dr. John Adriani of New Orleans, also believes that the information currently supplied doctors is sufficient for them to prescribe drugs safely. "But the doctor needs more information than what he gets from the package inserts, ads, and detail men," says Dr. Adriani. "The information put out by drug companies is all right for safety. But the 'why' and 'how' you've just got to go out and get yourself."

Considerably more angry about the hearings is Dr. Clinton S. McGill Jr. of Portland, Oreg. "It seems very clear that Senator Nelson does not want anyone to tell the story from the private practitioner's point of view, or even to allow us to defend ourselves against the scurrilous attacks that are now a part of the public record," Dr. McGill told a recent meeting of the Pharmaceutical Manufacturers Association. Dr. McGill accused the subcommittee of believing that "we doctors are simple boobs, so snowed under by drug advertising that we can't select the right therapeutic agents for our patients.

"Anyone who has even casual acquaintance with medical literature knows that long before any important new product is ever marketed, there will be a number of articles on it in our professional journals. Next, it will be described in some detail in the *JAMA* section on new drugs. All of this, mind you, before the product is distributed."

Dr. McGill defended the content of drug advertising and described detail men as "trained professionals who provide us with valuable information." He does not look with favor on government drug publications. "I am sure the physicians of this country have a great deal more confidence in our own council on drugs than we would ever have in a publication of the Department of Health, Education, and Welfare—at least as long as the present atmosphere exists."

Senator NELSON. Beginning today, and continuing throughout the month of March, the committee hearings will be devoted exclusively to major medical associations and a medical consultant who was formerly a professor of pharmacology.

Our witnesses today are Dr. Blaise Alfano and Dr. John C. Krantz, Jr., of the Huntingdon Research Center, Inc. of Baltimore, Md.

He is professor emeritus of the Department of Pharmacology of the University of Maryland.

Our first witness this morning is Dr. Blaise Alfano, executive secretary of the American Society of Abdominal Surgeons.

You have submitted a biographical sketch which will be printed in the record prior to your statement, Doctor.

(The biographical sketch of Dr. Alfano follows:)

BIOLOGICAL SKETCH OF BLAISE F. ALFANO, M.D.

Date of Birth: September 14, 1923—Boston, Massachusetts.
Boston Latin School: 1942
Harvard University, A.B., 1946:
- Accelerated course—(1942–1944 and summer of 1946) Degree awarded in 1952.
- Secretary-Treasurer, Harvard Student Council.
- Secretary to Philip Brooks House.
- Elected to 1946 Class Committee 1946 to date.
- 1946 Class Treasurer 1946 to 1956.

U.S. Navy active duty 1943–1946: Ensign, USNR, Aleutian Islands
Tufts Medical School: M.D. 1950.
Internship: Cambridge City Hospital—July 1, 1950 to June 30, 1951.
Surgical Residency: Cambridge City Hospital, July 1, 1951 to June 30, 1954.
Chief Surgical Resident: July 1, 1953 to June 30, 1954.
Instructor in Surgery: Tufts Medical School

Instructor Anatomy: Harvard Medical School, 1952.
Advanced Surgery given at Massachusetts General Hospital by Harvard Medical School—1954.
Hospitals:
Senior Surgical Privileges at:
Cambridge City Hospital, 1954 to 1964
Melrose-Wakefield Hospital—1954 to date
New England Sanitarium and Hospital 1954 to date
Winchester Hospital—1954 to date
Surgical teaching staff at Cambridge City Hospital—1954 to 1964
Societies and Associations:
American Medical Association.
Massachusetts Medical Society.
Middlesex East District Medical Society.
Secretary, American Board of Abdominal Surgery.
Executive Secretary, American Society of Abdominal Surgeons.
Fellow, International College of Applied Nutrition.
Founder-Diplomate, International Board of Applied Nutrition.
American College of Gastroenterology.
American Association for the Advancement of Science.
Association of Medical and Allied Publications.
Institute for Advancement of Medical Communication.
American Medical Writers' Association.
Medical Society Executives' Association.
Phi Beta Pi (Honorary) Medical Fraternity.
Board of Governors, International College of Applied Nutrition.
Associate Editor, Journal of Applied Nutrition.
Director of Publications, Journal of Abdominal Surgery.
Executive Secretary, Clinical Congress of Abdominal Surgeons.
Fellow, American Geriatrics Society.
Leaders in American Science.
Who's Who in the East.
Secretary, Section on General Surgery, A.M.A. 1962–1965.
Advisory Board—Middlesix County National Bank 1966.
Official Observer, Apollo 8 Launch, December 21, 1968.
Elected Chairman Advisory Board—Middlesex County National Bank—January 1969.

Senator NELSON. Dr. Alfano, we are pleased to have you here today. You may proceed to present your statement in any way you desire. If you wish to depart from the text at any time to elaborate on any aspect of your statement, feel free to do so. Your full statement will be printed in the record, as well as any other extemporaneous comments you wish to make. I assume if we have some questions from time to time, you will not mind being interrupted.

STATEMENT OF DR. BLAISE F. ALFANO, EXECUTIVE SECRETARY OF THE AMERICAN SOCIETY OF ABDOMINAL SURGEONS, MELROSE, MASS.

Dr. ALFANO. Fine.

I wish to thank Senator Nelson and the members of the Monopoly Subcommittee for this opportunity to speak before the committee.

American medicine is known and acclaimed throughout the world as providing the highest level of medical care. This is so despite the statements of the detractors who quote the statistics of infant mortality. This is an area that needs improvement, to be sure, but the raw statistics do not necessarily indicate a weak spot in medical care; close evaluation most likely will reveal that other factors play a significant role.

Senator NELSON. Let me interrupt, Doctor, on the point of infant

care. You note in those statistics and some reports indicate that the incidence is very high in those areas where the poorest people live. Is it not likely that the problem here is that there are poor people who cannot pay to get medical care?

Dr. ALFANO. That is one of the problems, a socioeconomic problem. There is also an education factor involved. There are some people in the country who are fearful of hospitals. That still exists. Their care is rendered outside of hospitals.

Senator NELSON. More so than people from other countries, who have a lower incidence of infant mortality? Why in this country?

Dr. ALFANO. I believe you will find in those countries with a lower incidence of infant mortality, they have a higher incidence of hospital deliveries and their prenatal care is, say, regulated. Most of these countries, I believe Sweden and Norway, have a low incidence.

Senator NELSON. It does say something about supplying medical care in this country, then? It is a significant factor?

Dr. ALFANO. It is not just medical care. I believe there are other factors besides medical care. If the doctors saw all these individuals, prenatally and through the delivery, we would find our incidence of infant mortality would be down. It would be the same or better than other countries. The fact is that the physicians do not have an opportunity to care for these people. Therefore, you have a higher rate of infant mortality.

Senator NELSON. Nonetheless, it does say something about the kind of care and delivery provided in this country—the richest country in the world. It indicates, does it not, that this problem deserves the attention of the public?

Dr. ALFANO. Yes. It certainly needs correction and attention, I would say, yes.

I am not saying that we cannot improve our system of medical care. I believe we can. Changes and improvements are occurring constantly as they have over the years.

I do submit that legislation that disrupts the physician-patient relationship, which is the basis of medical care, can cause deterioration of the system it purports to help. I refer to the proposal that when a physician prescribes a brand name drug the pharmacist may substitute a generic drug as he see fit, and the only determining factor is the price of the drug.

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

Dr. ALFANO. Yes.

Senator NELSON. Whose proposal it that? I am not aware of such a proposal.

Dr. ALFANO. There was a proposal—I believe Senator Long had a proposal. We have a proposal now in Massachusetts that states a pharmacist can substitute a generic drug for a trade name drug.

Senator NELSON. Committee counsel advises me that Senator Long's proposal only refers to the question of reimbursement; that is, that reimbursement under the medical programs would be solely at the price of the generic drug. It does not require that the doctor prescribe it, but the Government will not pay more than the price of the equivalent generic.

Dr. ALFANO. I am sorry, I do not have that bill with me here. But as I recall, they do have a factor where there could be discussion—

not only, as you say, the price factor. But at any rate, we do have in Massachusetts a bill now pending that generic drugs be substituted for brand name drugs. This stems, as I believe, anyway, from legislation that has been submitted or talked about here in Washington.

Senator NELSON. I will have to take another look at that proposal of Senator Long's. I am not aware that there is any proposal pending that——

Dr. ALFANO. There was. I do not believe it is pending now. It was in the previous Congress, I believe. I have not seen it for this Congress.

Senator NELSON. As I say, I do not remember specifically what that bill proposed. I do not believe there is any bill that just gives a blanket authorization to a pharmacist to substitute a generic for any brand name. I might be wrong, but I do not recall that there is such a proposal.

There have been proposals that would require, as I said, reimbursement only at the generic cost. That, ultimately, I suspect, will become the law in public-funded programs, because of these dramatic cases of price variances of equivalent drugs. You may be familiar with the Medical Letter case on prednisone. The price varied from 59 cents for 100 tablets to $17.90 for 100 tablets of the brand name Meticorten. This is just to the druggist. The Medical Letter flatly asserted that in their chemical tests and in their consultations with clinics, they were all of therapeutic equivalence, and they listed 22 of them. I suspect the public is not going to use public funds very long to pay $17.90 a 100 plus the markup, when the drug is available at 59 cents. Would you think they would?

Dr. ALFANO. No; I agree with you. But I do not believe that because you have a case or several cases, that should change the system. As I understand it—excuse me, Senator—the medical profession has a way of correcting this. You are speaking of Schering's product, I believe.

Senator NELSON. Yes, sir.

Dr. ALFANO. They had 100 percent of the market. Now they have, what is it, 5 percent, or less than 5 percent of the market.

Senator NELSON. They get a large percentage of the retail market, but they do not get very much of the general hospital market, the city of New York, institutional markets, Defense Supply or Veterans' Administration, because they get outbid all the time. The interesting thing about it, and this is true of all brand names, is that no one who testifies on this question ever explains the reasons behind this. After our hearings, Schering reduced the price on its Meticorten—prednisone—from $17.90 for 100 to $10.50. Parke, Davis reduced their price of Paracort—prednisone—later from $17.88 a 100 to $3.25 a 100. It is perfectly clear to anybody that Schering is gouging the public, but they can do it because doctors write the name, "Meticorten." If they write Meticorten, that is all the pharmacists can prescribe.

At that time, they were selling to pharmacists for $179 a thousand. That was the equivalent of their $17.90 a 100. However, to New York City, they offered it at $12 a 1,000. They wanted the New York City bid and knew they would be in competition. That is $1.20 a 100 versus the $17.90 they were charging the pharmacist on the same day, across the street from city hall. New York City awarded the contract to Lannett, who bid $4.58 a 1,000, which is 45 cents a 100.

Now, is there any reason in the world why any public program or any program ought to be paying $17.90 a 100 when it is available at 45 cents?

We have the same company, Schering, selling for $17.90 to pharmacists and bidding for the U.S. Defense Supply Agency at 82 cents a 100. Do you have any defense for that?

Dr. ALFANO. No; I certainly cannot defend that type of action, Senator. What I was stating was, I think the physicians learn of this over a period of time. That is why Schering's portion of the market has dropped down considerably.

Senator NELSON. It has been dropping as a consequence of some publicity here in Washington, I think.

But it is not only Schering. Let me give you Ciba's reserpine. Ciba sells that to the pharmacists for $39.50 a 1,000. However, they bid to the Defense Supply Agency not $39.50, but $3.95 a 100. The winner if you can imagine this incredible figure, the bid 89 cents. Now, 89 cents for a 1,000 versus $39.50. The only reason they can charge $39.50 in the retail marketplace is that they have used your publication and other medical publications to sell the brand name. So the doctor writes the brand name. The poor patient is getting gouged day in and day out.

Defense Supply is buying both brand names and generics. Defense Supply is making a good choice of a drug. I do not think there is any question about that. Why should the public pay that price?

This is what comes about, I think, from the continuous promotion of brand names, which you advocate in your statement, and which other doctors testifying before the committee have also. They have taken the drug company line on brand name and physicians become convinced that you have to use a brand name, then they become convinced that it has to be a certain brand name, like Meticorten. Thus, the public is constantly gouged.

Quite frankly, I think the drug industry has brainwashed the medical profession.

Dr. ALFANO. I am sorry you do not have confidence in the members of the medical profession, but it is not the fact of brainwashing the physicians. Physicians have faith and confidence in a particular pharmaceutical firm. They have had experience over a period of time with thousands of doses of medication. They are not willing to take a chance with an unknown preparation. A manufacturer not known to you—how can you feel secure in prescribing this for your patient?

Senator NELSON. This is the problem that troubles this committee. Every witness before the committee speaks with great admiration of the quality and integrity and scientific distinction of the Medical Letter, even the Pharmaceutical Manufacturers Association. Each witness, when asked, answered, we have a high regard for it.

Now, the Medical Letter here lists 22 brands of prednisone, Meticorten at $17.90, American Pharmaceutical at $1.80, Bryant Pharmacal, $1.65, Darby, 61 cents, Wolins Pharmaceutical, 59 cents. In their statement to the physicians over the country, they say the great price spread among the tablets purchased from different pharmaceutical companies suggest the desirability of prescribing by generic name and specifying at least for patients of little means that the perscription be filled with low priced prednisone tablets. Why would not the medical

profession rely upon the Medical Letter more than the claims of the advertisers in promotional shares? Which one would you put your confidence in—this Medical Letter or the particular name of the brand name company?

Dr. ALFANO. I do not think it is a simple answer either way. Personally, I would not use either one myself. You have to make your own judgments.

I know one or two of those names. I know one of them is a distributor, not a manufacturer. Therefore, they have gotten their particular drug that they are selling, I believe you said at 61 cents. They get it from somewhere else, somewhere along the line. But where is it from? I am afraid to give it to my patient until I know about it.

I will say, yes; I can try a particular known drug, run an experiment with my patients, carefully watch them, see them more frequently. It requires more recordkeeping. Then I can determine for myself as far as the efficacy or the therapeutic equivalent of that drug that I experiment with or am trying versus the one I have been using regularly. If I find it works out, I am satisfied with the results, costwise, it is better, naturally, I would use the one that costs less and yet produces the same effect. I think that is logical to do.

But not just because it has a price of 61 cents or $1 versus $17. I am not going to use it for price consideration primarily.

Senator NELSON. On what basis would an individual doctor, for example, decide to continue to prescribe Meticorten at $17.90 per 100 when Merck sells at $2.20? That is a distinguished brand name company.

Dr. ALFANO. I do not have the figures with me, but I will be glad to send them. But I believe Schering, which had 100 percent of the market, is down to 5 percent or less, which is an indication that the medical profession recognizes this factor of cost and has chosen other drugs than Schering's product.

Senator NELSON. I think we had testimony on Meticorten a year ago as to its share of the market. I do not have it before me. You might be correct that that is the share of the world market. They have a much higher share than that of the retail market.

When they have to bid in competition, they get beaten quite regularly, unless they lower the bids. It is the brand name retail marketplace, where brand name predominates, which is the important question. I will check and see what share they have now. But, of course, they have had a lot of publicity in the past year on their price and they did reduce that price to $10.50.

Dr. ALFANO. I believe the medical profession then is cognizant of this price differential and does not blindly follow, say, Meticorten, which has been advertised or so-called brainwashed. They do not use it indiscriminately or continually. They change products or companies who can provide a quality product at a lower price. I believe all physicians throughout the country would do that.

Senator NELSON. Well, they certainly dominated the retail marketplace for a long, long time when other equivalents were available. That is the point.

On this whole field of pricing structure, which is what we are discussing, let me give you another example. The defense continually made before this committe about the prices they charge—the witnesses

testify that they do a lot of research and use new drugs and so they are entitled to certain rewards and, of course, they get that in a 17-year patent. They are not entitled to anything after 17 years except fair and honest competition. But they do not get fair and honest competition in the marketplace even after the 17 years. The doctors are in the habit, after 17 years, of writing the brand name and they continue to do so.

I have had doctors say to me, when I explained the price differential, well, I have been writing Meticorten for x number of years and I suppose I will write it the rest of my life. That is the attitude of physicians, even though their patients could get it at one-thirtieth the price.

Now, I would like to ask you a question on this point. How would you explain that Schering, who sells for $179 a 1,000 to the pharmacist here, sells it in Berne, Switzerland, for $43? In other words, $17.90 a 100 here versus $4.37 in Berne, Switzerland, after assuming the cost of packaging and shipping it overseas?

Dr. ALFANO. Senator, first, I would like to say I am certainly not trying to defend the drug company, trying to justify some extremes in cost of drugs. I cannot explain various extremes in costs of drugs. I am not in the drug industry. I do not know these factors.

Senator NELSON. Well, I do not want to be unfair to you. I ask because the pattern of your testimony, like the pattern of a number of other very distinguished physicians who defended the pharmaceutical manufacturers—take their line on brand name, on the cost of the services they get, on every single point the pharmaceutical manufacturers make. Therefore, I think it is fair to raise the issue of the wide price differences with those who defend the arguments of the manufacturers. That is what a good part of this hearing is about, the fact that the doctors say we cannot rely on anything but brand names. Strangely, the best hospitals in America, the Defense Supply Agency, and the Veterans' Administration, all buy large amounts of generics. They have their own pharmacologists, they take competitive bids. They find no diflerences in those drugs versus the brand name drugs.

Dr. ALFANO. I know, Senator, but if I had the facilities, if I had the setup that the Defense Department has for investigating drug firms and testing out the drugs, I could purchase a large number of drugs and use them because I have tested them. As I understand, they reject what is it, 40 to 50 percent of the drugs submitted to them. But they, I think, are the only facility capable of testing as they do.

There was another point I wanted to state. The patients in this country are not that naive. I have had patients come back and complain of the cost of a particular drug. They make known to the doctor the cost. The doctor, in turn, will make it his business to find out what the costs of these particular drugs is when patients come in. It is not that this is unknown to the doctor. He does not know the cost—I believe that is the history of Meticorten. He had no choice, he had to use the higher priced drug, but as qualified drugs, so to speak, came on the market, the doctors used them. That is why Schering's share of the market has dropped. Otherwise, it would be as high as it was in the beginning. If, as you say, the doctors are brainwashed, are creatures of habit where they are not thinking concerning the cost of drugs.

Senator NELSON. With respect to the use of the phrase "brain-washed"—I only use it on the question of price and brand name. I am not using it any other way. In other words, all I am saying is the promotion is so effective that doctors become convinced that they should prescribe this particular brand name, and that holds the price of that brand up. As an example you can take almost any drug you want in which there has been a patent, it has been on the market a long time, the patent runs out. That brand name still holds a very strong place in the marketplace at a very high price compared to other available drugs.

For example, we can take dextroamphetamine. Smith Kline and French put out Dexedrine. They charge the pharmacist $22.60 for a 1,000 five-milligram tablets. They offer it to the Defense Supply Agency for $1. So. while they are convinced that because of their promotion, their brand name Dexedrine is going to be written by the doctor and there will be no substitute, they charge $22.60. When they want the Defense Supply Agency business, they bid $1. That is incredible to me.

In New York City, they did not bid, but the winning bid was 57 cents. So, New York is buying dextroamphetamine at 57 cents for a 1,000. The poor customer in the retail market place is paying $22.60 plus the druggist's markup, for Dexedrine, for the very simple reason that Smith Kline and French, through a vast program of promotion, has convinced the doctor to write Dexadrine. He writes it and his poor patient is paying $30 and $35 when New York City is buying it for 57 cents. That is what I am talking about when I say the companies have done a magnificent job of selling the brand name.

Every witness who comes in to testify on the side of the company gives that line of argument. They never answer why it is that they are able, the same company, to charge $22.50 and then turn around and offer to sell it to the Government for $1 when they have competition.

Dr. ALFANO. Certainly as I said before, I cannot speak for the drug company on their costs. But I can say that the drug—not that the drug company sells the drug. The drug sells itself. The doctors have used it and found it works and they know how it works. Therefore, they will continue to use it until they have another product that will come along that will do the job and cost less, but not use a drug because it costs 10 cents versus a drug that cost $1. A doctor first must consider the condition he is treating and his patient. Secondarily, the cost factor comes into treatment, not primarily.

Senator NELSON. Well, of course, to all the hospitals that have a formulary and to the Defense Supply and to all the rest, cost is a very important factor to them. Every major hospital in this country has its own therapeutics committee, sets up its own formulary. In that formulary, you will find brand name drugs and you find generic drugs, lots of them. The formulary, as you know much better than I, is designed by the best clinicians, representing all aspects of the profession in the hospital, along wth the pharmacist and so forth—a group evaluation of what drugs should be in the formulary. They do not pay anywhere nearly as much. In fact, you find the brand name companies bidding to the hospitals, just as they do to Defense Supply Agency, at a price way below what they are charging the pharmacists, because the brand name does not do them any good with the

Defense Supply Agency. The important question is, does the drug meet USP standards?

Dr. ALFANO. I believe it is more than just USP standards on that. They have their own testing for drugs.

Senator NELSON. They test on USP standards, I take it.

Dr. ALFANO. I will not speak on that I understand there is a clinical evaluation of these products. They inspect the drug companies, the factories where they manufacture.

Senator NELSON. I am not aware that they do any clinical evaluation when they take bids on drugs. They analyze them on their own to see if they meet USP standards.

Dr. ALFANO. It is my understanding that 44 percent of these drugs are rejected. That must mean they are rejected on substandard manufacturing reasons.

Senator NELSON. I would suspect they reject as many brand names as they do generic. The only test we have is the test of the FDA of 4,600 drugs, 2,600 of them generic, the other 2,000 brand name, for potency. Of the brand name drugs, 8.8 percent did not meet the USP potency test; 7.7 percent of the generics did not. So, in a miscellaneous test of 250 manufacturers of 4,600 drugs on potency, the generic drug was better quality, met the standards slightly better than the brand name.

What would be your observation about that? If that is the only test you went on, would you not be saying, you could not trust the brand name, I will gamble with the generics, because they meet the potency tests better?

Dr. ALFANO. If that is the only test you go by. Was not that test rejected as not valid? The one you quoted?

Senator NELSON. Dr. Goddard testified on that. Out of the 4,600, there was a mistake on something like half a dozen.

Dr. ALFANO. I will have to send that in. I do not have it here. But as I understand, that is dramatically different from the original figures you quoted.

(Material not received.)

Senator NELSON. Here is the testimony from Dr. Goddard. It has been in the record for a long time, unrefuted by anybody. You would imagine it would be refuted the next day by the pharmaceutical manufacturers, if it were possible.

In six samples involving five firms, after the review of the original data, they did concede that they had made an error. So they conceded six errors out of 4,600. It still would not change the percentage. The generic drug names met the standards of potency better than the brand name.

Dr. ALFANO. I believe there is something later than that. I could not give it to you now.

Senator NELSON. No; there has been nothing later. The quote is—Dr. Goddard—"Now the other original findings I still say are correct. We stand behind these as long as it is understood that this is not a representative sample of the marketplace." That is, they were miscellaneous collection from 250 manufacturers.

All I say is—

Dr. ALFANO. What does he mean, not representative?

Senator NELSON. Well, they did not try to take a representative sample. They were just drugs that were from 250 different manu-

facturers, with 2,600 of them generic drugs and 2,000 brand names. But it is the biggest and best test that we have, and it indicates that the generic drugs met the standard potency better.

Now, do you have any evidence—we have had none by any representative before the committee—of tests showing that brand names are better? The only test we have is that the generics win.

Dr. ALFANO. The only test, really, is in the field. You are working with patients, you are prescribing drugs, you know it works. I do not think we can come up with anything better than that. After all, that is what we are working on, treating patients. If we come out with good results, fine.

If you can show me that I can use another drug that costs less and is equivalent to the drug that I am using, which costs more, naturally, I will use the drug that costs less and does the job.

But certainly, I am not going to go ahead and run experiments on my patients every day, say giving unknown drugs until I can evaluate them. It would be impossible for an individual physician to carry out this type of experimentation with many, many patients. He can do it over a period of time.

Senator NELSON. Of course, it is not possible for an individual physician, as a practical matter, to make comparisons of the efficacy of a half dozen different drugs of the same compound, anyway. You get a testimonial. But you do not get scientific evidence. The doctor may very well conclude correctly, after experience, that this is a good drug and it works. He sees it work. That is his experience. That does not prove that another one does not work. It does not prove anything. It just proves that the one he is using, as far as he is concerned, does work.

Dr. ALFANO. Well, in the final analysis, that is what counts, is it not, the confidence the doctor has in his particular treatment? That is very important, regardless of the benefits of other types of drugs and medications that are around. He is using a particular drug, and it is important that he have faith and confidence in that particular drug.

How can I treat a patient when I do not have confidence myself in what I am giving this patient? I would be a nervous wreck. I would be out of practice of medicine inside of a week.

Senator NELSON. Well, I submit that the classic example is the Medical Letter again.

Dr. ALFANO. Well, I do not believe everyone has that sort of faith in the Medical Letter.

Senator NELSON. Pardon?

Dr. ALFANO. I do not believe everyone has that blind faith in the Medical Letter. I do not subscribe to it, I do not have it, but my chief of medicine feels it is fine, but there are certain limitations to it.

Senator NELSON. There are limitations to everything. The Medical Letter had the drug prednisone tested chemically, and 22 all met USP standards. Then they consulted with their clinicians around the country, distinguished professional men.

Dr. ALFANO. They do not say who they are, though, do they?

Senator NELSON. Well, they list the editorial board, of course. Now, their advisory board is Dr. Gardner, professor of pediatrics, State University of New York, Upstate Medical Center; Lewis S. Goodman, professor, head of the Department of Pharmacology at the Uni-

versity of Utah, College of Medicine; Dr. Lasagnia, associate professor of medicine, director of the Division of Clinical Pharmacology, Johns Hopkins Medical School; Dr. Lavietes, associate clinical professor of medicine, Yale University Medical School; Dr. Mark Lepper, professor of preventive medicine, University of Illinois Medical School; Dr. George E. Moore, clinical professor of surgery, State University of New York at Buffalo, director of Roswell Park Memorial Institute; Maxwell Wintrobe, professor and head of Department of Medicine, University of Utah, College of Medicine; Dr. Robert Wise, professor and head of Department of Medicine, Jefferson Medical College. They use other consultants. They consult with people who are in the field using this particular drug; then with the benefit of their chemical analysis and their consulting with clinicians, they come to a conclusion about the drug.

Now, nobody has refuted this, including the company. The company testified. They have not refuted this. No one has refuted it.

What I am saying to you is—certainly, you want to be sure that your drug is employed. But this committee, as one part of the hearings, is concerned about the pricing structure of the drug industry and the fact that in the retail marketing place by their brand name identification, they are able to charge an excessively high price which they cannot get from a general hospital or Defense Supply or Veterans' Administration. It is just a clear cut case of gouging the public. Incredible gouging.

They could not answer why they charged one-fourth as much in Berne, Switzerland, for their drug, after shipping it over, as they charged here. They said that the standard of living is lower over there. Then I pointed out that the standard of living is much lower in Mexico City and they charge three times as much in Mexico City. He said he would ask the comptroller of the company to look into that and write me. That was over a year ago. We have not heard yet.

But in my view, this is a case of gouging the public by the drug companies, with the support of a lot of the medical profession who say, "Stick to the brand name."

Now, it would seem to me that if I were practicing medicine, I would go get the best formulary from the nearest hospital, in other words, rely upon the judgment of the distinguished doctors at that hospital, and prescribe from their formulary. That would answer a lot of these questions.

Dr. ALFANO. I do not believe you would want that, Senator. You want your physicians then to be herded into one group. Physicians are individuals. They will decide what they feel is proper for their particular patients. I do not believe—you use the word "gouging". I am not going to try to justify variations in pricing, but I believe there are reasons why trade name drugs cost more than generic drugs. Trade name or ethical pharmaceutical firms provide services that we do not get from generic companies. In fact, most physicians do not know the generic companies. I believe I have in here in this statement some of the services rendered by the pharmaceutical firms.

For example, the medical department of the drug company. You certainly would not want the American public and the medical profession to go without the services of the medical department of a drug firm. We do not have medical departments in generic firms. Certainly,

that will cost money and if the generic firms had a medical department, their drugs would have to be up by that certain amount. Then if they had professional relations departments and other services that benefit the patient and the profession, the generic drugs, certainly, there would not be that wide difference in costs.

Senator NELSON. Well, that exact position has been put to this committee a number of times and I have responded with this question, which has not been answered yet: What is the purpose of the patent? If they discover a new drug, the Congress has said you can have 17 years to charge any price you please. And when you consider that Schering was charging $17.90 for a 100 tablets and Wolins was selling at a price of 59 cents a 100, you can imagine what kind of profit they made.

So they had 17 years. They know how much it costs for drug research, they know what their overhead is. They wanted to make a profit. It is the highest profit in America. So they had 17 years. What justification at the expiration of the patent is there for charging a high price? They are able to do it, I submit, Doctor, because that brand name becomes so well know they can stick with the high price and gouge the public. Otherwise, Wolins would be selling more of their product in the retail market, and so would American Pharmacal and Merck. So what answer is there? They have the patent. What else do they need?

Dr. ALFANO. I cannot discuss patents and other types of things. I know nothing about that type of thing. I am just stating that ethical pharmaceutical firms do offer services which are of benefit to the patient and to the profession which we do not get from generic firms. These costs, these services, do amount to a certain amount of money and this amount of money has to be applied to the drug as the patient purchases it.

As to justifying extreme costs, I cannot do that and I do not intend to try to justify an extreme cost. I am only stating that we do have benefits from ethical pharmaceutical firms.

Senator NELSON. On the question of whether anyone would rely upon or use a good hospital formulary, did I understand your answer to be that the doctor is an individualist and would not want to do that? Are you saying that you do not think the formulary system in our major hospitals is a good system, that the collective judgment of all the distinguished specialists and clinicians in that hospital is not better than the single judgment of a single practitioner?

Dr. ALFANO. All hospitals do not have a formulary system. I am on three hospitals. None of them have formulary systems. They are all accredited community hospitals.

I have not worked under a formulary system. There are problems with formulary systems where the physician is handicapped. Most physicians will not join the staff of a hospital where it is required that he use only the formulary system. He will join if he may use beside the formulary system drugs of his choice that possibly are not listed on the formulary system list.

But what I understood you to say is the doctor is out in practice outside the hospital. He comes to the hospital and he has to be governed by these drugs that are listed by the hospital pharmacy or formulary system. That, I believe, would be objectionable.

Senator NELSON. I would not say he would have to be governed, by any means. All I am saying; for example, is "I am a doctor, I am trying to help my patient, trying to get the best drug. If I am a sole practitioner, I like to get the best sources of information possible. I would be happy to check with the hospital and say, what are you using for prednisone? I have been prescribing a brand sold to the druggist for $17.90, and costing my patients, with the markup, $30 or $35. What do you use?"

They say, well, we are using Merck's at $2.20, Wolins at 59 cents.

What is your experience? Very good. We cannot find any difference.

That is the sort of thing I would consider; that the collective judgment and practice and experience of that hospital might be very useful to me and I would be glad to get that information.

But in any event, 88 percent of the accredited hospitals in America use a formulary. None of them that I know of—that is, of those who testified—have a formulary in which it was compulsory under all circumstances that the doctor use the drug in the formulary. If he has a specific reason for desiring a particular brand name, he has that leeway.

Dr. ALFANO. I do not believe they have any choice. The medical profession would not stand for a closed type of system. They would not go for it. The patients are their prime concern, not the hospital pharmacy or whatever it is in ——

Senator NELSON. What happens is that as a matter of practice, most all the drugs prescribed in the hospital come right out of the formulary. The exception is rare, percentagewise.

When the hospital in Atlanta went to a formulary 2 or 3 years ago, the doctors testifying here said they saved, I believe it was, a quarter of a million dollars and that they found the generics they used to be very good.

Dr. ALFANO. I think there are two different systems of formularies, though. There are some hospitals that you are required to use these particular drugs in. If you write a trade name, they will give the drug in stock for that drug. Then, there is a system whereby a formulary does exist and it is permissive as far as you may or may not use it, depending on how you feel concerning your patient at that time.

Senator NELSON. I imagine there are hundreds of them, so there is a great variety in their use. I only wanted to make the point that—of the doctors who testified here, those practicing in a hospital with a formulary—these doctors said that within their hospital any physician desiring a specific brand name, though it might not be in the hospital formulary, would be free to prescribe that particular brand. No one would quarrel with that.

Dr. ALFANO. You may rightly ask how does the cost of the drug interfere with the physician-patient relationship—does a more costly drug improve this relationship? Of course not. But anything that shakes the confidence of the physician or patient interferes with this necessary relationship. A physician who writes a prescription for a particular medication knowing full well that the pharmacist will substitute a generic drug in filling the patient's prescription does not have the confidence that the drug received by the patient will do the job. The doctor prescribed a known drug but the patient will take an unknown product. Will the generic drug have more of an effect than

desired, the same effect as the prescribed drug or will it provide less than the desired effect. Since the doctor is not sure that the medication received by the patient is doing the job properly he will have to see the patient more frequently. Thus the savings in the cost achieved by the use of the generic drug will be more than offset by the extra visit or visits.

Under our present system the physician prescribes a drug which is known to him and manufactured by a known reputable firm. More important however, the physician has personal knowledge and experience with the particular product. He can advise the patient, anticipate results and accurately judge when he should see the patient again. The doctor has a working knowledge of the particular product. Under the present system of generic drugs the doctor can never gain a working knowledge of the product.

Under the generic system each time a patient has a prescription filled for the same drug he could receive a drug produced by a different manufacturer. Each of the products can react differently since each manufacturer has his own method of producing the finished product. This problem is compounded by the fact that it is not possible to identify the manufacturer. Under these circumstances no physician can gain a working knowledge of a generic drug.

The most significant point of all, I believe, is the fact that a chemically equivalent drug does not mean it is therapeutically equivalent.

Senator NELSON. What evidence do we have of that specifically?

Dr. ALFANO. Well, studies of Max Sadove, an anesthesiologist in Chicago. He has done a study of the generic versus the trade-name drugs. Then there is a study of Pfizer on oxytetracycline. There is a difference which, I believe the FDA has confirmed.

Senator NELSON. We have not been able to get any convincing evidence from the manufacturers or anybody else that drugs that met USP standards are not therapeutically equivalent.

Dr. ALFANO. You have no evidence?

Senator NELSON. The best ——

Dr. ALFANO. Well, I will send you the material concerning these studies that there is a difference.

(Material not received.)

Senator NELSON. We have those studies. They have been refuted.

Dr. ALFANO. When were they refuted? I do not recall seeing this.

Mr. GORDON. In one of our earlier volumes, specifically volumes 1 and 2.

Dr. ALFANO. Was it not the chloramphenicol, too, that there was a difference?

Senator NELSON. That is the only drug we are aware of and there is no proof yet. Dr. Lee testified on that recently. There is no proof that the different blood level achievement of Chloromycetin versus the other chloramphenicols, indicates that one was any more efficacious, that there was any difference in therapeutic effect. There may be, but what happened was that in the tests, the brand name, Chloromycetin, achieved a higher blood level more quickly. The FDA took the other two, I believe, off the market because they did not achieve the same blood level. They wanted uniformity in blood level achievement. Dr. Lee says there is no evidence that either or any one of these was a more efficacious or a better drug than the other. They may find this to be so

some day. All they had was a different blood level achievement in a different period of time.

Dr. ALFANO. There is a study on oxytetracycline, I think. I can send you a copy of that.

(Material not received.)

Senator NELSON. But the evidence was that there was no therapeutic significance to the difference.

The following is a line of questioning of Dr. Lee, former Assistant Secretary of HEW, on this question of equivalency.

Mr. GORDON. I have one nitpicking question. You say there are only two or three which demonstrate an initial lack of equivalency and one of them has no practical clinical importance. Are there two or three? Which is it?

Dr. SILVERMAN. There are two. One of them, as you probably surmised, is chloramphenicol.

The second one is tetracycline. In the article in this publication, the scientists that wrote this article pointed out quite clearly that although differences were detected, this was not of any clinical importance.

Dr. ALFANO. That is tetracycline?

Senator NELSON. Yes.

Dr. ALFANO. There is one on oxytetracycline, a new one.

Senator NELSON. In any event, the USP, the formulary, and the FDA, can cite only one of two cases.

Dr. KRANTZ. May I speak to this, because it is very apropos of this?

Senator NELSON. Yes.

Dr. KRANTZ. The Department of Defense a few years ago, after having bought these brand name items at low price as generics, brought me 19 of them that did not show complete therapeutic efficacy. These are these drugs: Reserpine, thiopental sodium, tolbutamide, tedral, tobocurarine chloride, Warfarin, Heparin sodium injection, oxytocin injection, diphenylhydantoin sodium, digitoxin or digoxin, phenolsulfonphthalein, pentaerythrityl tetranitrate, succinylcholine chloride (Anectine), bromsulphalein solution, sustained release tablets, methenamine mandelate (enteric coating), Dexamyl.

Senator NELSON. We will check the record further. Counsel advises me that the task force on these drugs went into this and found out that——

Dr. KRANTZ. They came to me for the purpose of finding pharmacological data which would show the generic equivalency of these drugs.

Senator NELSON. Were these drugs you cited here—I have not read that report—were these drugs that did, in fact, meet USP standards?

Dr. KRANTZ. Oh, yes; they put them through the USP test. This is very simple for them to do.

Senator NELSON. Did they meet the USP standards or fail them?

Dr. KRANTZ. Met the USP standards but the diphenylhydantoin did not control epilepsy. The meprobamate did not produce sedation. The thyroid did not change the metabolic rate.[1]

Senator NELSON. You are certain that these are cases where the drug met the USP standards, not failed the standard tests when tested?

Dr. KRANTZ. The pharmacopeia standards are only standards of identity, purity, and also the rate of tablet disintegration.

Senator NELSON. Potency?

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[1] See pp. 4555–4557 of Dr. Krantz' testimony.

Dr. KRANTZ. Identity and purity.

Senator NELSON. The committee is well aware of that, Doctor. What I am saying is did each one of the drugs named under test meet the U.S. pharmacopeia standard or did they fail to meet the standard?

Dr. KRANTZ. I was so informed by the colonel who brought them to me, that they had met the pharmacopeia standards.

Senator NELSON. I would question it for this reason. We have discussed this question with the Directors of the National Formulary and U.S. Pharmacopeia and they flatly state that they cannot find any cases, excepting one or two, in which a drug met USP standards or U.S. Formulary standards and was proven not to be therapeutically eqivalent. Now, I will take these and recheck them, but this has been the testimony by the Director of the FDA, by the U.S. Formulary, the U.S. Pharmacopeia, and by a number of distinguished pharmacologists. If they met the standard, there have been only one or two cases where that was proved not to be therapeutically equivalent. If there is further evidence of exceptions, of course, the committee would like to have it.

Dr KANTZ. Well, this came from the Army source of supply in Philadelphia. The colonel came to see me in my laboratory about a year ago and asked me if we could develop pharmacologic tests which could prove their pharmacologic activity in addition to the fact that they had already proved their chemical identity.

Senator NELSON. Dr. Lee testified for the Department of Health, Education, and Welfare on December 23 respecting the Task Force Report. I will read what I said to him and what he said:

Just on one point of your conclusion—

that is the conclusion of the Task Force Report—

that when drugs are chemically equivalent and meet all the chemical standards, they are therapeutically equivalent except in rare instances, as you are aware. We have had distinguished pharmacologists and clinicians appear before this Committee and give the same testimony I assume that when you refer to the fact that you have relied upon the literature, and clinicians, and past experience and so forth, that that also involves the rather vast experience of the Defense Supply Agency, the Veterans Administration, and general hospitals and others who buy on competitive bidding. And on one occasion they get one brand of prednisone and one brand of another drug.

Dr. LEE. Tetracycline.

Senator NELSON. And their experience over the years has been that if they meet the same standard and have the same chemical composition, that they are therapeutically equivalent; is that correct?

Dr. LEE. That is correct. Because this is a highly charged and controversial area, the task force made a very extensive study. The task force study has been going on for well over a year. We consulted with the leading experts in the field; our staff reviewed the literature; we had the special studies carried out; we reviewed the experience of the Defense Supply Agency and other agencies who have had just the kind of experience that you have described. Our conclusions really are based on a detailed examination of the information that is available today.

Senator NELSON. Thank you.

I have to go vote, but the committee counsel tells me that he cannot find anything in your material, Dr. Krantz, that says these drugs, in fact, met USP standards. Could you show him where that is?

I will be back as soon as possible.

(A recess was taken.)

Senator NELSON. We will resume the hearing.

It was called to my attention during the recess that on our discussion about hospital formularies, that all hospitals must have formulary committees to be eligible to collect for medicare patients.

Dr. ALFANO. Committees, yes, but not formularies. You are talking about committees. A committee and a list are two different things.

Senator NELSON. What is the purpose of having a formulary committee if they do not select a group of drugs to fit the formulary? What is the point?

Dr. ALFANO. Supposedly, they check all the drugs that do come into the hospital pharmacy, regardless of whether it is a generic or trade name. The formulary committee makes sure that the hospital does not have a drug within the walls of the hospital, the type of drug that may be harmful or cause problems that may be detrimental to the hospital.

Senator NELSON. You are saying that under the medicare law, in your judgment, hospitals are not required to have a drug formulary in order to get medicare payments for medicare patients? Is that what you are saying the law is? I do not know what the law is.

Dr. ALFANO. I do not believe it is a law that you must have a formulary committee—a formulary. I believe they do require the Joint Commission on Hospital Accreditation to have a formulary committee, but not necessarily a formulary.

Senator NELSON. I am still puzzled about what the formulary committee would do if they did not devise a formulary for the hospital.

Dr. ALFANO. A formulary is a list of drugs. If it is so restricted, you can only use this list of drugs within the hospital. The formulary committee reviews all drugs that come into the hospital and are used within the hospital. They will prevent a drug coming into the hospital that may be harmful and cause a danger as far as the patients within the hospital or cause problems for the hospital corporation and the staff.

If I, as a doctor, want to come in with a drug that is not approved, not accepted, if we have no formulary committee, I could bring any drug I wanted to into the hospital. There is no protection, therefore, for the hospital and the hospital staff and the hospitalized patient. The formulary committee will prevent that from occurring.

Senator NELSON. Please continue.

Dr. ALFANO. Thus when a physician has a patient on a generic drug produced by an unknown manufacturer he is conducting an experiment because he does not know how the patient will respond. The patient must be seen more frequently in order that the physician can evaluate the therapeutic effect.

With a brand name product the physician over a period of time has obtained a working knowledge of the specific drug and does not have to see the patient as frequently as is required with an unknown product.

From the patient's standpoint the substitution of a generic drug can have a profound effect upon the patient's confidence. For example, the physician orders a particular drug while the patient is hospitalized and upon discharge writes a prescription for continuation of the medication at home. The druggist substitutes a generic drug which may be a round red pill rather than the oblong yellow medication the

patient received in the hospital. What is the result? After discussion with the pharmacist the patient is not convinced that he received the proper medication. The next natural thing to do is to contact the physician in order to determine if the medication dispensed is in fact the one prescribed. Unfortunately the physician cannot identify the generic drug by its shape, size, and color and must contact the pharmacist to determine if an error was made or if the patient actually has the medication which was prescribed. If you were that particular patient I'm sure that your confidence would be thoroughly shattered.

Senator NELSON. May I interrupt, Doctor? I would like to make the point that exactly the same thing happens all the time. As I said, 88 percent of accredited hospitals of America have a formulary. Every witness we have had from every major hospital has a formulary and uses generic drugs in the formulary. So to use your argument, the patient is in the hospital; the hospital gives him a generic brand drug. It is a little round red one. He gets out of the hospital, goes to the doctor and the doctor prescribes the little round yellow one and you shatter his confidence. Nonsense.

Dr. ALFANO. I can only testify from my experience. In my experience, if I prescribe a trade name drug, that is what the patient gets in the hospital. If I discharge the patient and the law requires that they substitute a generic drug, then they get a different one.

Senator NELSON. All I am saying is it works both ways. All the major hospitals in America are using a formulary. In those hospitals, the doctors are using the drugs in their formulary with rare exceptions. So the patient leaves the hospital, goes to another doctor, gets a little red pill instead of a little yellow one and his confidence is shattered. I must say even if it is shattered, it is shattered both ways.

Dr. ALFANO. I do not believe the formulary system is the way you understand it, really. The physicians on the staff, the formulary committee will make up a formulary and the drugs of choice are listed on that formulary. It is not made up primarily as a cost limit for the hospital.

Senator NELSON. Oh, it is a very important part of the cost. We have witnesses testifying to that. As I pointed out, one hospital saved a quarter of a million dollars a year.

Dr. ALFANO. If you are stating the formulary is made up for cost reasons, I condemn that type of system. I think the patient is the primary consideration.

Senator NELSON. I did not say that at all. All I am saying is the formulary is made up by a group of doctors representing the disciplines practiced in the hospital. I am just repeating what the expert testimony is, that using the knowledge and experience of a group of physicians who make up a formulary. It is expected that the doctors will use it and they do use it. They do have a caveat that if the doctor insists, has some reason to use a particular brand or another, he is completely free to do so. But this is an exception to the rule, not the rule.

So all I am saying is that in these hospitals, lots of patients are getting a generic drug. When they leave the hospital instead of getting a little round red one, they get a little round yellow one, a brand name. I simply submit that if it shatters their confidence one way, it shatters their confidence the other way. But I would be amazed if a great deal

of shattering were going on. If there were, perhaps the hospital should be required to continue to use on that patient the same generic drugs, the same brand drugs, so that the patient's confidence would not be shattered when the doctor changes from a generic to a brand or from a brand to a generic.

All I am saying is your argument is full of holes. It works both ways.

Dr. ALFANO. I do not believe so, because you are talking about a formulary system. The staff has a formulary committee. The staff then submits the drugs they wish to use. You have a staff that have on the formulary the drugs they wish to use, the drugs they use on their patients, inside the hospital and outside the hospital. There is no other change, no other outside force that comes between them. The formulary system belongs to the staff and is controlled by the staff.

Senator NELSON. Correct.

Dr. ALFANO. They have the drugs they wish on that. So it is not the same as you say, that they can have one drug in the hospital and another drug outside. The doctors on the staff submit the types of drugs they want on the formulary, because the formulary is derived primarily for the benefit of the patients and the staff, secondarily, for the cost. And I am sure—I do not have the figures, but if the hospital bought a large amount of a drug, a trade name drug or a generic drug, their prices or cost would be less than if they bought smaller amounts for, say, individual medications rather than a wholesale purchase. So there is a savings on both generic and trade name drugs.

Senator NELSON. There is no question about that. All I'm saying is one of the purposes of the formulary is economic. That is one of the purposes. The fundamental, primary idea in the selection of any drug is to be sure that you have a quality drug that does what the drug is supposed to do. That is fundamental. There would not be anyone who would argue about that.

Then another factor is the economics and it is an important factor, the difference between $17 a hundred and 59 cents is quite a bit. Any hospital that used a substantial number of drugs but did not develop a formulary to take competitive bids is a poorly managed hospital. When they design the formulary, they design it to be used. The testimony of the witnesses here is that it is used and it is the exception when a doctor insists that he wants to give Meitcorten or Paracort instead of Merck's prednisone or Wolin's. If he has a reason, he may. But that is the exception.

So patients are going into hospitals and often going back to their own or another physician, who is not associated with that particular hospital. And this physician decides that he will prescribe Meticorten instead of Paracort and the little red tablet becomes a little yellow one and you have shattered the patient's confidence. That is all I am saying. It works both ways.

So to use your argument, you just turn it around and use this one. It happens all the time. I wonder about how much shattering, but I suppose it happens.

Dr. ALFANO. I know it happens.

I recently spoke by telephone to a colleague at the Naval Air Station, Alameda, Calif., and asked if he had any problems with generic drugs versus brand name drugs. At the naval air station it is customary to use both brand name and generic drugs. He related one experience

that illustrates the problem. A patient was hospitalized in order to achieve a therapeutic blood level by a particular drug. Upon discharge, the patient was given a prescription for the drug and instructed on how to take the medication. The patient presented the prescription at the pharmacy and received the generic drug of the brand name product he received while in the hospital. A week later the patient returned to see the doctor. The patient stated he had not taken the prescription medication because it was different from the medication he received as a patient in the hospital. The patient had to be readmitted to the hospital and treatment was started all over again. It is quite obvious that there can be fatal consequences with interference to the physician-patient relationship.

Senator NELSON. Let me ask a question. That is one example. Now suppose a patient had been admitted to the hospital and had been getting a generic drug. He comes out of the hospital and the doctor prescribes a brand name drug. He goes to the pharmacy and sees the brand name drug as a little yellow one instead of a little red one. He refuses to take it. He has to go back to the hospital. What are you proving? In one case, it was a brand name he got in the hospital and rejected the generic. In the other case, he got out and refused to take the brand name. What are you proving? That the brand name is better than the generic?

Dr. ALFANO. I don't believe the practice is as you stated. The physician doesn't change medication on the patient that way. A physician will use medication and carry it on to the point where if that medication is not working any more, he will change the prescription and order a new medication.

Senator NELSON. Are you saying in this case at the hospital, the doctor prescribed the brand name and the pharmacist illegally substituted the generic name?

Dr. ALFANO. No, this is a system here. They have both brand name and generic drugs. While in the hospital, evidently, the brand name was used and at the pharmacy, the generic drug was dispensed. It could be the other way around.

Senator NELSON. Of course. But what does it prove?

Dr. ALFANO. It proves that you must have consistency as far as the medication. A patient gets confused. I have seen it happen.

Have you ever gotten medication, you get one type of medication, it is for a certain condition, and you go to a pharmacy and you have a different type of medication and it is foreign to you, that you do not question it? Do you feel, well, it is a different color and must be the same? It is irrational to say it is the same.

Senator NELSON. I assume you could have some instances on six or seven drugs and they switch. But you are using the case where the patient goes to the hospital and is taken care of in that hospital by the specialists, goes on back to a local physician in another city. The doctor there knows he is supposed to get prednisone, so he writes a brand name that he likes. It is not generic. So the patient's confidence is shattered again.

Dr. ALFANO. No, no, it isn't. It is understood. This is the patient-physician relationship that exists. There is no disturbance there. I write a prescription for a patient, tell the patient, you take it. They fill that prescription. You are talking about another doctor's prescription?

Senator NELSON. Yes, so his confidence is shattered.

Dr. ALFANO. No, it is not.

Senator NELSON. There are tens of thousands of patients who go into hospitals and get a drug and go back to a doctor in their rural communities. The doctor has been notified that the patient is supposed to get this particular drug. He will be notified, most likely, in generic terms, that he should be getting, for example, prednisone. So the doctor will say, well, I will select Paracort. In the hospital, he got Meticorten. So he is upset. Or in the hospital, he got Wolins' generic. So he is upset. All I am asking is, what are you proving?

Dr. ALFANO. You are trying to change this around, Senator, because the patient is treated by Dr. A in the hospital and has a certain medication. He goes home, Dr. B states, I will write a prescription for you to cover what you have been taking. Here is my prescription for the same medication made by a different company. There is no confusion by the patient. They accept the fact. They have a new prescription. It is the same medication, made by a different manufacturer. There is no confusion.

Senator NELSON. So he writes a prescription and all of a sudden, the patient loses his confidence because it is a different pill. But if the doctor explains to him, you have been getting a little round yellow one.

Dr. ALFANO. The patient knows that.

Senator NELSON. I know, but now I am going to prescribe one for you and it is going to be a little round red one. Don't let that upset you.

Dr. ALFANO. If he knows it, he had better tell the patient that, because the patient will be confused if he has a different type of medication. This has happened in practice. This is not a theoretical type of problem.

Senator NELSON. I am sure it happens, and I am sure the example I have given where the patient gets a generic in the hospital and he gets a brand name back in the town where he comes from and he refuses to take it and they have to put him back in the hospital, as far as I am concerned, that proves you should have continued to give him the drug under its generic name.

Dr. ALFANO. You have turned around what I was trying to say.

Senator NELSON. Just applying the same logic to both situations.

Please proceed.

Dr. ALFANO. This same sort of thing would happen when a patient refiled a prescription and, in the meantime, the pharmacist purchased the generic drug from a different company. Also, this would happen when the patient changed drugstores.

In all cases, the extra physician visits required to reassure the patient and to reestablish the contact between the physician, patient, and the medication in use would do away with all the savings achieved by requiring the use of generic drugs.

Confidence on the part of the patient in his physician is absolutely necessary for the physician-patient relationship, and vital to the patient's response to a course of treatment. A patient who loses confidence in his physician or is not secure in the medication received does not respond to the treatment, which results in a delay in returning to full productivity.

A physician cannot adequately treat his patient if he does not have full confidence in the medication taken by the patient. The individual

physician has developed confidence and faith in a particular drug and in the manufacturer over a period of time. Experience with a drug which consistently produces the desired effect results in confidence. No amount of advertising in journals, by mail, at conventions, or persuasion by the detailman can short circuit the process of developing confidence in a particular drug.

The pharmaceutical firms know that confidence on the part of the physician is essential for the existence of the company. As a result, these firms are constantly striving to produce quality medications and to improve their methods of production. A bad result with a drug or misleading information cutting corners, or a bad batch of a particular medication can be disastrous for a pharamaceutical firm. Each proprietary company is identified with every one of its brand-named drugs and puts its reputation on the line with each and every package that leaves the plant.

A generic drug is anonymous. By inspection there is no way of telling what the drug is, let alone the manufacturer. The generic drug firm if it so desires can cut corners and if a bad result occurs, the attention is not focused on the manufacturer. There is no need for the generic firms to gain the confidence of the medical profession because there is no way of identifying the drugs produced with the generic firm. Once there is product identification, the company is a brand-named firm and must have the confidence of the medical profession.

Senator NELSON. Let me ask a question here.

Again, what we seek to get in the evidence here—and we ask about this constantly—is what are the examples of adequacy or inadequacy of the generic drug versus brand name? We have been asking that for 2 years and really have not been getting any adequate answers. We get the assertion that you can't trust generics, you have to have confidence, you have to stick to the brand name company. But, we just do not get any real evidence that this is, in fact, so.

Dr. ALFANO. As I stated, I will send that report on oxytetracycline that has come out.

(Material not received.)

Senator NELSON. Committee counsel tells me that that would not quite fit the circumstance, because that drug is only produced by one company, Pfizer.

Dr. ALFANO. I do not have the report. I cannot go discussing it.

Senator NELSON. Is this Terramycin? If it is Terramycin, it is under patent to be produced by one company.

Dr. ALFANO. As I have said, I do not have it, and I could not come up with the answers.

But you could just, on chloramphenicol, have one product and show that—as far as I know, there has been evidence to show that the generic product was not therapeutically equivalent to the trade name product.

Senator NELSON. The FDA testified that that is not the case. I asked Dr. Ley who was here just last week. I asked him if FDA had any evidence that there was any difference in the therapeutic equivalency of the chloramphenicol they took off the market? He said there is no such evidence. They achieved a different blood level at a different period of time. That is all.

Dr. ALFANO. What was that period of time?

Senator NELSON. It is in part 6 of our hearings. All I am saying is that there is no evidence that Dr. Ley knows about, and I guess he would know it, because they have asked us about every single brand of drugs—but they wanted to achieve the same blood level over the same period. So they set that standard.

Dr. ALFANO. Was there any blood level?

Senator NELSON. Oh, yes.

Dr. ALFANO. I saw that thing in a generic product just in dissolving it. Over a half hour, it never dissolved.

Senator NELSON. We have that both ways. We have as many brand names that do those things as generics. As I said, according to the only test we have had on potency that is big, the brand name companies did not meet the standards of the generics.

Dr. ALFANO. I am saying here, Senator, once a generic name is identified, a generic drug is identified with a manufacturer, then it is essentially a brand name. It is identified. There is knowledge of this. I am not saying that the generic drugs are not worthy of being used or that type of thing.

Senator NELSON. As I am sure you know, a number of purely generic manufacturers manufacture compounds for the brand name companies. One of the distinguished companies is Strong, Cobb & Arner. Many brand name companies buy from Strong, Cobb & Arner.

Dr. ALFANO. Oh, yes, but while they have no name of manufacturer as to source, there is a question mark as far as the medical profession is concerned, and there should be.

Senator NELSON. All I am saying is that you hear the flat assertion all the time that brand names are better and yet the only test to date says that generics are better.

Dr. ALFANO. I am only saying that generics with a known manufacturer is a brand name. They do not have identification as you do with an ethical pharmaceutical firm. There are ways of identifying them with name, initials, and so forth.

Senator NELSON. I assume the pharmacist knows whether it is Lannett, American Pharmical or Merck or anything else. He knows. There it is. It is a little label on his jar, manufactured by this company. The tablets, except for one company, are not identified. The identity code is only used, so far as I know, by one company.

All I say is we continue to hear these assertions from the people who come before us, but when I ask for examples, I do not get them.

For example, let us take a recent case. This involves Parke, Davis. Have you heard of the *Tinnerholm* case involving Parke, Davis & Co., a 1968 case which involved a brand-named vaccine, sold under the name of Quadrigen by Parke, Davis & Co. In 1968, the Court said:

> Evidence in action against manufacturer of vaccine for damages resulting from infant's having been injected with vaccine by physician established that vaccine was defective and that defect was proximate cause of infant's injuries. Since that time he has been retarded in his mental development, being classified in the imbecile-idiot range.
>
> . . . evidence established that there existed sufficient number of both unrealistic and conflicting reports from field to have required manufacturer to take serious second look at its product before placing it on the market.

Then, in another case, the Court said:

Of the severe reactions reported, the first apparent instance in which death resulted was in March of 1959. It does not appear that Parke, Davis made any effort to determine the cause of the high incidence of reactions, and only a cursory attempt was made to investigate the cause of a death attributed to the use of Quadrigen.

This is just one brand name. We do not have such cases on a generic company. Were you aware of these cases?

Dr. ALFANO. No, Senator, I was not aware of that.

Senator NELSON. This raises an interesting example, Doctor. I will wager that hardly anybody in the medical profession is aware of these cases. But if this had been a generic company, you would have seen the Pharmaceutical Manufacturers Association grind out a load of propaganda attacking generics, reciting the deaths which resulted, saying it was a generic company, you cannot trust them, and all of the medical journals in the country would have run their stories. Because every time you make an attack like that, they get publicity. The case of chloramphenicol is an example.

So you have an interesting case here of a distinguished brand name manufacturer. Nobody knows about these cases. Because you can bet your hat that the Pharmaceutical Manufacturers Association did not spend money to notify the medical journals, and the medical journals have a tendency, from my reading of them in general—some of them much worse than others—to more or less ignore such things when it involves a brand name company that advertises in the journal. I think these are interesting cases and I shall put them into the record at the end of today's proceedings.[1]

Dr. ALFANO. I believe the example of Parke, Davis, when it was known that chloramphenicol or Chloromycetin caused aplastic anemia, I believe the record shows that the medical profession reacted to the bad result or this complication of the drug. Their sales dropped off. It was reported that way. You will probably find that the medical profession does not depend on outside agencies to get this type of information. The American Medical Association, I am sure, will list this result.

Senator NELSON. On this I think you will find there is an interesting relationship. Part of the committee consideration here is to ascertain the relationship between the medical profession and the manufacturers. What I am saying is that they would have ground out the story in big press releases and announcements and all the medical journals would carry it, attacking and saying, here is another example why you can't trust a drug under its generic name. The doctor reads that and says, oh, oh, you have to stick with the brand name. This is a fantastic propaganda machine.

Dr. ALFANO. I do not believe a doctor chooses on that basis, really. At least, I hope not. Otherwise, we are in trouble in this country.

Senator NELSON. You mentioned the case of chloramphenicol. I believe that was the most tragic case of misprescribing of drugs probably in modern history. But the organized medical profession did not make a point of informing its members—those who were misprescribing. This committee conducted extensive hearings, and because of the vast publicity and the lawsuits started around this country, the

[1] See information beginning at p. 4558, infra.

use of chloramphenicol dropped after our hearings. In the year 1968, it dropped from 40 million grams prescribed down to about 20.

But the testimony before this committee by distinguished doctors and pharmacologists and authorities in the field is that about 90 to 99 percent of the patients receiving chloramphenicol are receiving it for nonindicated cases, an incredible number.

Dr. ALFANO. Ninety to 99 percent, is that?

Senator NELSON. One of the witnesses testified that in his judgment, less than 1 percent of the people getting chloramphenicol are getting it for indicated cases and that of every death he had ever seen from chloramphenicol, not one had received it for an indicated case.

Dr. Dameshek, the distinguished hematologist who has written for the AMA on this question, testified that perhaps about 10 percent received it for indicated cases.

Our files are filled with letters, two more last week—I get some every week—of cases of doctors prescribing chloramphenicol for nonindicated cases—acne, infected gums, flu, sore throat—the last one, a woman died from getting it for flu—hangnails, all kinds of things.

How did it get that way? It got that way by some fantastic promotion in the medical journals in this country. That is what misled physicians. They did not correct it.

Dr. ALFANO. I have never seen it advertised for hangnail or flu or acne or that type of thing.

Senator NELSON. No; it is just advertised—Chloromycetin, when it counts. Very cleverly over the years, it has been promoted—at least it ends up this way—for use as a broad-spectrum antibiotic for all kinds of things. I do not think the doctors promoted it. I think it is the company's promotion that was effective through their detail men, through their advertising, through their promotion.

Or maybe somebody else has an explanation. The medical profession did not reform itself. The reduction in use has come about from the broad publicity this committee is getting.

Last week, Dr. Ley testified that still about 90 percent of the patients are getting it for nonindicated cases.

Dr. ALFANO. I am glad the committee has had a beneficial effect, but I believe we should not condemn the pharmaceutical industry or the PMA. I think it is a function of the medical societies, the medical organizations, to improve their continuing education programs. I believe you, through the committee, have probably functions in that regard. I do not believe you can condemn advertising per se as the cause of a problem that exists probably based on something else.

I am involved in continuing surgical education and there is a problem as far as stimulating the individuals to participate in courses and methods of instruction.

Senator NELSON. Well, what responsibility does the profession have? The fact is known. The medical journals, I suppost all of them—I do not know whether I have seen an ad in your journal on Chloromycetin, but I assume you have had them. I have seen them in all kinds of medical journals, including the AMA journal.

Dr. ALFANO. It is a good drug.

Senator NELSON. Yes, but the indication is——

Dr. ALFANO. It has uses.

Senator NELSON. But the indications are very, very limited.

Dr. ALFANO. I know, but when you do use it as a lifesaving drug, you have nothing else to use. This is it.

Senator NELSON. As you probably know, the National Academy of Sciences has said it is not the drug of choice for any case. But indications have been that it is only to be used if the disease is serious, if no other drug will do the job, and only if the disease will respond, the organism causing the disease will respond to this drug. But that is not the way it has been used.

The AMA itself is aware that 90 percent of the people are getting it for nonindicated cases and they still accept big drug ads promoting the drug. You would think the AMA would require them to put a big box in the ad saying, "This is being widely misprescribed," that they would run headline stories saying, "Doctors are misprescribing this drug and killing people with it"—would you not? Or else refuse to take the ads on the ground that the promotion has resulted in the misuse of the drug. What's the answer there?

Dr. ALFANO. I don't believe they have substantiated these claims by individuals and when they have, the medical profession will do something. I don't believe they have gotten it down to that, that only 10 percent of the cases are prescribed right. This has not been proved.

Senator NELSON. That is true.

Dr. ALFANO. I am not aware that the medical profession is—but it should be working toward that end—coming up with the facts as far as they can to determine which way they should act concerning certain drugs.

Senator NELSON. Five of our witnesses, doctors, stated that it was their guess, their best guess, that it was about this way, based upon what they have seen, each of them having a wide experience with the drug.

Dr. ALFANO. No, Dr. Dameshek; he is a hematologist. He would have the end result of a complication, not a wide use of that particular drug in his patients. I do not believe he would use it at all.

Senator NELSON. When he sees a patient and 90 percent of them got the drug for nonindicated cases——

Dr. ALFANO. That is retrospect, also. There is another problem in there. Looking back, you can get 10 doctors, a hundred doctors, you will not find they all agree 100 percent as to the course of treatment, type of drugs. Medicine has considerable variation in treatment and methods of treatment. You can have experts all disagreeing.

Senator NELSON. That is correct. But when you get one of them testifying that in every death he had seen from aplastic anemia, not a single patient had received it for an indicated case—if you see all five of them testify along the same line, so they conclude as they look at people with aplastic anemia that if nine out of 10 of them are getting it for a nonindicated case, that might give you a pretty good guess that where nine out of 10 people did get it for a nonindicated case, they just didn't get aplastic anemia.

Dr. ALFANO. No, I would not say you can project it that way on just a small sampling of indications. At least, I would not accept it that way.

Senator NELSON. Please go ahead.

Dr. ALFANO. Awareness of the name of a manufacturer by the physician and indeed by the patient is in the best interests of the public. The manufacturer must produce a drug of the highest quality

possible because he knows that an inferior batch of one drug will adversely affect his entire line of products. He must protect his reputation as does any other manufacturer. In fact, the drug manufacturer is more vulnerable than other manufacturers because the word travels fast throughout the medical profession when something goes wrong. This is certainly in the best interest of the public.

I would like to point out that the pharmaceutical firms provide services for the patients and medical profession which are essential for proper medical care. Generic drug firms do not provide these services.

A vital and indispensable service offered by the ethical pharmaceutical firms is a medical department available 24 hours a day every day of the year. If a physician finds he has an untoward reaction caused by a particular medication he can call upon the medical department for assistance and advice. When a drug does not seem to have the desired effect the medical department is available to help solve the problem. It must be remembered that the medical department has accumulated the reports of physicians from all section of the country representing the sum total of millions of doses for each medication. How can we overlook the importance of this one particular service for the sick of our country. We must not gloss over this service by stating we know and appreciate the contributions made by the pharmaceutical firms but comparisons show that the generic drugs are cheaper for the most part and therefore the patient has been gouged by the brand name drug firm. This price differential would not be as great if the generic drug firms offered the services of a medical department.

I don't believe that this committee or the American public would tolerate the loss of the services of the medical departments of the ethical pharmaceutical firms. Indeed, this committee should insist that the generic drug firms provide the services of a medical department similar to the services provided over the years by the medical departments of the proprietary drug firms.

The medical department is only one of many services provided by the pharamaceutical firms and these services cost money which is reflected in the cost of drugs.

Another example is the professional relations department which will respond to a wide variety of requests made by the individual physician.

Pharmaceutical firms are always ready to supply a rare drug or a drug in short supply for a single patient. A simple telephone call by a physician starts in motion the mechanism to bring to a patient the required lifesaving drug. The cost in man-hours expended for the benefit of one patient plus the other costs involved are not recovered by the drug firms. It is a service.

Senator NELSON. Doctor, let me interrupt for one moment. It is all included in the cost of production like any other overhead cost. They put it in the price of the drug. It is a cost of operation, just as an advertisement is a cost of operation. They recover it from the drugs all right, otherwise it would not be the highest profit industry in this country.

Dr. ALFANO. I know, but it is a service to the patient. The generic firms do not offer this to the doctor or the patient.

Senator NELSON. I just want to say it is included in the cost of the drug.

Dr. ALFANO. Oh, sure, this accounts for part of the cost of the drug, right.

Senator NELSON. Of course.

Dr. ALFANO. A detail man is more than a salesman. In my area most of these men are registered pharmacists. The detail man provides the physician with information on new products plus a review of established drugs.

True, he endeavors to have the physician use his firm's products. It's logical because without sales the firm would go out of existence. However, the detail man's first job is to inform the physician about the drug, how it works, the side effects, and contraindications.

He must provide the research reports and reprints of clinical trials of the drug, answer questions and supply or obtain whatever additional data the doctor may desire.

A drug detail man is more than salesman, he is a professional who is well informed about drugs. A liaison between his firm and the individual physician, he is the man turned to by the hospital, the pharmacist, and the physician to obtain whatever is required either in drug information or services.

Research at the rate of more than a million dollars a day is carried on by the pharmaceutical firms. Naturally, each company strives to come up with a product which will return the money spent for research. But this does not happen with predicted regularity. But all this is not lost because both the positive and negative results contribute to mankind.

Pharmaceutical firms support continuing medical education. They support postgraduate programs by grants to pay for emminent speakers. The firms do not require that their products be mentioned or discussed in the post graduate programs. In fact, they made a point of stating that all they desire is a credit line indicating the company is sponsoring the program in part.

They support continuing medical education because they know it is vital for the medical profession and the public. Certainly they are aware that a better informed profession will result in benefits to the entire pharmaceutical industry.

The pharmaceutical firms provide almost unlimited quantities of new drugs to clinical investigators in order to determine the effectiveness and safety of the new product. Financial support is given to carry out the clinical trials of a new drug which entails the keeping of extensive records, almost constant laboratory examinations and close observation of the patient.

After a drug has successfully passed the clinical trials, the drug firms support scientific exhibits which present the results of the clinical trials. It is in the interest of the pharmaceutical firm to support a scientific exhibit which is centered around one of its products. However, a scientific exhibit is an excellent method of making known to the profession the existence of a new drug. Scientific exhibits use the generic name of drugs in the display material and mention the trade name and the manufacturer as a footnote. Most important, the physician who participated in the clinical trials is available at the booth to answer questions and to add whatever additional explanation may be needed. The scientific exhibit's purpose is to make known the existence of a new drug and the results of the drug with patients during clinical trials.

Without scientific exhibits, published reports and reprints the benefits of a new drug could possibly take years before it reached the members of the medical profession, and also their patients.

If the generic firms provided these services there would be little difference in prices between the generic drugs and the proprietary drugs.

Senator NELSON. May I interrupt a moment? I raise the question again of how you can assert that with confidence? If so, how can you explain that Schering can sell its drugs for $1.20 a hundred to New York City and sell it for $4.25 a hundred in Berne, Switzerland, but stayed in the marketplace until after these hearings at $17.90 a hundred? Why were they not selling it here at less than the price at which they were selling it in Berne, Switzerland. You say they have to have these prices in order to do all these services. Why do they not have to have that price when they sell to New York City, Defense Supply, or Berne, Switzerland?

Dr. ALFANO. As I said before, I cannot explain these extremes. I am talking about the average, the usual that is going on in medicine, not specifically isolated types of examples or a handful or whatever number of examples are available.This does not occur throughout the entire industry.

Senator NELSON. Every single brand name drug that was patented has the same time—17 years. Every company sells it cheaper to New York City by far, than they do in the marketplace.

Dr. ALFANO. What I am saying is, there is a difference. The cost is increased by these services. I am not trying to justify an extreme cost by these particular types of services. These services are provided by the ethical pharmaceutical firms and not provided by the generic firms.

Senator NELSON. But this is continually asserted by the manufacturers as the reason for their prices. All I point out is they get a patent. That is the only protection they are entitled to. Nobody else in America who gets anything patented is able to stay in the retail marketplace once the patent runs out at an exorbitantly high price. For example, you have invented a new lawnmower, you are selling it at a high price because the patent has been in effect and it is a good lawnmower. Then the patent runs out. You can't get by in the marketplace selling it in competition with other lawnmowers, because the consumer can make a judgment that another one is just as good at a cheaper price. But the consumer cannot make the same judgment on drugs. The drug companies know he cannot. The purchaser for New York City or the Defense Supply Agency, or the Veterans' Administration, that buyer can make the judgment and he does. And the drug company dramatically drops its price.

So on the same day they are charging 30 times as much to the pharmacist, they are offering it for one-thirtieth as much because they know they have to compete with other brand names and the generics. In the retail marketplace, however, the buyer is not qualified to make any distinction at all. The doctor writes a brand name. He prescribes and the buyer, the patient, pays.

These great discrepancies apply to all the drugs that I have looked at. Everybody comes in with the assertion that they have to have this price because they do all these services, but nobody ever explains how

they can make a profit of $1.20 and make a profit in Berne, Switzerland, of one-fourth as much.

I just say to you, Doctor, and I do not want to be unfair to you because a number of other witnesses have said the same thing—I just say that in my judgment, your statement is not supported by the facts and what you are repeating is what the pharmaceutical manufacturers have been saying year after year. Most of the medical profession also has been saying this. Most of the medical profession has never heard what the industry charges in New York City or in Switzerland and London and Rome. We have checked all these cities. The physicians do not know what is being done over there. If they did, I think they would say to the companies, how do you explain that you are selling it cheaper, one-fourth as much, in another country and my patient has to pay four times as much?

I have never heard a doctor say that. I know why. He has not heard about it. But he has heard from the company at the rate of $4,000 or $5,000 advertising each year to each physician. So the company has convinced the physician.

What you are saying to me—and I am not critical of you for it—is what nine out of 10 doctors say to me when they talk to me across the country. I had a meeting in Wisconsin with four doctors. One of them started to say to me, here's the reason why the firms have to charge more.

I said, you just hold that for a minute, and I called another doctor aside and said, here is what he is going to tell me, and I lined up all the arguments by the pharmaceutical industry. And we went back to the group and the doctor told me every one of these items. Because that is what he has heard from PMA. The evidence supports that every single one of the doctors and the pharmaceutical manufacturers said the same thing.

Dr. ALFANO. I am telling you what I say did not come from the PMA. About 2 years ago, I wrote to the pharmaceutical firms asking for the services provided by these companies. If you wish, I could send a couple of suitcases of material down to you. This is what I got from being in the practice and being exposed to the services provided. I do not believe I have anything in here that comes from the pharmaceutical manufacturers, at least that I received and put into this statement.

Senator NELSON. I believe that a number of my good friends make the same argument. I am not saying there is anything illegal about that. I am just saying that the manufacturers have made what to the doctors have been a compelling, convincing case and the doctors believe it. All I say is I do not think the doctors know the whole story, because when I have asked the doctors about these prices, they have never heard it before. They can't explain it. But the record can't stand without having these examples saying, why can they sell in Berne, Switzerland at $4.50 and sell here at $17.90. I call that gouging.

Dr. ALFANO. Have the companies not been in to explain the differences in costs?

Senator NELSON. Yes; when I asked Mr. Conzen—I had the whole list of foreign prices—he said, they charge less in Berne, Switzerland, because the standard of living is lower over there. But they charge more in Mexico City by three times than in Berne, Switzerland. When

I asked him about that, he said he did not know the answer and he would have to ask the comptroller of the company. I said you ask him and write me. That is a year ago and I have not heard.

Dr. ALFANO. I do not believe the medical profession can answer these questions of cost and the differences, really. However, I have more faith in myself and my colleagues, that they will not knowingly write prescriptions for a high-priced drug when they know full well that there is an available drug that will do the job and cost a lot less.

Senator NELSON. I am confident of that. I think the medical profession is a profession of integrity, but they do not know these facts. That is the problem. So when the spokesmen of the medical profession say the drug companies do all these very fine things and the generic companies do not, therefore that shows the price differential——

Dr. ALFANO. It accounts for a proportion of that price. The price can't be equal when one is providing certain services and another is not. There have to be differences. What the difference is, I could not give you. That I do not know.

Senator NELSON. But to make this unqualified defense all the time of the industry, not being able to explain—as a matter of fact, not knowing—that the company they are defending is selling at one-twentieth the price to New York City and the Veterans' Administration, and one-quarter the price in Berne, Switzerland—I am just saying this argument does not hold water because they are charging a fraction of that price in other parts of the world and in the Defense Supply Agency.

I see I have a rollcall vote. I will try to be back in a couple of minutes.

(Short recess.)

Senator NELSON. Please forgive me, Doctor. Will you proceed?

Dr. ALFANO. A compendium which lists all prescription drugs under their generic names together with all the necessary prescribing information and a supplement of the brand names, the suppliers and the prices at which the drugs are available at first seems to be a laudable endeavor. As I understand it, the compendium would list 7,000 drugs with 21,000 dosage forms. This type of listing would not be practical since it could not be easily used by the prescribing physician. For example, the PDR contains about 600 drugs and is more than 2 inches thick; the compendium would contain almost eight times the number of drugs listed in PDR and would be at least 16 inches high. Even if special paper were used the book would be 15 inches high because it would contain 10,000 to 12,000 pages. The compendium would not be used and the PDR would continue to be used by the busy physician.

Why is it necessary to list all of the 7,000 prescription drugs when in reality physicians are in the habit of using a small number of drugs. When it becomes necessary to prescribe an infrequently used drug, the physician can obtain the required information from the appropriate reference material.

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

Dr. ALFANO. Yes.

Mr. GORDON. You are a surgeon?

Dr. ALFANO. Yes.

Mr. GORDON. Can you give us an idea of the number of drugs, on the average, the abdominal surgeon prescribes in a year?

Dr. ALFANO. The number of drugs?
Mr. GORDON. Number of different drugs.
Dr. ALFANO. No; I could not. I have actually been out of practice the last 6 or 7 years, so I could not give it to you right from actual experience now.
Mr. GORDON. Could you give us an idea?
Dr. ALFANO. A surgeon uses less drugs than, say, an internist or a general practitioner.
Mr. GORDON. Would you say about 25 or ——
Dr. ALFANO. Well, about 25 would be a reasonable number that are constantly being used—pain medications, infection, control of infection, that type of thing.
Mr. GORDON. I see. Around 25.
Dr. ALFANO. I could be way off on that. I am guessing, really.
Mr. GORDON. What would be his principal source of information about toxic and dangerous properties of a new drug?
Dr. ALFANO. On a new drug that he is using now?
Mr. GORDON. Yes.
Dr. ALFANO. We have had a survey in the past on why does a physician, why does one of our members use a particular drug? What causes him to use that particular drug? Twenty-three percent stated an article in the journal was the No. 1 reason they used——
Senator NELSON. You are talking about surgeons?
Dr. ALFANO. Members of the American Society of Abdominal Surgeons, right.
Senator NELSON. You are talking about your journal, or all articles in——
Dr. ALFANO. No, no; any medical journal.
Senator NELSON. Twenty-three percent, did you say?
Dr. ALFANO. Twenty-three percent; yes, sir.
Mr. GORDON. How about the rest?
Dr. ALFANO. I have that, I am pretty sure. Do you want to know what influences a physician to use a particular drug?
Mr. GORDON. No; the surgeons.
Dr. ALFANO. The surgeons; yes. This was a survey sent to members of the American Society of Abdominal Surgeons.
Senator NELSON. How many do you have?
Dr. ALFANO. 9,000.
Senator NELSON. How many responded? 9,000 responded?
Dr. ALFANO. No. The questionnaire was sent to 1,500 surgeons and a total of 20.53 percent of the surgeons responded and completed the questionnaire.
Senator NELSON. When was the survey conducted?
Dr. ALFANO. 1964.
Senator NELSON. And what other sources did they use?
Dr. ALFANO. Presentation at a medical meeting—at a meeting. It does not say medical meeting—presentation at a meeting, 19.8 percent. The detail man, 19.6 percent. Exhibits at a meeting, 11.6 percent. Recommendations from a colleague, 11.5 percent. Journal advertisement, 7 percent.
Senator NELSON. Advertisement in a——
Dr. ALFANO. In a journal.

Senator NELSON. Medical journals in general, you are talking about?

Dr. ALFANO. Yes; because a surgeon would get, say, the Journal of the American Medical Association.

Mr. GORDON. What percentage is that?

Dr. ALFANO. Seven percent. Advertising sent by mail, 4.6 percent. Miscellaneous, 2.5 percent. That first figure, journal article, exactly is 23.4 percent.

Senator NELSON. This was a survey as to where they got their information or began to use a new drug, is that what you are talking about?

Dr. ALFANO. Yes; the factors that influenced them to use a particular preparation, what caused them to use this particular preparation, brand new, the first time they used it.

Mr. GORDON. What percentage did you get for detail men?

Dr. ALFANO. 19.6.

Mr. GORDON. And the percentage of those learning from colleagues?

Dr. ALFANO. 11.5 percent.

Mr. GORDON. It could be, of course, that the colleague could well have secured his information from, say, the detail men or advertising or a journal. We just do not know. That does not mean too much, really.

Dr. ALFANO. No, no, but this is—that is right, the colleague has to get the information originally from some particular spot. I would say it probably follows the same, though it would be a journal article or a presentation at a meeting or a detail man.

Senator NELSON. Please continue.

Dr. ALFANO. I suppose if a smaller listing of prescription drugs was undertaken it would be a duplication of the PDR and would serve no additional purpose but would create the problem of what drugs to list and who would make the selection.

It appears that the American Medical Association's drug evaluations currently being developed would serve the purpose of the medical profession because it would include the 500 most commonly prescribed drugs. It also would give a comparison of drugs within the same class.

Information on the pharmacology of the drugs would be included in the AMA publication much of which is lacking in the package inserts. The proposed compendium would lack the pharmacology necessary to knowing all about a drug since the compendium, as I understand it, would be made up of the package inserts.

Senator NELSON. We have had some testimony on the concept of a compendium. We have introduced legislation, but as to what the nature or makeup of a practical compendium would be, we have not really gone into it in any depth, nor have we received the advice of all the appropriate sources, the medical profession and organizations and the manufacturers and so forth. So I would guess when we have hearings on a compendium, if such a bill were recommended by the committee, it would be one that was developed as a consequence of testimony from a broad number of authoritative sources. As to whether it would be package inserts or something else, I do not know and I would not want to form a firm opinion until I listened to the appropriate experts in the field.

Dr. ALFANO. If it is the intent of the compendium to bring before

the physician a list of the generic drugs and a price comparison then this could be done by a supplement to the AMA drug evaluations.

However, if the intent of the compendium is to change the prescribing habits of the medical profession then I don't believe that this can be accomplished by the compendium.

The chairman of the Monopoly Subcommittee stated in invitation to speak before the committee that some witnesses have expressed concern about the dependence of medical organizations upon funds derived from the drug industry. I can speak for the American Society of Abominal Surgeons and state that the society does not depend upon funds from the drug industry. The society can function without any outside help.

In 1961 drug advertising accounted for 7 percent of the cost of publishing the Journal of Abdominal Surgery. In 1962 it was 8 percent; 1963, 17 percent; 1964, 21 percent; 1965, 28 percent; 1966, 49 percent; 1967, 61 percent; 1968, 41 percent.

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

Dr. ALFANO. Yes.

Senator NELSON. When was the journal founded?

Dr. ALFANO. The first issue was February of 1959.

Senator NELSON. We have the percentage figures here supplied by the Legislative Reference Division of the Library of Congress.[1] Do you have the dollar figures?

Dr. ALFANO. Yes.

Senator NELSON. That is, the dollar figures of advertising?

Dr. ALFANO. I have the net advertising income.

Senator NELSON. What does that mean?

Dr. ALFANO. That means the advertising income—for example, in 1961, it was $5,533 of advertising income. Subtracted was the commissions that went to the advertising agency plus our own space representative who gets a commission.

Senator NELSON. So the figures you are going to give us now are the net, not the gross?

Dr. ALFANO. Not the gross, billing, yes. For example, 1961, it was $5,533 as a gross. The net was $2,846.

Senator NELSON. Could you give them to us for each year?

Dr. ALFANO. Yes. 1961, $2,646; 1962, $3,520; 1963, $8,657; 1964, $10,592; 1965, $15,214; 1966, $41,941; 1967, $55,734; 1968, $42,138.

Senator NELSON. What was the figure for 1967?

Dr. ALFANO. $55,734.

Senator NELSON. Now, were these all net figures?

Dr. ALFANO. Those are the net figures, yes.

Senator NELSON. I see.

Mr. GORDON. What percentage of your total income would that be?

Dr. ALFANO. That is what I have over here—no, that was the percentage of the cost of publishing the journal. I do not have the percentage of the total income that I can give you. I gave you—these figures are the percentage of the total cost of publishing the journal. For example, 1968, the cost of publishing the journal was $103,850; that $41,000 represents 41 percent.

[1] See Appendix XIII, "A Study of Pharmaceutical Advertising in Selected Medical Journals," pp. 4863–4998, infra.

Senator NELSON. Of the cost of publication?
Dr. ALFANO. Right.
Senator NELSON. I see.
Then what's the other income from, subscriptions?
Dr. ALFANO. Yes.
Senator NELSON. Do these two factors constitute the total income, subscriptions and advertising?
Dr. ALFANO. Yes, subscriptions, advertising, and there is a small amount from reprints of articles that are published in the journal. An author may wish to have a hundred or a thousand reprints, whatever he desires. There is a cost for that.
The income from drug advertising allows a publication to publish more articles per issue and special features which benefits the profession and the public. For example, I would like to have more advertising income in order to develop a monthly feature on surgical anatomy and surgical technique. This is a very expensive endeavor since it requires the talents of medical artists and surgical anatomists. I hope that all will agree that this is a worthwhile endeavor.
Mr. GORDON. Doctor, may I interrupt? When you say you would like to have more drug advertising to publish more articles, what you are really saying is you would like to have the public, the drug-consuming public, pay for this. Surgeons do very well financially. Why should they not pay through higher membership rates or higher subscription rates?
Dr. ALFANO. Well, I have not tried that system. You mean assess the individuals who receive the journal higher amount?
Mr. GORDON. When you say you want more advertising, you are really saying that you want the consuming public to pay for it.
Dr. ALFANO. Well, the public, I am hoping, are the ones who benefit from the results of the journal, or from the journal itself. They are the ultimate ones to benefit from it.
Mr. GORDON. But it is pretty indirect.
Senator NELSON. Please continue.
Dr. ALFANO. A medical publication does not come in contact with the drug companies who advertise in the publication or the drug companies who are potential advertisers. A medical journal has a space representative who contacts the advertising agencies representing the drug companies. Thus, there are two independent companies between the medical journal and the drug company.
The men and women engaged in medical publications have earned the respect and trust of their readers and that is really what counts regardless of what some outsiders may say in an attempt to undermine the integrity of medical publications and the sponsoring medical societies.
Senator NELSON. In any event, does not the fact that a medical journal—any medical journal—that depends in substantial part on advertising by a drug firm, does it not really end up having, even unconsciously, a subtle effect upon the position the journal might take on the kind of promotion that is in the ad, or criticism of the industry itself? The publication is relying—it does not make any difference whether it is a medical publication or newspapers or what have you, when they receive substantial moneys from an important advertiser, is it not just potentially inherent in the case that they are going to be

quite reluctant to be very critical of the one who is supplying the money that is important to the publication?

Dr. ALFANO. I do not believe so. Not in medicine, sir. You can probably find it in other types of advertising, but in medicine, if there is a just criticism of the drug company or the entire industry, that criticism will be made regardless of the number of advertisers in the journal. Because this industry that is limited to 350,000 doctors; therefore, the profession is not a captive of the individual drug companies or the industry. If there is a valid justified criticism, I believe every medical journal and every society would make it known and would not hesitate because they have advertising or money coming in because of ads in their particular journal.

I would never be afraid to put anything in the journal criticizing the drug industry. If I have something that is valid, I will put it in.

Senator NELSON. Well, is it not just human nature, the nature of human beings, whether it is medical publication or any other, that if an important source of money is coming from a particular place, it creates a potential bias. It could be conscious or unconscious.

I read some of these publications. I am not referring to yours—I have not read it, so I do not direct this at you at all. But I read quite a few of the publications that rely heavily upon drug company advertising. Sometimes I cannot quite identify the hearing they are talking about because of the bias they put into the stories. Actually they are these hearings. If you just look at them regularly, you will find a lot of bias in favor of the company. I suppose that is just natural.

If that publication is critical and tough on an advertiser, who they think is doing something wrong, that advertiser is likely not to spend any money with them. I do not see how that is avoidable.

So it just seems to me that medical journals and medical publications are compromised by the substantial amount of money that they rely upon from an industry which needs independent critical evaluation from the medical profession all the time. I do not see how you avoid that.

Dr. ALFANO. Well, I believe the checks and balances—the American individual is critical. They are critical individuals. If you have an association with a publication that tries to put something over on its membership, that publication, that society will hear about it, because they have hundreds of thousands of members who are reading. They will not stand for something which they feel is not correct or proper. I do not think they can put something over on the members is what I am saying, because of money from advertising.

Senator NELSON. There is no doubt in my mind that as professions go, I am biased toward the medical profession. I was raised in a family with lots of doctors. I think there is not any profession that has a higher percentage of conscientious people in it. I think it probably has more conscientious people than any other profession because of the nature of the person who is inclined to select that profession in order to take care of the health of someone else. But that does not mean they are all perfect. We all know that. I happen to be a lawyer, but I think there is more dedication, a higher percentage of the people who are really dedicated, in the medical profession, doing good for other people, than there is in my profession, though we have a substantial number of highly dedicated people, too.

So I would not raise any question about that. I think if a publication conscientiously misrepresented or defended a bad cause in the medical field, practically all individual doctors would be very critical of it. So I am not raising that question.

I simply say that if you are a publication and you rely heavily upon an advertiser—in this case, it is drugs—you just may omit criticizing them. You do not have to mislead by commission, you can mislead by omission. I think it is true of almost every magazine or paper that relies heavily upon some industry for advertising.

I do not see tough criticisms in various publications of the major advertiser in that publication, when it is a daily newspaper. They are pretty careful. If something breaks and they have to cover the news, maybe they do.

But here is a case where the profession has the primary obligation to the public and its patients. And it is important that the profession at all times be vigorously, conscientiously evaluating all aspects of medicine, including the promotion of drugs and the use of drugs and advertising policies and claims for drugs. The fact is that there are just endless examples of the drug companies making claims for their drugs that are not acceptable to the FDA.

Dr. ALFANO. They do not appear in journals, to my knowledge, that type of ad. They cannot. The journal must have the approved information.

Senator NELSON. Counsel advises me that last year—within about the last year and a half—as a consequence of paid drug ads in publications, medical publications, the FDA required 29 "Dear Doctor" letters—in other words, 29 times in the last year and a half, because of misleading advertising, the FDA has required the company to write a letter to every single doctor in America correcting the misleading claim. That is quite a bit. But it appeared in the journals.

Dr. ALFANO. These were ads that appeared in journals?

Senator NELSON. In medical journals.

Dr. ALFANO. Excuse me, the Medical Tribune is not a medical journal.

Senator NELSON. I do not want to mislead you. Some of them were in these other publications which rely exclusively upon drug advertising.

I recognize a distinction between a publication that receives 100 percent of its money from drug advertising and one that receives 50 percent. But if they receive a large percentage, I think that they cannot really be independent and objective in the fashion they ought to be in order to protect the interests of medicine itself. Do you really?

Dr. ALFANO. I believe the scientific medical journals, journals that are published by societies, they are published by these same individuals who you state are the most dedicated group in the country. I do not believe they would be influenced one way or the other by the amount of money that comes in by an ad. If they have something valid to say in criticism of a particular company or of the industry, they would put it in.

Now, there are more than just scientific medical journals that carry the same ads. I am only speaking as far as the medical journals that are published by medical societies.

Senator NELSON. Counsel advises me that 19 of the 29 "Dear Doctor" letters were based upon ads in medical journals.

Dr. ALFANO. I know, I have seen these "Dear Doctor" letters. I have received them and some of the criticism, they are not that important as regards the patient and the result of the medication. There is a dispute between the FDA and the drug companies that I do not know that much about. But it does not seem that it makes that much difference. But these letters come out and, as you say, there were 19. But I am sure they do not affect the policy that the journal, if it is something vital, will certainly make it known in the next edition that they did publish an article that was misleading and they would make it known.

Mr. GORDON. Doctor, are you aware that certain criminal cases have been brought against drug companies for advertising in medical journals?

Dr. ALFANO. I do not believe so. Which ones are you referring to?

Mr. GORDON. Well, the criminal cases are Pree MT, Esidrix K, Esidrix, and the civil case is Enduron.

Dr. ALFANO. I do not know about those cases.

Senator NELSON. I have another rollcall and I do not want to hold you over. We are late as it is. I think this is an important question, however. As I say, I do not think it is so much a question of reputable journals misleading intentionally. I do not think they do that. But the argument remains that you might omit to do something that you ought to do—I mean broadly, any journal; because that is the nature of human beings. I find it very hard to be critical of a good personal friend of mine because I like him. I overlook defects or something wrong with somebody I like, and so do you. And you end up in a position—that is, the medical journals end up—in a position, it seems to me, where just in the nature of the case, they compromise themselves and condone some of these things that they ought not to.

Dr. ALFANO. There is no close relation between a journal and a drug company as such. As I stated, there are other individuals or companies that come between the journal and the drug company.

Senator NELSON. But the financial relationship, when it reaches a substantial amount—is a close financial relationship. And if you are depending upon that and you would like to have more advertising, or any of the rest of them would, I do not see how any publication can avoid being compromised by it. It is the nature of the animal, I think.

Dr. ALFANO. I disagree. I do not believe that this type of thing exists where they would knowingly withhold information which essentially is unethical for a medical publication or a man who is editor of a publication to withhold information. He must make known—whatever he knows must be made known to his colleagues.

Senator NELSON. I would not suggest that they willingly withhold, but maybe they fail to criticize. I think Chloromycetin is a dramatic case in point.

Now, many of the medical journals carried articles by distinguished authorities on the drug explaining and emphasizing that it is overprescribed, was being widely misprescribed, at the same time they were receiving it, carrying lots of clever advertising promoting the drug. This is a terrible case, it is a terrible indictment of those in the profession who misused the drug and the promoters of the drug. I would have a thought that every medical journal in America ought to have

front page, cover stories, and if necessary, a national meeting about it. I never saw that. It took the dramatic publicity from these hearings to do it. The medical profession should have done that.

Of course, they will say, we ran an article a few years ago. We ran one another time. But the fact is the wide misprescribing continued and the leaders of the medical profession knew it and they did not stop it.

Dr. ALFANO. These are the opinions of certain individuals. You mentioned Dr. Dameshek, that 10 percent only needed or it was necessary to use Chloromycetin. I say when this is substantiated and it is an absolute fact, you will find it in all the medical journals that *x* drug should not be used because it has more dangers than it has benefits. Until that happens, I do not believe that you should expect a journal or a society to arbitrarily take action against a particular drug, particularly the one you mentioned, which is known to be an excellent drug, with its indications.

Senator NELSON. There is not a medical organization or a leading distinguished authority in America who has doubted the drama of this situation—that it is being widely misprescribed. I have a file you could cry reading. I get letters every month. I have a file that high: "My daughter came home from college with a sore throat and got Chloromycetin and died." One from a husband last week with a 30-year old wife who had Chloromycetin for the flu and died. "My son had a hangnail and died"—"an infected gum, and died." Every single case nonindicated. Every single case.

I did not see the profession or the journals screaming to the high heavens about it. I think it is an indictment.

Dr. ALFANO. Did the profession get that information? I have not seen a letter come to our organization or the journal concerning these specific cases of misuse. However, you must remember, there are 831 million patient visits a year. Certainly there are going to be exceptions to good medical care out of that 831 million patient visits. But I do not believe because you have some examples that you have to condemn the whole profession or the system.

Senator NELSON. But when you have distinguished authorities saying in their judgment, 90 percent is for nonindicated cases, one of them saying 99 percent in his judgment, nobody is refuting it. Maybe it is only 85 percent, maybe it is 95, but it is terribly high. And these publications all take ads.

Dr. ALFANO. It may be 89 percent in his case, it may be 1 percent to someone in practice out in the suburbs. I do not know what those figures are.

Senator NELSON. There are certainly a number of doctors who never misprescribe at all. We know that. But this figure is awfully big and it dropped by half when the hearings started.

I have imposed on you enough and I appreciate very much your taking the time to come. I do not want to have you come back again. I thank you for your willingness to testify today.

I will be back in about 10 minutes.

(Short recess.)

Senator NELSON. Dr. Krantz, I am sorry we have had some interruptions. The Senate would be a lot better place if I were running it, but I am not.

Our next witness is Dr. John C. Krantz, Jr., of Huntingdon Research Center, Inc., in Baltimore. Dr. Krantz is a professor emeritus of the Department of Pharmacology at the University of Maryland.

Go ahead, Doctor. We are very pleased to have you here today and we apologize for being delayed so long in getting to your testimony.

STATEMENT OF JOHN C. KRANTZ, JR., PH. D., HUNTINGDON RESEARCH CENTER, INC., BALTIMORE, MD.

Dr. KRANTZ. Senator, Mr. Counsel, every animal is capable of a cry characteristic of its species; man alone speaks. All along the tortuous road of ascent, articulate speech has been the sharp line of distinction between man and other primates. Speech gave him a history, speech enabled him to transmit knowledge, and speech has marched with a fidelity that is unwavering in the vanguard of advancing civilization.

But when speech or any form of communication is unclear it may serve as the source of misunderstanding and mischief. In medicine, with the prescribing of drugs, it can be the difference between the "quick and the dead." St. Paul, in his letter to the Church in Corinth, gave us the word, "Except ye utter by the tongue words easy to be understood, how shall it be known what is spoken? For ye shall speak into the air."

This thesis is a plea for simplicity in the nomenclature of drugs. I have been advocating this principle for four decades. Its first target was the preposterous use of the Latin titles in the official compendia and on prescriptions. I have witnessed the complete demise of this anachronism.

For three decades I taught pharmacology to medical students in the School of Medicine in the University of Maryland. It was extraordinarily difficult to have the student become familiar with two names and sometimes three or four for the same drug. It was more difficult to explain to an intelligent person why this cumbersome and confusing practice existed. This confusion did not prevail only with the student but also with trained physicians.

My proposal is simple and would bury the so-called created generic name in the same cemetery with the Latin titles. I propose that a new drug be assigned a name by its manufacturer, approved by the FDA and/or USAN, with a suitable suffix, representing the manufacturer.

For example:

Benadryl—Parke, Davis—not diphenhydramine hydrochloride.
Dramamine—Searle—not, dimenhydramate.
Isordil—Ives—not isosorbide dinitrate.
Capla—Wallace—not mebutamate.

Such a name then becomes the only name that the drug has other than the true chemical name that may appear in small print on the label.

At the termination of the patent, other manufacturers could synthesize and market the product, using the assigned name without the originator's suffix. Thus, the names Benadryl, Dramamine, Isordil and Capla would be the equivalent of the generic name used today.

This has happened in the case of aspirin. Manufacturers are free to market aspirin but, Aspirin—Bayer has withstood the ravages of time and competition. This leaves us still with the age old problem of

"generic equivalency." The advocates of the purchase of generic named drugs, on the basis of economy, are only correct in a comparatively few cases.

1. The report of the study of this problem by the AMA asserts, "Except in a few cases, there is no economy achieved in the purchase of generic named drugs."

Senator NELSON. May I interrupt there a second?

Dr. KRANTZ. Yes.

Senator NELSON. About a year ago, two drug chains, Peoples and Gray's—I am going by memory here—I think representing about 300 drugstores, both announced that they were going to stock a line of generic drugs, that the manufacturer would be Strong, Cobb & Arner.

Dr. KRANTZ. The Cleveland company? I think it is the Cleveland company; a very fine company.

Senator NELSON. They have a good reputation, I understand. This is on price. The stores have announced that the average price of their generic drugs would be one-half the price of the brand names, on the average. So that is in direct contradiction to the AMA report.

Is this a study that the AMA did about a year ago in December?

Dr. KRANTZ. And published in their newsletters.

Senator NELSON. I am going to have to take another look at it, but I think there were some fatal defects in it. They did some buying at drugstores and then announced a price. They made purchases at the retail level and ended up by saying that they did not gain anything in price. This is very simple to explain.

Under all the laws of this country, if a doctor prescribes a generic name, the pharmacist can supply anything he wants, any brand. If he prescribes a brand name in some 40-odd States, there can be no substitution. Maybe it applies in all States now, I do not know. But I think it is 42.

Now, all that happens is that if you go to a drugstore, as the AMA, I understand did, and you ask for prednisone and the store is only carrying meticorten, you pay the same price as if you went into the store and asked for meticorten.

So I was impressed by that study of theirs, really, because I think that was a fatal defect in it.

I shall look at the record and be sure I am not mistaken in what I state here. If I am, I shall correct it.

Dr. KRANTZ. Senator, if you follow this suggestion, you will eliminate all those worries. You will not have that problem any longer.

Senator NELSON. Well, I think the suggestion made—we have had some testimony along this line of simplification, and I think the suggestion you make here is a very simple one and might very well be exactly what ought to be done.

Dr. KRANTZ. May I continue?

Senator NELSON. Yes.

Dr. KRANTZ (reading). 2. The purchase of generic-named drugs on price from manufacturers of unknown reputation involves the risk of an inferior or even an ineffective product. This is tantamount to throwing dice for the destiny of the patient.

Senator NELSON. Might I say there, Doctor, we mentioned Strong, Cobb & Arner. I am not qualified to make any independent judgment of my own about the quality of any product put out by any company.

Strong, Cobb & Arner, I understand, sells to many companies and, from everything I have heard, has a fine reputation.

Dr. KRANTZ. That is right.

Senator NELSON. As to your item No. 2, what risk would there be to a pharmacist who announced, as Peoples & Gray's did, that we are going to stock a brand of generics by Strong, Cobb & Arner because we know that they are a distinguished company with good quality.

Dr. KRANTZ. None whatsoever.

Senator NELSON. Thank you.

Dr. KRANTZ. You say I qualify this by stating that unknown reputation.

3. There is no substitute for integrity and pharmaceutical expertise of the manufacturer. To be sure, the originator of the product would be the most likely source of a dependable, uniformly formulated and active product.

Notice I say, most likely. To assert that skilled pharmaceutical scientists employed by reliable manufacturers cannot formulate efficacious and uniformly dependable dosage forms of medicaments is equivalent to saying that pharmacy and biopharmaceutics do not exist.

As a member of the Committee on Revision of the U.S. Pharmacopeia, I have also advocated the use of trade names in the monographs. But there are those who stated if, for example, the title Capla-Wallace were used in an official compendium, the trade mark rights would be abrogated. I have recently read the law pertaining to these matters and am of the opinion that this was an unfounded judgment. The advantages of this suggestion are as follows:

1. One name for each drug enhances safety and ease in prescribing.

If we stop right after "safety," this justification is enough for doing this.

2. The manufacturer is always identified with the product.

3. The manufacturer stands to gain by such a process of simplification by having his name or insignia attached to the only name of the drug.

Senator NELSON. Well, I would certainly agree that from the evidence we have had over the past 2 years from other distinguished witnesses, that the question of simplifying the names in identification of the drugs is an important question.

I would certainly agree with you, based upon other witnesses, like you who have testified on this question, that it ought to be done. I do not know the best way to accomplish it, I am not certain in my own mind, but I think the present system is, as you say, very cumbersome and confusing.

Well, I thank you very much.

Mr. GORDON. Do you have that list of drugs you talked about before?

Dr. KRANTZ. It is the only list I have.

Senator NELSON. Doctor, what is the significance of—I have not had a chance to study it—the document you have submitted with the list of drugs?

Dr. KRANTZ. Well, the statement was made this morning that these generic-equivalent drugs are always, or generally, the therapeutic equivalent of the trade mark item. I simply stated that a colonel from the Army—I suppose it would be their purchasing agent——

Mr. GORDON. Do you know his name?

Dr. KRANTZ. No. I do not know his name, but I have it in my records at home. It has been about a year ago since he appeared. He came and told me one day that they had purchased a number of these items by price and they had not worked well in the patients. They have not given the required therapeutic results that they expected.

So I delineated a series of tests that we could do on animals that would enable him, in turn, to be sure within a reasonable doubt that the item that he was purchasing would be tantamount to the trade mark item. At the present time, we are considering the same situation for the Maryland Hospital Association, which includes some 56 hospitals and spends roughly $13 million a year on drugs.

It is their contention that if they could buy with certainty a drug that was generically labeled instead of trade mark labeled, they may save some money.

So if we apply these tests, I think we can assure them that they are, within reason, the therapeutic equivalent.

Senator NELSON. I see no indication here of the test that was made on each of these drugs, if it was made, to determine whether it might be up to USP standards. Who made that test?

Dr. KRANTZ. Some of these products are not in the Pharmacopeia, you see. Tedral, for example, one of them, is not an official product.

Senator NELSON. Of those that are, where was the test made to see whether it met the USP standards? Who made it?

Dr. KRANTZ. I presume it was made by the laboratory of the Army procurement group, but I do not know.

Senator NELSON. So you are not certain whether or not any of these drugs met USP standards?

Dr. KRANTZ. No; I did not have any of the drugs.

Senator NELSON. I think that this is a crucial question.

The testimony before the committee has been that if the drug meets USP standards, it is their judgment that it is therapeutically equivalent and there has not been any significant evidence except as perhaps to one drug, and that is a maybe, that if they met USP standards, they were therapeutically equivalent. We do not know, then, whether the drugs you mentioned, met USP standards?

Dr. KRANTZ. I agree.

Senator NELSON. We recognize, and I know you do, as an expert, that brand name companies and generic companies manufacture drugs and, for reasons of quality control, a certain percentage of them do not meet USP standards. As I have said earlier in the hearing, the one big test made showed that generic companies had a better percentage in meeting a potency test than did the brand name companies, by 1 percentage point.

So these are not submitted, then, as part of that?

Dr. KRANTZ. Oh, no, no.

Senator NELSON. I see.

Mr. GORDON. I might also mention that tolbutamide is not sold by the generic name. It comes only under the brand name of Orinase. It is manufactured by only one company, Upjohn.

Dr. KRANTZ. I thought the patent had expired.

Mr. GORDON. Not yet. It will expire soon, but has not yet. As of now, only Upjohn manufactures that.

Dr. KRANTZ. Up to this time, and this was about a year ago, the patent had not expired on Miltown and Equanil, which was the same

drug, meprobamate. I asked the colonel about this, because I was interested in the inclusion of meprobamate in the pharmacopeia, because I was director of Scope——

Mr. GORDON. I said that, with respect to tolbutamide, there is no other company making this but Upjohn.

Dr. KRANTZ. You cannot be sure.

Mr. GORDON. Is Tedral a brand name?

Dr. KRANTZ. This is an asthmatic remedy that contains aminophyllin ephredrine and some other agents—I do not remember.

Mr. GORDON. Is this a brand name or a trade name?

Dr. KRANTZ. A trade name.

Mr. GORDON. So you have trade names on your list?

Dr. KRANTZ. There is no other name. It is a mixture.

Mr. GORDON. I still cannot understand what the significance of this list is.

Dr. KRANTZ. Let me explain it to you very carefully and very slowly: Our laboratory engages in scientific research, developmental procedures, and so forth. This colonel from the Procurement Office of the Army in Philadelphia called and asked if he could have an appointment.

He came down and spent a whole afternoon with me and told me his problem was this: By Government mandate, he is forced to buy drugs on price. Now, we have bought these drugs that he has mentioned there and they have not, in the hands of our doctors, met the standards, or met the clinical equivalency would be better—clinical equivalency—of the trademark product.

Senator NELSON. May I interrupt there? Did your lab conduct the clinical tests, how many patients were involved, and where were they conducted?

Dr. KRANTZ. I do not know this. This was in the Army. They were giving them to soldiers and people in veterans hospitals, I presume.

Senator NELSON. So we do not know what kind of tests they conducted and whether it was a scientific, clinical test or not. We do not know whether the drugs met USP standards or not?

Dr. KRANTZ. That is correct. It is simply an opinion.

Senator NELSON. We do not know how many were generics and how many were trade names, either?

Dr. KRANTZ. Well, I got the impression from him—this conversation has been over a year ago, so it is not all clear in my mind—that there were several companies that were making these items prior to expiration of the patents. Now, I can readily see how most any company could make something comparable to Tedral by simply mixing the ingredients. They know the formula, it is available, so they could call it most anything they wanted—psuedo-Tedral or anything of the sort.

Senator NELSON. Of course, if it is under patent, they could not market it.

Dr. KRANTZ. I doubt if it is patentable, a mixture of this kind.

Senator NELSON. All right. Thank you very much, Doctor. We appreciate your taking the time to come here. I apologize for having delayed so long in getting you on.

The committee will stand in recess until Tuesday, March 18, at 10 a.m.

(The supplemental information submitted by Senator Nelson follows:)[1]

[From Federal Supplement, vol. 257—cases argued and determined in the U.S. District Courts—U.S. Customs Court—pp. 991–998]

SHANE STROMSODT, a minor, by Robert M. Stromsodt, his guardian ad litem, Plaintiff,

v.

PARKE-DAVIS AND COMPANY, a corporation, Defendant.
Civ. No. 3992

United States District Court, D. North Dakota, Northeastern Division—
September 28, 1966,

Product liability case involving defendant's ethical drug which allegedly caused injuries to infant plaintiff. The District Court, Ronald N. Davies, J., held that evidence established that defect in defendant's drug caused damage to brain and central nervous system of infant, that such defect constituted breach of implied warranty of merchantability, that defendant was chargeable with negligence in failing adequately to test product and adequately to warn of dangers inherent in its use and that infant was entitled to award of $500,000,00.

Judgement for plaintiff.

1. Druggists ⇐10

Evidence established that competent, producing cause of damage to brain and central nervous system of infant was defect in defendant's ethical drug, a quadruple antigen with a prophylaxis against diphtheria, pertussis, tetanus and poliomyelitis, and that chronologically and etiologically, infant's condition was traceable directly to the drug administered to him.

2. Sales ⇐284(1)

Defect in drug resulting in damage to brain and central nervous system of infant to whom drug was administered constituted breach of implied warranty of merchantability.

3. Sales ⇐255

Asserted lack of privity is not defense in North Dakota in an action by ultimate consumer against manufacturer of drug for breach of implied warranties, where, through advertising or other media of education and information, defendant manufacturer has persuaded medical profession to prescribe defendant's drug.

4. Druggists ⇐9

Finding that defendant drug manufacturer breached implied warranty of merchantability and that infant plaintiff's injuries were caused thereby did not preclude finding that manufacturer was also chargeable with negligence in failing adequately to test product and adequately to warn of dangers inherent in its use.

5. Druggists ⇐10

Evidence established that adequate test performed prior to marketing of defendant's ethical drug would have disclosed product's potency instability as well as cause of greater incidence of reaction and that defendant was negligent in failing to adequately test product, in suit for damage to brain and central nervous system of infant resulting from defect in defendant's drug which was administered to infant.

6. Druggists ⇐9

Even though drug manufacturer met all of government regulations and requirements in production and marketing of drug, manufacturer still owed duty to warn of dangers which were inherent in use of drug and of which it knew or should have known in exercise of reasonable care.

7. Druggists ⇐9

For drug manufacturer to be liable for injuries caused by use of its drug on basis of its failure to warn of dangers which are inherent in use of drug and

[1] See p. 4537, supra.

of which it knows or should know in exercise of reasonable care, danger must be reasonably foreseeable and injury must be proximately caused by failure to warn.

8. Druggists ⇐10

Evidence established that defendant drug manufacturer knew or should have known that its ethical drug, a quadruple antigen with a prophylaxis against diphtheria, pertussis, tetanus and poliomyelitis might cause encephalopathies in some users and that it was negligent in failing to give adequate warning of that danger, in action for damage to brain and central nervous system of infant resulting from use of drug.

9. Druggists ⇐9

Even if case of encephalopathy was the first occurring after administration of defendant's ethical drug, that did not preclude finding that such as foreseeable by defendant and that defendant was negligent in failure to give adequate warning.

10. Damages ⇐132(3)

Where plaintiff as a baby suffered convulsions following administration of defendant's defective drug and at time of trial, when plaintiff was seven years old, he walked unsteadily, lacked coordination, spoke but a few words, had none of basic childhood skills normally possessed by children of this age, plaintiff suffered permanent and irreversible injuries to his brain and central nervous system and plaintiff would in all probability be institutionalized shortly for inability of his parents to give him necessary care, plaintiff was entitled to award of $500,000.

Melvin M. Belli, of Belli, Ashe, Gerry & Ellison, San Francisco, Cal., Mart R. Vogel of Wattman, Vogel, Vogel, Bright & Peterson, Fargo, N.D., Carlton G. Nelson, and Jerome J. Mack, of Nelson & Mack, Grand Forks, N.D., for plaintiff.

Harold D. Shaft, of Shaft, Benson, Shaft & McConn, Grand Forks, N.D., for defendant.

MEMORANDUM AND ORDER

RONALD N. DAVIES, District Judge.

This is a product liability case tried to the Court without jury, involving the ethical drug Quadrigen made by the Defendant, Parke-Davis and Company, containing four antigens: diptheria toxoid, tetanus toxoid, pertussis (whooping cough) vaccine and poliomyelitis vaccine. It was also described as a quadruple antigen with a prophylaxis against diphtheria, pertussis, tetanus and poliomyelitis. Jurisdictional requirements of 28 U.S.C.A. § 1332, have been met.

The Plaintiff was originally shown as "Robert M. Stromsodt, guardian ad litem of Shane Stromsodt, a minor." By ex parte order entered by this Court April 1, 1966, leave was granted Plaintiff to amend the caption of the amended complaint to include "and Robert M. Stromsodt, individually." The Defendant moved the Court to set aside this order, urging that it was given no opportunity to object to it and contending that the North Dakota Statute of Limitations had run as against any claim of Robert M. Stromsodt, individually. A ruling was reserved on this motion.

To make certain that the issues are solidly joined in this cause, and that its ultimate resolution may not be attacked by reason of any real or fancied future claim to which the Defendant may think itself exposed, the Defendant's motion upon which ruling was reserved, must be and it is hereby granted. The Defendant's motion to dismiss the cause of action as to Robert M. Stromsodt, individually, must be and it is hereby granted. for the reason that the complaint fails to state a cause of action as to Robert M. Stromsodt, individually. This case is ordered captioned as it appears herein, that is, "Shane Stromsodt, a minor, by Robert M. Stromsodt, his guardian ad litem. Plaintiff, versus Parke, Davis and Company, a corporation, Defendant," and as so styled it will be adjudicated.

In 1953 Parke, Davis commenced studies for the purpose of determining the feasibility of combining poliomyelitis vaccine with the company's trivalent antigen sold under the trade name "Triogen," containing diphtheria toxoid, tetanus toxoid and pertussis vaccine. Parke, Davis' product, Quadrigen, which has heretofore been described, was finally developed and licensed March 25, 1959, and its manufacture authorized by the Department of Health, Education and Welfare (HEW). Commercial marketing of the drug under the trade name "Quadri-

gen" commenced in July of 1959 with Quadrigen having an expiration dating period of twelve months after manufacture, and six months after issue.

On April 13, 1961, the Division of Biologics Standards (DBS) of the National Institutes of Health (NIH) issued a memorandum to manufacturers of multiple antigen products containing pertussis and poliomyelitis vaccines that the products could contain no less than 14 units of pertussis potency (previously 12) and be labeled with an expiration date of six months after manufacture, and four months after issue. This change was necessitated when studies indicated a significant loss of pertussis potency in quadruple antigen vaccines after marketing. No comparable loss of pertussis potency had been found in triple antigen products not containing poliomyelitis vaccine.

DBS then determined that some lots of inactivated poliomyelitis vaccine contained a live vacuolating agent (SV 40), from the monkey kidney cells on which poliomyelitis virus was grown. Resultantly, a memorandum was issued May 20th, 1961, requiring the subsequent lots of vaccines containing components grown on monkey kidney cells be free of live SV 40.

On August 23, 1961, DBS issued a regulation or letter placing a new toxicity test requirement on all products containing pertussis vaccines; and on September 21, 1961, provided a new reference vaccine for the pertussis potency test which effected an additional increase in the potency requirement. The new toxicity test required additional treatment of the pertussis component. This treatment adversely affected the pertussis potency to the extent that the potency requirement could not consistently be met. Various articles appearing in medical literature indicated that the poliomyelitis component and the preservative being used might be the cause of the instability in multiple vaccines. Production and marketing of "Quadrigen" was finally halted in November, 1962.

Shane Stromsodt was born in Grand Forks, North Dakota, May 24th, 1959. His mother's pregnancy and his birth were entirely normal and uneventful, according to her physician, Dr. John H. Graham. On August 26th, 1959, Shane was taken for examination to Dr. Graham's office; and on that date Quadrigen was administered to him intermuscularly. The infant seemed to suffer no ill effects, and his mother recalled no reaction which caused her any alarm. On October 1, 1959, some five weeks later, Shane was again taken to Dr. Graham's office, examined and once more Quadrigen was injected into the child's body, between four and five o'clock that afternoon. Mrs. Stromsodt bundled up the child and took him to the family car in which her husband, Robert, was waiting. She reached the car some five or ten minutes after Shane had received the Quadrigen, removed the blankets from about the child, and noticed a fine red rash on his face.

The Stromsodts drove to their home where Shane was undressed, and the rash was noticed on his face and the upper part of his body. Mrs. Stromsodt gave Shane his bottle immediately after the family had had their meal. Shane promptly vomited the bottle's contents, something he had never done before. Mrs. Stromsodt laid the child on the bed and testified the baby had a "seizure." She described his eyes as rolling back in his head, his heels and head dug into the bed, his back arched and his fingers grasping. Mrs. Stromsodt believes the convulsion may have lasted five minutes. Having no idea of what was happening, she watched Shane, and when the seizure was over, telephoned Dr. Graham. She described to the Doctor what had happened to Shane and added that she thought the baby had the measles. The Doctor, however, thought it was a reaction from the shot given Shane and instructed Mrs. Stromsodt to watch him and to telephone next morning if the child was no better. Shane seemed normal the next morning, and Mrs. Stromsodt did not call the Doctor nor see him again until November 4, 1959, when the baby was taken to Dr. Graham's office for a third shot. Shane slept most of the next two days following the initial seizure, but he had two more convulsive attacks after the first one, both of which were prior to November 4, 1959.

When Shane was taken to Dr. Graham's office, November 4, 1959, Mrs. Stromsodt recited his condition to the Doctor. She told him the baby had suffered from two "spells" since the last Quadrigen shot, that he had been sleeping more and "it seemed like he wasn't doing anything any more." In short, the child was not progressing normally. The Doctor concluded that Shane should not be given Quadrigen because of the severe reaction suffered by the infant following the October 1 injection of that drug, and thus, on his third trip Shane was given Triogen which contained diphtheria toxoid, pertussis vaccine and tetanus toxoid (DPT). Poliomyelitis vaccine was not given on this date.

Shane continued to have difficulties which stemmed from the October 1st introduction of Quadrigen into his body and repeatedly had seizures until January, 1960. Mrs. Stromsodt testified the baby was making no progress. On January

13, 1960, the Stromsodts sought the advice of a specialist in pediatrics and took Shane to Dr. Samuel L. Pettit in Grand Forks. The Doctor prescribed phenobarbital for the child and testified that he finally prescribed a conventional dosage of one-quarter grain phenobarbital three times a day for Shane, which amounts he continues to receive.

When trial of this case began Shane was nearly seven years old. The record show he walks unsteadily, lacks coordination, speaks but a few words has none of the basic childhood skills normally possessed by children of his age and can neither read nor write. Uncontroverted medical testimony disclosed that he has damage to the brain and central nervous system. Shane is definitely, permanently and irreversibly injured, and in all probability his parents shortly will be unable to give him the necessary care and the boy will have to be institutionalized.

[1] A careful weighing of all the credible medical testimony in this case leads this Court to the inescapable conclusion that the competent producing cause of Shane Stromsodt's condition was Quadrigen, and that chronologically and etiologically Shane's condition is traced directly to the Quadrigen administered to him October 1st, 1959.

Of the several theories under which the Plaintiff seeks to recover in this action, only two are sustainable and require discussion here. They are breach of an implied warranty and negligence.

BREACH OF IMPLIED WARRANTY

"The liability in negligence of a manufacturer or other supplier for damage caused by his product is based on the supplier's failure to exercise reasonable care. Hence, negligence is a tort concept based on fault.

"Although the courts are occasionally confused about the matter, warranty, on the other hand, is not a concept based on fault or on the failure to exercise reasonable care. But this does *not* mean that warranty is necessarily contractual or nontortuous in nature. Liability in warranty arises where damage is caused by the failure of a product to measure up to express or implied representations on the part of the manufacturer or other supplier. Accordingly, an injured person is not required to prove negligence in a warranty-products liability case.

"This has been concisely summarized as follows:

> " 'There seems to be some confusion in understanding the nature of implied warranty liability. In the first place, concepts of negligence and fault, as defined by negligence standards, have no place in warranty recovery cases. Proof of negligence is unnecessary to liability for breach of implied warranty and lack of it is immaterial to defense thereof. Since the warranty is *implied* [emphasis by court] either in fact or in law, no express representations or agreements by the manufacturer are needed. Implied warranty recovery is based upon two factors: (a) The product or article in question has been transferred from the manufacturer's possession while in a "defective" state, more specifically, the product fails to be "reasonably fit for the particular purpose intended" or of "merchantable quality," as these two terms, separate but often overlapping, are defined by the law; and (b) as a result of being "defective," the product causes personal injury or property damage.' " 2 Frumer & Friedman, Products Liability, Chapter 3, Sec. 16.01[1].

[2] None of the experts called by either party could or would state which particular ingredient in Quadrigen caused the damage to Shane Stromsodt Plaintiff's witness, Dr. Ronald Okun, testified that there was evidence to show that pertussis endotoxin made the other components of Quadrigen more liable to cause an anaphylactic sort of reaction in a patient. Other evidence indicated that the product was rendered defective by the instability of potency in the pertussis vaccine. The evidence justifies the conclusion that the Plaintiff's injuries and damages were caused by a defect in the Quadrigen, and that such defect constitutes a breach of the implied warranty of merchantability.

[3] The asserted lack of privity is not a defense in North Dakota to a claim based upon breach of an implied warranty. See Lang v. General Motors Corporation, 136 N.W.2d 805 (N.D.1965) Thi sapparently would be particularly true in actions by the ultimate consumer against a manufacturer for breach of implied warranties where "through advertising or other media of education and information defendant has convinced and persuaded the medical profession to prescribe its drug, since it is in the very competitive field of supplying drugs and medicines for the alleviation of human suffering as well as for its own pecuniary advantages." Bennett v. Richardson-Merrell, Inc., D.C., 231 F.Supp.150

NEGLIGENCE

[4] The finding that Parke, Davis breached the implied warranty of merchantability and that Plaintiff's injuries were caused thereby does not preclude a finding that the Defendant is also chargeable with negligence in failing adequately to test the product and adequately to warn of the dangers inherent in its use.

The insert,[1] under "Reactions", reads:

"When given in accordance with suggested methods, local and systemic reactions following the administration of Quadrigen are usually mild. The incidence is usually no greater than is normally experienced with trivalent vaccine. Local reactions and fever of short duration may occur, however, and parents should be cautioned not to apply local treatment, such as wet dressings or heat. Any child who shows a febrile reaction should be kept quiet, should be offered water repeatedly and may be given one or more doses of aspirin as indicated. Occasionally, a residual induration or circumscribed nodule may persist for a week or more.

"In instances of more marked reaction, the immunization may be completed with monovalent antigens or other combinations of antigens.

"Local reactions have been known to be more severe when the child is in the incubative stage of pertussis. Encephalitic symptoms occasionally occur with acute pertussis though rarely with the use of the prophylactic vaccine. Such severe symptoms of the central nervous system include convulsions and lethargy. They may be followed by mental or physical manifestations, sometimes permanent, or even by death; but fortunately such reactions are extremely rare.

"The poliomyelitis vaccine components of Quadrigen contains small amounts of penicillin and streptomycin used in culturing the virus. During the adsorption process most of the antibiotic content is removed. In fact, residual antibiotics in the adsorbed product are usually not demonstrable by ordinary laboratory technics. However, consideration should be given to the possibility of allergic reactions in individuals sensitive to these antibiotics and they should be tested for sensitivity where this possibility exits.

"The value and importance of maintaining continuing antibody levels in the infanct in relation to the possibility of provocation of paralytic poliomyelitis by injection are self-evident. In modern clinical practice the administration of medication by hypodermic injection is generally accepted, and the hazard of thereby provokng poliomyelitis is increasing. If, however, basic immunity against poliomyelitis as evidenced by circulating antibody has been achieved, provocation is quite unlikely. Also, it should be noted that Quadrigen is considered *less* likely to provoke paralysis than is the trivalent product not containing poliomyelitis vaccine. With products not containing poliomyelitis antigen the patient is at some risk following each injection. With Quadrigen, on the other hand, after the first injection, basic immunity is developing and risk is greatly decreased for subsequent inoculations. Furthermore, if current recommendations are followed, the course of immunization will be started during the first 6 months of life under the protection of passive maternal antibody. However, the hazard of provocation in the face of an epidemic, particularly with the first dose of Quadrigen, cannot be ignored and the physician should exercise discretion, as with any injectable."

Clinical trials of Quadrigen prior to marketing were conducted by Dr. Clarence D. Barrett of Detroit beginning in 1956 and terminating in 1959. These tests used Quadrigen considered "fresh" in that the product was less than six months of age from the date of "pooling" of the poliomyelitis component with the DPT fraction. The trials were designed to determine antibody response and the earliest age in infancy at which immunization against poliomyelitis, diphtheria, tetanus and pertussis would be started, using a multiple antigen against

[1] Exhibit 46 is a tiny bottle of Quadrigen contained in a small cardboard box which included also Parke-Davis' insert showing what the product was designed to do. It is observed that the bottle itself contained no warning whatever, the cardboard box in which it was enclosed contained no warning whatever. The insert itself, a single sheet of paper containing in the main very small print, showed the nature of the product, when to immunize, dosage and administration, recall or booster doses, reactions and storage instructions, and was printed on a sheet measuring approximately four by seven inches, in which were compressed approximately 1,444 words, excluding the reference list on the bottom of the reverse side.

all four diseases. No clinical reactions of any serious consequence were reported or observed.

Quadrigen was then made available to selected members of the medical profession who were requested to comment on their use of the product. These "field trials" indicated a marked increase in reactions among patients given Quadrigen over those being given DPT and poliomyelitis vaccine. Of the severe reactions reported the first apparent instance in which death resulted was in March of 1959. It does not appear that Parke-Davis made any effort to determine the cause of the high incidence of reactions, and only a cursory attempt was made to investigate the cause of a death attributed to the use of Quadrigen.

[5] It appears to this Court that adequate tests performed prior to marketing would have disclosed the product's potency instability as well as the cause of greater incidence of reaction, especially in view of the number and seriousness of the reactions being reported. This was not a situation where an epidemic existed or where need justified the risk of premature marketing since products were already available to the medical profession that satisfactorily accomplished that Quadrigen was designed to do.

[6] Although all of the Government regulations and requirements had been satisfactorily met in the production and marketing of Quadrigen, the standards promulgated were minimal. The Defendant still owes a duty to warn of dangers of which it knew or should have known in the exercise of reasonable care. Love v. Wolf, 226 Cal.App.2d 378, 38 Cal.Rptr. 183. See also Ebers v. General Chemical Co., 310 Mich. 261, 17 N.W. 2d 176; Brown v. Globe Laboratories, 165 Neb. 138, 84 N.W.2d 151; Gonzalez v. Virginia-Carolina Chemical Company, 239 F.Supp. 567 (DC, SC, 1965).

[7, 8] The danger must be reasonably foreseeable and the injury must be proximately caused by the failure to warn. *The Defendant knew or should have known that Quadrigen might cause encephalopathies in some users and to warn of the danger.*

[9] Though this may have been the first case in which encephalopathy [2] occurred after the administration of Quadrigen, it does not preclude the finding of foreseeability and negligence. See Roberts v. United States, 316 F.2d 489 (3 Cir., 1963).

The warning "Local reactions have been known to be more severe when the child is in the incubative stage of pertussis" on the insert accompanying the product, not only would not have warned members of the medical profession, but might have misled them to believe that only in cases where the child was in the incubative stage of pertussis would encephalitic symptoms occasionally occur.

There is no competent evidence in the entire record, medical or other, to show that Shane's condition arose out of or from any susceptibility or predisposition, nor that the child had any congenital disease or disorder or defect of any kind, nor that he had any allergy or idiosyncrasy, nor that heredity was a factor that might account for his present condition.

This Court being of the opinion that the Defendant is liable both for breach of an implied warranty and for negligence, it becomes unnecessary to forecast whether the Supreme Court of North Dakota would apply Sec. 402 A of the Restatement of Torts in a situation such as is here presented.

As pointed out in 2 Frumer-Freidman, Chapter 3, Sec. 16A [4]:

"Strict liability in tort in the products liability area is in its infancy. Therefore, the precise scope of the rule and the defenses thereto have not as yet been clearly defined. It is believed, however, that strict liability in tort is for the most part no different than strict liability in warranty, that similar results can be achieved under either theory. Comment *m* to § 402A of the Restatement of Torts seems to agree. It states:

> " 'There is nothing in this section which would prevent any court from treating the rule stated as a matter of "warranty" to the user or consumer.'

"But in the next sentence it is pointed out that,

> " 'if this is done, it should be recognized and understood that the "warranty" is a very different kind of warranty from those usually found in the sale of goods, and that it is not subject to the various contract rules which have grown up to surround such sales.'

"If a court does not require, *inter alia*, privity of contract, a sale, or notice of a breach of warranty, does it matter that the defendant is being held strictly liable in warranty rather than in tort? The answer seems obvious.

[2] Any degenerative disease of the brain.

If a court imposes strict warranty liability irrespective of contract and sales rules, then strict liability in warranty and tort are synonymous."

The Plaintiff has sustained the burden of proving, by a fair preponderance of the credible evidence adduced upon trial, that Parke-Davis has breached an implied warranty, and in addition, has been guility of tortious negligence. The verdict which this Court reaches, and the damages awarded, are supported by either one or both of these theories.

[10] It is my conclusion that the sum of $500,000.00 constitutes a fair, just and adequate award to Shane Stromsodt, considering the totality of circumstances in this lawsuit.

Counsel for the Plaintiff are directed to prepare and submit through the Clerk of this Court findings of fact, conclusions of law, order for judgment and judgment with the least practicable delay.

[From Federal Supplement, vol. 285—cases argued and determined in the U.S. District Courts—U.S. Customs Court—pp. 432–454]

ERIC R. TINNERHOLM, an infant under the age of fourteen years, by his Guardian ad Litem, Carl F. Tinnerholm, and Carl F. Tinnerholm, Individually, Plaintiffs,

v.

PARKE, DAVIS & Co., Defandant.

No. 62 Civ. 4006.

United States District Court, S. D. New York—May 15, 1968

Action against manufacturer of vaccine for damages resulting from doctor's administration of vaccine to infant. The District Court, Tenney, J., held that evidence established that manufacturer breached its implied warranty and warranty of merchantability and manufacturer was guilty of negligence. That Court further held that plaintiffs were entitled to damages in the sum of $651,783.52 to reimburse father for loss of services and medical expenses incurred and for infant's loss of wages, future medical expense, and pain and suffering.

Judgment accordingly.

1. Druggists ⇐10

Evidence established that release of endotoxin into fluid contained in vaccine injected into infant was cause of unusually high fever which, in turn, caused severe and permanent brain damage.

2. Druggists ⇐10

In action against manufacturer of vaccine for damages resulting from infant being injected with vaccine, plaintiffs need not disprove every possible ground of causation suggested by manufacturer nor must findings of court meet standards of laboratorian.

3. Sales ⇐427

Liability for "breach of warranty" arises where persons or property are damaged because of product's failure to live up to an express or implied representation by manufacturer or other supplier.

See publication Words and Phrases for other judicial constructions and definitions.

4. Sales ⇐427

"Breach of warranty" is distinguished from negligence liability in that it is not based upon fault or upon failure of such manufacturer or supplier to exercise reasonable care.

5. Sales ⇐260

An "express warranty" will arise where manufacturer, supplier or other seller positively represents a fact concerning goods he sells.

See publication Words and Phrases for other judicial constructions and definitions.

6. Sales ⚖434

Allegation that vaccine was fit for use as immunizing agent against various ailments and was of good merchantable quality constituted an allegation of "implied warranty".

See publication Words and Phrases for other judicial constructions and definitions.

7. Sales ⚖279

Warranty of "merchantability" is that thing sold is reasonably fit for general purpose for which it is manufactured and sold.

See publication Words and Phrases for other judicial constructions and definitions.

8. Sales ⚖273(1)

Implied warranty of fitness for particular purpose is distinguished from merchantability warranty in that in merchantability warranty there is reliance on particular seller's skill and judgment.

9. Sales ⚖55

In action by New York residents against manufacturer of vaccine for damages resulting when infant was injected with vaccine, court was bound by New York law of warranty.

10. Sales ⚖255

Under New York law, doctrine of privity did not apply to action against manufacturer of vaccine for damages resulting from infant's being injected with vaccine by physician.

11. Sales ⚖246

Even if sale is necessary in order to impose warranty liability, such requirement was fulfilled in action against manufacturer of vaccine for damages resulting from vaccine having been administered to infant by doctor.

12. Druggists ⚖10

Evidence in action against manufacturer of vaccine for damages resulting from infant's having been injected with vaccine by physician established that vaccine was defective and that defect was proximate cause of infant's injuries.

13. Sales ⚖441(1)

In action against manufacturer of vaccine for damages resulting from vaccine administered to infant, evidence established that manufacturer breached an implied warranty in manner that increased chances of party injected with vaccine of contracting an encephalopathy.

14. Sales ⚖441(3)

In action against manufacturer of vaccine for damages resulting from doctor's administering vaccine to infant, evidence established that manufacturer breached its warranty of merchantability.

15. Druggists ⚖9

Finding of implied warranty liability did not preclude court from finding manufacturer of vaccine liable in negligence for damages resulting from doctor's administering vaccine to infant.

16. Federal Civil Procedure ⚖2571

While finding of implied warranty liability would not preclude finding liability based on negligence, plaintiffs are limited to one recovery.

17. Druggists ⚖10

In action against manufacturer of vaccine for damages resulting from doctor's administering vaccine to infant, evidence established that manufacturer was negligent in failing to adequately test its product, for releasing product for commercial distribution in face of certain danger signs emanating from test results, and in failing to adequately warn medical profession of risks inherent in its use.

18. Druggists ⇐9

Where drug manufacturer develops new drug subsequently found to produce harmful side effects which manufacturer failed to discover in course of testing product, manufacturer is liable in negligence if drug in fact was inadequately tested or manufacturer failed to exercise due care in development of product prior to its release on market for commercial distribution.

19. Druggists ⇐9

Where it was well known that variations in temperature could have marked effects on safety and effectiveness of vaccine, and it was also know that many lots could not be shipped under refrigerated or storage conditions, it was incumbent upon manufacturer of vaccine to subject their pre-release lots to those foreseeable variations in temperature to which their product would be exposed prior to point of inoculation so as to insure that this exposure would not produce deleterious effects.

20. Druggists ⇐9

Although it would be negligence for manufacturer to disregard regulations established by National Institutes of Health in manufacture of its drug products, manufacturer could not exempt itself from liability in negligence for failure to exercise due care in area not covered by specific regulation.

21. Druggists ⇐9

Manufacturer of vaccine was negligent in using, as basis for its representation that vaccine yielded no greater local or febrile reactions than was experienced with former vaccine, a clinical study which lacked controls for diagnostic and reporting procedures and used vaccines which contained ingredient that had been in cold storage for two years.

22. Druggists ⇐10

In action against manufacturer of vaccine for damages resulting from doctor's administering vaccine to infant, evidence established that there existed sufficient number of both unrealistic and conflicting reports from field to have required manufacturer to take serious second look at its product before placing it on market.

23. Druggists ⇐9

Where products were already available to medical profession which satisfactorily accomplished that which new vaccine was designed to do, there was no epidemic or need justifying risk of premature marketing.

24. Druggists ⇐10

In action against manufacturer of vaccine for damages resulting from doctor's administering vaccine to infant, evidence established that manufacturer was negligent in not adequately warning medical profession of dangers inherent in vaccine's use.

25. Druggists ⇐9

Drug manufacturer is under duty to warn medical profession of dangers inherent in its biological drugs which, in exercise of reasonable care, it knew or should have known to exist.

26. Druggists ⇐9

Watering down substance of warning so as to give false assurance to medical profession that drug or biological can be safely administered, thereby minimizing danger which exists in use of product, amounts to inadequate warning.

27. Druggists ⇐9

Doctors have right to and in fact do rely on brochures sent to them by drug manufacturers regarding safety and use of their products.

28. Druggists ⇐9

Drug manufacturer who, after reporting results of its test to Food and Drug Administration, and on strength of those reports markets its products, discovers new harmful side effects produced by drug, yet fails to send out warnings of this new development to foreseeable users, is negligent.

29. Druggists ⟸9

Any significant increase found to exist in reaction rate of particular drug must be disclosed by manufacturer.

30. Druggists ⟸9

Where manufacturer of vaccine had noted that study revealed that seven per cent of children inoculated with vaccine suffered fevers of 104 degrees and above, manufacturer was under duty to timely amend brochure included with its product in order to inform medical profession of information which would reasonably be expected to affect doctor's decision to use vaccine.

31. Druggists ⟸9

Manufacturer of vaccine marketed in 1959 was under duty to warn medical profession of possibility of allergic reaction.

32. Damages ⟸1

Under New York law damages are compensatory, not punitive.

33. Parent and Child ⟸7(1)

Father is entitled to recover for loss of injured child's services and for medical attendance and expenses.

34. Damages ⟸60

"Collateral source" doctrine has been severely limited in its application.

35. Damages ⟸60

Where liability for care of mentally defective infant may be asserted by state against infant and his father, doctrine of "collateral source" does not apply. Mental Hygiene Law N.Y. § 24 and subds. 5(b), 9(b).

36. Mental Health ⟸32

Where state has provided care for mentally defective infant, damages awarded father for past period of institutionalization are subject to lien of state and defendant may move to have lien determined. Mental Hygiene Law, N.Y. § 24 and subds. 5(b), 9(b).

37. Damages ⟸43

In absence of proof that nursing services performed by infant's mother were other than would normally have been rendered by mother to her child, damages for such services would not be awarded.

38. Damages ⟸133

Father was entitled to damages in amount of $2,500 for loss of services of infant who became mentally retarded as result of receiving vaccine at age of three months.

39. Damages ⟸32, 37, 43

Infant who became mentally retarded from being administered vaccine at age of three months was entitled to damages to cover future medical expenses, to reimburse him for future loss of wages, and to cover past, present and future pain and suffering.

40. Damages ⟸135

Evidence established that $160,000 would be fair amount to insure adequate future medical care for infant who became mentally retarded from administration of vaccine at age of three months.

41. Damages ⟸133

Infant who became mentally retarded from administration of vaccine at age of three months was entitled to $50,000 as damages for loss of future earnings even though he would be confined to institution during most of his life and would not start work until age 21.

42. Damages ⟸132(3)

Infant who as result of being administered vaccine suffered from high fever, underwent two spinal taps and craniotomy, was partially paralyzed and subject to seizures and was mentally retarded was entitled to $400,000 as damages for pain and suffering.

Fuchsberg & Fuchsberg, New York City, Jacob D. Fuchsberg, Richard E. Shandell, New York City, of counsel, for plaintiffs.

Costello, Ward, Tirabasso & Shea, New York City, Joseph M. Costello, New York City, David C. Dethmers, Detroit, Mich., of counsel, for defendant.

TENNEY, District Judge.

This product liability case. which was tried to this Court without a jury, involves the ethical drug Quadrigen, made by defendant Parke Davis & Co., and administered to the infant plaintiff herein. Quadrigen contains four antigens:[1] diphtheria toxoid, tetanus toxoid, pertussis (whooping cough) vaccine and poliomyelitis vaccine. The action has been brought on behalf of the infant plaintiff by his father, and by the father individually, charging negligence in various respects and breach of an express and implied warranty. There is no dispute that the injuries suffered by the infant plaintiff are catastrophic.

The plaintiff, Eric Tinnerholm, was born on August 30, 1959, in Huntington Station, Long Island, New York. He was the third child born to his parents, the plaintiff Carl F. Tinnerholm and Mrs. Tinnerholm, the other two children then being five and four years of age. His birth was normal, as was his mother's pregnancy, and at the end of the first and second months of his life he was taken to the family physician, Dr. Gerald Feinberg, for routine check-ups. The infant was apparently a big, healthy boy who ate and slept well and was active and alert.

Some time between 11:00 A.M. and noon on Saturday, November 28, 1959, Mrs. Tinnerholm, by prearrangement, took Eric to Dr. Feinberg's office for his first immunization injection. She was informed that this immunization was not the usual 3-in-1 that her other children had received, but that it was a 4-in-1 which added poliomyelitis vaccine to the antigens with which she was already familiar. Eric suffered no immediate side-effects following the injection and continued in apparent good health through that Saturday and Sunday. On Monday he appeared extremely quiet and seemed to look toward the wall most of the day, although the parents apparently thought nothing of this at that time. On Tuesday morning, December 1, 1959, at about 4:00 A.M., the child was found tangled up in his bedclothes and whimpering, but on being picked up and patted he quieted down and presumably went back to sleep. There was no indication of temperature at that time. However, some time later, between 6:30 and 7:00 A.M., the child was found by his mother huddled under the covers, lethargic and bathed in perspiration. His temperature at that time was 108°, he was very white, his lips were blue, and he was limp. While Mrs. Tinnerholm gave the child an alcohol bath, Dr. Feinberg was summoned by the boy's father.

When the doctor arrived around 7:30 A.M. he confirmed the 108° temperature which was shortly reduced to 106° by the alcohol bath. The doctor's examination further disclosed a small amount of emesis and some coughing. The remainder of the examination was negative.

Eric was admitted to Huntington Hospital at 8:45 A.M. where he was again examined by Dr. Feinberg, who found the child's neck supple, an absence of masses, and a negative Brudzinski.[2] Dr. Feinberg's original diagnosis was fever of unknown origin. Eric remained in Huntington Hospital until December 18th. during which period he was cared for by two pediatricians, Doctors Gordon and Kagan, and also examined by a neurologist, Dr. Sengstaken. Dr. Kagan examined the boy on the day of his admission to the hospital and found him to be pale, hyperpneic,[3] the eyes dull and apathetic, with focal seizures and twitching of the right side. There was a dullness and loss of landmarks in the ears and some redness at the back of the throat. On the basis of his examination, Dr. Kagan believed that the boy had either a bacterial infection of the bloodstream (sepsis) or meningitis. However, subsequent laboratory testing ruled out both the sepsis and meningitis, for a spinal culture revealed clear fluid with only three cells, a normal finding, indicating the absence of infection. There was, however, an elevated protein content of 10 milligrams percent, indicating some abnormality attacking the brain. A repeat lumbar puncture ten days after admission again showed an absence of cells and a protein content of 56 milligrams percent, lower than the previous 100 milligrams percent, but still above normal. During this first hospitalization Eric developed recurrent seizures, and on the fifth day a flaccid paresis or paralysis of the right arm and leg was noted and which per-

[1] An antigen is a substance which causes antibodies to be produced by the organism into which it is injected.

[2] A Brudzinski is a neurological test which includes the forward flexion of the neck or the head on the neck. which, if done without resistance and without pain, indicates there is no meningeal irritation.

[3] Abnormally rapid breathing.

sisted until his discharge on December 18, 1959. Since that time he has been retarded in his mental development, being classified in the imbecile-idiot range. He is unable to stand or walk or talk, is incapable of toilet training, and in order for him to be able to sit he must first be propped up. There is a spasticity in posturing of the right upper limb and the right lower limb, indicating a spastic weakness of these extremities. He still suffers occasional seizures and has a mental age in the range of five months.

Is it possible to determine, with reasonable medical certainty or reasonable medical probability, that something peculiar to Quadrigen was the proximate cause of the injuries suffered by the infant plaintiff? The question must be answered affirmatively. Dr. Charash, one of plaintiffs' experts, concluded that the child suffered a pertussis-vaccine encephalopathy,[4] basing his conclusion on the temperal relationship between the immunization and the onset of illness; the unusual and spectacular sudden rise and subsequent rapid reduction in temperature; the appearance of unilateral seizures and weakness; the essentially extraordinary discrepancy between the very high protein and the absence of white cells in the spinal fluid; and the flatness of the fontanel. For the same reasons, he discounted the possibility of a viral encephalitis,[5] one of the possible alternatives raised by defendant. Likewise, the suggestion that the infant may have developed a brain abscess from otitis media is not supported by the evidence. *What was it, then, that was peculiar to Quadrigen that it can be stated, with reasonable medical certainty or probability, that it caused the injuries already described?* In order to answer this question it is necessary to discuss in some detail pertussis and pertussis vaccine as incorporated in Quadrigen.

Pertussis, or whooping cough, is a communicable respiratory disease caused by a bacterial organism. The disease may attack the brain to the extent that convulsions, high fever, and occasionally hemorrhages in the brain are produced. Sometimes this is accompanied by hemiplegia or paralysis of half the body, and not infrequently there is a resultant mental retardation. The disease is particularly dangerous for children during their first year of life, since little or no maternal immunity is passively transferred to the newborn. Immunity, however, may be obtained through the injection of a vaccine.

A vaccine, by introducting an antigenic factor into the body of the recipient, is intended to stimulate the production of antibodies, which antibodies confer protection against the disease. In the process, lymphocytes, a form of cell contained in the lymph glands, absorb the antigenic factor and produce an antitoxin against the particular disease. With some infectious diseases, such as diphtheria and tetanus, it has been possible in developing a vaccine to isolate the soluble toxin or poison excerted by the bodies of these bacteria, and to inactive this toxin with formaldehyde, thus converting the toxin into what is called a toxoid. This toxoid preserves the ability to immunize against the disease by stimulating the production of antibodies in the recipent, but it has lost its poisonous qualities.

The pertussis organism, however, is a unique, very complex one containing many different factors. There is an exotoxin, an endotoxin, a protective antigen, a factor that gives the Schwartzman phenomenon,[6] a factor sensitizing to histamine, yeast, protein extracts, vaccines and endotoxin, to infection by gram negative bacteria and by influenza, to X-rays, pressure, the stress of cold, and to a marked degree sensitizing to ceretonium, one of the important neuro-hormones of the brain. The exotoxin in the pertussis organism is thermo labile, i.e., it is destroyed by heat, and all vaccines with which we are concerned are heated during preparation and the thermal labile exotoxin destroyed. However, the endotoxins inside the cell are not destroyed by heat. It is this endotoxin, also called a lipopolysaccharide, to which febrile reaction following administration of pertussis vaccine is usually attributed. In addition to the protective antigen already mentioned, there are some fourteen or fifteen different antigens, and nobody knows which, of all these antigens, is the one which stimulates production of the antibodies conferring protection against pertussis (whooping cough).

By reason of the complexity and mystery of the pertussis organism it was impossible to isolate the toxin conferring protective activity and make a toxoid out of it, as in the case of diphtheria and tetanus. Therefore, it was necessary to administer the entire bacteria organism, treating it in some way by heat or otherwise to kill the organism but preserve the antigenicity. As a result, whereas there were practically no reactions to diphtheria or tetanus toxoids, there were

[4] Encephalopathy is any degenerative disease of the brain.
[5] Encephalitis is an inflammation of the brain.
[6] The Schwartzman phenomenon is the production of ulcers on injection under the skin of a rabbit.

not uncommonly reactions to pertussis vaccine such as a swollen injection area and some fever. Occasionally, there was severe plain from the site of the injection, and on rare occasions convulsions, high fever and the neurological sequelae of brain hemorrhage, hemiplegia and mental retardation, just as with the disease itself. The cause of these neurological manifestations following the use of pertussis vaccine is not definitely known either on a pathological, histological or clinical basis. These manifestations, however, were first brought to the attention of the medical profession in April of 1948. Thereafter there were developed additional controls over the production of pertussis vaccine. Under the new regulations the encephalopathic type of reaction was minimized. The use of phosphate adjuvants [7] made possible a decrease in the amount of pertussis in the formula; new maximum as well as minimum potency standards were set; and the toxicity of the pertussis component was reduced by extra heating and by the toxicity test. The potency test is performed by injecting groups of mice with varying dilutions of vaccine, and, then, after a period of time, challenging the mice with virulent organisms. The toxicity test was performed by injecting a group of ten mice of specified weight with a specified dose of vaccine and weighing the group at specified intervals. I will have further occasion herein to discuss in greater detail the matter of tests as to their adequacy in the present case. Mention has been made above of the use of phosphate adjuvants which permitted a reduction of the amount of pertussis in the formula. Today, at least in American vaccines, an aluminum salt is used as an adjuvant. An adjuvant serves as a depot or button which will slow the release of the antigen rather than having it released all at once when the vaccine is merely suspended in a liquid. When aluminum phosphate was first used, there was some apparent increase in toxicity and the amount of the aluminum phosphate was reduced approximately one-half with a resultant substantial reduction in toxicity. Thereafter vaccines with the aluminum phosphate were no more toxic than other adsorbed vaccines.

One other aspect of the manufacture of pertussis vaccine should be mentioned at this time. All vaccines packed in multi-dose vials require a preservative to keep them sterile (not to preserve their potency). In the development of pertussis vaccines until the development of polio vaccine the universal preservative used was Merthiolate. At the time there was no information that the Merthiolate affected the vaccine for better or for worse, but it has recently been discovered that Merthiolate acts as a stabilizer of the vaccine, that in its presence the vaccine tends to decrease in toxicity in storage at the same time that its potency is stabilized at a level at least for the first six months.

In the early 1940's, there was developed the method of combining pertussis vaccine with diphtheria and tetanus toxoid into a combined antigen product colloquially known as "DDT". No apparent decrease in toxicity or reactivity was noted as a result of such combination. Defendant marketed such a product under the trade name "Triogen".

After the Salk poliomyelitis vaccine had been developed, it was decided by defendant to attempt to mix the polio vaccine with the "Triogen" in order to develop commercially a quadruple antigen product. In connection with the development of polio vaccine it had been learned that Merthiolate had a deleterious effect upon the polio virus, caused by the action of released mercury ions. Eli Lilly & Company incorporated Versene within its vaccine, which prevented the release of the mercury ions. However, Versene was incompatible with the aluminum phosphate used as an adjuvant by defendant in Triogen, and since defendant anticipated that it would want to develop a vaccine combining the polio vaccine with Triogen, it decided to use benzethonium chloride, or Phemerol which was defendant's trade name for this product.

Unknown to defendant the benzethonium chloride had an unusual effect on the pertussis vaccine contained therein. It appears that there was a loss of potency, a reduction in the protective activity of the pertussis vaccine when benzethonium chloride rather than Merthiolate was used as the preservative. This loss occurred only when the vaccine was exposed to variations in temperature. While there is no knowledge as to the manner in which benzethonium chloride affects the unidentified protective antigen of the pertussis vaccine, considerable knowledge has been accumulated as to the physical effects of benzethonium chloride on pertussis bacteria placed in a solution including benzethonium

[7] An adjuvant in immunology is any substance that, when mixed with an antigen, enhances the antigenicity and gives a superior response.

chloride. It has been demonstrated that benzethonium chloride partially disappears from the solution during storage, coming down from twenty-five parts per million to only seven parts per million. Benzethonium chloride is a quatenary ammonium compound and has a positive charge, whereas the bacterial cell wall has a negative charge. By attraction, the benzethonium chloride is adsorbed to the cell. Such adsorption on the bacterial cell wall may cause its denaturation and favors the leaching of the toxin from the bacterial cell, resulting in the leakage of the contents of the organism. Certainly, it is reasonable to conclude that the effect of the use of benzethonium chloride was to release the endotoxin from the bacteria cell into the fluid that was injected. One such endotoxin, the lipopolysaccharide, causes fever, and fever can produce convulsions and brain damage. Indeed, fever is one of the recognized etiologies or causes of post-pertussis vaccine encephalopathies.

[1, 2] It is reasonable to conclude, as I do, with reasonable medical certainty or probability that the release of the endotoxin into the fluid injected into the infant plaintiff was the cause of the unusually high fever which, in turn, caused the severe and permanent brain damage. I find defendant's suggestion that the cause of such damage was a viral encephalitis caused by some unspecified virus, a sepsis or meningitis, or an allergic reaction, totally unconvincing. It is not plaintiffs' burden to disprove every possible ground of causation suggested by defendant, nor must the findings of the Court meet the standards of the laboratorian. Plaintiffs' experts have furnished impressive evidence to support the conclusions reached herein, evidence which has clearly withstood the attack of defendant's experts. Having found Quadrigen to have been the causative factor, I turn now to the question of warranty, express and implied, and the further question of negligence.

Warranty Generally.

[3, 4] Liability for breach of warranty arises where persons or property are damaged because of a product's failure to live up to an express or implied representation by the manufacturer or other supplier. It is distinguished from negligence liability in that it is not based upon fault or upon the failure of such manufacturer or supplier to exercise reasonable care. 2. Frumer & Friedman, Products Liability § 16.01[1] (1967) (hereinafter referred to as "Frumer & Friedman"); cf. Rheingold, Products Liability—The Ethical Drug Manufacturer's Liability, 18 Rutgers L.Rev. 947, 977 (1964) (hereinafter referred to as "Rheingold").

[5–8] An express warranty will arise where a manufacturer, supplier or other seller positively represents a fact concerning the goods he sells. 2 Frumer & Friedman § 16.02; cf. Uniform Commercial Code § 2–313. In the instant case, plaintiffs allege that defendant warranted Quadrigen as "safe, effective and free from harmful side effects * * *." Amended Complt. ¶ 20.[8] An implied warranty, on the other hand, is imposed by operation of law. 2 Frumer & Friedman § 116.02. *The implied warranties allegedly breached in the case at bar are the warranties of merchantability and fitness for a particular purpose.* Amended Complt. ¶ 28. The warranty of merchantability is that "the thing sold is reasonably fit for the general purpose for which it is manufactured and sold." Henningsen v. Bloomfield Motors, Inc., 32 N.J. 358, 161 A.2d 69, 75 A.L.R.2d 1 (1960); 2 Frumer & Friedman § 16.04[2][d]; see Burr v. Sherwin Williams Co., 42 Cal.2d 682, 268 P.2d 1041 (1954); Twombley v. Fuller Brush Co., 221 Md. 476, 158 A.2d 110 (1960); Ryan v. Progressive Grocery Stores, 255 N.Y. 388, 175 N.E. 105, 74 A.L.R. 339 (1931); Rheingold at 978 (reasonable fitness for ordinary purpose for which sold). The implied warranty of fitness for a particular purpose is virtually self-explanatory, the major distinction from the merchantability warranty being reliance on the particular seller's skill and judgment. 2 Frumer & Friedman § 16.04[2][d]; see Henningsen v. Blomfield Motors, Inc., supra.

Privity and Related Problems.

a. Privity.

The last decade has seen a vigorous frontal assault on the previously near-impregnable "citadel of privity" so that in many states the insulation of the man-

[8] In paragraph 20 of the amended complaint, plaintiffs also claim that defendant expressly warranted that Quadrigen "was fit for the use as an immunizing agent against various ailments and was of good merchantable quality." These are normally considered to be implied warranties and do not appear to be expresly warranted in the Quadrigen package insert or advertisements to the medical profession. Indeed, in paragraph 28 of the complaint, plaintiffs make these same allegations in their cause of action for breach of implied warranty.

ufacturer of defective goods from direct liability for breach of warranty, express or implied, is a thing of the past. See generally the excellent state-by-state analysis of the privity problem in 2 Frumer & Friedman § 16.04; Kessler, Products Liability, 76 Yale L.J. 887 (1967); Prosser, The Assault Upon the Citadel (Strict Liability to the Consumer), 69 Yale L.J. 1099 (1960).

The decision which provided the impetus for the collapse of privity was Hennington v. Bloomfield Motors, Inc., supra, wherein the New Jersey Court held that public policy demanded the extinction of the privity doctrine because of mass marketing conditions causing the manufacturer to become remote to the ultimate consumer, sales being accomplished through intermediaries, and product demand being created by use of advertising media. It was obvious, indicated the Court, that manufacturer contemplated the cultivation of the ultimate consumer and that at least with respect to the purchase of a car, the implied warranty of merchantability should extend to the ultimate purchaser of such vehicle and those persons who would reasonably be anticipated to use it, such as members of the purchaser's family and those occupying or using the vehicle with his consent.

[9, 10] Of course, no extended discussion is necessary to show that this Court is bound by the New York law of warranty. And it is clear that if the requirement of privity is not dead in this jurisdiction, it has at least been dealt a deliberating blow by the New York Court of Appeals in Greenberg v. Lorenz, 9 N.Y.2d 195, 213 N.Y.S.2d 39, 173 N.E. 2d 773 (1961); Randy Knitwear, Inc. v. American Cyanamid Co., 11 N.Y.2d 5, 226 N.Y.S.2d 363, 181 N.E.2d 399 (1962); and Goldberg v. Kollsman Instrument Corp., 12 N.Y.2d 432, 240 N.Y.S.2d 592, 191 N.E.2d 81 (1963). See generally 2 Frumer & Friedman § 16.04 [2] [b] [x]. In Greenberg v. Lorenz, supra, the Court held that a retailer impliedly warrants the wholesomeness of food and household goods to all members of the buyer's household since a presumption should arise that the purchase was made for all such persons. Randy Knitwear, Inc. v. American Cyanamid Co., supra, dispensed with the requirement of privity in an express warranty case. Frumer & Friedman point out that the real importance of *Randy Knitwear* was that it paved the way for the New York Courts to abrogate privity as a requirement in implied warranty cases since the Court noted (1) a trend away from privity; (2) privity was an outmoded technical rule; (3) that the separate indemnity actions required by the privity rule were a waste of time spent in litigation (obviously both on the part of the courts and the various parties who would be involved); and (4) that warranty was historically a tort action. Id. at § 16.04 [2] [b] [x]. Finally, in Goldberg v. Kollsman Instrument Corp., supra, the New York Court of Appeals went about as far as *Henningsen* by holding that an airplane assembler could be liable for the death of an airplane passenger under an implied warranty theory. It was held, however, that the manufacturer of a component part was not liable since "adequate protection is provided for the passengers by casting in liability the airplane manufacturer which put into the market the completed aircraft." 12 N.Y.2d at 437, 240 N.Y.S.2d at 595, 191, N.E. 2d at 83.[9] It is apparent that the refusal to hold the component part manufacturer was not because of lack of privity. 2 Frummer & Friedman § 16.04[2] [b] [x].

From the foregoing, it should appear obvious in the instant case that privity presents no bar to recovery.[10]

b. Necessity of a Sale

In Perlmutter v. Beth David Hospital, 308 N.Y. 100, 123 N.E.2d 792 (1954), the Court held that a hospital administering a blood transfusion is rendering only a service and is not making a sale. Whether a sale is necessary to impose warranty liability today is questionable (see 1 Frumer & Friedman § 19.02; Rheingold at 974), but even assuming such a requirement, it is submitted that *Perlmutter* would not bar a recovery in the instant case. Faced with the argu-

[9] For an apparent extension of Goldberg v. Kollsman Instrument Corp., see Rooney v. S. A. Healy Co., 20 N.Y.2d 42, 281 N.Y.S.2d 321, 228 N.E.2d 383 (1967), where the defendant supplier sold used protective masks to the City of New York. The Court of Appeals held defendant had breached the implied warranty of merchantability since the defect was in design.

[10] Gottsdanker v. Cutter Laboratories, 182 Cal. App. 2d 602, 6 Cal. Rptr. 320, 79 A.L.R. 2d 290 (1960), used a novel but valid approach to solve the privity problem. The reasoning of the *Gottsdanker* Court was that both food and drugs are intended for human consumption and that such consumption is one of the basic reasons for the food exception. Therefore, the courts should extend the exception to drugs. Of course, in light of the New York cases cited supra, there is no need to resort to the *Gottsdanker* reasoning herein. See generally 3 Frumer & Friedman § 33.02 [2][a]; Rheingold at 978.

ment that cases such as *Perlmutter* would prevent recovery, in Gottsdanker v. Cutter Laboratories, 182 Cal.App.2d 602, 6 Cal. Rptr. 320 (1960), the live-polio vaccine case, the California Court stated:

"Clearly it is the patient, and not the doctor, who is the ultimate consumer of the vaccine. While a sale is essential to impose liability under the implied warranties, the intial sale to distributor or retailer of pharmaceuticals is sufficient to impose upon the manufacturer the responsibility of fulfilling the implied warranties which run to the benefit of the persons whom the manufacturer intended to be, and who in fact became the 'consumers'." Id. at 605, 6 Cal.Rptr. at 324.

[11] The *Cutter* rationale is a sound one. Moreover, the case at bar is distinguishable from *Perlmutter* (as was *Cutter*). Similarity would have been present if the physician who had administered the vaccine to Eric Tinnerholm had been sued for breach of warranty. See 3 Frumer & Friedman § 33.02[b]. Under the law as it existed at that time, plaintiffs would possibly have been denied any recovery. But the later decisions of the New York Court of Appeals in Greenberg v. Lorenz, Randy Knitwear, Inc. v. American Cyanamid Co., and Goldberg v. Kollsman Instrument Co. would allow a direct recovery against the manufacturer, a result not inconsistent with *Perlmutter*. Accordingly, I find that even if the technical requirement of a sale is necessary, such requirement has been fulfilled under the *Cutter Laboratories* decision and *Perlmutter* presents no obstacle to recovery.

With these hurdles cleared, I turn to a consideration of the warranty causes of action.

Express Warranty

The package insert (Plaintiff's Exh. 1) which was apparently sent to the administering physician with his purchase of Quadrigen stated that:

> When given in accordance with suggested methods, local and systemic reactions following the administration of Quadrigen are usually mild. The incidence is usually no greater than is normally experienced with trivalent vaccine. Local reactions and fever of short duration may occur, however, and parents should be cautioned not to apply local treatment, such as wet dressings or heat. Any child who shows a febrile reaction should be kept quiet, should be offered water repeatedly and may be given one or more doses of aspirin as indicated. Occasionally, a residual induration or circumscribed nodule may persist for a week or more.
>
> In instances of more marked reaction, the immunization may be completed with monovalent antigens or other combinations of antigens.
>
> Local reactions have been known to be more severe when the child is in the incubative stage of pertussis. Encephalitic symptoms occasionally occur with acute pertussis though rarely with the use of the prophylactic vaccine. Such severe symptoms of the central nervous system include convulsions and lethargy. They may be followed by mental or physical manifestations, sometimes permanent, or even by death; but fortunately such reactions are extremely rare.

Whether this statement establishes an express warranty and a breach thereof need not be reached herein, for it is clear, as will be hereinafter developed, that the defendant has breached a warranty implicit in the package insert. However, certain of the problems which need be considered in express warranty causes of action will be briefly discussed. Discussion of the sufficiency of the warning will be reserved for that portion of this opinion wherein the negligence issues are considered.

The unique characteristic of drug-product-liability litigation is that while the product is actually meant for the patient, the sales pitch is made to the physician in an attempt to get him to prescribe a particular product or course of treatment to the ultimate consumer. Rheingold at 976. Thus, advertising will take the form, among other things, of promotional literature to the physician, statements of "detail" men who solicit purchases by the physician, package inserts, labels and the like, and/or articles in medical journals. Id. at 965. Can liability of the manufacturer be sustained even though the consumer has not relied on any representation? One New York decision has held that the physician is an agent of the patient for the special purpose of receiving statements from the manufacturer. Wechsler v. Hoffman-La Roche, Inc., 198 Misc. 540, 99 N.Y.S.2d 588 (Sup.Ct. 1950). A number of commentators have expressed the view that the representation need not be made directly to the injured consumer. See, e. g., 2

Frumer & Friedman § 16.04[04]; 2 Harper & James, Torts § 28.7 (1956); Rheingold at 976–77. Nevertheless, if direct communication is dispensed with, it would appear that a plaintiff must still prove reliance by the physician. See id. at 977.

Dr. Feinberg, the administering physician, testified that he had read the package insert (TR 610, 616). According to him, it presented no more than he had already been taught in his formal medical education and in his practice (TR 460–63, 617). But, as will be discussed *infra*, the evidence clearly indicates the greater incidence of febrile reactions resulting with the use of Quadrigen, so that the statement as it appears in the package insert is incorrect. Moreover, the statement regarding encephalitic reactions is, at the very least, an ambiguous one (TR 610–18).

However, whether these statements can be properly characterized as express warranties which were breached need not be reached in light of my subsequent decision with respect to the implied warranty of merchantability.

Implied Warranty

In Picker X-Ray Corp. v. General Motors Corp., 185 A.2d 919, 922 (D.C.Mun. Ct.App.1962), it was stated that:

> Implied warranty recovery is based upon two factors: (a) The product or article in question has been transferred from the manufacturer's possession while in a "defective" state * * *; and (b) as a result of being "defective" the product causes personal injury or property damage.

The critical problem, then becomes the meaning of the word "defective". One commentator has attempted to distinguish between pure and impure drugs, the former being "those sold as the manufacturer intended, but with the harm arising as a side effect because of some inherent quality" and the latter being defined as "those sold other than as the manufacturer intended, and containing deleterious impurities." Rheingold at 970. According to this article, additional considerations flow from a finding that the drug is pure. Id. at 983. The problem with this definition is that in the instant case it is unclear whether a pure or impure drug is involved. It can be argued that Quadrigen was pure because its ingredients were as the manufacturer intended. On the other hand, it can be as persuasively contended that the drug was impure because the endotoxin that was released from the bacterial cell into the fluid was "a deleterious impurity" and thus the drug was defective.

Another commentator suggests a more reasonable test: "[T]he issue as to whether a substance not intended to be present is natural or foreign is completely immaterial on the ground that a product is to be regarded as defective *if a reasonable man would not have sold it had he known of the presence of the substance in the product.* Keeton, Products Liability—Liability Without Fault and the Requirement of a Defect, 41 Texas L.Rev. 855, 861–62 (1963). (Emphasis added.)

The commentary to the Torts Restatement provides perhaps the best working definition of a defect: "the product is, at the time it leaves the seller's hands, in a condition not contemplated by the ultimate consumer, which will be unreasonably dangerous to him." Restatement (Second) of Torts § 402A, commenting at 351 (1965).

[12] Whatever definition is used, in my opinion the proof amply sustained the fact that Quadrigen was defective and that the defect was the proximate cause of the injury sustained by Eric Tinnerholm. Compare Stromsodt v. Parke-Davis & Co., 257 F.Supp. 991 (D. N.D.1966). I need not discuss the evidence with respect to the biological and clinical testing of Quadrigen by Parke-Davis and the National Institutes of Health at this time although such matter has been fully considered by me in reaching conclusions on the warranty issues. The matter of testing will be amply discussed in the negligence portion of this opinion. However, certain of the articles that have been written in the field and received in evidence, the deposition of Dr. Margaret Pittman of the Division of Biologics Standards (hereinafter referred to as "DBS") of the National Institutes of Health (hereinafter referred to as "NIH"), and testimony elicited at the trial are all important, have been considered by me in reaching this conclusion and will be discussed at some length herein.

[13] The occurrence of encephalopathics following administration of vaccines containing a pertussis component has been long known but the specific element that causes this explosive assault to the brain has not been discovered. See Berg, Neurological Complications of Pertussis Immunization, British Medical Journal 24 (July 5, 1958); Byers & Moll, Encephalopathies Following Prophylactic

Pertussis Vaccine, 1 Pediatrics 437 (1948). However, the fact that an encephalopathy can be caused by pertussis vaccine would not mean that liability would be incurred for breach of warranty in the instant case. Rather, the finding of an implied warranty breach is predicated on the fact that by manufacturing Quadrigen in the method chosen by defendant, the changes of contracting an encephalopathy were enhanced.

Aside from the clinical and laboratory studies of the benzethonium chloride preserved Quadrigen *which, in my opinion, indicate a defect in defendant's product,* the earliest literature which noted a problem with Quadrigen was published in 1960. Massachusetts Department of Public Health, Pertussis Immunization, 263 New England Journal of Medicine 410 (Aug. 25, 1960). The investigation indicated by this group "established that the potency of the pertussis-vaccine component in the quadruple antigen products * * * was relatively unstable." Pittman, Instability of Pertussis-Vaccine Component in Quadruple Antigen Vaccine, 181 Journal of the Am. Medical Ass'n 113 (1962). It is interesting to note this Pittman article points out that with the adoption of a unit of potency in 1953 with an upper limit placed on potency, no cases of fatal encephalopathy due to pertussis vaccine were reported to DBS although "occasional nonfatal neurological reactions" continued to occur. Id. at 114. Dr. Pittman hypothesized that "the preservative and the tissue-cell enzymes present" in the quadruple antigen vaccines "may be factors which contribute to instability." Id. at 118.

In 1964, a study was made with bordetella pertussis cells which showed that various substances influenced leakage from the bacterial cell. Niwa, Yamadeya & Kuwajima, Leakage of Cell Components of Bordetella Pertussis, 88 Journal of Bacteriology 809–10 (1964). Although benzethonium chloride was not used in that study, certain chemical substances similar thereto were employed (TR 1529–30).

Finally, in 1965, in an article co-authored by Dr. Pittman, it was stated:

"*Recent work has shown that pertussis vaccine in DTP–P*[*diphtheria-tetanus-pertussis-polio vaccine*] *preserved with benzethonium chloride is unstable in potency * * *. This surface-acting preservative, no doubt, contributed to the greater toxicity of DTP–P * * * by favoring the leaching of the toxin from the bacterial cell.* It is well known that alkalinity favors lysis and thereby promotes toxicity." Pittman & Cox, Pertussis Vaccine Testing for Freedom-from-Toxicity, 13 Applied Microbiology 447, 453 (1965). (Emphasis added.)

When testifying at her deposition, Dr. Pittman attempted to water down her statement by contending that she considered this statment to be a mere hypothesis (Pittman deposition of Nov. 17, 1967, at 83 (hereinafter referred to as "Pittman I")), but that it was based on scientific experimental data (id. at 83–84). The statement in her article, written when she was not involved in the instant litigation, seems far more significant than her later attempt to diminish its importance. Dr. Pittman, throughout her testimony, appears to consider the instant litigation a personal attack and an indictment of DBS as well (Pittman deposition of Nov. 27, 1967, at 214–15 (hereinafter referred to as "Pittman II")).

Dr. Pittman also testified that leakage would be immediately ascertainable in the toxicity tests conducted by the defendant and DBS (Pittman I, at 79–80). However, she later stated she had absolutely no idea as to the extent of leakage or how long it would take (Pittman II, at 79–81), so it is most difficult to see how she could predict with any certainty that the toxicity tests would reveal the leakage phenomenon.

The foregoing documents lend significant credence to the testimony of one of plaintiffs' expert witnesses, Dr. Lapin, who stated that in his opinion Quadrigen was toxic and that the administration of the vaccine to the infant plaintiff caused the injury involved in this litigation. Coupled with this is the complete failure of defendant to offer any reasonable alernative cause of Eric Tinnerholm's injury.

The "defect" involved was, in my opinion and as already stated hereinbefore, the leakage of endotoxins from within the bacterial cell and it has been shown by a preponderance of the credible evidence that such defect was the proximate cause of the injury.

Nor can defendant argue that this was a marked improvement over Triogen so that it should be shielded from liability even if the above finding is correct. I will state now, and will have occasion to reiterate later that no need justified a risk of marketing Quadrigen at an early date. Other products which performed the same function as the indicated vaccine without the danger involved were on the market and readily available to the medical profession. Although there is

testimony that it is beneficial to the patient and the medical profession to reduce the number of infections, when balancing this with the tragic occurrence in the case at bar and perhaps several other cases, the reduction of injections argument pales into insignificance.

[4] Accordingly, it is my opinion that the defendant has breached its warranty of merchantability to the plaintiff. In view of this discussion, the issues involving liability for breach of the warranty of fitness for a particular purpose need not be considered.

Negligence

[15–16] The finding of implied warranty liability does not preclude this Court from finding the defendant liable in negligence. *Stromsodt* v. *Parks-Davis & Co.*, supra, 257 F.supp. at 995. However, it is fundamental law that plaintiffs will be limited to one recovery.

[17] Defendant herein is chargeable with negligence in failing to adequately test its product, for thereafter releasing the product for commercial distribution in the face of certain danger signs emanating from the test results, and in failing to adequately warn the medical profession of the risks inherent in its use.

[18] It is established law that where a drug manufacturer develops a new drug subsequently found to produce harmful side effects which the manufacturer failed to discover in the course of testing the product, the manufacturer is liable in negligence where it appears that the drug in fact was inadequately tested or that the manufacturer failed to exercise due care in the development of the product prior to its release on the market for commercial distribution. 3 Frumer & Friedman § 33.01[2]; *Roginsky* v. *Richardson-Merrell, Inc.*, 378 F.2d 832 (2d Cir. 1967); *Stromsodt* v. *Parke-Davis & Co.*, supra.

The tests which the various lots of vaccine had to undergo prior to their release on the market were generally biological and/or clinical in nature. Not only was it required that each lot fall within the acceptable standards of potency and toxicity established by DBS, but also the reports from the doctors in the field as well as those testing the vaccine under clinical conditions had to indicate that the drug was safe for use and that it produced no untoward adverse reactions in the recipients.

Both the potency and toxicity tests were first performed in the laboratories of the manufacturer. Once satisfactory results were achieved, the manufacturer would send the lot to DBS which, in turn, would conduct its own independent study. If the DBS test results confirmed the manufacturer's report or protocol, the lot would be approved for release on the market. If, on the other hand, the DBS results conflicted with the results set forth in the manufacturer's protocol, the lot would be returned to the manufacturer for re-testing.

As hereinbefore stated, the potency test was performed by injecting groups of mice with varying dilutions of vaccine, and, after a period of time, challenging the mice with virulent organisms. The protective activity of the vaccine was judged by the number of mice which survived the challenge at the various dilution levels. In addition, it was required that the pertussis vaccine component have no greater potency than 12 protective units per total human immunizing dose (THD).[11] Because a standard deviation is inherent on a test of this nature, a vaccine would be deemed satisfactory if the result of one test or an average of the combined results of two or more tests indicated that the calculated protective activity of the vaccine fell within the allowable range of 8 to 36 protective units. Any result falling outside this range indicated that the particular lot was not fit for public use and consequently was unacceptable for distribution.

The standard toxicity text was preformed by weighing a group of ten mice, injecting them with a test dose of vaccine and weighing them again at the end of periods of 72 hours and 7 days. A vaccine was accepted as being free from toxicity if at the end of 72 hours the group weight of the mice was no less than it had been at the initial weighing, and at the end of 7 days was greater than it had been initially. A lot automatically failed the test if it was determined that a mouse had died from the vaccine.

Although Parke-Davis found no problem in meeting the potency requirements in the testing of its triple antigen vaccine, Triogen, it is apparent from the

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[11] "THD" is the total dose of vaccine, administered in a series of three separate inoculations, that any one individual is required to be given in order to insure full immunizing protectivity. The "12 protective units" standard represents the number of bacteria within a total human dose which successfully immunizes the recipient from the disease without itself causing harmful side effects.

correspondence between Parke-Davis and DBS during the year 1959 that beginning with the very first experimental lots of Quadrigen submitted to DBS for testing, i.e., Lots X–7513 and X–7514, Parke-Davis was having difficulty obtaining satisfactory potency values. On January 9, 1959, Dr. Workman of DBS wrote to Parke-Davis that:

"Our potency assays on the pertussis component of this lot (X–7514) showed values of only 7.9 and 3.8 units per total immunizing dose and thereby suggest the potency of the pertussis component is too low. In view of the extreme difference between your and our results, however, we would be willing to give further consideration to this lot if you are willing to retest. * * *" Plaintiffs' Exh. 3.

Letters of a similar nature were written concerning Lots 049033, 059294, 049032, 049034, 054044, 055961, 051639, 058836 and others, which lots initially produced test results between 2.7 and 7.25 protective units per THD. Some of these lots were re-tested and eventually withdrawn from processing.

Evidencing Parke-Davis' dilemma, on March 5, 1969, only 4 months prior to the time Quadrigen was commercially marketed, George D. Brigham, Director of the Biological Division of Parke-Davis, wrote a letter to Dr. Workman regarding Lot X–7514:

"As you know from recent reports, we have been having difficulties in obtaining satisfactory potency values in our preliminary production lots of Quadrigen. In view of these results, we are planning to increase the H. pertussis content to 20 opacity units instead of 15 opacity units as was originally intended." Plaintiffs' Exh. 3.

In a follow-up letter dated March 13, 1959, from Dr. Brigham to Dr. Workman, it was further stated:

"You indicate in your letter that you are concerned with the low values we have been obtaining in the pertussis component of our multiple antigens. As far as we are aware, *our only problem seems to be with the quadruple antigens i.e. except for an occasional lower than usual result, our other pertussis-containing products are given satisfactory potency tests.* Naturally, we have been concerned with the low pertussis test results in Quadrigen and as indicated in earlier correspondence, we plan to increase the concentration of organisms to a minimum of 20 opacity units per cc. as an immediate step to correct the situation." Plaintiffs' Exh. 3D. (Emphasis added.)

It seems significant to this Court that Parke-Davis, realizing the inherent potential of the pertusis component for causing fatal reactions, and faced with the unique problem of exceptional deficiencies in the potency values of its premarket lots, simply sought to strengthen the pertussis component without considering the possible existence of a defect in the combination itself. This proposed solution, however, also presented problems. On June 4, 1959, Dr. Brigham wrote Dr. Workman with reference to Lot 52230, the first commercial lot:

"We noted the *unusually high value obtained in the pertussis vaccine potency test.* In view of these high results we conducted a re-test on thi slot. A supplemental protocol summarizing the test is attached indicating 21.5 units per total human dose. This confirms our thought that a re-test would probably show average results within an acceptable range." Plaintiffs: Exh. 3F. (Emphasis added.)

It appears clear to this Court that Parke-Davis in its rush to commercialization of its product either overlooked or neglected to consider the possibility that Quadrigen was too unstable a vaccine and therefore too unpredictable to be released on the market at that time.

[19, 20] Parke-Davis was equally negligent in failing to test its product under market conditions. Inasmuch as it was well known that variations in temperature could have marked effects on the safety and effectiveness of a vaccine, and it was also known, as testified to by Dr. McLean of Parke-Davis, that many of the lots could not be shipped under refrigerated or storage conditions, it was incumbent upon Parke-Davis to subject their pre-release lots to those foreseeable variations in temperature to which their product would be exposed prior to the point of inoculation so as to insure that this exposure would not produce deleterious effects. This was not done. As it developed, tests taken in 1960 by the Massachusetts Department of Health and subsequently by DBS, indicated that although samples of the quadruple antigen vaccine which were held in storage under refrigerated conditions showed no perceptible loss of potency, those purchased on the market revealed a loss of potency below the minimum requirements for a pertussis vaccine. Although events subsequent to the injury herein cannot be considered in determining the manufacturer's negligence, it could not have been

clear during 1959 that tests under market conditions were necessary and that the defects subsequently discovered in 1960 were foreseeable.[12]

Similarly, Parke-Davis was experiencing difficulty in its attempt to meet the minimum standards of toxicity. Even as late as August 1959, one month *after* Quadrigen had been released to the commercial market, certain lots which had been submitted by Parke-Davis to DBS for toxicity testing were being repected. On August 25, 1959, a letter from Dr. Workman to Dr. Brigham, regarding Lot 054043, indicated:

"Our tests of the pertussis component for freedom from toxicity do not conform with the results reported in your protocol. Three tests were performed and 6 of 30 mice died by the end of 7 days." Plaintiffs' Exh. 3.

In a letter dated September 16,1959, Dr. Bringham replied that Parke-Davis' own re-test of Lot 054043 resulted in the deaths of 4 of the 40 mice inoculated. Defendant admitted that although this lot passed a 10-mouse test given earlier, the lot "appears upon more extensive testing to have enough toxicity to fail to pass the Minimum Requirements test in a certain percentage of cases." Plaintiffs' Exh. 3.

Clinical trials of Quadrigen prior to marketing were conducted by Dr. Clarence D. Barrett, Director of the Division of Material and Child Health of the City of Detroit, beginning in 1956 and terminating in 1959.[13] Although these trials were primarily designed to determine antibody response in children of various ages and to determine the earliest age in infancy at which immunization with Quadrigen could be started, Parke-Davis used these trials in its license application as a basis for the proposition that the clinical experience involving Quadrigen yielded no greater local or febrile reactions than was experienced with the triple antigen product.

[21] Because of the nature of the vaccine used in the Barrett study and the lack of controls placed on the diagnostic and reporting procedures, it was negligent for Parke-Davis to have used this study as its basis for making the above representation. The pertussis component which Dr. Barrett used had been in cold storage for the two-year period immediately preceding the inoculations. If had been discovered that during this period of time the potency of the pertussis component had fallen below the NIH's minimum requirements for an acceptable vaccine. Nevertheless, it was used in the study. Although in the standard commercial production lots the benzethonium chloride is combined with the pertussis component at the point of manufacture and allowed to remain in combination throughout the entire storage period, such was not the case with the vaccine used in the Detroit study. There, the preservative was not combined with the pertussis component until the time that the children were to be inoculated. Consequently, the clinical trial could not validly test the extent to which the addition of the benzethonium chloride (one of the few important changes being made in the quadruple antigen product) increased the reactivity of the product. Although the vaccine used may have been sufficient to determine the antibody response in the children tested, never having been subjected to market conditions and representing a quadruple antigen of lesser strength and of a different manufacturing process than the one eventually to be released on the market, it should not have been used as a barometer for judging local and febrile reactions.

Even had the vaccine used been an acceptable one for this purpose, the absence of controls over the diagnostic and reporting procedures made any conclusion with regard to the nature and extent of the reactions an invalid one. Mothers, most of whom came from the lowest socio-economic stratum of urban Detroit, had been asked to report, by telephone, all illnesses or reactions suffered by the children following their inoculations. No doctor or medical assistant at any time took the temperatures of the children either on the day that the vaccine was administered or subsequent thereto unless a mother, suspecting a reaction, brought her child back to the clinic. Needless to say, it was somewhat

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[12] It must be noted that in 1959 there were no regulations requiring a drug manufacturer to test its product under market conditions prior to releasing it for use to the general public. It is the opinion of this Court, however, that although it would be negligent for a manufacturer to disregard the regulations established by the National Institutes of Health in the manufacture of its drug products, a manufacturer cannot exempt itself from liability in negligence for failure to exercis due care in an area not covered by a specific regulation. See Stromsodt v. Parke-Davis & Co., supra at 997; Frumer & Friedman § 3301[3].

[13] Barrett, Timm, Molner, Wilner, Fahey & McLean, Multiple Antigen for Immunization Against Poliomyelitis. Diptheria, Pertussis and Tetanus, 49 American Journal of Public Health 644 (1959); Barrett, Timm, Molner, Wilner, Anderson, Carnes & McLean, Multiple Antigen for Immunization Against Poliomyelitis, Diphtheria, Pertussis and Tetanus, 167 Journal of the American Medical Association 1103 (1958).

presumptuous to assume the mothers' ability to recognize a "reaction", to assume their possession of thermometers with which to determine whether their children were experiencing febrile reactions, to assume the availability of telephones with which to communicate the fact that a reaction had been suffered, and hypothesizing the fact that telephones were available, to assume the dependability of the mothers to make the requested reports. To allow any implication to be derived from this study with regard to the incidence of reactions following the inoculation of the children was negligence on the part of the defendant herein.[14]

[22] Quadrigen was then made available to selected members of the medical profession who were requested to comment on their experience with the product. Enough of the "field trials" indicated a marked increase in reactions among the patients given Quadrigen over those being given the triple antigen product with a separate inoculation of the poliomyelitis vaccine to have required Parke, Davis to experiment further with their newly-developed quardruple antigen. There were some reports indicating up to 75 per cent reactions in the children tested whereas other reports indicated that no reactions whatsoever had been suffered. Some of these contrasting reports involved experiences with the same lot of vaccine. In other reports which indicated reaction rates as low as 2 per cent, the "Remarks" sections indicated that "slight fever" was not reported, "high temperature" was designated "no reaction", and "103-degree temperature" designated as a "slight reaction". In one report, only temperature of 105 degrees qualified as a "reaction". Many of the reports which indicated unrealistically low reaction rates were from doctors who, by the nature of their covering letters, seemed primarily interested in obtaining more of the free vaccine. In addition, it is most significant that the deposition testimony of Dr. John E. Gajewski, employed during 1959 in Parke-Davis' Department of Clinical Investigation and thereafter as Assistant Director of Medical Correspondence, indicated that during the period between July 1959 and September 1961 the reported incidents of febrile reactions with Quadrigen showed more frequent and higher temperature elevations. Similarly, and in the face of the testimony of Dr. Feinberg and Dr. Lapin that it was a rare instance when the triple antigen vaccine produced a fever of 104 degrees, the results of a study conducted by Dr. Sauer, the inventor of the original pertussis vaccine, submitted for publication on June 10, 1959, and published in the fall of that year, evidenced that of the large groups of infants inoculated with Quadrigen 5 per cent reacted with temperatures of 104 degrees and as much as 2 per cent reacted with temperatures of 105 degrees. All in all, it appears to this Court that there existed a sufficient number of both unrealistic and conflicting reports from the field to have required Parke-Davis to take a serious second look at its product before placing it on the market.

Of particular note was Parke-Davis' cursory attempt to investigate the cause of a reported death attributed by the treating physician to his use of Quadrigen. Although the autopsy report, received subsequently by Parke, Davis, stated that the immediate cause of death was bronchial pneumonia, the hospital record revealed that the patient had exhibited high fever, convulsions, opisthotonus, vomiting and lethargy several hours after a Quadrigen inoculation. The conclusion of the autopsy report is not necessarily inconsistent with a finding that the child experienced a pertussis encephalopathy prior to his death in that although bronchial pneumonia may have been the immediate cause of the infant's expiration, such condition can frequently be brought about by some other condition, which, in this case, in light of the small hemorrhages found in the subarachnoid portion of the brain, could well have been the vaccinal encephalopathy as was originally diagnosed. Nevertheless, there should have been an immediate and thorough investigation conducted by Parke-Davis into the possible connection between the Quadrigen inoculation and the infant's death two days subsequent thereto, especially in view of the fact that the quadruple antigen was soon to be released on the commercial market. This was not done nor did Parke-Davis attempt to notify the NIH of the possible existence of a Quadrigen-related death.[15]

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[14] Although a separate study had been conducted by Dr. Barrett in 1958, using fresh experimental vaccine and employing stricter controls over the diagnostic and reporting procedures, this study showed increased febrile reactions with the use of Quadrigen, and was not the principal study relied upon in support of the license application. To the contrary, it was the Detroit study discussed in the accompanying text which Parke-Davis attached to its application and upon which it relied most heavily.

[15] See note 12, supra.

[23] In considering the above discussion, it should be understood that the entry of Quadrigen on the market in July 1959 was not a response to a situation in which an epidemic or need existed justifying the risk of premature marketing since products were already available to the medical profession which satisfactorily accomplished that which Quadrigen was designed to do. Stromsodt v. Parke-Davis & Co., supra 257 F.Supp. pp. 996–997.

[24] In addition to defendant's negligence in failing to further test its product in the face of evidence that the quadruple antigen was unstable, and in the absence of a public need justifying its premature release on the market, defendant was similarly negligent in not adequately warning the medical profession of the dangers inherent in its use.

25[–28] It is the opinion of this Court that a drug manufacturer is under a duty to warn the medical profession of dangers inherent in its biological drugs which, in the exercise of reasonable care, it knew or should have known to exist. Sterling Drug, Inc. v. Cornish, 370 F.2d 82, 84–85 (8th Cir. 1966); Stromsodt v. Parke-Davis & Co, supra, 257 F.Supp. at 997; Love v. Wolf 26 Cal.App.2d 378, 38 Cal.Rptr, 183 (1964); Alfieri v. Cabot Corp., 17 A.D.2d 455, 235 N.Y. S.2d 753 (1st Dep't 1962), aff'd, 12 N.Y.2d 1098, 240 N.Y.S.2d 163, 190 N.E.2d 535 (1963); Marcus v. Specific Pharmaceuticals, Inc., 82 N.Y.S.2d 194 (Sup.Ct.1948); Frumer & Friedman, supra § 33.01[3]; Restatement (Second) of Torts § 388 (1965); Rheingold at 993, 994. "Watering down" the substance of a warning so as to give false assurance to the medical profession that a drug or biological can be safely administered, thereby minimizing the danger which exists in the use of a product, amounts to an inadequate warning. Love v. Wolf, supra, 38 CalRptr. at 193, 197; Alfieri v. Cabot Corp. supra; Rheingold at 993, 994. Inasmuch as doctors have the right to and in fact do rely on the brochures sent to them by the manufacturers regarding safety in the use of their products, Gielskie v. State, 18 Misc.2d 508, 191 N.Y.S.2d 436, 439 (Ct.Cl.1959), rev'd on other grounds 10 A.D.2d 471, 200 N.Y.S.2d 691 (3rd Dep't 1960), aff'd, 9 N.Y.2d 834, 216 N.Y.S.2d 85, 175 N.E.2d 455 (1961), a manufacturer is negligent who, after reporting the results of its tests to the FDA and on the strength of those reports markets its products, discovers new harmful side effects produced by the drug, yet fails to send out warnings of this new development to the foreseeable users, i.e., doctors and dispensaries, Sterling Drug, Inc. v. Cornish, supra, 370 F.d at 85; De Vito v. United Airlines Inc., 98 F.Supp. 88, 96 (E.D.N.Y. 1951); Gielske v. State, supra; Rheingold at 995.

Since the relevant portions of the warning which Parke-Davis issued in the form of a package insert are specifically set forth in the express warranty portion of this opinion, there is no need to recite them at this time.

Knowing that the only advantage in administering Quadrigen rather than the trivalent vaccine was the reduction from two to one of the number of inoculations required for each immunization, it is reasonable to assume that had the doctors been informed that greater reactivity could be expected from the quadruple antigen, they would not have subjected their patients to needless risk by using this product. Fully realizing this, Parke-Davis, employing the technique of ambiguity and a shrewd use of descriptive adjectives, was able to gloss over those facts which would have dissuaded the doctors and dispensaries from using their product, thereby lulling the medical profession into a false sense of security.

[29] The brochure states that "[t]he incidence [of reactions with Quadrigen] is *usually* no greater than is normally expected with trivalent vaccine." (Emphasis added.) This statement is misleading in that it reasonably permits one to conclude that the results from the studies conducted by the manufacturer have shown that Quadrigen has produced no greater reactions in the recipients thereof than did Triogen, with the exception of an insignificant number of isolated instances. Of course, this was not true. If Parke-Davis thought that in this instance it could legitimately use the word "usually" to mean "in a majority of the lots tested", it was clearly in error, for under that interpretation the manufacturer could conceal from the medical profession a 49 per cent increase in the reaction rate of its products. For example, if Product A and Product B produce reaction rates of 50 per cent and 60 per cent, respectively, in all the lots tested, it is conceivable that a manufacturer could represent that there is "usually" no greater reaction found to exist in Product B than in Product A, relying on the fact that only 1 additional person out of every 10 tested reacted to Product B. This method of linguistic distortion is grossly misleading. Clearly, any significant increase found to exist in the reaction rate of a particular drug must be disclosed.

[30] As hereinbefore stated, a study conducted by Dr. Sauer, submitted for publication in June 1959, revealed that 7 per cent of the children inoculated

with Quadrigen suffered fevers of 104 degrees and above. Parke-Davis alleges that the reason such study was not mentioned in its brochure was that the Sauer report had not been published until after Parke-Davis had written its package insert. However, it would appear from the evidence that Parke-Davis was fully familiar with the contents of this report in light of Dr. Sauer's continuing association with defendant since the early days in the development of the pertussis vaccines. As the cases cited above hold, it was Parke-Davis' duty timely to amend its brochure to inform the medical profession of any significant new developments or information which could reasonably be expected to affect a doctor's decision to use the product. Had Parke-Davis promptly amended its literature to include the results of the study conducted by Dr. Sauer, the medical profession would have been apprised prior to the day that the infant plaintiff was inoculated of the unusual reactivity produced by Quadrigen.

[31] Having raised the possibility at trial that plaintiff's injury could have been caused by an allergic reaction and therefore due to plaintiff's own particular hyper-sensitivity (a possibility rejected by me herein), it would appear sufficient to note in passing that defendant was under a duty in 1959 to warn the medical profession of this possibility, especially in view of the fact that such an etiological theory had been recognized since 1947. Berg, Neurological Complications of Pertussis Immunization, British Medical Journal 26 (July 5, 1958). Inasmuch as Parke-Davis did see fit to warn of a possible allergic reaction to penicillin and streptomycin, the two antibiotic residuals from the poliomyelitis vaccine, it similarly should have warned of that possibility with regard to the pertussis component.

Finally, the warning that "[l]ocal reactions have been known to be more severe when the child is in the incubative stage of pertussis" was ambiguous in that it reasonably could have misled the members of the medical profession to believe that only in cases where the child was in the incubative stage of pertussis would encephalitic symptoms occasionally occur. Stromsodt v. Parke-Davis & Co., supra, 257 F.Supp. at 997. This was Dr. Feinberg's interpretation and, in the opinion of this Court, could reasonably have been followed by others.

After due consideration and for the reasons set forth herein, it is the opinion of this Court that the defendant was negligent both in its failure to adequately test its product prior to releasing it on the commercial market and for its failure to adequately warn the medical profession of the dangers inherent in its use. As stated by the late Justice Jackson, dissenting in Dalehite v. United States:[16]

"This is a day of synthetic living, when to an ever-increasing extent our population is dependent upon mass producers for its food and drink, its cures and complexions, its apparel and gadgets. These no longer are natural or simple products but complex ones whose composition and qualities are often secret. Such a dependent society must exact greater care than in more simple days and must require from manufacturers or producers increased integrity and caution as the only protection of its safety and well-being. Purchasers cannot try out drugs to determine whether they kill or cure. * * * Where experiment or research is necessary to determine the presence or the degree of danger, the product must not be tried out on the public, nor must the public be expected to possess the facilities or the technical knowledge to learn for itself of inherent but latent dangers. The claim that a hazard was not foreseen is not available to one who did not use foresight appropriate to his enterprise."

[32] Finally, as to the damages claimed, I have been guided by the principle enunciated by the New York courts that damages are compensatory, not punitive. Little purpose would be served by further detailing the catastrophe irrevocably visited on this infant child.

[33] The plaintiff father is, of course, entitled to recover for the loss of the child's services and for medical attendance and expenses. Kalina v. General Hospital, 31 Misc.2d 18, 20, 220 N.Y.S.2d 733,735 (Sup.Ct.1961), aff'd, 18 A.D.2d 757, 235 N.Y.S.2d 808 (4th Dep't 1962), aff'd mem., 13 N.Y.2d 1023, 245 N.Y.S.2d 599, 195 N.E.2d 309 (1963). The parties have stipulated that his out-of-pocket payment for hospital and medical expenses for the infant total $3,470.55 and payments made by him to the State hospitals total $2,812.97, for which he is entitled to recover herein. Eric has been confined to State institutions since January 30, 1962 and will require institutional care, either of a public or private nature, for the rest of his life.

[34–36] Defendant suggests that since the infant plaintiff might be cared for at State expense, the doctrine of Drinkwater v. Dinsmore, 80 N.Y. 390 (1880)

[16] 346 U.S. 15, 51, 73 S.Ct. 956, 97 L.Ed. 1427 (1953).

should be applied. Such "collateral source" doctrine, however, has been severely limited in recent years in its application. Klein v. United States, 339 F.2d 512 (2d Cir. 1964); Feeley v. United States, 337 F.2d 924 (3rd Cir. 1964); Cunningham v. Rederiet Vindeggen A/S, 333 F.2d 308 (2d Cir. 1964). Moreover, it is inapplicable in the present case since liability for such expenses may be asserted herein against plaintiff father and plaintiff infant. The present cost of maintaining the infant at Suffolk State School is $6,000, which the State may recover from the father. New York Mental Hygiene Law, McKinney's Consol.Laws, c. 27, § 24. Even though it has accepted lesser payments in past years, it may recover the full reimbursement rates less the payments already made, § 24(9) (b), which potential recovery for the past period of institutionalization is fixed at $33,000. Such sum is subject to the lien of the State under § 24(5) (b). Defendant may, for his own protection and if so advised, move to have such lien determined.

[37, 38] I have not included any amount to cover the nursing services rendered by the infant's mother during the period from December 1, 1959 to January 30, 1962, for lack of proof that such survices were other than would normally have been rendered by a mother to her child. I do award the plaintiff father $2,500 for the loss of the child's services during minority.

[39, 40] The damages properly awarded to the infant are to cover future medical expenses, to reimburse him for future loss of wages, and to cover past, present and future pain and suffering. With respect to future medical expenses, it seems clear that Eric will require institutionalization for the rest of his life. However, in view of the injury, I believe from the evidence that a present life expectancy of 50 years is a reasonable approximation. Also, recognizing the continuing rise in medical costs and the fact that Eric may well be entitled to private nursing and therapy additional to what may be received under State care, I believe that $160,000 would be a fair amount to ensure him adequate future medical care. Loss of wages may also properly be awarded. Grayson v. Irvmar Realty Corp., 7 A.D.2d 436, 184 N.Y.S.2d 33 (1st Dep't 1959).

[41] The defendant contends that since the infant will be permanently confined to an institution he will have little need for damages attributed to loss of earnings. The only authority cited for this proposition is Scolavino v. State, 187 Misc. 253, 263, 62 N.Y.S.2d 17 (Ct.Cl.) modified, 271 App. Div. 618, 67 N.Y.S.2d 202 (3rd Dep't 1946), aff'd. 297 N.Y. 460, 74 N.E.2d 174 (1947), and is clearly inapposite since the condition of the infant in that case prior to the accident made his future employment impossible, i.e., loss of future earnings was not attributable to the accident. Accordingly, taking into account a 5-percent discount factor and making the valid assumption that Eric would not have commenced to work until age 21, I award him $50,000 for loss of future earnings.

[42] To the out-of-pocket losses suffered by this infant must be added the general damages for pain and suffering. Little purpose would be served in further dwelling on the various aspects of his past, present and permanent condition. He has undergone two spinal taps and a craniotomy, is partially paralyzed and subject to seizures. He is not comatose, however; he is not a vegetable. Accordingly, after careful consideration of this case and of others in which somewhat similar injuries were involved,[17] I consider an award of $400,000 for pain and suffering reasonable and just.

In summary, I find as follows:

I. For plaintiff Carl F. Tinnerholm—	
(a) Reimbursement for medical expenses paid	$ 6,283.52
(b) For Past medical expenses for which liable	33,000.00
(c) Loss of Services	2,500.00
II. For the infant plaintiff Eric Tinnerholm—	
(a) Future medical expenses	160,000.00
(b) Loss of future earnings	50,000.00
(c) Pain and suffering	400,000.00

The foregoing represents the Court's findings of fact and conclusions of law. A judgment shall be entered for plaintiffs in conformity herewith.

(Whereupon, at 1:40 p.m., the subcommittee recessed, to reconvene at 10 a.m., on Tuesday, March 18, 1969.)

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[17] See, e.g., Christopher v. United States, 237 F. Supp. 787 (E.D. Pa. 1965) (29-year old man—paraplegic—$350,000); Schwartz v. United States, 230 F. Supp. 536 (E.D. Pa. 1964) (43-year-old man—facial cancer—over $600,000); Wolfe v. General Mills Inc., 35 Misc. 2d 996, 231 N.Y. S.2d 918 (Sup. Ct. 1962) (30-year-old man—brain injury—$240,000).

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

TUESDAY, MARCH 18, 1969

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

The subcommittee met, pursuant to recess, at 10:05 a.m., in the Caucus Room, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

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

Senator NELSON. This morning the Subcommittee on Monopoly reopens its hearings. We have as our witness today the distinguished Dr. Edward Annis, past president of the American Medical Association, and now one of the 15 trustees of the association.

Dr. Annis, we are very pleased to have you here before the committee this morning. Perhaps for the record, you should introduce your associates.

STATEMENT OF DR. EDWARD R. ANNIS, PAST PRESIDENT OF THE AMERICAN MEDICAL ASSOCIATION; ACCOMPANIED BY DR. THOMAS HAYES, DIRECTOR, DEPARTMENT OF DRUGS, AND SECRETARY, AMA COUNCIL ON DRUGS; AND BERNARD P. HARRISON, DIRECTOR, LEGISLATIVE DEPARTMENT, AMA

Dr. ANNIS. Yes, Senator.

Mr. Chairman, members of the committee, I appreciate this opportunity and I would like now to introduce Dr. Thomas Hayes, director of our department of drugs, secretary of the American Medical Association's Council on Drugs, and a member of the Department of Medicine of the University of Illinois. The Senator in the past has expressed his desire to Dr. Hayes to attend this hearing and we are very pleased that he could be with us. With us also is the director of the Legislative Department of the American Medical Association, Mr. Bernard Harrison.

Senator NELSON. Doctor, you may proceed to present your statement in any fashion you desire. Certainly at any time you wish to elaborate or extemporize on any part of your statement for the record, we will be happy to have you do so. Your statement will be printed in full in the record, along with the appropriate material that you have submitted along with your statement. I assume if we have some questions in the course of your presentation, you will have no objection

to my asking them, but most of the questions, I will ask when you finish.

Dr. ANNIS. Mr. Chairman, if it meets your approval, I will not extemporize during my original presentation. This has been prepared pursuant to your request so that we can have a record. We have condensed it as much as is possible. If I would be allowed to present our entire statement first—I would like to withhold extemporaneous remarks and answers to the chairman until after that presentation, if this meets with your approval.

Senator NELSON. Fine.

Dr. ANNIS. In correspondence between this committee and our association, it has been requested that I include in my discussion these topics:

1. The AMA itself.
2. The evaluation of advertising appearing in AMA publications.
3. Revenue of the association from advertising in its publications.
4. AMA views on a comprehensive drug compendium.
5. Prescription labeling.

All of these subjects are included in this statement, along with exhibits of supporting data which I shall not read, but which will be available for your further information. In addition, I will offer some brief comments which I believe you will find pertinent.

I would like to hope that what I say here today is as carefully reviewed in the Nation's press and in other communications media as the testimony of earlier witnesses has been. If it is, I know it will buttress the public's confidence in American medicine, which I feel has been weakened by some statements this committee has heard.

This Nation is blessed with many hundreds of medical organizations and medical journals, along with hundreds of thousands of physicians and allied medical and health personnel, devoted to improving the health care of the people.

Medicine in this country is already good. That fact can be attested to by millions of men, women, and children who are helped by physicians—and by drugs—every day.

The goals of this committee will not be achieved, and the best interests of the Government and of the Nation's people are not served by undermining confidence in the medical profession or any of the other professions and occupations working to maintain or restore good health.

Mr. Chairman, let me now turn to the topics I promised to cover.

THE AMERICAN MEDICAL ASSOCIATION

The AMA was founded 122 years ago in a nation and a world entirely different from those we now know. In 1847, there were only 29 States with a combined total population less than the present population of the New York and Chicago consolidated areas.

Three primary desires motivated the conscientious physicians and medical school faculties of that day to found a national professional association in medicine.

One was the need to establish and maintain a code of ethics by which physicians' behavior and professional performance could be judged by their peers and the public.

Second was the need to combat the flourishing trade in quackery and nostrums which was endangering the health and lives of Americans.

Third was the need to improve and accredit medical education and to establish high standards which persons must attain before being permitted to practice as physicians.

All three of these objectives are implicit in the purposes of the association, first written into the AMA constitution when it was adopted May 5, 1847: "To promote the science and art of medicine and the betterment of public health."

In 122 years, the association has grown into the world's largest medical association, with 217,000 members—including members who are in the Armed Forces or other Government service and some who are not "active," such as physicians of other nations and dentists and other scientists outside the M.D. discipline who have been accepted into membership because of their contributions to health.

The AMA is a federation of 54 State and territorial medical associations, each of which is autonomous. Remember, it was the State and regional medical societies that existed in 1847 which created the American Medical Association as their national voice; not the other way around.

Each State association—one in each State plus the District of Columbia, Puerto Rico, the Canal Zone, and the Virgin Islands—has its own house of delegates as its policymaking body, made up of representatives elected by the county, city, metropolitan or regional medical societies within its geographical jurisdiction. All together, there are 1,955 of these local medical societies in the United States.

The policymaking body of the AMA is its 242-member house of delegates, of whom 215 are elected by the State and territorial medical associations on the basis of one delegate for each 1,000 members. Five other delegates represent the Army, Navy, Air Force, Veterans' Administration and U.S. Public Health Service. The remaining 22 are from the AMA scientific sections, each representing a medical specialty.

The wishes of the house of delegates—as expressed through the adoption of resolutions or reports—are translated ito action by the officers of the association; by the staff of the AMA; by one or more of the committees, councils, or commissions; or by the State and local medical associations and societies, according to their nature.

Limitations of time make it impratical—if not impossible—to list all of the activities and projects of the AMA on a national scale. But as just one example, the current inventory of books and pamphlets shows 676 designed primarily for physicians; and another 321 primarily intended for public education. Those latter items most commonly are distributed to the public by the State and local associations and by individual physicians. Mr. Chairman, what follows is a partial list of these publications, exhibit A, and a recent brochure entitled "The Search" containing the 1968 Annual Report of the American Medical Association. I believe that both exhibits will be of interest to the committee and I ask that they be included in the report at this point.

Senator NELSON. They will be printed in the record.

Dr. ANNIS. Thank you.

(The documents referred to follow:)

Exhibit A

A PARTIAL LIST OF AMA PUBLICATIONS

AVAILABLE FOR DISTRIBUTION

(Other Than Subscription Items)

Hard and Soft Cover Books

The Best of Law and Medicine (192 pp.)
U.S. Adopted Names for Drugs (150 pp.)
Manual on Alcholism (100 pp.)
The Physician's Career (100 pp.)
The Extended Care Facility (152 pp.)
Current Medical Terminology (976 pp.)
Standard Nomenclature of Athletic Injuries (158 pp.)
Emergency Department, A Handbook for the Medical Staff (144 pp.
Alcohol and the Impaired Driver, A Manual on the Medicolegal Aspects of Chemical Tests for Intoxication (236 pp.)
Utilization Review, A Handbook for the Medical Staff (116 pp.)
Health Education (430 pp.)
School Health Services (414 pp.)
Healthful School Living (324 pp.)
Today's Health Guide (640 pp.)
Let's Talk About Food (148 pp.)
The Look You Like (144 pp.)
Chemical Tests for Intoxication (104 pp.)
Survey of Medical Groups in the U.S. (148 pp.)
Health Appraisal of School Children (56 pp.)
Continuing Medical Education (128 pp.)
New Drugs (591 pp.)

Pamphlets and Brochures

Keeping Healthy
A Letter To You, Mother, About Measles and Your Child
Allergies
Allergies from the Air and What to Do About Them
Anesthesiology
Arthritis
Blood Tests
Cancer: Facts You Should Know
Constipation
Diabetes
How to Prevent Heart Disease
Immunization
Old King Cold
Smoking: Facts You Should Know
TB Control: Prospects for Eradication
Tonsils and Adenoids
Veneral Disease Is Still a World Problem
When Hearing Fades
Your Blood Pressure

(A Partial List....
Pamphlets and Brochures - cont.)

Health Education
- Education of Children for the New Era of Aging
- Health Promotion for Adults
- Mental Health and School Health Services
- Suggested School Health Policies
- Why Health Education?
- Health Aspects of the School Lunch Program
- Health of School Personnel

Quackery
- Chiropractic: The Unscientific Cult
- Did You Know That...? Chiropractic
- Facts on Quacks
- Health Quackery
- Health Quackery-Arthritis
- Health Quackery Devices
- Mechanical Quackery
- The Merchants of Menace
- Health Quackery-Chiropractic
- Health Quackery-Cancer

Alcoholism
- How Teens Set the Stage for Alcoholism
- The Illness Called Alcoholism
- Test Your Alcohol Quotient
- To Your Health (Alcoholism)

Diet and Nutrition
- Can Food Make the Difference
- The Healthy Way to Weigh Less
- Vitamin Supplements and Their Correct Use
- Your Age and Your Diet

Sex Education
- Approaching Adulthood
- A Story About You
- Facts Aren't Enough
- Finding Yourself
- Infertility
- Parents' Responsibility
- Contraceptive Drugs and Devices

Skin Care and Grooming
- The Aging Skin
- Man's Oldest Fallout Problem: Baldness
- The Case of the Sunburned Mannequins
- Color Her Hair Beautiful

(A Partial List....
Pamphlets and Brochures - cont.)

Skin Care and Grooming - cont.
- Color Is Only Skin Deep
- Common Sense About Moles
- Dandruff
- A Dermatologist Talks About Warts
- Excess Hair-A Common Problem for Women
- Housewife and Her Hands
- Feminine Shaving Practices
- Psoriasis: The Scaling Disease
- Shaving Advice For Men
- Something Can Be Done About Acne
- Sunlight and the Skin
- Time Out For Good Grooming
- Vascular Birthmarks and Your Child
- What to Expect from Your Deodorant
- Cosmetic Surgery

Doctors and Patients
- 8 Ways to Cut Your Doctor Bills
- How to Be a Good Patient
- Let's Use Not Abuse Health Insurance
- Medicines and How to Use Them
- Surgery
- What Is Hypnosis?
- What to Look for in a Nursing Home
- When A Mental Patient Comes Home
- When To Call Or See Your Physician
- Why Wait?
- Your Family Health Record
- Your Health Examination

The Human Body
- The Miracle of Life
- The Wonderful Human Machine

Safety and First Aid
- Are You Fit to Drive?
- Artificial Respiration Card
- Danger Lurks
- Emergency Medical Identification Card
- Emergency Medical Identification Symbol
- First Aid Manual
- Protecting Your Home from Unlabeled Poisons
- Safety Belts Save Lives
- Tetanus-the Second Deadliest Poison

Child Care
- A Child in the Family
- Prenatal Care
- When Your Child Needs Glasses

(A Partial List....
Pamphlets and Brochures - cont.)

Adolescent Years
- Why Girls Menstruate
- Why the Rise in Teenage Gonorrhea?
- Why the Rise in Teenage Syphilis?
- Your Teenager And Smoking

Fitness and Sports
- The ABC's of Perfect Posture
- Exercise and Fitness
- First Aid Chart for Athletic Injuries
- A Guide for Medical Evaluation of Candidates for School Sports
- Height/Weight Folder for Boys
- Height/Weight Folder for Girls
- Johnny Makes the Team
- Physical Fitness
- Safeguarding the Health of the Athlete
- Seven Paths to Fitness
- Tips on Athletic Training
- What Makes a Good Hobby?
- What You Should Know About Saunas

Senior Citizens
- Health Aspects of Aging
- How the Older Person Can Get the Most Out of Living
- A New Concept of Aging
- Stay Young, Think Young

For Young Children
- Your Friend The Doctor
- Your Body and How It Works

Drug Dependence
- The Crutch That Cripples - Drug Dependence
- Amphetamines
- Barbiturates
- Glue Sniffing
- LSD
- Marihuana

For Physicians
- Mental Retardation Handbook
- Patient's History Form
- Who Helps the Physician Help the Retarded
- Prenatal Record
- Nursery Record of a Newborn Infant
- Newborn Nursery Daily Worksheet
- Labor Record
- Summary of Labor and Delivery
- Physician's Record of Newborn Infant
- Obstetrical Discharge Summary

(A Partial List....
Pamphlets and Brochures - cont.)

Timely Tips

Buckle Down and Stay Safe
Pull a Switch to Exercise
How Are You Fixed for Poisons
Battling the Cold
Recipe for Family Feeding
Tune-Up for Motoring
The Better to See and Hear
Well Done is For Steak
Operation: Diet Right
Prognosis: Medical Career
Pick Your Shots
How to Be a Medical Watchdog
Key Facts About Tetanus
How's Your Medical ID?
Take Stock of Your Assets
Smarter Than Ponce de Leon
Operation Lift
How Do You Shape Up?
Don't Test Your Poison Defense
Have You Checked on Health
Upstairs, Downstairs, All Through the House
Silent Killer
Let Breakfast Fight Your Battles
Badge of Safety
"VD"
How To Be A Good Patient
Aid For Acne
Measles Vaccine
Handle With Care
Stock Up for First Aid
Partners for Better Health
Beware of Food
The Everyday Exercise-Walking
The Facts About Hay Fever
Night Driving - Double Trouble
Treat Your Feet Right
The Cigarette - A Dubious Companion
Two In Every Hundred
Building a Better Mousetrap

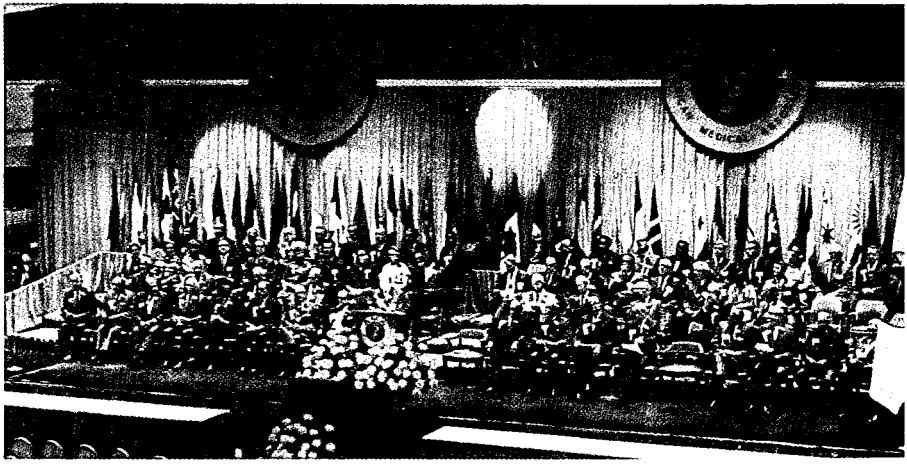
Also Spanish Language Series

EXHIBIT A-1

the Search

1968 ANNUAL REPORT of the AMERICAN MEDICAL ASSOCIATION

"The Death of Socrates," by Jacques Louis David (French, 1748-1825), courtesy of The Metropolitan Museum of Art, Wolfe Fund, 1931.



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FOREWORD

WHAT IS THE AMA?

It is the publisher of the world-famous *Journal of the American Medical Association (JAMA);* ten medical specialty journals; a family health magazine; a newspaper for physicians and others interested in the socio-economic aspects of medicine, and numerous books, proceedings, reports and papers on medical science and medical care.

It is the sponsor or co-sponsor of approximately a thousand meetings, large and small, every year on a host of scientific and non-scientific subjects of interest to physicians and others in the health field.

It is a primary source of medical and health information for the public, the government, schools and writers of books, newspaper stories, magazine articles or television scripts.

Alone, or jointly with other health and scientific organizations, it is the accrediting body for hospitals, extended care facilities, medical schools, internships, continuing education programs for physicians, and educational courses for persons pursuing allied health professions and occupations.

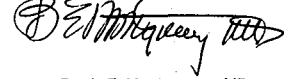
More than anything else, however, the AMA is a state of mind . . . a state of mind that aspires to that of the man honored on the cover of this report.

Socrates sought the truth, and in imparting it to his generation, passed it to all succeeding generations. Physicians, too, seek truth and impart it to their colleagues, to their professional successors and to society so that mankind may live not only a longer life, but a better, richer life.

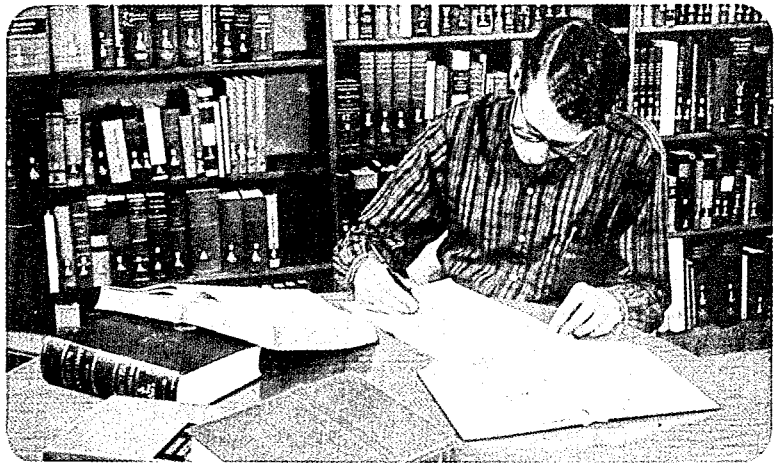
As an organization, the AMA reflects the desire of physicians to join together for the "maintenance of their honor and respectability, for the advancement of their knowledge and the extension of their usefulness"—as the Association founders said in 1846.

It also manifests the belief stated in the last two years by the House of Delegates that "the health and well-being of the patient has always been—and must continue to be—the first concern of the physician," and that "adequate health care should be available to all who need it."

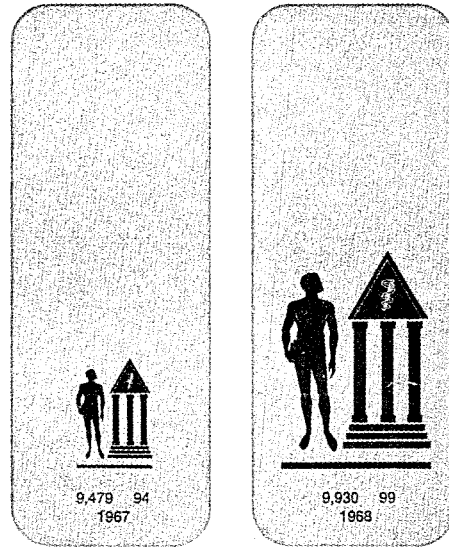
This report of some of the activities of the AMA for the year 1968 is designed to highlight the diverse programs in which the AMA is engaged. I commend it to your attention and I hope you will find it useful as a source of information.



Burtis E. Montgomery, MD
Chairman
Board of Trustees



SEEKING MORE MEDICAL MANPOWER



Nobody quarrels with the idea that there is a shortage of health services. But a lot of arguments can be started by asking, "Why?"

Is there a shortage in the supply, or an excess of demand? Is the shortage only in patient care services, or can it be traced also to areas of teaching, research and the establishment and control of environmental health conditions?

Where people are unable to get immediate medical attention, is it because there is no physician nearby? Or is the problem caused by lack of transportation, lack of knowledge about how to get care, poverty which inhibits some from seeking help, and insurance plans that encourage hospitalization and crowd existing facilities?

How efficiently is today's medical and health personnel being used? How much time does a physician spend doing things that don't require his professional knowledge, judgment and skill? How often is the same thing true of other professionals and technicians? Adding 10 per cent to the productivity of today's physicians would, in effect, add 30,000 physicians to the nation's resources, a figure approximately equal to the yearly production of 300 additional medical schools. A similar increase for all health workers would add the equivalent of 350,000 skilled people.

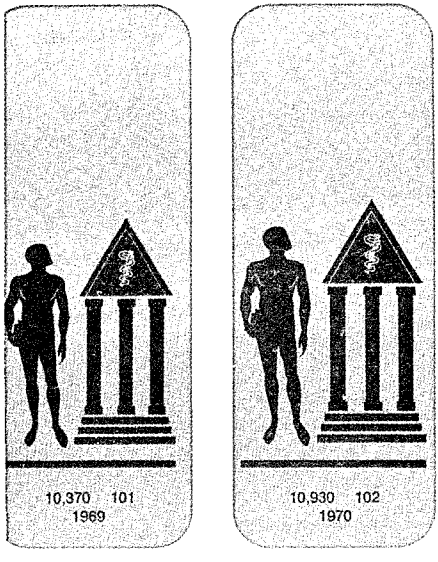
Answers are being sought to two obvious questions: How can more medical and health personnel be developed? How can today's workers best be utilized?

As one step in seeking the answers, the AMA and the Association of American Medical Colleges issued two joint statements in 1968 calling for expanded enrollment in existing medical schools and establishment of new schools; curricular innovations and other changes in the educational programs which could shorten the time required for a medical education; and innovation in educational programs to encourage diversity in the character and objectives of medical schools.

From a first-year enrollment of 9,479 in the nation's 94 medical schools in 1967, the figure has grown to an estimated 9,930 in 99 schools in 1968; and it is expected to reach 10,370 in 101 schools in 1969 and 10,930 in 102 schools in 1970. The five schools which opened for the fall term of 1968 were the University of California School of Medicine at Davis, the University of California San Diego School of Medicine, the University of Connecticut School of Medicine in Hartford, Mount Sinai School of Medicine of the City University of New York, and the University of Texas Medical School at San Antonio.

AMA also is working closely with the National Medical Association to attract more young men and women from minority groups into medicine and to find ways of providing both financial and educational help where necessary.

In addition to its interest in the education of physicians, the AMA also evaluates and approves educational programs for nine groups allied to medicine—medical technologists; x-ray technicians; medical record librarians and technicians; occupational, physical and inhalation therapists; cytotechnologists, and certified laboratory assistants. Standards are currently being developed for programs for radiation therapy technologists, nuclear medicine technologists and technicians, and medical assistants.



FIRST YEAR ENROLLMENT
PER MEDICAL SCHOOL

"American" is AMA's first name, but its interests and activities are by no means limited to these shores.

During the past year, for example, 229 foreign guests from 47 nations visited the headquarters of the American Medical Association.

AMA is the largest of 29 national medical groups that organized the World Medical Association in 1947, now representing more than 700,000 physicians in 59 national associations. A member of the WMA governing Council, AMA has played an important role in such projects as the International Code of Medical Ethics, the Declaration of Helsinki (ethical principles for clinical research), and the Declaration of Sydney (organ transplants).

In cooperation with the U. S. Agency for International Development (AID), AMA organized and administers the American Project of Assistance to Medical Education in Vietnam, bringing together departments of the University of Saigon's Faculty of Medicine and counterparts in U. S. medical schools, now including Emory University and the Universities of Louisville, Nebraska, Washington, Missouri, Georgetown and Oklahoma. American professors help Saigon's teaching program and Vietnamese faculty and graduates are selected for advanced training and observation of educational methods here.

In three years of the Volunteer Physicians for Vietnam Program, more than 500 U. S. physicians have contributed more than 80 man-years of voluntary medical service to South Vietnam's civilian population. Also done in cooperation with AID, the program has attracted U. S. physicians from 49 states, the District of Columbia, Canal Zone and seven overseas locations.

Through AMA's "Doctor-to-Doctor" program, 1,747 American physicians now are corresponding with 2,424 overseas colleagues, sending them medical journals and exchanging information and knowledge.

Readers in 139 foreign countries subscribe for 32,000 copies of the *Journal of the AMA*, the 10 specialty journals, *The AMA News* or *Today's Health*. Another 3,000 copies are sent free to 117 countries. A bimonthly *International Health Bulletin* goes to 2,000 readers here and abroad.

A Spanish edition of AMA's *Current Medical Terminology (CMT)* is being prepared through a Barcelona publisher. *CMT* is a reference book for selecting preferred medical terms, including certain synonyms and generic terms, to provide maximum convenience in usage and publication. AMA is working to make *CMT* the international language of medicine.

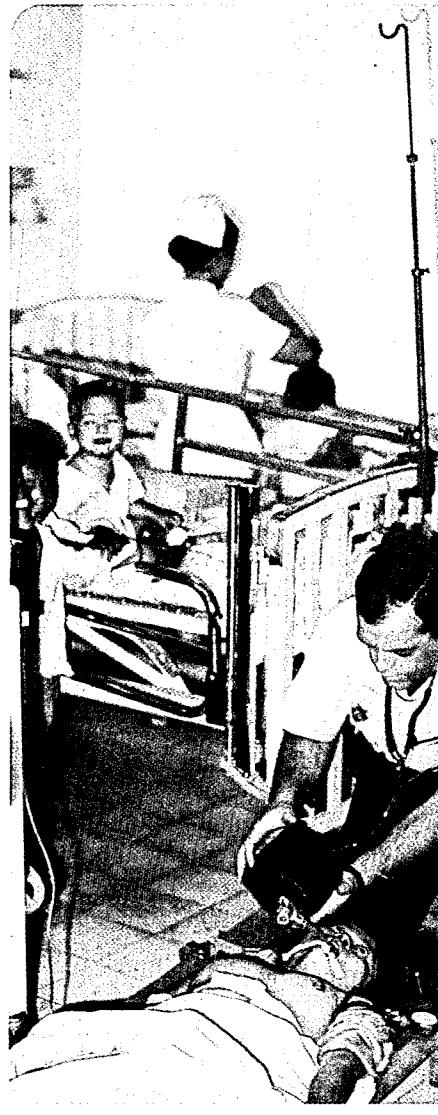
AMA also—

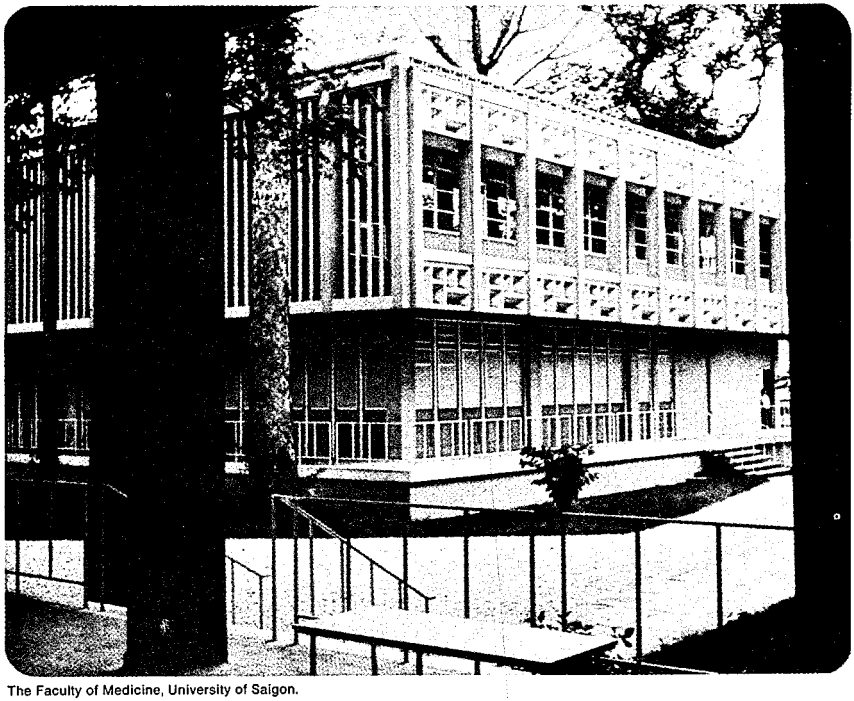
. . . has filled more than 300 requests from around the world for free medical textbooks through its Medical Missionary Program;

. . . has named 22 AMA representatives to foreign national medical meetings or international congresses during the past year;

. . . and maintains liaison with 90 per cent of the 73 volunteer foreign aid agencies recognized by AID.

The fourth AMA Conference on International Health is being planned for the latter part of 1969.





The Faculty of Medicine, University of Saigon.

EXPANDING MEDICINE'S HORIZONS

In more innocent years past, the natural desire of young people to undergo new experiences—and to horrify their elders—led to such activities as goldfish swallowing and telephone booth stuffing.

Today that same desire—apparently coupled with greater sophistication, a social climate of conflict and a disciplinary philosophy of permissiveness—is leading increasing numbers of young people into drug abuse.

Parents, physicians, educators, lawmakers and others share growing concern about the problem and ways to combat it.

As one step toward meeting the challenge, AMA has launched a nationwide educational program on drug abuse.

The production and distribution of a comprehensive educational packet of materials aimed at both physicians and laymen has laid the groundwork for a program that can be carried out at the community level. In the packet, among other things, are the AMA's basic booklet on the subject, *The Crutch That Cripples* (which ran in the September and October issues of *Today's Health),* and a series of *JAMA* articles reviewing the latest scientific findings on marihuana, other hallucinogens, stimulants, sedatives and narcotics.

The strategic position of physicians as leaders of the health team and their understanding of drug abuse and its possible consequences make state and county medical societies and their members best suited to implement such a program, which already has been well accepted by educators, civic leaders, the military and allied medical and health organizations.

Materials developed for the educational program are tailored to community needs.

TELLING IT LIKE IT IS—DRUG ABUSE

EVALUATING DRUGS FOR PHYSICIANS

A pharmaceutical laboratory develops a new drug. It is clinically tested and then approved by the federal government for marketing. It is available to patients on prescription through licensed pharmacists.

How does the physician find out that this new drug is available? Even more important, where can he get accurate, unbiased information on exactly what it will do; what possible side effects can it cause; what conditions within the patient forbid its use?

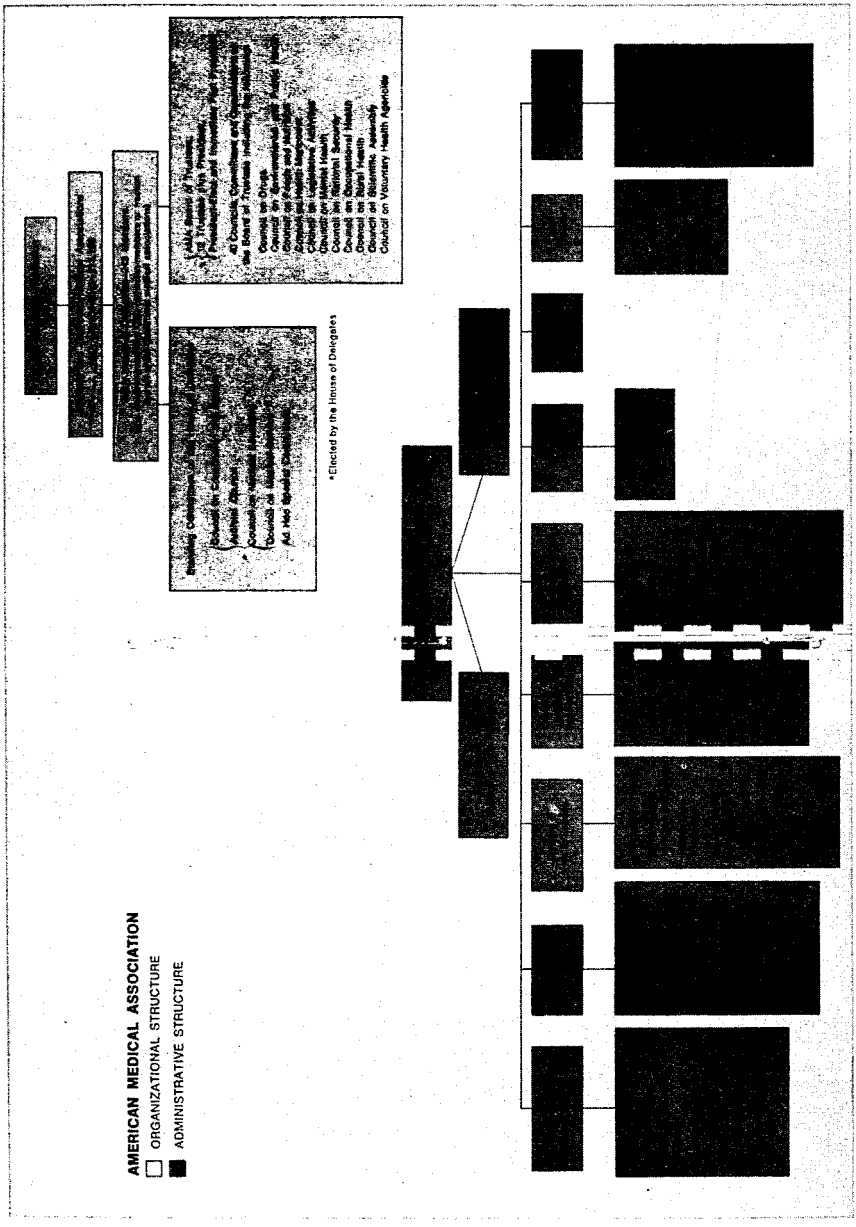
There are a number of sources of such vital information. An important one is AMA.

To provide timely drug information to practicing physicians, the *Journal of the AMA* carries periodic reports on new drugs based on an evaluation of the published literature plus unpublished information received from drug manufacturers—which includes pharmacology and toxicology studies in animals. Before publication, each report is reviewed by AMA and other experts in the field.

AMA's annual book, *New Drugs*, has been an outstanding source of drug information for practicing physicians. It contains information on, and evaluations of, new drugs made available during the previous decade.

Now in preparation is a new publication, to be called *AMA Drug Evaluations (ADE)*, which will include everything *New Drugs* contains plus data on commonly prescribed older drugs, both single entities and combinations. Expected the latter part of 1969, *ADE* initially will have more than 70 chapters covering as many as 1,400 drugs, with comprehensive indexes of names, pharmacologic actions, therapeutic uses and adverse reactions.

Staff services for the United States Adopted Names Council, which names new drugs, are provided by AMA, which also maintains a registry of adverse reactions to drugs and is developing methods for surveillance of drug usage in hospitals.


AMERICAN MEDICAL ASSOCIATION
ORGANIZATIONAL STRUCTURE
ADMINISTRATIVE STRUCTURE
*Elected by the House of Delegates

Television can sell products, personalities and ideas.

Can it sell good health practices? AMA believes it can. So does the television industry, which is cooperating by broadcasting one-minute public service messages on the subject.

Produced and distributed monthly by AMA, the health announcements are used regularly by more than 600 television stations from coast to coast. Many stations use them as often as 90 times a month.

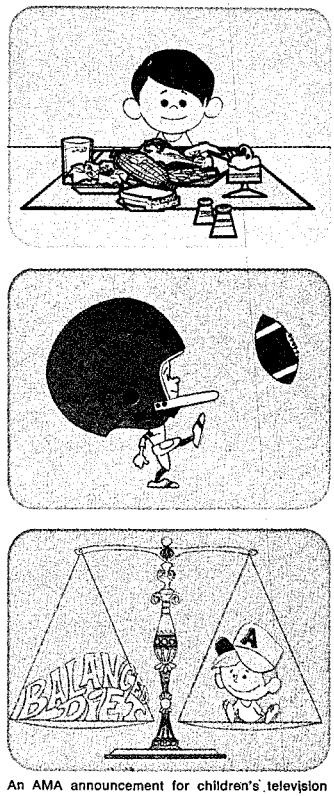
Purpose of the messages is to stimulate awareness of how to stay well by protecting one's own health and safety. These spot announcements are designed to relieve fear, reinforce good health practices and discourage abuses. Subjects range from the selection of a proper babysitter to drug abuse or the measles vaccine.

The messages are animated to be more attention-getting for adults and more easily understandable for children.

The most successful single announcement, in terms of exposure, has been one titled *Faith.* It urges viewers to "Let the faith that sustains you grow strong," and reminds them that "Faith, too, is a physician, with whose help you need never fear." Since its production in 1963, *Faith* has been seen by 50,000,000 people.

Certain messages are being expanded to five minutes for use on children's programs. The first, *Your Body,* has been seen across the country on such programs as "Romper Room." A second, *Your Friend the Doctor,* now is being distributed.

SERVING THE PUBLIC VIA TV



An AMA announcement for children's television programs shows importance of a balanced meal.

INTERPRETING LAW AND LEGISLATION

Imagine a physician trying to keep up with every recent court decision related to health, medicine or physicians. Or imagine him finding time in his busy practice to analyze every piece of pending national or state legislation to see if it would affect his patients or medical practice.

Sound impossible? It is. Yet America's physicians are extremely well informed on medicolegal matters because of the continuing efforts of AMA.

Every bill in Congress that affects health or medicine is analyzed, and pertinent information is distributed to medical societies. There were 1,600 such bills in the 89th Congress and 1,435 in the 90th.

Hundreds of state bills also are analyzed and indexed, providing a valuable source of help for state society legislative committees considering bills for physician support.

Every week a report on *Law and Medicine* appears in the *Journal of the AMA*. More than 80 of the articles that appeared between January, 1966, and February, 1968, were combined in one publication in 1968. Material on legal problems involving medicine or physicians also is published in *The AMA News*.

The Citation, distributed every other week, summarizes individual court decisions involving physicians or medicine. It is the only publication of its type in the country.

In addition, more than 200 printed medicolegal items are available from AMA, including model forms, acts and agreements. AMA compiles information on taxes, corporate practice, professional liability, ethics, blood transfusions and blood grouping, hospital records and other subjects pertaining to law and medicine.

AMA also oversees the maintenance of medical ethics. It keeps extensive files on health quacks and helps collect evidence for their prosecution.

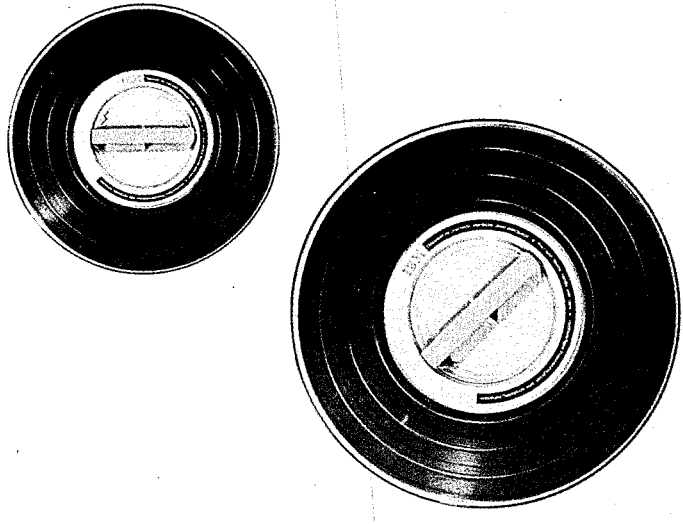
"In a split second, my life flashed before my eyes!"

The hero of a paperback novel describing a moment of mortal danger? Not at all. Simply the comment of a physician seeing AMA's computerized physician records for the first time.

The visitor was seated in front of a television screen as his code numbers were pressed by the operator. In one fifth of a second—the time it takes to blink—his complete record appeared on the screen, including date of birth, medical education, type of practice, American Board affiliations, specialty society memberships and other pertinent information. AMA keeps more complete records on physicians than any other profession has on its members. To answer the approximately 200 requests a day for information, clerks formerly had to go through files, find, remove and read the record cards.

Now the computer—an IBM 360-40, known to the key-punch operators, programmers, systems analysts and operators as Mod-40—does the job for them in a

BRINGING RECORDS TO LIFE



tiny fraction of the time.

Keeping physician records—of AMA members and non-members alike—is the computer's biggest job now. However, Mod-40 is capable of serving every division of AMA in addition to organizations affiliated with or close to AMA, such as the Woman's Auxiliary and AMA-ERF, component and constituent medical societies and medical specialty organizations.

Mod-40's components include the console, through which it is controlled; memory banks to store millions of items of information for instantaneous retrieval; and input-output devices that accept information for storage and produce figures, charts or reports on the screen or in printed form.

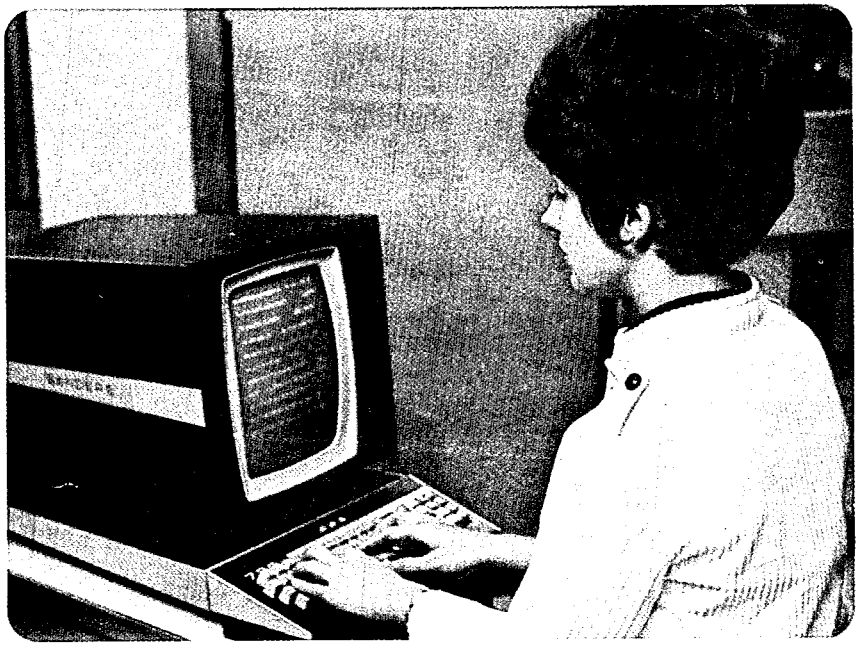
Data fed into the computer is stored on discs and tapes. The full information on the nation's 318,000 physicians is contained on six reels of tape. Information also is stored in a "data cell," which can file 400,000,000 characters and symbols. The average physician's record consists of 1,500 characters of information.

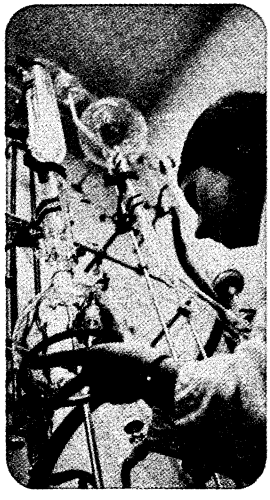
In addition to keeping statistics on physicians, Mod-40 prepares mailing lists, survey and research reports and AMA booklets and directories. It keeps statistical records and makes weekly revisions of the AMA membership report.

New assignments are being sought for it. All accounting and budgeting operations are being computerized, and additional work already is scheduled for other departments or sections of AMA.

Computer technology is advancing at such a swift pace that it is necessary for Mod-40's "keepers" to undergo continual re-training. A new generation of computers is developed every five years and each innovation leads to changes, improvements, new uses and new operating procedures.

The inner complexities of Mod-40 are somewhat a mystery even to its highly trained programmers and operators. "We know what goes into her," one said, "and we know how to get what we want out of her. But we really don't know how she does it."





REACHING FOR KNOWLEDGE

Put 25 scientists and MD's in a modern laboratory with the latest equipment. Relieve them of all administrative or teaching duties, allowing them to devote their full time and energies to pure research. Give them the help of some 35 research assistants, technicians, engineers, secretaries and others, and permit them to call on the facilities of AMA and AMA-ERF. And what do you have?

You have the Institute for Biomedical Research, which, in its second full year of operation, has become an increasingly visible landmark on the scene of biomedical research in this country and in the world.

It is not possible to hold up any one criterion of productivity for an institute completely devoted to basic research, but much of its impact and its worth can be measured by published works in the most reputable and influential scientific journals.

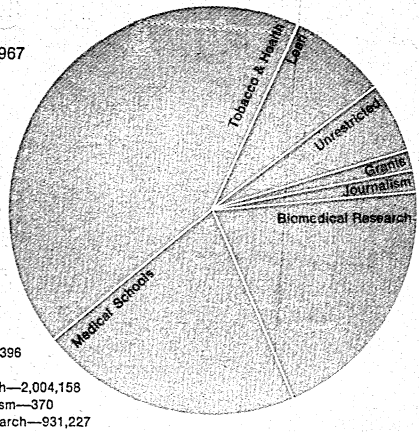
More than 80 scientific papers have appeared over the names of Institute staff members in such journals as the *Proceedings of the National Academy of Sciences, Journal of Biological Chemistry, Science, Virology, Journal of Physical Chemistry, Archives of Biochemistry and Biophysics and Experimental Brain Research.* Thus, the voice of the Institute is being heard in the forums of the world where basic biomedical research is reported and discussed.

All of this is in keeping with the mission of the Institute: to further the development of knowledge in those fundamental aspects of biology which broaden and deepen the foundations of an expanding science of medicine.

The Institute now consists of an animal research facility and laboratory departments of experimental medical ecology, virology, molecular biophysics, regulatory biology and neurobiology.

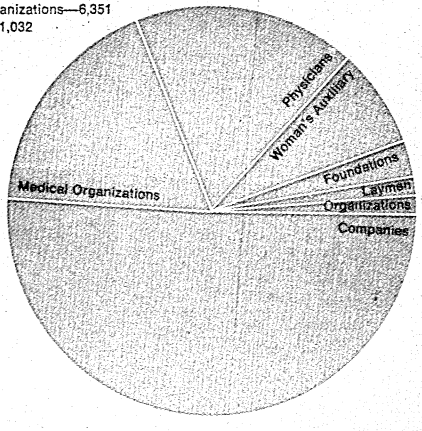
With the approval of the House of Delegates, the Institute will move to a location adjacent to the University of Chicago campus. George W. Beadle, PhD, retired president of the University of Chicago and Nobel prize winner in medicine and physiology, assumed direction of the Institute December 1, 1968. No date has been set for the move to the new location.

SUMMARY 1967



PROGRAM
Schools—$ 930,396
Loan—350,800
Tobacco & Health—2,004,158
Medical Journalism—370
Biomedical Research—931,227
Unrestricted—304,210
Grants—3,758
$4,524,919

SOURCE
Physicians—$ 798,059
Woman's Auxiliary—373,442
Companies—2,365,519
Medical Organizations—838,874
Non-Medical Organizations—6,351
Foundations—131,032
Laymen—10,642
$4,524,919



PUTTING MINDS AND DOLLARS TO WORK

No dollar goes further or does more good than one that supports research . . . helps operate a medical school . . . teaches physicians and medical students journalistic skills so they can communicate more clearly with their colleagues . . . or makes loans available so a medical student, intern or resident can go on with his studies.

And that's exactly what dollars do when physicians and others contribute them to AMA's Education and Research Foundation.

AMA-ERF programs include loan guarantees, the Institute for Biomedical Research, contributions to medical schools, tobacco and health studies, training in medical journalism, and basic medical investigation by independent researchers.

During the year, $959,000 was contributed to medical schools by AMA-ERF, providing a source of unrestricted funds which may be used as each dean sees fit. These funds came principally from physicians (68%) and their wives through the Woman's Auxiliary to the AMA (30%). The remainder came from medical and non-medical organizations and laymen. In the past 15 years, physicians of the U. S. have given almost $68,000,000 to medical schools, both directly and through AMA-ERF.

The Student Loan Guarantee Fund so far has guaranteed 36,707 loans totaling $41,223,000. The guaranteed loans are made available by commercial institutions to cover only essential training and living expenses. The borrower does not start repaying until he has completed his training.

The Woman's Auxiliary, which carries out many fund-raising projects, has contributed $3,268,000 in 16 years to AMA-ERF, increasing its gift every year—from $15,700 in 1951-52 to $389,800 in 1967-68.

About 80 independent investigators in 50 institutions in this country and abroad are studying the effects of tobacco on health, supported by grants allocated through AMA-ERF.

Assets			Liabilities and Reserves		
Current Assets			Current Liabilities		
Cash	2,794,108.68		Accounts Payable	1,618,743.03	
Notes & Accounts Receivable	1,350,450.59		Accrued Taxes	293,311.91	
Inventories	1,350,946.52		Total Current Liabilities		1,912,054.94
Total Current Assets		5,495,505.79	Deferred Income		
Deferred Charges			Dues & Subscriptions		2,599,903.96
Deposits	112,233.75		Total Liabilities		4,511,958.90
Prepaid Expenses	309,941.27		Reserves		
Total Deferred Charges		422,175.02	Reserves for Replacement of Building and Equipment	15,894,766.81	
Fixed Assets			Reserves to finance anticipated needs in the future	3,116,843.44	
Land	1,126,047.14		Total Reserves		19,011,610.25
Building less Accumulated Depreciation	7,234,976.95				
Furniture & Equipment less Accumulated Depreciation	899,785.08				
Total Fixed Assets		9,260,809.17			
Investment-Securities					
U.S. Government Securities	1,138,935.96				
Common Stock	5,895,427.22				
Total Investment-Securities		7,034,363.18			
Other Assets		1,310,715.99			
Total Assets		23,523,569.15	Total Liabilities & Reserves		23,523,569.15

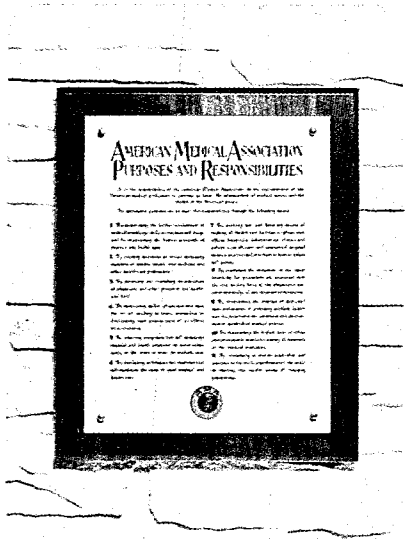
BALANCE SHEET—DECEMBER 31, 1967

It is the responsibility of the American Medical Association, as the representative of the American medical profession, to continue to foster the advancement of medical science and the health of the American people.

Its continuing purposes are to meet this responsibility through the following means:

1. By encouraging the further development of medical knowledge, skills, techniques and drugs; and by maintaining the highest standards of practice and health care.
2. By creating incentives to attract increasing numbers of capable people into medicine and other health-care professions.
3. By advancing and expanding the education of physicians and other groups in the health-care field.
4. By motivating skilled physicians who have the art of teaching to apply themselves to developing new generations of excellent practitioners.
5. By fostering programs that will encourage medical and health personnel to serve voluntarily in the areas of need for medical care.
6. By developing techniques and practices that will moderate the costs of good medical and health care.
7. By seeking out and fostering means of making all health-care facilities—physicians' offices, hospitals, laboratories, clinics and others—as efficient and economical as good medical practice and attention to human values will permit.
8. By combining the utilization of the latest knowledge for prevention and treatment with the vital healing force of the physician's personal knowledge of and devotion to his patient.
9. By maintaining the impetus of dedicated men and women in providing excellent health care by preserving the incentives and effectiveness of unshackled medical practice.
10. By maintaining the highest level of ethics and professional standards among all members of the medical profession.
11. By continuing to provide leadership and guidance to the medical profession of the world in meeting the health needs of changing populations.

THE PURPOSES AND REPONSIBILITIES OF THE AMERICAN MEDICAL ASSOCIATION



Dr. ANNIS. And a moment ago, I mentioned the committees, councils and commissions of the AMA. There is one whose responsibilities are most pertinent to this presentation. It is the council on drugs. I would like to take a few moments to describe some of its functions and achievements.

THE COUNCIL ON DRUGS

In 1847—the year of its founding—the AMA House of Delegates passed a resolution calling for regulation of pharmaceutical matters and patent medicines.

In 1905, the board of trustees of the AMA established the council of pharmacy and chemistry to consider medicinal preparations offered to physicians for use in the prevention, diagnosis, or treatment of disease.

The primary purpose of the council has been to encourage the practice of what physicians call "rational therapeutics," which simply means prescribing drugs on the basis of knowledge of the disease and knowledge of the actions of the proposed remedy.

Since its beginning, the council has engaged in programs of drug evaluation leading to the publication of authoritative, unbiased information on drugs and drug therapy. And as the scope of drug therapy has changed, the council has enlarged and revised the scope of its evaluation programs.

In 1957, after the use of single-entity drugs had become dominant and individually compounded prescriptions had declined, the council changed its name to the council on drugs.

As you can see, the AMA's drug evaluation program is the result of more than 60 years of experience and has taken many forms, of which I shall mention only a few.

From 1907 through 1957, the association published an annual book—this is the one that I received when I was in medical school—"New and Nonofficial Remedies." That was followed from 1958 until 1964 by "New and Nonofficial Drugs," which reflected the need for more clinically oriented information.

An improved annual book first appeared in 1965, called "New Drugs." It provided, for the daily use of the physician, authoritative information on single-entity drugs introduced during the previous 10 years, plus comparative reviews of older drugs in a particular therapeutic group.

A roster of the members of the Council on Drugs is included in this statement as exhibit B. I request that it be made a part of the record at this point.

Senator NELSON. It will be made part of the record.

Dr. ANNIS. Thank you.

(The exhibit referred to follows:)

Exhibit B

COUNCIL ON DRUGS
AMERICAN MEDICAL ASSOCIATION

ROSTER

Adriani, John, M.D. Chairman	New Orleans, Louisiana; Specialties - Anesthesiology, Surgery, Certified by American Board of Anesthesiology; Professor of Surgery, School of Medicine, Tulane University; Member of Subcommittee for Anesthesia and Surgery Committee; National Research Council.
Azarnoff, Daniel L., M.D.	Kansas City, Kansas; Specialty - Internal Medicine; Associate Professor of Medicine and Pharmacology and Director of Clinical Pharmacology of the Department of Medicine, University of Kansas, School of Medicine; Research Interests - Clinical Pharmacology; lipid metabolism and atherosclerosis.
Bass, Allan D., M.D.	Nashville, Tennessee; Specialty - Pharmacology; Professor and Chairman, Department of Pharmacology, Vanderbilt University School of Medicine; Research Interests - Cancer chemotherapy, Mechanism of steroid action, Autonomic pharmacology.
Cluff, Leighton E., M.D.	Gainesville, Florida; Specialty - Internal Medicine, Certified by American Board of Internal Medicine; Professor and Chairman, Department of Medicine, University of Florida College of Medicine; Member, Committee on Infections, American Hospital Association; Recipient, Cancer Research Award NIH, 1962.
Curry, John J., M.D.	Silver Spring, Maryland; Specialties - Cardiology, Internal Medicine, Certified by American Board of Internal Medicine; Associate Clinical Professor of Medicine, Georgetown University School of Medicine; Research Interests - Pulmonary physiology, Hemodynamics in cardiovascular field, Allergy.

David, Norman A., M.D.	Portland Oregon; Specialty - Pharmacology; Professor and Head, Department of Pharmacology, University of Oregon Medical School; Research Interests - Chemotherapy of amebiasis, Pharmacology of sedative and hypnotic drugs, Chronic effects of opium drugs and synthetic analgesics, others.
Freis, Edward D., M.D.	Washington, D.C.; Specialty - Internal Medicine (Cardiovascular Disease), Certified American Board of Internal Medicine; Professor of Internal Medicine, Georgetown University, School of Medicine; Chief, Cardiovascular Research Lab, University Hospital Georgetown University, Washington, D.C., 1949; Senior Medical Investigator, Veterans Administration Hospital, Washington, D.C., 1959; Research Interests - Clinical evaluation and hemodynamic analysis of hypotensive drugs, blood and fluid volume changes in disease, cardiovascular physiology in man.
Moser, Robert H., M.D.	Washington, D.C.; Specialty - Internal Medicine; Chief of Medicine, Walter Reed Hospital; Editoral Staff, Archives of Internal Medicine.
Paulsen, Charles A., M.D.	Seattle, Washington; Specialties - Internal Medicine, Endocrinology; Associate Professor of Medicine, University of Washington; Member of Endocrinology Society, American Society of Internal Medicine.
Rogers, Daniel, M., M.D.	Wenham, Massachusetts; Chairman, Board of Health, Wenham, Massachusetts; Massachusetts Chapter, American Heart Association; Governor's Task Force on Mental Illness; Member of American Academy of General Practice.
Shirkey, Harry C., M.D.	Honolulu, Hawaii; Specialty - Pediatrics, Certified by American Board of Pediatrics; Professor and Chairman, Department of Pediatrics, Professor of Pharmacology, University of Hawaii; Research Interests - Pediatric-Pharmacology, Therapy, Toxicology Drug Standardization.

Smith, Donn Le Roy, M.D.	Louisville, Kentucky; Dean and Professor of Physiology, Louisville University, School of Medicine.
Woods, Lauren, M.D.	Iowa City, Iowa; Specialty - Pharmacology; Professor and Chairman of the Department of Pharmacology, University of Iowa; Research Interests - Metabolism of Drugs, CNS compounds.
Hayes, Thomas H., M.D. Secretary	Chicago, Illinois; Specialties - Administrative Medicine and Internal Medicine; Director, Department of Drugs, American Medical Association; Clinical Associate of Medicine, Department of Medicine, University of Illinois, College of Medicine.

ADVERTISING EVALUATION

Dr. ANNIS (reading).

Earlier in this statement, I mentioned the 997 books and pamphlets produced by the AMA for distribution to physicians and the public. None of those contain advertising. At that time, I did not include the regular publications of the association, saving them for my discussion of the criteria used by the AMA to determine the acceptability of advertising. This is the second of my major subjects.

The AMA publishes the "Journal of the American Medical Association"—known as JAMA and recognized to be the outstanding medical journal in the country.

In addition, the association regularly publishes 10 specialty journals. They are the "American Journal of Diseases of Children." "Archives of Environmental Health," "Archives of General Psychiatry," "Archives of Internal Medicine," "Archives of Otolaryngology," "Archives of Ophthalmology," "Archives of Dermatology," "Archives of Pathology," "Archives of Surgery," and "Archives of Neurology."

Besides the scientific journals, the AMA publishes "Today's Health," a monthly consumer magazine of articles on family health and safety; "The AMA News," a weekly newspaper containing items of general interest to physicians; and a large number of special publications.

JAMA, the specialty journals, "Today's Health" and "The AMA News" all contain advertising. The scientific publications restrict their advertising to products that are germane to, effective and useful in the practice of medicine. The advertising of certain products, such as tobacco and alcoholic beverages, is specifically excluded.

The AMA has a department of advertising evaluation which reports directly to Dr. Hugh H. Hussey, director of the AMA Division of Scientific Activities. Dr. Hussey is a former dean of Georgetown University School of Medicine.

It is important to note that administratively, the department of advertising evaluation is not answerable to the advertising department. It is a separate function, responsible only to the member of the AMA staff charged with directing the association's activities in scientific areas.

The wording and illustrations of advertising, to be acceptable in JAMA or the specialty journals, must meet standards established by the "Principles Governing Advertising in the AMA Scientific Publications." Advertising for "Today's Health" or "The AMA News" must meet written principles and policies governing their acceptance for those publications.

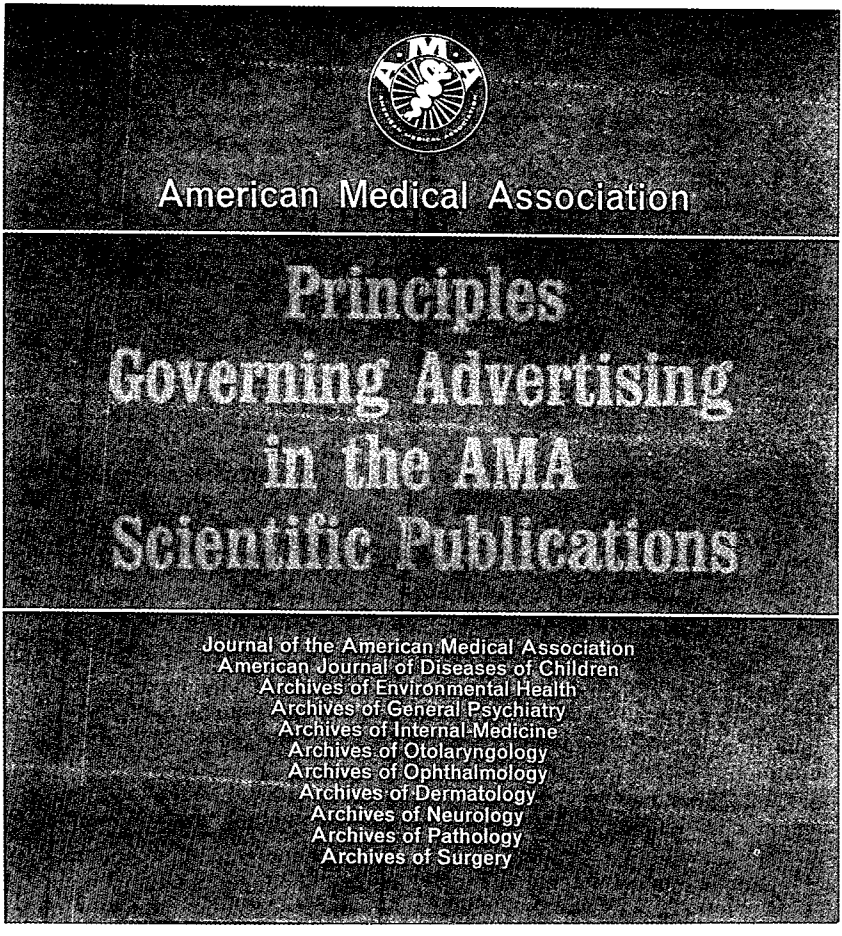
The principles I have referred to are attached to this statement as exhibits C, D, and E. I ask that they be inserted in the record at this point.

Senator NELSON. They will be printed in the record.

Dr. ANNIS. Thank you.

(The exhibits referred to follow:)

EXHIBIT C


American Medical Association
Principles Governing Advertising in the AMA Scientific Publications
Journal of the American Medical Association
American Journal of Diseases of Children
Archives of Environmental Health
Archives of General Psychiatry
Archives of Internal Medicine
Archives of Otolaryngology
Archives of Ophthalmology
Archives of Dermatology
Archives of Neurology
Archives of Pathology
Archives of Surgery

THE AMERICAN MEDICAL ASSOCIATION seeks to promote the science and art of medicine and the betterment of public health. In serving these aims, the AMA communicates regularly with the members of the medical profession, with professional persons in allied fields, and with the public. A substantial part of this communication is carried on through the regular production and distribution of its publications.

In keeping with its avowed purposes, the Association will do all it reasonably can to insure the accuracy, comprehensiveness, timeliness, and relevancy of the advertising content of these publications. The evaluation of advertising copy will be based on the consideration of available data concerning the product or service. It will not be based on tests conducted by the AMA.

The appearance of advertising in AMA publications should not be construed as a guarantee or endorsement of the product by the Association. The fact that an advertisement for a product, service, or company has appeared in an AMA publication shall not be referred to in collateral advertising without specific, written authorization from the American Medical Association.

As a matter of policy, the AMA will sell advertising space in its publications when (1) the buyer believes purchase of such space represents a sound expenditure, (2) the inclusion of advertising material does not interfere with or seriously detract from the purpose of the publication, and (3) the advertising copy meets the standards established for that publication.

Office of Advertising Evaluation
American Medical Association

general principles

These general principles are applied by the American Medical Association in determining the eligibility of products and services for advertising in AMA scientific publications—*The Journal of the American Medical Association* and the ten specialty journals. The Association reserves the right to change these principles in the light of developments in medicine or in industry.

ELIGIBILITY FOR ADVERTISING

1. Products or services eligible for advertising shall be germane to, effective in, and useful in the practice of medicine and shall be commercially available.

2. Pharmaceutical products will not be eligible for advertising until a New Drug Application has been approved by the Food and Drug Administration.

3. "Institutional-type" advertising germane to the practice of medicine and "public service" messages of interest to physicians may be considered eligible for appearance in the scientific publications.

4. Alcoholic beverages and tobacco products are not eligible for advertising.

5. The Association may decide that certain products or services are not eligible for advertising in AMA's scientific journals if advertisements for these specific products or services in other media consistently or significantly depart from the standards set forth in the following sections.

Data Requirements

1. DRUGS.—For convenience, advertisements for drugs (including vaccines and biologicals) may be separated into four categories, as follows:

(a) *New Drugs or New Claims for Drugs Which Have Not Previously Been Advertised in AMA Publications.* A new drug is here defined as any pharmaceutical product which has not been advertised previously in AMA scientific journals. Example of a new claim: use of an established antimalarial drug, such as chloroquine phosphate, in rheumatoid arthritis. In all such cases, the Office of Advertising Evaluation will require supportive scientific evidence for review. It is suggested that clinical and laboratory data on new drugs be submitted to the Office of Advertising Evaluation at the time a New Drug Application is filed with the Food and Drug Administration. This will make it possible, in many cases, to obtain product and advertising clearance prior to the introduction of the drug. However, the Association will not grant final clearance of advertising until notified that the New Drug Application has been approved by the FDA.

(b) *Drugs Which Represent an Additional Brand of a Product That is Already Eligible.* The advertisement alone may be submitted. Supportive data are not required.

(c) *Drugs Which Represent a Modification of an Eligible Product.* Example: Some modification of a previously eligible drug, such as a new salt or ester. All pertinent clinical and laboratory data should be submitted to the Office of Advertising Evaluation.

(d) *Mixtures of Drugs.* Clinical and laboratory data should be submitted for review by the Office of Advertising Evaluation. Clearance depends primarily on showing justification for the rationality of the combination.

2. APPARATUS, INSTRUMENTS, AND DEVICES.—The Office of Advertising Evaluation determines the eligibility of products and the suitability of claims for medical equipment intended for preventive, diagnostic, or therapeutic purposes. Advertisements for products which have not been advertised previously in AMA scientific journals, and new claims for eligible devices should be accompanied by complete scientific and technical data concerning the product's safety, operation, and usefulness. The data should include the results of clinical and

laboratory examination. The data may be either published or unpublished. Samples of apparatus, devices, equipment, or instruments should not be submitted unless specifically requested by the Office of Advertising Evaluation.

3. FOOD PRODUCTS AND VITAMIN PREPARATIONS.—Advertisements for food products and vitamin preparations may be separated into four categories as follows:

(a) *General Purpose Foods.* Those foods promoted for use by the population in general. Examples are bread, processed meats, fruits, and vegetables. Advertisers of such products should submit descriptive literature, labels, and a statement of composition where pertinent.

(b) *Special Purpose Foods.* These are foods for special dietary uses subject to the labeling conditions imposed by section 403j of the Federal Food, Drug and Cosmetic Act. Examples are foods manufactured and promoted for use by certain specific segments of the population, such as infants, invalids, as well as others requiring foods with certain properties, e.g., foods for carbohydrate-restricted diets, sodium-restricted diets, and other therapeutic diets. Advertisers of such products should submit copies of labels, statements of composition, and analytical data. When pertinent, they should be supported by data demonstrating the effectiveness of the product for its intended use. If new claims are made for a previously advertised product, clinical data substantiating such new claims must be submitted.

(c) *Supplemental Vitamin Preparations.* Rational mixtures of the vitamins recognized to be essential in human nutrition or metabolism in amounts not differing greatly from the recommended dietary allowances are eligible. However, with the exception of iron-containing and calcium-containing preparations that are intended for use during pregnancy, vitamin mixtures to which minerals are added (as contrasted to trace minerals which are inherent in the manufacturing process) are not eligible for advertising.

(d) *Therapeutic Vitamin Preparations.* Rational mixtures of the vitamins recognized to be essential in amounts not greater than five times the recommended dietary allowances are eligible. However, preparations containing a mixture of all or most of the following antianemic factors—vitamin B_{12}, folic acid, intrinsic factor, iron, ascorbic acid, and copper—are not eligible for advertising. If claims not generally recognized are made for any of the vitamins, such claims must be substantiated by clinical studies in support of such claims.

4. BOOKS.—A book may be requested for review so that its eligibility for advertising can be determined.

5. MISCELLANEOUS PRODUCTS AND SERVICES.—Products or services not in the above classifications may be eligible for advertising if they satisfy the general principles governing eligibility for advertising in AMA scientific publications.

advertising copy

After a product or service has been declared eligible to be advertised in the scientific publications of the AMA, the Office of Advertising Evaluation must approve each advertisement. The AMA's decisions will be guided in all cases by the following principles:

1. The advertisement should clearly identify the advertiser and the product or service being offered. In the case of drug advertisements, the full generic name (including salt and ester designation) of each active ingredient must appear in eight-point type or larger.

2. Advertisements should not be deceptive or misleading. Layout, artwork, and format should be such as to avoid confusion with the editorial content of the publication. The word "advertisement" may be required.

3. Unfair comparisons or unwarranted disparagements of a competitor's products or services will not be allowed.

4. Claims for superiority must be supported by evidence acceptable to the Association. Unsubstantiated superlatives or extravagantly worded copy will not be allowed.

5. Quotations or excerpts from a published paper are acceptable only if they do not distort the meaning intended by the author. Claims made within quotations must conform to the same standards as unquoted claims.

6. Advertisements will not be accepted if they conflict with the principles of medical ethics.

procedures of the AMA office of advertising evaluation

(SCIENTIFIC JOURNALS)

The AMA Office of Advertising Evaluation is responsible for applying the foregoing principles and standards to advertising copy submitted for inclusion in AMA scientific journals. It will do so in accordance with the following procedures:

1. *Submission of Data.*—The Office of Advertising Evaluation requires that scientific data be submitted to substantiate claims made for new products (such as drugs, devices, and foods) or new claims for products which have appeared previously in AMA scientific journals.

2. *Type of Data Needed.*—Data should include pertinent reports—published and unpublished, favorable and unfavorable—of clinical and laboratory investigations covering the efficacy and relative safety of the product under consideration. These data should be based upon sound studies and should be sufficiently comprehensive to permit a critical evaluation of the subject matter. While the quantity of the scientific data required will depend on the type of product, the nature of the medical problem involved, and the claims made in the advertising copy, the quality of the evidence is regarded as highly important; in this respect, the importance of suitable controls is emphasized. Compilations of subjective individual case reports and testimonials are not considered acceptable evidence. The unpublished portions of all submitted data will be regarded by the Office of Advertising Evaluation as confidential, and consultants will be requested to treat them accordingly.

3. *Consultation.*—The AMA Office of Advertising Evaluation frequently seeks the opinions of consultants and recognizes the statements formulated by AMA Councils and Committees in determining the eligibility of products and the suitability of claims. The consultants to the Office of Advertising Evaluation are persons who have been selected for their competence in the specialties involved. The names and affiliations of the consultants are not made available.

Time Requirements of the Office of Advertising Evaluation

Although the Office of Advertising Evaluation cannot guarantee adherence, in all cases, to a fixed time schedule, every effort will be made to expedite completion of AMA consideration in the following time intervals:

Advertisements for Eligible Products with No New Claims.—From the time copy is received, 5 working days should be allowed for AMA consideration.

Advertisements Involving New Claims for, or Modifications of Currently Eligible Products, Or Both.—From the time copy and, if necessary, supportive data are received, 10 working days should be allowed for AMA consideration.

Advertisements for New Products.—From the time copy and supportive data are received, 15 working days should be allowed for AMA consideration. Unless accompanied by supportive data, proposed advertisements for new products cannot be considered by the Office of Advertising Evaluation.

In those cases in which AMA consideration cannot be completed prior to the expiration of the foregoing time intervals, the advertiser or agency will be so informed.

As a matter of policy, the AMA periodically will review its advertising principles with the view of keeping pace with changes that may occur in the industry and in the profession. It is hoped by this practice of continuous review and reevaluation to insure and improve the timeliness, relevancy and appropriateness of the advertising content of AMA scientific publications.

Correspondence, proposed advertisements, supportive data, etc. should be addressed to:

Office of Advertising Evaluation
American Medical Association
535 North Dearborn Street
Chicago, Illinois 60610

EXHIBIT D

NON-HEALTH ORIENTED PRODUCTS AND SERVICES

principles governing advertising in Today's Health

advertising in today's health

TODAY'S HEALTH, published monthly by the American Medical Association, provides interesting and authoritative information to the public concerning the care and well-being of the readers and their families. It is distributed to physicians for their office reception rooms and to persons who wish to subscribe.

The acceptance of an advertisement for TODAY'S HEALTH by the American Medical Association does not constitute in any way an endorsement or guarantee by the Association. The evaluators will make every reasonable effort to ensure the accuracy, timeliness, and relevancy of the advertising content of the magazine. No laboratory testing of products is done by the A.M.A. In no case may the appearance of an advertisement for a product, service, or company in TODAY'S HEALTH be mentioned in collateral advertising unless specific written authorization has been obtained from the American Medical Association.

The following principles are used to determine the eligibility of products and services and the suitability of advertising copy. The American Medical Association reserves the right to change its principles governing advertising in accord with current developments. The Association also reserves to itself all final decisions regarding the eligibility of any products and services and the acceptability of proposed advertisements.

eligibility

Products and services that are offered by responsible advertisers and which, when used properly, contribute to the general welfare of the consumer are eligible for advertising in TODAY'S HEALTH.

Products or services NOT eligible for advertising in TODAY'S HEALTH include:

1) Products (e.g., tobacco and alcoholic beverages) or services which, in the opinion of the Association, may be detrimental to the user, and any products related to the use of such a product or service;
2) Product or service claims which can not be supported by data acceptable to the Association;
3) Products or services that are advertised in other media in a manner inconsistent with the following principles.

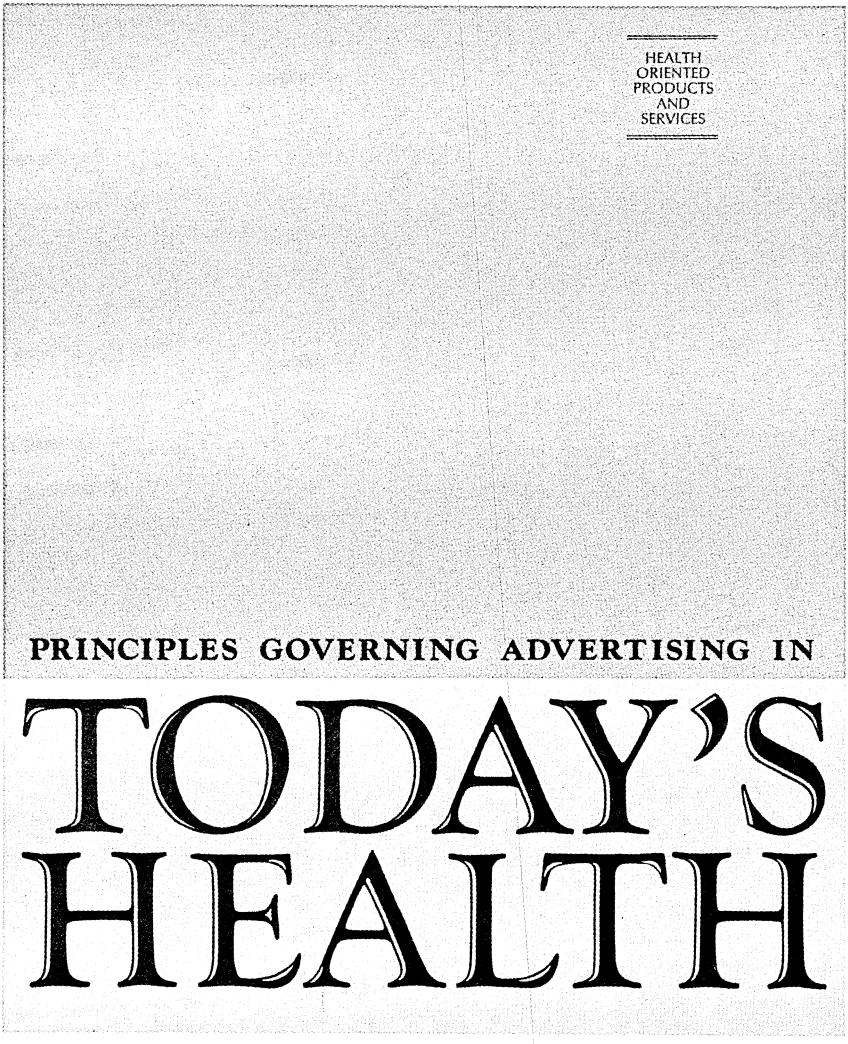
advertising principles

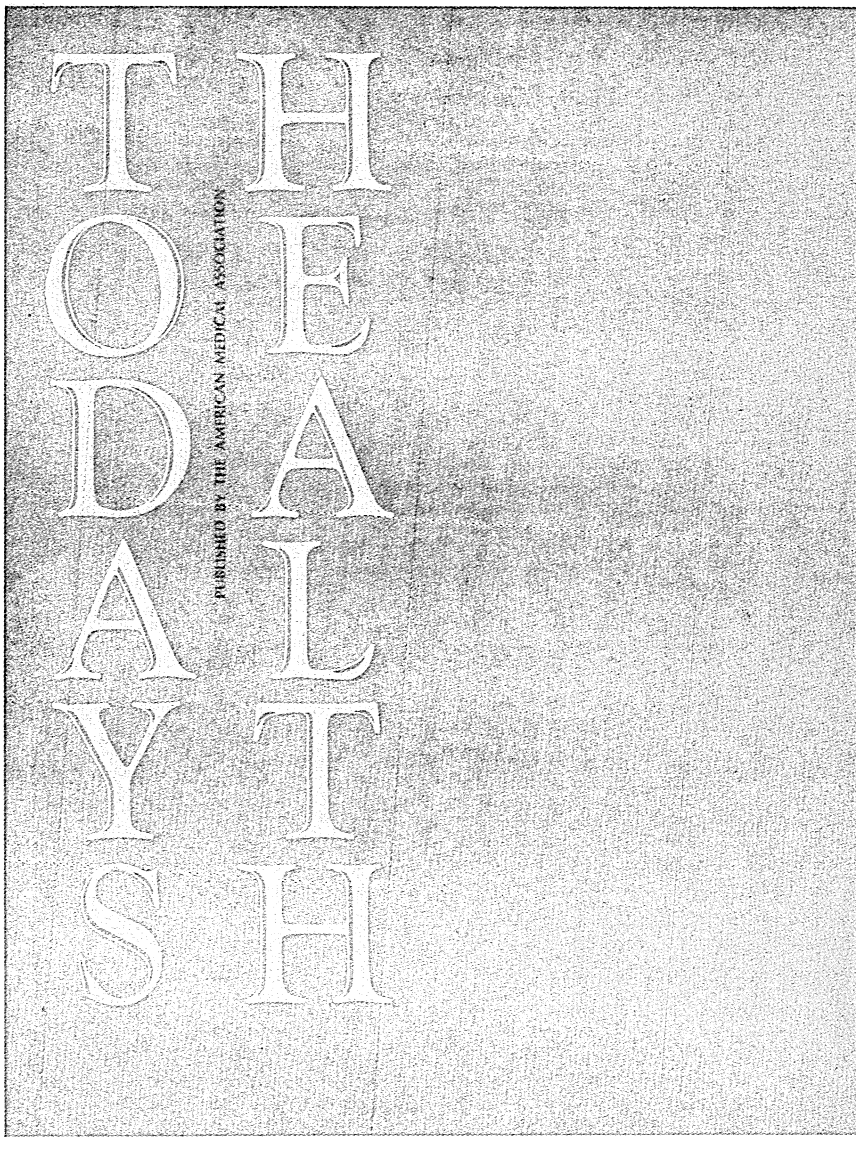
Each presentation of advertising copy of an eligible product or service must be approved individually by the American Medical Association, which shall make the final decisions regarding the suitability of copy, artwork, and format.

The following principles will be utilized to evaluate advertisements:

1) The advertisement must clearly identify the advertiser and the product or service.
2) The message, text, and artwork must be in good taste and in harmony with the purpose of the magazine.
3) The advertisement should present the positive merits of the product or service and not discredit or disparage those of competitors. Fair comparisons based on substantial evidence are acceptable.
4) The advertisement shall be designed to avoid deceiving or misleading the reader in any way.
5) The format should be such as to avoid confusion with the editorial content of the magazine.
6) Claims made within quotations must conform to the same standards as unquoted claims.

EXHIBIT D-1


HEALTH
ORIENTED
PRODUCTS
AND
SERVICES
PRINCIPLES GOVERNING ADVERTISING IN
TODAY'S
HEALTH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ADVERTISING IN TODAY'S HEALTH

Today's Health, published monthly by the American Medical Association, provides interesting and authoritative information to the public concerning the health and welfare of the individual and society. It is distributed to physicians for their office reception rooms and to persons who wish to subscribe.

The acceptance of an advertisement for *Today's Health* by the American Medical Association does not constitute in any way an endorsement or guarantee by the Association, although the evaluators will make every reasonable effort to ensure the accuracy, timeliness, and relevancy of the advertising content of the magazine. No laboratory testing of products is done by the A.M.A. In no case may the appearance of an advertisement for a product, service, or company in *Today's Health* be mentioned in collateral advertising unless specific written authorization has been obtained from the American Medical Association.

The following principles are used to determine the eligibility of products and services for which health claims are made and the suitability of advertising copy. The American Medical Association reserves the right to change its principles governing advertising in accord with developments in medicine or in industry. The Association also reserves to itself all final decisions regarding the eligibility of any products and services and the acceptability of proposed advertisements.

ELIGIBILITY

Products and services that are offered by responsible advertisers and which, when used properly, contribute to the health or general welfare of the consumer are eligible for advertising in *Today's Health*.

Products or services NOT eligible for advertising in *Today's Health* include:

1. Products (e.g., tobacco and alcoholic beverages) or services which, in the opinion of the Association, may be detrimental to the user, and any products related to the use of such a product or service;

2. Certain products with particularly intimate uses;

3. Products or services for which the claims for efficacy are not supported by data acceptable to the Association;

4. Needlessly complex combinations of drugs;

5. Products or services which, in the opinion of the Association, should be used only on the advice or prescription of a physician; and

6. Products or services that are advertised in other media in a manner inconsistent with the following principles.

ADVERTISING PRESENTATION

Each presentation of advertising copy of an eligible product or service must be approved individually by the American Medical Association, which shall make the final decisions regarding the suitability of copy, artwork, and format.

The following principles will be utilized to evaluate advertisements containing health claims:

1. The advertisement must clearly identify the advertiser and the product or service. A complete statement of composition, qualitative and quantitative, of over-the-counter medications must be submitted to the Office of Advertising Evaluation. Such information need not be included in the text of the advertisement, except when this information is considered necessary for purposes of identification.

2. The message, text, and artwork must be in good taste and in harmony with the purpose of the magazine.

3. The advertisement should present the positive merits of the product or service and not discredit or disparage those of competitors. Fair comparisons based on substantial evidence are acceptable.

4. The advertisement shall be designed to avoid deceiving or misleading the reader in any way.

5. The format should be such as to avoid confusion with the editorial content of the magazine.

6. Scientific evidence acceptable to the Association must be submitted to substantiate health claims made for any product or service.

7. Claims made within quotations must conform to the same standards as unquoted claims.

THE AMA NEWS Exhibit E

ADVERTISING ACCEPTANCE POLICIES

The acceptance of advertising to be carried in The AMA NEWS is governed by the following policies:

A. ELIGIBILITY FOR ADVERTISING

1. Products or services eligible for advertising in The AMA NEWS must be of interest to physicians and their families as consumers.

2. Products or services directly involved in the prevention, diagnosis or treatment of disease or which involve copy claims pertaining to health of people are NOT eligible for advertising in The AMA NEWS.

3. In addition to the above limitations, advertising will be accepted only from responsible business firms which guarantee to stand back of claims made in their advertising copy.

4. Advertisements which offer the reader information concerning investment opportunities must comply with the above standards and, in addition, must avoid reference to a specific security issue.

5. Advertisements for alcoholic beverages and products to be smoked are not acceptable.

B. SUITABILITY OF ADVERTISING COPY

1. The advertisement should clearly identify the advertiser and the product or service being offered.

2. Advertisements should not be deceptive or misleading to physicians or their families.

3. Layout and format should be such as to avoid confusion with editorial or news items.

4. Unfair comparisons or the disparagement of a competitor's goods will not be allowed.

5. Advertisements will not be accepted if they appear to violate the principles of medical ethics, are indecent or offensive in either text or art work, contain attacks of a personal, racial or religious character.

6. Claims made in advertisements for insurance coverage must conform to the above standards and, in addition, must conform to the following specific criteria:

   (a) Claims relating to policy benefits, losses covered, or premiums must be complete and truthful.

   (b) Claims made shall include full disclosure of expectations, reductions and limitations affecting the basic provisions of the policy

   (c) Claims incorporating quoted testimonials must meet the same standards as unquoted claims.

   (d) Each advertisement for insurance must include a statement indicating the number of states in which the company is licensed.

Dr. ANNIS. All proposed advertising is screened through the filter of the appropriate written principles. If the product is found ineligible, the advertising is rejected. If claims in the proposed ad are questionable, substantiating data are requested and the material is reviewed again in the light of the new information.

Finally, the advertisement is reviewed: for clarity; that it makes no unwarranted comparisons or claims of superiority; and that it does not conflict with the principles of medical ethics.

On the whole, we believe that no publication surpasses our own standards for acceptable advertising. However, it should be remembered that the AMA does not attempt to substitute its principles for the advertising surveillance authority vested in the FDA by Congress. We evaluate prescription drug advertisements to make sure the Journal of the AMA continues to fulfill its scientific purposes and remain acceptable to the profession. In making these decisions, we are aware of the ever-changing world of medical science. As new knowledge becomes available, our judgment factors must change accordingly.

ADVERTISING REVENUE

The third subject I promised to cover logically comes at this point. It is the advertising revenue received by the AMA.

Your correspondence indicated that the committee is interested in the income received by the AMA from pharmaceutical manufacturers who advertise in JAMA. We do not have a breakdown purely for pharmaceutical advertising. However, I can give you figures for total advertising revenues for JAMA and the specialty journals.

I want to preface these figures by making it clear that they represent gross income—not net. To obtain a net figure, it would be necessary to substract the expenses of producing the journals, including salaries and wages for the staffs; buying the paper; printing; mailing; and other items. I can assure you the costs are substantial.

For the years 1963 through 1968, gross advertising revenues for JAMA ranged from a low in 1963 of $7,831,000 to a high of $10,605,000 in 1966. The revenue in 1968 was $8,643,000. For the specialty journals combined, the gross figure for those years ranged from $1,413,000 in 1963 to $2,234,000 in 1968.

(Gross advertising revenues follow:)

GROSS ADVERTISING REVENUES

Year	JAMA	Specialty journals
1963	$7,831,000	$1,413,000
1964	7,968,961	1,563,702
1965	9,983,795	1,710,510
1966	10,605,625	1,725,695
1967	10,546,000	1,978,000
1968	8,643,000	2,234,000

Dr. ANNIS. Advertising rates for medical journals are expressed most commonly in cost per page of advertising and the cost per thousand copies of the journal according to its total circulation.

For JAMA, the rate for one black-and-white page rose from $1,600 in 1963 to $2,120 in 1967 and 1968. The cost per thousand was $8.05 in 1963; fell to $7.89 in 1964; and reached $9.89 in 1968, having dropped 2 cents from 1967.

(Advertising rates for JAMA follow:)

ADVERTISING RATES FOR JAMA

Year	Rate for 1 page, black and white	Cost per thousand
1963	$1,600	$8.05
1964	1,600	7.89
1965	1,840	8.88
1966	1,840	8.65
1967	2,120	9.91
1968	2,120	9.89

Dr. ANNIS. I have already referred to the association's substantial expenses. I think it is of interest that the AMA has more than $12 million budgeted for scientific programs in 1969; and more than $6 million for medical service programs. Most of the medical service programs are directed toward health education of the public and community health planning.

Almost another million dollars is budgeted for support of other medical organizations such as the World Medical Association, the Joint Commission on Accreditation of Hospitals, and the National Health Council.

Two million dollars is earmarked for international health programs; and maintenance of complete biographical records on all physicians in the United States takes another million and a half dollars a year.

The programs of the AMA Education and Research Foundation receive $1 million a year from the association.

Mr. Chairman, I have attached as exhibit F a copy of the association's 1969 budget, which lists major program expenditures. I ask that it be inserted in the record at this point.

Senator NELSON. It will be printed in the record.

Dr. ANNIS. Thank you.

(The exhibit referred to follows:)

EXHIBIT F

American Medical Association, 1969 Budget

1. Scientific programs	$12,357,903
2. Medical service programs	6,058,459
3. Communications programs	1,232,687
4. Support to other medical organizations	759,700
5. Support to nonmedical organizations	23,625
6. International health programs	2,031,757
7. Legislative programs	299,228
8. Professional ethics	89,919
9. Medicine and religion program	148,907
10. Archive—Library service	238,431
11. Public affairs	1,230,100
12. Legal services	397,528
13. Physician records	1,422,962
14. AMA–ERF programs	1,003,300
15. Administrative costs	6,605,041
Total	33,899,547

Dr. ANNIS. The American Medical Association's programs and policies have never been, are not now, and will never be shaped by any

dependence on the drug industry. And to insure that there is no "conflict of interest," the AMA has consistently separated the editorial management, advertising acceptance, and business management of each of its scientific publications.

The editorial staff of JAMA is in one division; the advertising acceptance responsibility is in a separate division; and business management and sales are in still another.

The editorial content of a journal must be objective if it is to be acceptable to members of our profession. If that content were shaped or influenced by commercial considerations, the profession would quickly reject the publication.

COMPENDIUM

Turning to my fourth topic, legislative proposals have been made regarding publication of a drug compendium which would, in effect, contain information presently included in package inserts for all available prescription drugs.

The purpose of the compendium is to compile in one volume complete information on those drugs. It is intended to be, in fact, the single authoritative source of readily accessible drug information for the physician. Under most proposals, drugs would be identified both by their generic and their brand names.

You will recall that during my earlier discussion of the AMA Council on Drugs, I mentioned annual publications in the drug field—specifically, New and Nonofficial Drugs, and New Drugs.

Today, an important activity of the council is to create a publication that is expected later this year, to be called AMA Drug Evaluations, or ADE.

We agree wholeheartedly that the medical practitioner needs another source of reliable, unbiased, and current information on drugs and new developments in drug therapy. It is necessary also that the source be in a form that makes the facts he needs available with a minimum of effort and in a minimum of time.

ADE will identify various diseases, disturbances, and conditions for which drugs are prescribed.

Drugs used in the treatment of the conditions will then be listed alphabetically by their generic names, along with other necessary information, such as actions, uses, principal adverse reactions, dosage, available dosage forms, and the names of manufacturers.

In addition—and this is a most important feature—will be information providing a comparison of the therapeutic effectiveness of drugs having similar uses.

A mere compendium, in the sense that it would be a listing of drugs, would leave significant information gaps. Our drug evaluation publication would not.

Evaluations are now being prepared for essentially all marketed therapeutic agents that are new, single entity drugs; official in the U.S. Pharmacopeia or National Formulary; frequently used or prescribed; or otherwise notable. For example, they might be otherwise notable either because of their therapeutic nature or their unusual toxicity.

The book will be thoroughly cross-indexed, including listings by drug name, by pharmacologic and chemical factors, by therapeutic uses and by adverse reactions. It will be revised and updated regularly.

And because it will contain special information on newer products, it will, in effect, absorb the earlier publication, New Drugs, by making that same information available in a more usable form, along with substantial amounts of other information.

We believe sincerely that AMA Drug Evaluations will be the most useful publication in the physician's library regarding drugs.

And that is not only our opinion. A sample chapter of the publication, on anticonvulsants, was published in JAMA May 20, 1968. I offer it with this statement and ask that it be included as exhibit G at this point in the record.

Senator NELSON. It will be printed in the record.

Dr. ANNIS. Thank you.

(The exhibit referred to follows:)

Exhibit G

Reprinted From The Journal of The American Medical Association
May 20, 1968, Vol. 204, pp. 702-710B

Council on Drugs

A new publication of the Council on Drugs will provide authoritative, unbiased information on drugs in a new format designed to meet the everyday needs of the practicing physician. The Council herewith presents a sample chapter of the new book, and invites physicians to comment on the book's usefulness by completing the questionnaire following p 710.

AMA Drug Evaluations

A New Book on Drugs

The American Medical Association's Council on Drugs announces a new publication on drugs designed to provide an improved service to the medical profession. From its inception in 1905, the Council on Drugs (originally called the Council on Pharmacy and Chemistry) has encouraged rational therapy by providing authoritative and unbiased information on drugs. Throughout its long history, the Council has modified its drug evaluation programs in accordance with new developments in the drug field, and it has continued to alter the concepts and format of its publications to reflect the changing needs of the physician. Its earlier evaluation program had been limited to those drugs considered to have well-established clinical usefulness, but in 1955 this program was expanded to consider all commercially available, newer single-entity drugs. The older books published by the Council—*New and Nonofficial Remedies*, *New and Nonofficial Drugs*, and, more recently, *New Drugs*—are now being replaced by *AMA Drug Evaluations (ADE)*, a comprehensive reference book that will include information on both old and new single-entity drugs and mixtures. The book is being prepared through a joint effort of the Council, the staff of the AMA Department of Drugs, drug evaluators outside the Department working part-time, and many voluntary expert consultants; as with *New Drugs*, the cooperation of much of the pharmaceutical industry will continue to be sought for the furnishing of data relevant to some parts of *ADE*.

The design calls for continuing the practice of having in each chapter an introductory statement that discusses the overall therapeutic category, followed by brief descriptions and evaluations of all drugs in the class, old or new, if they fall within a very broad priority list. The more detailed monographs on newer agents will be included as an appendix, which will represent a continuation of *New Drugs*.

The priority list of drugs, including mixtures, that will have individual evaluations includes virtually all therapeutic agents in official compendia, *USP* and *NF*; the drugs most commonly prescribed or used by physicians in the United States; and, as in *New Drugs*, all single-entity preparations introduced during the past ten years. In addition, other selected drugs will be evaluated if they are judged to be of particular importance because of such qualities as notable value, unusual toxicity, notoriety, or need for notoriety. Many nonpriority drugs that are not individually evaluated will be listed in the book if they are distributed nationally; these will be listed and indexed to give information on their therapeutic category and availability. To make the information readily accessible, *ADE* will be extensively indexed; comprehensive indexes on drug names (nonproprietary and trademarks), pharmacologic actions, therapeutic uses, and important adverse reactions are planned.

The evaluations of the older drugs and mixtures will often contain fewer details than the monographs on newer, single-entity drugs. Nevertheless, an effort will be made whenever possible to give comparative statements on relative effectiveness and relative safety and to inform of notable hazards and necessary precautions in the use of the drugs. The inclusion of a particular drug in the book will not imply endorsement by the Council; an evaluation may be favorable toward a drug, unfavorable, or a combination of both, depending on the merits. Whenever the facts clearly warrant, a drug will be described as an agent of first choice, reserve choice, or last resort.

The evaluative or interpretive information in the book, particularly on controversial matters, must necessarily disagree with the opinions of some other sources. Statements will be based on the convergent trend of the best information available from such sources as scientific literature, unpublished data, and advice of consultants. Reportorial information will be selective and condensed to represent what the Council regards as the most useful to the physician in his selection and use of the drugs. Accordingly, such information as rare, relatively minor, or unconfirmed reactions, precautions that relate to clearly obvious or highly remote situations, and unusual or speculative uses of a drug

Reprint requests to Secretary, Council on Drugs, American Medical Association, 535 N Dearborn St, Chicago 60610.

may be omitted. It is hoped that *ADE* thus will provide a convenient reference from an authoritative source to give the practicing physician the most important information to help in his prescribing practices. For other details, for basic data, and even for varying points of view, the physician is encouraged to consult and compare the many sources of information on drugs he uses: journal articles, standard textbooks, official compendia, manufacturers' labeling, prominent bulletins and periodicals on drugs and therapeutics, and symposia.

The sample chapter that follows is presented both to familiarize the physician with the Council's plans and to invite comments and recommendations. Most of the book is in a stage of preparation that still permits flexibility in content and design, and subsequent editions are intended to follow. Therefore, since the Council's aim is to meet the needs of its physician readers, responses to the attached questionnaire can have an important influence on the further development of the book. The book is expected to be published in approximately one year.

The accompanying chapter on "Anticonvulsants" is not completely a self-contained unit. The reader will notice several cross-references that presently are only hypothetical, as the associated material is still to be published; nevertheless, they are included to help illustrate the design of the forthcoming book.

After reading the sample chapter, please fill out the questionnaire following page 710 and return it to the AMA.

Chapter 29

ANTICONVULSANTS

Anticonvulsants are used to terminate certain acute convulsive episodes, but their principal use is prophylactic to reduce the number and severity of seizures in patients with epilepsy. Seizures may be classified in various ways; for therapeutic purposes, the following is convenient: major motor (grand mal or focal), petit mal (absence), minor motor, and psychomotor.

Although their specific modes of action are not fully understood, a number of drugs have anticonvulsant activity and are effective in preventing or reducing the frequency of seizures in most patients with epilepsy. The objective of therapy is to control the seizures and at the same time maintain the patient in as normal a physiologic state as is possible. Drug therapy must be individualized for every patient; within the limits of adverse effects and toxicity, the correct dosage of any drug or combination of drugs is that which is "enough" to accomplish the stated purpose. The choice of drugs depends upon the type of seizure. Further, many patients with epilepsy have more than one type of seizure, and drugs effective for one of these types may not help or may even unmask another. The most common causes of failure of treatment are improper classification of type of seizure, failure to recognize a progressive neurologic disease, failure to use the proper drugs or proper dosages, too frequent changes in drug therapy, premature withdrawal of drugs, poor indoctrination of patients, and failure to recognize the social and economic needs of patients. With the exception of patients who do not adhere to their prescribed regimen, the largest group of failures is related to the administration of insufficient dosages of appropriate drugs and failure to use two or more of them concomitantly when they are needed.

The patient should be started on a small or moderate dosage of the drug that is considered to be suitable. This dosage should be increased gradually at intervals until the seizures are controlled or until the appearance of minor toxic symptoms makes further increases inadvisable. If more than minor toxic phenomena develop, the medication should be withdrawn and another substituted. When the drug used initially is well tolerated but only reduces the frequency of the seizures, another compound should be added. The dosage information given with the subsequent discussions of individual drugs falls within the ranges given in official compendia, those recommended by one or more manufacturers, or those considered reasonable by other authorities. However, the size, age, and condition of the patient, his response to treatment, and the possible synergistic or antagonistic effect of concomitant medication must always be considered. Reductions in dosages of anticonvulsants for children in comparison with adult dosages are not always as great as would be expected from the difference in age and size.

Phenobarbital is still considered the mainstay of anticonvulsant therapy; it is among the safest of the available drugs and is useful in the management of most types of seizures. The other long-acting barbiturates, **mephobarbital** [MEBARAL] and **metharbital** [GEMONIL], are alternate drugs, the actions of which, with proper dosage adjustment, closely resemble those of **phenobarbital. Primidone** [MYSOLINE], which is chemically related to the barbiturates and has similar action, is frequently useful in refractory epilepsies, especially of the major motor and psychomotor types.

The hydantoins, such as **diphenylhydantoin** [DILANTIN], **mephenytoin** [MESANTOIN], and **ethotoin** [PEGANONE], are used primarily in major motor and psychomotor seizures; they are usually not effective in treating petit mal. They may be effective, as may the barbiturates, in certain nonconvulsive epileptic equivalents, a syndrome of recurrent autonomic symptoms associated with an abnormal electroencephalogram. **Diphenylhydantoin** is considered the drug of first choice among the hydantoins; it is safer than **mephenytoin** and more effective than **ethotoin.** However, each of these alternative hydantoins may be considered for trial in special circumstances (see the individual drug evaluations following this introductory statement).

The hydantoins are cumulative in effect; therefore, the dosage schedule must be adjusted gradually over a long period to obtain control without producing toxic reactions. Ordinarily, a hydantoin should be added to a regimen after an initial trial with the relatively safer **phenobarbital** has not provided adequate control. Alternatively, many clinics and some of the Council's consultants prefer **diphenylhydantoin** as the initial drug. The Council's moderate preference for **phenobarbital** is based on considerations of relative safety, although this drug does introduce the inconvenience of drowsiness for many patients. Other drugs can be added if a combination of a hydantoin and **phenobarbital** do not completely control the seizures. **Primidone** [MYSOLINE] ordinarily should not be *added* to this regimen, but it may be *substituted* for the **phenobarbital** in refractory epilepsy of the major motor and psychomotor types. Also, psychomotor epilepsy may respond to **methsuximide** [CELONTIN]. **Phenacemide** [PHENURONE] may be effective in controlling psychomotor or various other seizures, but since it is extremely toxic, it is only of limited usefulness and should be used only if other medications are ineffective. Inorganic bromides (eg, **sodium bromide, potassium bromide**) also have anticonvulsant activity against grand mal, but because of their toxicity, interest in them is chiefly historical. However, they may have a limited place in the treatment of children with grand mal.

Methsuximide [CELONTIN], **phensuximide** [MILONTIN], **ethosuximide** [ZARONTIN], **trimethadione** [TRIDIONE], and **paramethadione** [PARADIONE] are useful primarily in the treatment of petit mal. **Ethosuximide** is the drug of choice in this group, but **phensuximide** may be considered for initial treatment in mild cases because it is moderately safer. **Acetazolamide** [DIAMOX], and perhaps ketogenic diets, control petit mal in some patients. Recently, selected new benzodiazepine derivatives, particularly **diazepam** [VALIUM], have also shown promise and relative safety. Among the remaining drugs, **trimethadione** is probably the most likely to be effective, but it is also the most dangerous. Petit mal rarely responds to **phenobarbital** alone; nevertheless this drug, because of its broad anticonvulsant spectrum, should be tried initially unless there is convincing evidence, including a characteristic electroencephalogram, that the patient has classical petit mal uncomplicated by any other type of seizure. Less satisfactory agents like **meprobamate** [EQUANIL, MILTOWN], **quinacrine** [ATABRINE], or the amphetamines may be tried if other medications do not control petit mal. For patients who have petit mal and other seizure types, drugs effective in controlling those other types must be combined with the drugs selected for the treatment of petit mal.

Minor motor seizures are akinetic and myoclonic types that are often refractory to drug therapy. They may occur alone or in association with petit mal or grand mal. Drugs effective for both seizure types may be used alone or in combination. The minor motor seizure syndrome of infancy or childhood sometimes responds to **corticotropin** or adrenocortical steroid therapy or to a ketogenic diet program. Recent experience with various benzodiazepine derivatives indicates that some of the compounds in this group have effectiveness in minor motor epilepsy; of the benzodiazepine derivatives currently marketed in this country, **diazepam** [VALIUM] has given the most favorable results.

Sometimes, epileptic seizures that apparently are under good control by drugs will escape from control. When a barbiturate or hydantoin is involved, the escape may result from a physiologic adjustment in which the patient's metabolism of the drug is increased. With these particular drugs, an increase in dosage will ordinarily reestablish control, and once this is accomplished, there is no reason to expect a repetition of the escape unless the disease itself happens to worsen. Trauma or emotional stress may cause an increase in the dosage requirement, which should be borne in mind if a patient requires surgery.

Spontaneous remissions, particularly of petit mal seizures, are common if convulsive disorders have begun during childhood but are rare if they have begun during adulthood. Anticonvulsant therapy therefore must be prolonged; as a rule, drugs are continued until the patient has been completely free of seizures for two to four years. When a decision is made to discontinue their administration, the dosage of one drug at a time should be reduced gradually, since sudden withdrawal of any of these drugs may precipitate a recurrence of seizures or even status epilepticus. However, when a serious adverse reaction to a drug occurs, the agent should be discontinued immediately and another anticonvulsant should be given to protect the patient during this period.

Status epilepticus is a serious emergency that requires prompt and vigorous treatment to prevent permanent harmful effects or death. It may be terminated by the intravenous administration of **phenobarbital.** This drug is preferable to shorter acting barbiturates, since its effect is practically as rapid but lasts longer. The full calculated anticonvulsant dose should be given initially since the use of fractional doses may result in the paradoxic situation of drug-induced depression but continued status epilepticus. **Diphenylhydantoin** [DILANTIN] may be given intravenously or intramuscularly, but its onset of action is delayed for 5 to 15 minutes. It has the advantage of usually not depressing respiration, but intravenous administration must be slow to avoid serious hypotension. Recently **diazepam** has been shown to be effective when given parenterally. **Paraldehyde** given parenterally is still used occasionally. When anesthetic agents are necessary, they should be given under the supervision of an anesthesiologist, when possible, and resuscitative equipment should be available.

Major motor seizures, usually with severe, protracted, clonic convulsions, are sometimes associated with the withdrawal syndrome in persons with physical dependence on barbiturates, alcohol, or certain other sedative drugs. Barbiturates will often help prevent these dangerous convulsions; the hydantoins are usually of little value.

Adverse Reactions and Precautions

Many minor reactions to anticonvulsant drugs may be overcome by reducing the dosage of the responsible agent, which may, however, necessitate the addition of another anticonvulsant agent to the regimen.

Most anticonvulsants produce gastrointestinal disturbances in at least some patients, especially during the early stages of treatment. The symptoms may be reduced either by administering the drugs after meals or by decreasing the dosage.

Many of the anticonvulsants have sedative effects, and drowsiness is sometimes a significant complaint. Again, this effect is most noticeable during the early period of treatment; if it persists, a reduction of dosage may be indicated. Sedative drugs may cause alterations in mood, which occasionally are serious (see the chapter on Sedatives and Hypnotics).

Other anticonvulsants also can cause mental disturbances. **Phenacemide** [PHENURONE] is particularly prone to cause serious personality changes including psychoses and suicidal depressions.

Ataxia occurs commonly with the hydantoins and, if persistent, requires reduction in dosage. There is evidence that the hydantoins can cause cerebellar damage if a dosage that produces ataxia is administered for a prolonged time. For practical purposes, however, this danger appears remote since the reaction is so troublesome in itself that it demands correction by dosage adjustment. Very young patients can present an exception, as drug-induced ataxia may be confused with the natural unsteadiness of the toddler. Ataxia also may occur with the use of barbiturates.

Many anticonvulsants commonly cause skin eruptions, which are usually morbilliform or acne-like and may disappear when the dosage is reduced or the drug is temporarily discontinued and cautiously readministered. However, a skin reaction may herald the development of a severe reaction that may warrant withdrawal of the drug. Lupus erythematosus, Stevens-Johnson syndrome, angioneurotic edema, serum sickness, and polyarteritis have been associated with anticonvulsant medication. Anaphylaxis is extremely rare. Other reactions that occasionally have been noted with some anticonvulsants include alopecia and hypertrichosis.

Because the barbiturates are particularly prone to aggravate porphyria, their use should be avoided in patients with that disease.

Several of the anticonvulsant drugs may cause reversible visual disturbances such as diplopia and nystagmus; one of the most notable, hemeralopia (defective vision in a bright light), occurs with the oxazolidinediones, **trimethadione** [TRIDIONE] and **paramethadione** [PARADIONE].

Certain untoward effects are frequently characteristic of a particular anticonvulsant and may not occur with a chemically related drug; for example, **diphenylhydantoin** [DILANTIN] frequently causes gingival hyperplasia, but this reaction seldom occurs with **mephenytoin** [MESANTOIN], and apparently never with **ethotoin** [PEGANONE].

Lymphadenopathies simulating malignant lymphomas have occurred with several of the anticonvulsant drugs. Hydantoins have been implicated most frequently. Although it is questionable whether **diphenylhydantoin** is as prone to cause these pseudolymphomas as is **mephenytoin,** it is responsible for a greater number of reactions since it is more widely used. The signs and symptoms may show a temporary progression but usually begin to disappear within one to two weeks after therapy is stopped. A few cases of true lymphoma and of Hodgkin's disease have been reported in which a causal relationship to hydantoin therapy seems possible.

Megaloblastic anemias, which respond to **folic acid** or **leucovorin** (folinic acid) therapy, also have been reported with several anticonvulsants. Accordingly, periodic blood studies are indicated when such drugs are taken. Usually, the drug may be continued if the anemia responds well to treatment. However, because of the possibility that **folic acid** may interfere with the anticonvulsant action, routine prophylactic treatment with **folic acid** in patients without anemia is not suggested.

Among the most dangerous reactions that develop during therapy with anticonvulsant drugs are those that result from damage to the marrow, liver, and kidneys. Severe blood dyscrasias have sometimes been associated with **phenacemide** [PHENURONE], **mephenytoin** [MESANTOIN], **paramethadione** [PARADIONE], **trimethadione** [TRIDIONE], and less frequently with other drugs. Baseline blood counts should be made before initiating treatment with these drugs. Although periodic blood studies during treatment will detect mild leukopenias of uncertain clinical significance, they cannot be relied upon to predict the more serious reactions that ordinarily occur precipitously (eg, agranulocytosis, thrombocytopenia, aplastic anemia). There is some chance that an aplastic anemia might be detected early, before symptoms develop, if one were so fortunate as to have a hemoglobin determination at a time during its beginning decline, but even moderate expectation of such detection would require an impractical frequency of blood studies in view of the extreme rareness of the reaction with most drugs. Since early recognition of the presence of a dyscrasia and discontinuance of the offending drug are essential, the patient should be advised to report promptly such symptoms as sore throat, fever, easy bruising, petechiae, epistaxis, or other signs of an infection or bleeding

tendency. Clinical and laboratory evaluation is necessary if such symptoms occur. Although the risk of dyscrasias is diminished after the first year of treatment with these medications, the physician should be constantly alert to their possible occurrence at any time. The mortality rate from aplastic anemia is particularly high and, if the patient does survive, recovery is slow. Except for **mephenytoin** and **phenacemide,** however, this reaction is fortunately very rare with the anticonvulsants that cause it at all.

Severe liver disease, sometimes fatal, has occurred with **phenacemide** [PHENURONE] and more rarely with some of the other anticonvulsants, including hydantoins. Before treatment with these drugs is begun, it is advisable to make baseline liver function studies, and patients should be instructed to report promptly any symptoms of hepatitis such as jaundice, dark urine, anorexia, abdominal discomfort, or other gastrointestinal symptoms. Since this drug-induced hepatitis is probably idiosyncratic, the monitoring of treatment with periodic laboratory studies in asymptomatic patients is of doubtful reliability in predicting a reaction. **Phenacemide** may present an exception, as there is some evidence that hepatitis can develop insidiously with its use; liver function abnormalities, eg, decreased prothrombin activity, may herald serious disease.

Nephropathies have developed occasionally during treatment with anticonvulsants, especially in patients receiving the oxazolidinediones, **trimethadione** and **paramethadione.** Unlike the blood dyscrasias and hepatitis, these reactions may develop insidiously without producing symptoms in the early stages. Therefore, urinalyses should be made before treatment and periodically during treatment. The development of any significant renal abnormality is an indication for discontinuing the drug.

From the preceding discussion, the question arises of just what type of laboratory monitoring is advisable for patients taking anticonvulsants who have no symptoms suggesting marrow, hepatic, or renal damage. As noted, baseline studies of the functional state of these organs are needed before initiating treatment with drugs known to cause damage even occasionally. Tests should be repeated and perhaps extended if signs or symptoms of a reaction develop. Periodic urinalyses and evaluations for anemia are of value with drugs known to cause nephropathy or megaloblastic anemia, as these conditions may occur well in advance of their symptoms. The problem is whether to subject patients to frequent testing for idiosyncratic blood dyscrasias and hepatitis when nothing suggests the presence of these disorders. The Council's consultants have expressed widely divergent views on whether such testing is of any significant medical value with most anticonvulsants. It is known that various minor laboratory abnormalities may appear and cannot be relied upon to herald the development of a serious reaction. Moreover, when a dangerous idiosyncratic reaction does occur, signs or symptoms will probably appear about as soon as a diagnosis can be made reliably by laboratory methods (with the possible exceptions of hepatitis from **phenacemide,** and aplastic anemia from **mephenytoin** and **phenacemide**). Accordingly, and with due respect to those consultants who disagree, the Council regards routine laboratory monitoring with most drugs as optional, rather than mandatory, if the only issue is whether an asymptomatic patient is taking a drug that rarely produces a blood dyscrasia or hepatitis by some apparently idiosyncratic mechanism. This is in contrast with the situation where a drug has a direct toxic action on the marrow or liver.

A frequently cited paradoxic effect of anticonvulsants is the tendency of agents effective for one type of seizure to aggravate or precipitate seizures of another type. However, epileptic disorders tend to be mixed as to seizure type and, very probably, the apparent aggravation of one type is a manifestation of the natural course of the disease and merely reflects the therapeutic ineffectiveness of the particular drug for that type of seizure. Causally related precipitation of seizures by anticonvulsant drugs probably is rare, and some consultants doubt that it occurs. There is no question, however, that abrupt withdrawal of anticonvulsants can precipitate seizures. Thus, when a drug is to be discontinued, the dosage should be reduced gradually unless rapid withdrawal and substitution of another drug is mandatory because of a serious adverse reaction.

In general, there has been little systematic investigation of the anticonvulsant drugs for teratogenic effects, but a lack of reported teratogenicity after extensive use provides some circumstantial evidence of probable safety. Thus, whenever practical, it would seem prudent to use older and more extensively used anticonvulsants if it is necessary to treat epilepsy in a pregnant woman.

As a general rule, the more toxic compounds should not be used if an equally effective and less potentially toxic preparation is available. However, minor adverse effects should be expected and accepted with any drug. The anticonvulsant drugs in frequent current use, and a few that are rarely used, are listed and briefly described in the individual evaluations that follow. Not every known adverse reaction is mentioned, but an effort has been made to include those that are notable because of danger to life, unusual frequency of occurrence, proneness to cause significant discomfort, or peculiarity to a particular drug.

Barbiturates

Phenobarbital

Most broadly useful anticonvulsant. Initial therapy of choice in most epilepsy (see general statement). Principal effectiveness is in major motor and psychomotor seizures. Sedative-hypnotic effect, as well as ataxia, may present problems. Produces hyperactivity in some children instead of

sedation. Amphetamines, which do not interfere with anticonvulsant action, sometimes useful for relieving drowsiness. Occasional skin eruptions; rare progression to exfoliative dermatitis. Abrupt termination in epilepsy may cause withdrawal convulsions, but true addiction and barbiturate inebriation unlikely in usual doses for epilepsy. Contraindicated in patients with porphyria.

Usual Dosage.—Oral: Adults: Usually 120 to 200 mg daily in divided doses. Range: 50 or 100 mg at bedtime to 300 mg in divided doses. *Children:* 1 to 6 mg per kilogram of body weight per day in divided doses.

Preparations.—Various, including: Elixir 20 mg/5 ml; tablets 16, 32, 50, 64, and 100 mg. Many manufacturers.

Phenobarbital Sodium

Used parenterally in status epilepticus, but may depress respiration. Parenteral diphenylhydantoin may be given concomitantly.

Usual Dosage.—(Status epilepticus) *Intramuscular, Slow Intravenous: Adults:* 200 to 320 mg. *Children:* 3 to 5 mg per kilogram of body weight represents a reasonable guide.

Preparations.—Various, including: Powder 120, 130, and 320 mg; solution 130 mg/ml in 1 ml containers; 160 mg/ml in 2 and 10 ml containers; tablets (hypodermic) 60 mg. Many manufacturers.

Mephobarbital [MEBARAL]

Metabolized to phenobarbital and has effects similar to phenobarbital, but larger doses are used.

Usual Dosage.—Oral: Adults: 200 mg at bedtime to 600 mg daily in divided doses. *Children:* Under 5 years, 16 to 32 mg three or four times daily; over 5 years, 32 to 64 mg three or four times daily.

Preparations.—Mebaral (Winthrop): Tablets 32, 50, 100, and 200 mg.

Metharbital [GEMONIL]

Similar to phenobarbital, but less potent on basis of weight. Dosage adjustment can compensate for this difference. Has same relation to barbital as mephobarbital has to phenobarbital.

Usual Dosage.—Oral: Adults: Initially, 100 mg at bedtime to 300 mg daily in divided doses. Increase to as much as 600 to 800 mg daily if required. *Children:* 5 to 15 mg per kilogram of body weight daily in divided doses.

Preparations.—Gemonil (Abbott): Tablets 100 mg.

Primidone [MYSOLINE]

Not really a barbiturate by traditional classification, but closely related chemically. However, larger doses are needed. Principal usefulness is as substitute for barbiturates in patients not responding adequately to regimen of barbiturate and hydantoin. No compelling reason why it may not be used as initial anticonvulsant in major motor and psychomotor epilepsy, but it is more commonly reserved for refractory cases because it often causes marked sedation. Sedation often diminishes with continued administration. Dosage build-up should be gradual to avoid incapacitating drowsiness. Ataxia and various relatively minor reactions resemble those of barbiturates. Skin eruptions occasionally occur. Megaloblastic anemia may occur; responds to folic acid.

Usual Dosage.—Oral: Adults: 250 mg to 2 gm daily in divided doses. *Children under 8 years:* One-half adult dosage.

Preparations.—Mysoline (Ayerst): Suspension 250 mg/5 ml; tablets 50 and 250 mg.

Hydantoins

Diphenylhydantoin Sodium [DILANTIN]

Drug of choice among the hydantoins. Often used in conjunction with phenobarbital. Used in major motor and psychomotor epilepsy. Has little or no sedative activity in usual doses. Ataxia occurs with larger dosages; if persistent, it indicates overdosage, and the dose must be reduced. Ocular signs and symptoms such as nystagmus and diplopia may also necessitate reduction of dosage. Skin eruptions rather frequent; only rarely serious. Gingival hyperplasia common, and often is severe in children; scrupulous oral hygiene helps prevent it. Hirsutism and excessive activity are less common but do occur, especially in the young. Rare but serious idiosyncratic reactions include hepatitis, marrow depression, megaloblastic anemia, lupus erythematosus, Stevens-Johnson syndrome, and lymphadenopathy resembling malignant lymphoma (see general statement).

Useful parenterally for control of status epilepticus. Unlike barbiturates, seldom depresses respiration. However, onset of action is slower than barbiturates. Also, if intravenous administration is too rapid, dangerous hypotension may occur.

Usual Dosage.—Oral: Adults: Initially, 100 mg three times daily; most common maintenance dose is 300 to 400 mg daily but may reach 600 mg. *Children:* 3 to 8 mg per kilogram of body weight daily in divided doses.

Intramuscular, Intravenous: (Status epilepticus) *Adults:* 150 to 250 mg. Inject intravenously no faster than 50 mg per minute. *Children:* Reduce dosage according to weight or body surface area.

Preparations.—Dilantin (Parke, Davis): *Oral:* Capsules 30 and 100 mg. *Injection:* Powder 50 mg/ml when properly diluted with special solvent provided in 100 and 250 mg vials.

Diphenylhydantoin [DILANTIN]

See Diphenylhydantoin Sodium.

Preparations.—Dilantin (Parke, Davis): *Oral:* Capsules (delayed action) 100 mg; capsules (Dilantin in oil) 100 mg; tablets (pediatric) 50 mg; suspension 100 mg/4 ml.

Ethotoin [PEGANONE]

Moderately effective in grand mal and slightly so in psychomotor epilepsy, but usually unsatisfactory if used alone. Toxicity resembles that of diphenylhydantoin but incidence of at least some

and possibly all reactions is lower. In summary, the drug is less toxic but also less effective than diphenylhydantoin.

Usual Dosage.—Oral: Adults: Initially, 1 gm daily in divided doses; for maintenance, 2 to 3 gm daily in four to six divided doses. *Children:* 0.5 to 1 gm daily in divided doses.

Preparations.—Peganone (Abbott): Tablets 250 and 500 mg.

Mephenytoin [MESANTOIN]

Effective in major motor and psychomotor epilepsy, but more dangerous than diphenylhydantoin and thus should be reserved for cases refractory to the drugs of choice. Has a sedative effect usually absent with diphenylhydantoin; otherwise lacks or has lower incidence of some of the more *minor* adverse effects of diphenylhydantoin (eg, ataxia, gingival hyperplasia, hirsutism, gastric distress). However, life-threatening and other serious reactions are considerably more common: severe skin eruptions, blood dyscrasis (eg, aplastic anemia, leukopenia, agranulocytosis, thrombocytopenia, megaloblastic anemia), liver damage, lupus erythematosus, and pseudolymphoma.

Usual Dosage.—Oral: Adults: Initially, 50 to 100 mg daily, with weekly increases of the same amount until maintenance dose, usually 200 to 600 mg, is established. Further increases to 800 mg or more occasionally required. *Children:* Initially as for adults; maintenance dose usually 100 to 400 mg, depending on age of patient and severity of seizures.

Preparations.—Mesantoin (Sandoz): Tablets 100 mg.

Succinimides

Ethosuximide [ZARONTIN]

Drug of choice for petit mal. Also effective for minor motor seizures in some patients, but generally ineffective for psychomotor or grand mal epilepsy, or in patients with considerable organic brain damage.

Major untoward effects appear to be less frequent than with trimethadione or paramethadione; the most frequent are gastrointestinal disturbances. Drowsiness, ataxia, headache, dizziness, euphoria, hiccup, skin eruptions, and psychologic or psychiatric aberrations have been reported. Aplastic anemia, thrombocytopenia, leukopenia, pancytopenia, and eosinophilia have been reported rarely. See the monograph in the New Drugs section for further details.

Usual Dosage.—Oral: Adults and Children over 6: 500 mg daily initially; increase daily dose by 250 mg every one to two weeks until seizures are controlled or untoward effects develop. Dosages exceeding 1 gm per day are seldom more effective than smaller dosages. *Children under 6:* Initial daily dosage is 250 mg.

Preparations.—Zarontin (Parke, Davis): Capsules 250 mg.

Methsuximide [CELONTIN]

May be helpful in petit mal and minor motor seizures, especially when used with other anticonvulsants. Also may be used as the second or third drug to reduce the incidence of psychomotor attacks. Grand mal, if present, must be controlled with other medication. Untoward effects occur frequently and may be of minor or major consequence. These include gastrointestinal disturbances and reactions affecting the central nervous system (drowsiness, headache, dizziness, diplopia, and ataxia). Hypersensitivity reactions, such as skin eruptions, fever, hiccup, and periorbital hyperemia, occur only rarely. Many minor untoward effects may disappear spontaneously or be controlled by reducing dosage, but a rash may herald a more serious reaction. Severe mental depression may occur, and patients who have psychomotor seizures particularly should be watched closely for behavioral changes, for these may progress to an acute psychosis unless the drug is discontinued. Renal and hepatic damage may occur. Hematologic reactions, including aplastic anemia, although rare, have also been reported.

Usual Dosage.—Oral: Adults and Children: Initially, 300 mg daily; this may be increased at weekly intervals until a daily dose of 1.2 gm, given in divided amounts, is attained. The optimal dose is the minimal amount that will control seizures without causing serious untoward effects.

Preparations.—Celontin (Parke, Davis): Capsules 150 and 300 mg.

Phensuximide [MILONTIN]

Used in control of petit mal seizures. Less effective and less potent than ethosuximide and trimethadione. However, it is the safest of the succinimides. Its relative lack of serious toxicity justifies its inclusion among drugs that may be considered for initial trial in petit mal (see general statement), although substitution of a more effective agent usually will be necessary. Adverse effects may include nausea, weakness, drowsiness, and skin eruptions. The confirmed reaction of greatest concern reported to date is nephropathy, particularly in children, which apparently is reversible on withdrawal of the drug. Agranulocytosis, if indeed it is caused by this drug, has been very rare.

Usual Dosage.—Oral: Adults and Children: 500 mg to 1 gm two or three times daily.

Preparations.—Milontin (Parke, Davis): Capsules 250 and 500 mg; suspension 250 mg/4 ml.

Oxazolidinediones

Trimethadione [TRIDIONE]

Principally effective in control of petit mal seizures. Although among the more effective agents for this purpose, should be reserved for refractory cases because of toxicity. Serious reactions, some of them fatal, include skin eruptions that may progress to exfoliative dermatitis or erythema multiforme, nephropathy, hepatitis, and marrow depression with aplastic anemia, neutropenia, or

agranulocytosis. Pseudolymphomas, lupus erythematosus syndrome, and myasthenia gravis-like syndrome also have been reported. Drowsiness may occur. Reversible visual disturbances, particularly hemeralopia, are quite common. Hiccup sometimes occurs during early treatment. Hair loss may occur.

Usual Dosage.—Oral: Adults: 0.9 to 2.1 gm daily in three or four divided doses. *Children:* Reduce initial dosage in proportion to age and weight.

Preparations.—Tridione (Abbott): Capsules 300 mg; solution 150 mg/4 ml; tablets 150 mg.

Paramethadione [PARADIONE]

Similar to trimethadione and has similar indication, ie, petit mal that is refractory to safer drugs. Somewhat less toxic than trimethadione but also less effective. Reactions that occur tend to be the same as with trimethadione, but some occur less frequently. A few (eg, pseudolymphoma, lupus erythematosus) have not yet been reported with paramethadione.

Usual Dosage.—Oral: Adults: 0.9 to 2.1 gm daily in three or four divided doses. *Children:* Reduce initial dosage in proportion to age and weight.

Preparations.—Paradione (Abbott): Capsules 150 and 300 mg; solution 300 mg/ml.

Miscellaneous

Bromides

Usually as sodium bromide or potassium bromide. Historically of interest as the first antiepileptic. Moderate anticonvulsant activity against grand mal. Routinely cause sedation. Skin eruptions are frequent. Of greatest importance is cumulative poisoning that causes severe toxic psychoses. Bromides are regarded as obsolete for routine use, although they may still have a role in grand mal in children in whom other drugs, for various reasons, prove unsuitable.

Usual Dosage.—Oral: Recommendations have varied. The following are reasonably consistent with several suggestions: 20 to 60 mg per kilogram of body weight per day in divided doses up to 1 gm three times daily total.

Preparations.—Common preparations are tablets or elixirs of various strengths. Many manufacturers.

Phenacemide [PHENURONE]

An effective anticonvulsant that may be useful in *refractory* psychomotor, grand mal, petit mal, and mixed seizures. However, it is a very dangerous drug and should be used only when adequate control of seizures cannot be achieved with other drugs. Potentially fatal reactions include hepatitis, blood dyscrasias (aplastic anemia, agranulocytosis), and toxic psychoses, often with suicidal tendencies. Nephropathy occasionally occurs. Rashes and gastrointestinal symptoms are rather common.

Usual Dosage.—Oral: Adults: Starting dose, 250 to 500 mg three times daily. If necessary, an additional 500 mg daily may be added at weekly intervals. Usual maintenance dose is 2 to 3 gm daily in divided doses. *Children:* Age 5 to 10, approximately one-half adult dosage.

Preparations.—Phenurone (Abbott): Tablets 500 mg.

Acetazolamide [DIAMOX]

Has been reported useful in children with petit mal, but effectiveness declines with continued administration. See chapter on Drugs Used in Glaucoma for properties and other uses.

Usual Dosage.—Oral: Adults and Children: 8 to 30 mg per kilogram of body weight daily in divided doses.

Preparations.—Diamox (Lederle): Capsules (sustained release) 500 mg; tablets 125 and 250 mg.

Meprobamate [EQUANIL, MILTOWN]

May be helpful in some cases of petit mal. When used alone, seldom controls any but the mildest cases. See chapter on Antianxiety Agents for properties and other uses.

Usual Dosage.—Oral: Adults: 400 to 800 mg three times daily. *Children:* Age 3 and older, 100 to 200 mg two or three times daily increased as needed to as much as 2.4 gm daily in older children.

Preparations.—Equanil (Wyeth): Suspension 200 mg/5 ml, tablets (uncoated) 200 and 400 mg, tablets (coated) 400 mg, capsules (sustained release) 400 mg; Miltown (Wallace): Tablets 200 and 400 mg; Meprospan (Wallace): Capsules (sustained release) 200 and 400 mg; Meprotabs (Wallace): Tablets (coated) 400 mg. Other manufacturers.

Paraldehyde

Effective in status epilepticus, but should be reserved for cases in which phenobarbital has failed. Beware of decomposed drug. Intravenously, should be given slowly in a drip; otherwise, it induces severe coughing that, at best, makes administration difficult, and at worst, can cause pulmonary hemorrhages. Some fatalities have occurred. Compatibility with blood has been questioned. Intramuscular injection, though often very irritating, is reasonably safe if adequate care is taken to avoid peripheral nerves. The Council's consultants have divided sharply on whether this agent should be used parenterally, and if so, by which route. Bronchopulmonary disease is a relative contraindication. The sedative effect may be intensified and prolonged in the presence of liver damage.

Usual Dosage.—(Status epilepticus) *Intramuscular. Intravenous:* Suggestions have varied, and available recommendations of manufacturers are vague. However, dosage for status epilepticus frequently exceeds that given for more benign conditions. About 0.15 ml per kilogram of body weight is reasonable; sometimes a moderate additional dose will be needed, especially for smaller children. Intravenous injection must be slow, preferably by drip, with the drug diluted by physiologic saline, and with caution to avoid extravasation.

Preparations.—Paral (Fellows-Testagar), Paraldehyde (Tilden-Yates): 2, 5, and 10 ml containers.

Quinacrine Hydrochloride [ATABRINE]

May be effective in petit mal, but should be used

only if other drugs have failed. Its toxicity is severe and its effectiveness is not great. See the chapters on Antimalarial Agents, Anthelmintics, and Antineoplastic Agents for properties and other uses.

Usual Dosage.—Oral: Adults: 100 mg daily. *Children:* 1 to 2 mg per kilogram of body weight per day.

Preparations.—Atabrine Hydrochloride (Winthrop): Tablets 100 mg.

Diazepam [VALIUM]

This drug was introduced as an antianxiety agent, but like other benzodiazepine derivatives, it has anticonvulsant properties. Eventually, it probably will not prove the best anticonvulsant of this group, but it is the preferred one of these now marketed in this country. Conflicting reports of effectiveness in various epilepsies have appeared. The drug has shown much promise in petit mal, but perhaps of greatest importance is its value parenterally in terminating status epilepticus and its frequent effectiveness in minor motor epilepsy, which is so often refractory to the conventional anticonvulsants. Its greatest drawback in maintenance therapy is the eventual tolerance that develops to the therapeutic effect. However, this problem also occurs with other agents in minor motor epilepsy. The most common adverse effects with oral use are drowsiness, dizziness, fatigue, and ataxia, all dose related. Paradoxic excitement or stimulation sometimes occurs. Parenteral administration for status epilepticus requires observation for respiratory depression and hypotension, and the slight possibility of cardiac arrest must be borne in mind; however, from the limited information available, the overall safety of the drug appears to compare favorably with other agents used for this life-threatening emergency. See the monograph in the New Drugs section for other properties and uses.

Usual Dosage.—Oral: Adults: 4 to 40 mg daily in divided doses, beginning with a low dose and increasing it gradually. Consider starting with only 2 mg in elderly or debilitated patients. The effect of the drug is cumulative. *Children:* Somewhat reduced dosage, beginning with 2 to 4 mg daily in divided doses.

Intravenous: (Status epilepticus) *Adults:* 5 to 10 mg injected *slowly*. *Children:* 2 to 5 mg injected *slowly*. Intramuscular injection may be substituted if the convulsions make *slow* intravenous injection impossible. The drug should not be mixed physically with other agents or diluted with intravenous solutions.

Preparations.—Valium (Roche): Solution (injection) 5 mg/ml in 2 ml containers; tablets 2, 5, and 10 mg.

Corticotropin and Various Adrenal Corticosteroids

Of value in minor motor epilepsy. See the chapter on Adrenal Corticosteroids for detailed discussion of these agents.

Dosage varies with the agent used.

Mixtures

Several fixed combinations of anticonvulsants are marketed. They are listed below only to acknowledge their availability and not necessarily to encourage their use. The usefulness of such fixed combinations is limited since, in the management of epilepsy, the dosage of each drug used concomitantly should be established *individually*. After this has been done, if the doses present in an available mixture happen to correspond to the ratio and quantities required by the patient, the use of such a combination product would seem justified, for the convenience of the patient, unless a subsequent adjustment of dosage becomes necessary. However, some available combinations are unrealistic, since the usual dose of one ingredient carries with it only a trivial dose of the other. Some others contain irrational ingredients that are not effective therapeutic agents for epilepsy. Still others contain more than two ingredients and appear to be entirely too cumbersome for practical use in view of the importance of individualizing the dosage of every drug the patient receives.

ALEPSAL (Fougera): phenobarbital 97 mg, belladonna powder 20 mg, caffeine 26 mg/tablet

BARBA-NIACIN (Cole Pharmacal): phenobarbital 32 mg, niacin 16 mg/tablet

BARBA-NIACIN FORTE (Cole Pharmacal): phenobarbital 97 mg, niacin 48 mg/tablet

DILANTIN with PHENOBARBITAL (Parke, Davis): diphenylhydantoin sodium 100 mg, phenobarbital 16 or 32 mg/capsule

ELMALOIN with PHENOBARBITAL (Elder): diphenylhydantoin sodium 100 mg, phenobarbital 15 mg/capsule

HYDANTAL (Sandoz): mephenytoin 100 mg, phenobarbital 20 mg/tablet

MEBROIN (Winthrop): mephobarbital 90 mg, diphenylhydantoin 60 mg/tablet

NEO-SEDAPHEN (Smith, Miller & Patch): pentobarbital sodium 30 mg, phenobarbital sodium 10 mg, sodium bromide 300 mg, potassium bromide 200 mg, calcium bromide 100 mg/5 ml

PHELANTIN (Parke, Davis): diphenylhydantoin 100 mg, phenobarbital 30 mg, methamphetamine hydrochloride 2.5 mg/capsule

QUADRA-SED (Smith, Miller & Patch): pentobarbital sodium 15 mg, phenobarbital sodium 15 mg, butabarbital sodium 15 mg, secobarbital sodium 15 mg/5 ml

SEDALIXIR (National): pentobarbital sodium 8 mg, phenobarbital 16 mg/5 ml

SEDAPHEN (Smith, Miller & Patch): phenobarbital sodium 20 mg, sodium bromide 300 mg, potassium bromide 200 mg, calcium bromide 100 mg/5 ml

SEDOBARB #1 (Whittier): phenobarbital 16 mg, pentobarbital sodium 32 mg/tablet

SEDOBARB #2 (Whittier): phenobarbital 32 mg, pentobarbital sodium 65 mg/tablet

Dr. ANNIS. This advance chapter was run in JAMA for good reason. To find out if we were heading in the right direction to meet the physician's need for usable drug information, we asked physicians who received the ADE chapter to give us their reactions.

To summarize the results, 96 percent said a drug evaluation book like the one in the sample chapter would supply the type of information needed in their practice; 96 percent said the information in the sample chapter was presented in a readily accessible form; and 91 percent said the extent of information presented in the sample chapter was "about right" rather than "inadequate" or "excessive."

Details of that study are included in this statement and I request that they be included in the record at this point as "exhibit H."

Senator NELSON. They will be printed in the record.

Dr. ANNIS. Thank you.

(The exhibit referred to follows:)

EXHIBIT H

Analysis of ADE Questionnaire

(Total Number, 3,761)

The questions and results were:

1. Would a book containing evaluations of all drugs that are commonly prescribed, as illustrated in the accompanying sample chapter, supply the type of information you need in your practice?

Yes	3,622
No	110
No comment	29
Percent favorable response	96.3

2. As a reference on drugs, is the information in the sample chapter presented in a readily accessible form?

Yes	3,601
No	116
No comment	44
Percent favorable response	95.7

3. An effort has been made to present the most useful information for most circumstances in which a drug may be used. In view of this intention, do you believe the extent of information presented is: inadequate, about right, excessive?

Inadequate	165
Excessive	137
About right	3,418
No comment	41
Percent favorable response	90.6

4. Do you have a copy of New Drugs?

Yes	1,243
No	2,677
No comment	33
Percent having new drugs	31.9

PRESCRIPTION LABELING

Dr. ANNIS (reading). Also in connection with drugs and drug information, my fifth subject is labeling prescription drugs.

The AMA Council on Drugs has considered the question of labeling prescription drugs many times. The council's recommendations last appeared in JAMA in 1965. Mr. Chairman, I ask that the article, which is attached to this statement, be included in the record at this point as "exhibit I."

Senator NELSON. It will be printed in the record.

Dr. ANNIS. Thank you.

(The exhibit referred to follows:)

Exhibit I

Reprinted From the Journal of the American Medical Association
December 20, 1965, Vol. 194, page 1311

To Label or Not to Label

In a less sophisticated era, when the art of medical practice outweighed scientific knowledge, physicians did not tell their patients the identity of the medications they prescribed. Today, this practice is being gradually abandoned, and increasing numbers of physicians ask pharmacists to indicate on the label the names and strengths of the drugs they prescribe. The Council on Drugs believes that all physicians should adopt this policy, and make an exception only when such disclosure would be detrimental to the welfare of the patient. In a prior discussion of this subject,[1] the Council made a number of the following points:

The patient has the right to be informed about his illness and the medications prescribed.

In emergency situations, such as accidental poisoning, overdosage, or attempted suicide, immediate identification of a prescription drug from the label may be lifesaving.

The information is invaluable when the patient changes physicians, moves to another locality, or contacts the prescribing physician at a time when his records are not readily available.

The information on the label is of value in group practices in which the patient may not always have the same attending physician.

It is advisable that patients with allergies know what is being prescribed.

This specific information on the label helps to prevent mix-ups between two or more drugs being taken concurrently, or between medications being taken by different members of the family.

Should it become necessary to issue a warning against the use of a particular drug, the name on the label serves as a danger signal to those who have been given prescriptions for the product.

In its earlier consideration of this subject, the Council on Drugs passed the following resolution[1]:

> The Council resolves that it favors labeling of prescriptions as a general practice, and furthermore, it is recommended that prescription pads contain boxes for a "yes" or "no" on whether to label; if these boxes are not filled in by the physician, the prescription will be labeled.

That resolution was received favorably by many. However, pharmacy organizations and several state medical societies have opposed the method that the Council suggested for implementing its recommendation. The Professional Relations Committee of the American Pharmaceutical Association agreed with the position expressed by Apple and Abrams,[2] who concluded that unless a prescriber specifically requests labeling, ". . . a pharmacist should not by himself, or upon request by a patient, disclose the ingredients in the prescribed medication by labeling." This reflects the feeling of the pharmacist that he needs a directive to label from the physician, who alone has the authority to make such a decision.

Physicians and pharmacists who are opposed to labeling as a routine measure and feel that it may create or accentuate various problems have the following objections:

The practice may lead to self-medication and to "patient-prescribing" for others.

A patient who knows the drug name may compare prices at different pharmacies, and thus tempt pharmacists to bid for business on a price basis rather than on a basis of professional service.

The information may only confuse and trouble the patient.

The practice reduces the stature of the physician and lowers the status of the prescription to practically that of an over-the-counter item.

Patients may put other drugs into bottles labeled with the previous contents, which may then lead to charges that a pharmacist dispensed the wrong medication.

Labeling could make it easier to channel drugs into illegal markets.

The Council believes that the advantages of labeling outweigh these objections in almost every instance; the Council always has recognized that there are occasions when such labeling is inadvisable for psychological or other reasons, and that the physician is the one who must decide.

However, only in exceptional circumstances is it desirable not to reveal the identity of prescribed drugs under today's conditions. Moreover, the physician's explanation to his patient regarding the purpose of a prescribed drug and what may be expected from it, together with the public's growing awareness of the effects of drugs—both beneficial and harmful—will help to minimize problems that may occur occasionally.

After consultation with officers of the national pharmacy organizations and after further deliberation, the Council on Drugs strongly reaffirms its position that in the best interest of the patient the prescription container should, as a rule, be labeled with the name and strength of the drug. To implement this recommendation, the Council suggests that the physician use two sets of prescription blanks, one of which is for routine use and is imprinted with an order to label. This procedure is consonant with the ethics of medicine and pharmacy, and with the physician's responsibility to decide whether the prescription label should or should not identify the drug.

The Council further urges that the physician always designate the number of refills he wishes the patient to have, and that he prescribe only the number of doses usually required in any specific condition, since adjustments in dosage are often necessary to obtain the desired result in individual cases. The Council also recommends that any prescription that does not indicate the number of refills, or that is labeled "p.r.n." or "ad lib," not be refilled.

The Drug Abuse Control Amendments that were recently passed by the Congress regulate the refilling of prescriptions for stimulant and depressant drugs. No prescription for drugs in these classes can be renewed more than five times, or more than six months after the date of issue unless the physician gives additional authorization for refilling.

The physician's responsibility for the medication regimen of his patient is clear, and he should therefore heed the pharmacist's requests for specific instructions on renewals.

The Council hopes that this statement will clarify its position on the question of labeling and refilling of prescription drugs, and earnestly solicits the cooperation of physicians, pharmacists, and other health personnel in implementing these important public health recommendations.

References

1. Labeling of Prescription Drugs, editorial, *JAMA* 185:316 (July 27) 1963.

2. Apple, W.S., and Abrams, R.E.: Problems in Prescription Order Communications, *JAMA* 185:291-293 (July 27) 1963.

Dr. ANNIS. May I summarize the council's views? It recommends that in most instances the physician should request that the prescription label indicate the name and strength of the drug prescribed.

Some of the reasons given are these:

The patient has the right to be informed about his illness and the medication prescribed.

The information is invaluable when the patient changes physicians.

It is advisable that patients with allergies know what is being prescribed.

Specific information on the label helps to prevent mixups between two or more drugs being taken at the same time; or between medications being taken by different members of the family.

However, the council also offered the fact that there are situations when the physician might determine that such information should not be contained on the label. Those situations usually involve psychological considerations for specific patients.

Mr. Chairman, I would now like to add some further remarks that the AMA considers of importance to these hearings.

Almost at the beginning of this statement, I listed the three primary reasons for which the American Medical Association was founded 122 years ago; to established a code of ethics; to combat quackery; and to improve medical education.

That last point—education—includes the entire spectrum of training and education necessary to produce and maintain a competent physician:

Premedical education.

Medical school.

Postgraduate education through internship or residency training.

Continuing education of practicing physicians.

The proper use of drugs is a vital part of all medical education, beginning with medical school.

A survey of medical schools by the AMA in 1966 revealed that an average of 173 classroom hours was devoted to pharmacology during the sophomore year. The range was from a low of 62 hours to a high of 396 hours.

In the junior and senior years, instruction in drug therapy is presented as a part of each clinical service and through clinical pathology conferences which all students are required to attend.

It is not possible to give the total hours of drug therapy instruction received by the student because there is continuous education in that area throughout medical school and during the internship and residency years.

The same observation can be made about continuing medical education courses. The AMA publishes a list of such courses each year. The latest list, and I have with me a copy for the committee, shows 1,922 courses offered to physicians by 372 institutions and organizations. I will leave it with the committee. This is, I think, the 11th or 12th—the 14th consecutive year which this has been made available, so physicians anyplace in the country will know where they can go for continuing education.

Senator NELSON. Thank you.

Dr. ANNIS. While there are no courses titled "Drug Therapy," with very few exceptions, each course necessarily includes information and

discussion of the therapeutic agents used in the treatment and control of the problems being covered by the course.

The medical profession has great respect for the results of drug research. It recognizes that a great number of the specific medical advances of the last three decades have been in the area of chemotherapy—of drugs.

These advances have come about because of the varied support of research and development—by the private drug industry, through academic contributions supported by private and Federal grants and directly from the Federal Government.

If financial support for research and development were confined to only one of those sources, it is possible—even probable, I think—that the research would be directed into whatever approach was of most interest to the sponsoring body. That could mean fewer innovative discoveries and applications.

Speaking of the application of drug discoveries, the American Medical Association has always advocated the rational use of therapeutic agents by physicians in treating patients and has consistently expressed its firm belief that the physician should have for his patient the very best drug available for the patient's condition.

At the same time, the AMA has urged that physicians be aware of the economic factors connected with the use of drugs.

In this regard, I would like to present the essence of a position adopted by the AMA House of Delegates:

> Physicians should be free to use either the generic or the brand name in prescribing drugs for their patients; and physicians should supplement medical judgments with cost consideration in making this choice.

A copy of the report is included as exhibit J and I ask that it be inserted in the record at this point.

Senator NELSON. It will be printed in the record.

Dr. ANNIS. Thank you.

(The exhibit referred to follows:)

Exhibit J

Excerpt From
"Proceedings of the AMA House of Delegates"
November 1966

Prescribing and Dispensing of Drugs

This report is intended to state the position of the American Medical Association regarding the considerations which are pertinent in determining under what circumstances the physician should prescribe generically or by brand name.

The present policy of the American Medical Association is that physicians should be free to prescribe drugs generically or by brand name for all of their patients, whether they are paying, medicare, or indigent patients, the primary consideration being the best interests of the patient. Medical considerations must be paramount in the selection of drugs. In addition, the physician also has an obligation to be mindful of the economic consequences of the treatment he prescribes.

The issue of cost is not simply a matter of prescribing drugs generically as opposed to brand name prescribing. Often there will be substantial variations in the cost of the same drug marketed under different brand names by a number of reputable manufacturers. However, generic prescribing alone will not assure that the least costly brand will be dispensed or that the savings will be passed on to the patient. Nor will generic prescribing alone assure the physician that his patient is receiving the product of a manufacturer in whom he has confidence.

If the physician prescribes by brand name, he designates the source of supply. If the physician prescribes generically without naming a manufacturer, the pharmacist or some other third party chooses the source of supply.

The attending physician should not delegate this choice, that is, he should not prescribe generically, unless he is convinced that he can rely upon the quality and purity of the drug that will be dispensed to his patient. If this is not the case, then the physician himself should designate the source of supply by prescribing by brand name or by adding the name of his choice of supplier to the generic name of the drug.

Cost Considerations

If medical considerations lead the physician to the conclusion that he should not delegate the choice of supplier to anyone else, then he must make the decision. And in doing so he should supplement medical considerations with considerations of cost to his patient.

It is a fact that, in many cases, drugs prescribed by physicians in the United States are available from more than one dependable supplier. They are also available to patients from a large number of retail pharmacies. Thus, in selecting a dependable supplier of the drug of his choice, the physician has an opportunity to serve his patient at the lowest possible cost. The physician should inform his patient of the medical considerations which have led him to the decision to prescribe a particular brand. He should also encourage the patient to be cost conscious in having the prescription filled.

If medical considerations lead the physician to the conclusion that he can safely delegate the choice of a supplier to a pharmacist, a hospital formularly committee or some other third party, he does not abrogate his responsibility to protect the economic as well as the medical interests of his patient. Just as it does not follow that generic prescriptions automatically ensure therapeutic effectiveness, it is also a fact that generic prescriptions do not automatically ensure the lowest possible cost. If the third party filling a generic prescription does not reflect the same concern as the prescribing physician, his patient may be charged a higher price than would have been the case given a brand name prescription. Thus, in choosing to prescribe generically, the physician should be assured that whoever actually makes the choice of supplier can and will take into account not only the medical needs of his patient but will protect the patient's economic interests as well.

With this clarification of the medical and the economic consequences which can flow from the physician's decision to prescribe by generic or by brand name, the Board of Trustees recommends that the House of Delegates:

(1) Reaffirm the present policy of the Association which states that physicians should be free to use either the generic or brand name in prescribing drugs for their patients; and

(2) Encourage physicians to supplement medical judgments with cost considerations in making this choice.

Dr. ANNIS. This committee has heard testimony that drugs should be prescribed by their generic names only. That recommendation usually is founded on the assumptions that drugs of the same generic name are therapeutically equivalent; and that a prescription written by generic name will automatically save the patient money. Neither assumption is necessarily true.

The AMA believes firmly that no system of prescribing drugs should be compulsory for a physician. Instead, a full range of drugs must be available so he can select for his patient the one he believes will achieve the best response.

To cope with differences among some patients in their responses to drug therapy, the physician must be allowed the greatest possible freedom in prescribing from a supply of drugs that is as large and as flexible as possible.

It takes more than laboratory testing—more than just chemistry—to prove therapeutic equivalence among drugs. It takes proper clinical testing.

Even assuming equivalence of chemical composition among drugs, other factors are involved. Among these are crystalline size, nature of incipients, flavors, coloring agents, tableting pressures and the number, thickness, and orientation within the tablet of coating films.

The physician who prescribes a drug needs to know what to expect from that drug. A generic prescription, filled by a drug the pharmacist selects, may be filled with any drug within that generic classification. If the prescription is refilled, the product of a different manufacturer may be used. As a result the physician may be unable to evaluate fully the patient's response to that course of drug therapy.

Mr. Chairman, and members of the committee, that completes the statement of the American Medical Association before these hearings.

I have tried at least to touch on, if not to discuss in elaborate detail, subjects that we believe are important both to this committee and to the medical profession. If there are any questions at this time, I shall be glad to do my best to answer them.

I will be glad to be assisted by both Dr. Hayes and Mr. Harrison. We appreciate this courtesy.

Senator NELSON. Thank you very much, Dr. Annis. We appreciate this statement of the American Medical Association.

You made some reference in the beginning to statements by some witnesses that may reflect in a fair way on the profession. Let me say that in my judgment based upon some natural bias, coming from a medical family, I consider the medical profession the finest of the professions, though I am a lawyer. And though we have highly motivated people in all professions and we have some who are not, I think my own unscientific estimate from experience is that there is a higher percentage of highly motivated people in medicine for a very simple reason, that I think more people go into this profession because they want to do something for people. That has been the history of medicine more than perhaps any other profession.

I want to say, too, that the fact that Congress conducts hearings of various kinds involving all aspects of the social structure of the country and the economic structure and the professions does not mean that the hearings which may bring out testimony critical of some industries, some profession, or something else, does not mean that that is a

general indictment of the industry or the profession or that the Congress feels that that industry or profession or economic or social group is not making a very fine contribution to society.

I have introduced a fair amount of consumer legislation involving pesticides and the chemical industry, the tire industry, tire safety standards, the auto industry, and a number of others. I remember when I introduced the tire and auto safety bills, I was attacked in some quarters as being against the auto industry, which it could be said is the greatest, at least in terms of its size, of any industry in the country. I had to point out repeatedly that the fact that I thought there were some things wrong in that industry in terms of the work they are doing in safety, and in terms of the quality of tires the auto industry was using, this is not a general indictment of the industry.

There is not any group in the country that has a relationship with the public that is perfect. The purpose of this hearing is to raise issues in which the public has an interest. The problems and issues raised before this committee have not been raised by the members, by me, or the members of the committee. They have been raised by witnesses who come before the committee, and, like anybody else, I could agree with some and disagree with others, based upon what they have to say.

But in the last 2 years there have been a large number of very reputable witnesses who have been critical of certain practices in the medical profession, of the medical journals, and of the drug industry. They have been very distinguished men who have been willing to come before the committee and express their opinions about these various matters.

Of course, there have been others who have come before the committee to respond or to criticize those who have criticized. We have made it a point in this committee, which I think we must, to be fair, when we are discussing anything involving the drug industry, and that has been the main thrust of these hearings, that any company that was criticized would have an opportunity forthwith to respond to that criticism and whenever they have asked for the opportunity, we have set up the earliest possible date in order to let them respond to anything that was said before the committee.

We also have made it the policy of this committee to hear from all viewpoints respecting any issues raised. And we have been trying to do that. We cannot hear from everybody at once, of course, because we would have to hold the hearing in a stadium.

But anyway, the fact that these questions are raised before the committee, as you well appreciate, puts me in an adversary position, in the view of many, since that is the kind of issue that is being raised here. In other words, it is a hearing to raise public questions of importance which are critical of certain practices in the drug industry.

Many times, it has been said, "Well, you are just hearing the bad things about the drug industry." Well, we know a great deal about the good things. However, that is why we have always been happy to permit the drug industry or the Pharmaceutical Manufacturers Association to appear, or anybody else, and delineate in a great detail as they desire the contributions, the work of the particular organization they represent.

While we will be pleased to have your summary of the vast amount of work the American Medical Association does—I realize it is, just

as you have said, a concise, short presentation of an organization that has a long and distinguished history in this country. Nevertheless, since it is the function of this committee to probe these very questions, I necessarily have to ask the hardest questions I can think of. Sometimes they are not very hard. And some of the questions I ask may not be very perceptive. In fact, some may be considered foolish. That is because nobody on this committee, particularly myself, poses as an expert on any aspect of this field or as an expert in the issues before this committee. The committee conducts hearings and hears testimony of experts who have conflicting views so that the whole story will be in the hearing record, so that it may be read and evaluated and so that the Congress sitting in the position, so to speak, of a jury, may make some kind of evaluation as to what the testimony means and whether or not legislation is required in some area respecting the public interest.

Now, I try, as I said, to make my questions as tough and probing as possible. Some witnesses even think, if you can imagine it, that some of my questions are offensive, and some people even think the questioner is offensive. That is not my intent.

I want to say also that I try to ask the most probing questions I can, affecting all the issues that have been raised here. I note that very frequently I am quoted as advocating some position because of the questions I ask.

Dr. ANNIS. I can appreciate that, Senator, I have had that directed toward me a few times, too.

Senator NELSON. I ask questions that occur to me, saying why is this not a good idea, and then I am put in the paper as saying I advocate doing such and such, and then there will be an editorial someplace, in one of the medical publications, saying how foolish the proposal I advocated was when, in fact, I did not advocate anything. I am just asking for information. I may conclude after hearing all the testimony that I agree with the proposition implicit in the question I asked. Or I may not.

Now, having said that, I would like to ask some questions.

First, on the continuing question of generics versus brand names and labeling of drugs and so forth, it seems to me, after 2 years of listening to testimony, and after reading the arguments made by the drug manufacturers, that there is a continuous and very successful attempt by the manufacturers to convince the medical profession that you cannot ever trust generic drugs, and that you have to prescribe brand names, particularly the brand name of a particular company. We have not received any adequate testimony from either side—when I say adequate, I mean we have not had any conclusive testimony that a brand name is better than a generic. The FDA is presently testing a whole series of very commonly used drugs to try to settle this question. The test I refer to, a previous test made by the FDA, is of some 4,600 drugs, of which 2,600 were generic drugs and 2,000 brand name, and they tested them only for potency. On that particular test, the generics came out slightly better than the brand names.

Pharmaceutical manufacturers attacked it on the grounds that it was not accurate and the FDA, after reexamining it, conceded that there were six instances, I think, out of the 4,600, that were erroneous.

In any event, as I recall, about 8.8 percent of the brand names failed the potency test; that is, they were slightly under or above the USP standards, and 7.7 percent of the generics failed that test.

So the problem continues, and the drug companies have been very persuasive in trying to make sure that generics are not trusted by much of the medical profession. However, we have had a number of distinguished witnesses who simply say that they prescribe by generic name—that if the drug meets USP standards, there is no evidence, of any consequence, that they are not therapeutically equivalent.

First, let me ask you about the question of labeling which you referred to in the latter part of your statement. You recommend that the doctor use the generic name in prescribing, I believe, is that correct?

Dr. ANNIS. My recommendation, Senator, is that a physician be given the opportunity to prescribe generically as he will do in some instances.

Senator NELSON. I was referring to labeling; I am sorry.

Dr. ANNIS. But if he so prescribes, or by brand name, if he feels that he is a little more certain. The recommendation for labeling is one that has come as a result of long discussion by many of the able members on our council on drugs, supported by many others in the profession. With the growth of new drugs with the expanding names, whether they are generic and hard to decipher, to spell, or to pronounce; or whether a simple brand name, it is increasingly difficult, with the tremendous mobility of our population—people moving around—to know what they are taking. So the recommendation for labeling is that in most instances, except for a few where for psychological reasons it is not good for a patient to realize what you are giving him is acetylsalicylic acid—plain aspirin—when they think they need an exotic one—except in those rare instances—for the most part the physician would be wise and it would be safer, and therefore better for the patient who is moving around, and better for another doctor, should they be traveling or should they move, to know exactly what they are getting.

So that if, for example, you write a prescription for a tolbutamide for a diabetic, you might write "Tolbutamide" with the name of a producer. You might write it, as I often do, one or the other producer, whichever the pharmacist may have on hand. But label it so that it will say tolbutamide, whatever company. I do not treat diabetes, but if I did, the patient would know the drug.

Then if they are visiting on a weekend, or if they have a reaction—because they ate inadequately, or because of an upset stomach and their diabetes the effect of the medicine to control their diabetes is too great and they have a reaction from the drug, any doctor can take a look at it and know what the patient is getting. This is a protection for the patient. It gives more information. They know what they are treating, they know what drug is being used and it helps immeasurably.

I have many patients from out of town, who come down to Miami. They will come in and bring two or three bottles with them, with a prescription number. Not infrequently, I have had my secretary call various parts of the country to find out from the druggist what the prescription for Mrs. Jones is. Then I will know.

For some people, you can't tell them what they are taking. They will not only think it is good for them, but they will prescribe it for Aunt Lillie when she is visiting.

We think it is good practice, it gives greater information and shares with the patient a little of the responsibility in their own care and it will give tremendous aid for our increasingly mobile population in being immediately able to let the doctor know what they are taking,

and the dosage they are taking. This is so important in many drugs, how frequently they take it, and also, how long they have been taking it. Many drugs are not considered dangerous if taken for a week. The same drug you might give for a week, you would not want anybody to refill, and you sure do not want them taking it for a month or two or three. This basically is the summary of the philosophy behind this recommendation.

Senator NELSON. I think we have had a number of distinguished physicians testify on this precise point. No one so far as I know, has testified to the effect that the physician should not have a choice of whether it is a brand name or generic, but in order to accomplish this, is it not necessary to have some legislation that would require that the label carry the generic name, and then, of course, the doctor may decide that it should be Lilly or Parke, Davis or Merck or something else. It may very well have that on the label, also.

Do you see any other way to secure, without legislation, a requirement that the label shall bear the generic name excepting in those cases where the doctor notes that he does not wish a patient to have the drug identified?

Dr. ANNIS. Well, Senator, in most instances compulsory labeling would cause no hardship. But, especially in the field of psychiatry, sometimes in other fields, for psychological or emotional reasons—if you were to tell someone who is disturbed—an exception must be provided. This is one of the fields that I have to listen to my colleagues. Let me cite an example. There are meprobamates, Miltown or Equanil. These patients will say, "I read about that Miltown, I tried that years ago, and it is of no value." Yet the prescribing physician, the psychiatrist, the internist, the obstetrician, would be very reluctant to let this patient know she is being given Miltown, so he might prescribe meprobamate made by someone else or meprobamate USP.

There are many reasons why physicians will not tell the whole story. Psychiatrists dealing with children are totally reluctant to disclose all to their patients.

This is the reason that our recommendations, following the Council on Drugs, with the concurrence of most of these very distinguished men who have been before your committee in the field of physiology and medicine, recommend strongly an increase in the practice of labeling, but they still leave to the physician the discretion. If it became a matter of law, it is mandatory, then we overcome the part of treatment, the mysticism, for example, that some physicians in certain areas of medicine—in psychiatry—feel is part and parcel of good treatment. This is where the objection comes.

In my practice I cannot conceive of but very few instances where a compulsory labeling would make any difference.

Senator NELSON. It has been the testimony of a number of distinguished witnesses that it ought to be described generically on the label, with the caveat that if a doctor does not think it should be, it will not be put on the label. So I am wondering why legislation requiring it, except when the physician directs otherwise, is not the only way you are really going to accomplish this.

Dr. ANNIS. I would not have too strong an opinion against that as long as the physician—this is the only thing—as long as the physician taking care of this patient has the right to discriminatory judgment in the interest of the patient. This is all we ask for.

Senator NELSON. I would call upon the AMA to support legislation to that effect, as I say, with the freedom of the physician to decide if he does not wish to have the generic label on it.

I have a letter from Dr. John Adriani, who is chairman of the council on drugs, endorsing that himself. He said, referring to an educational television program he was on, "I was the participant who expressed the opinion that all drugs should be sold by the generic name, that the generic name should appear in large print and the trade or brand name be put in smaller type below it, or the generic name in parenthesis."

Dr. ANNIS. I am acquainted with Dr. Adriani and also this television show. Dr. Adriani is an anesthesiologist and a very capable one in a university in Louisiana. There are many people who concur with this basic approach. The thing that they are fearful of is anything that makes it mandatory that physicians prescribe in only one way or that they always label in one way. This is where you take away from the physician his opportunity to discriminate.

Senator NELSON. Thus far, we have not had any one who advocated that you not reserve that right to the doctor.

One of the problems raised continuously to which I referred a bit back, is the brand name versus generic name. A year or so ago two drug chains, People's and Gray's, involving, if my memory is correct, about 300 pharmacies, announced that they were stocking across the board generic drugs supplied by Strong, Cobb & Arner, and that the average price of prescriptions would be about one-half of the brand name. Everybody testifying and appearing before the committee has been familiar with that company and spoken very highly of it.

The question I am getting at is it seems we have to have adequate legislation, adequate personnel in the FDA, to guarantee inspection and quality control so that we can forever get rid of this argument about brand name being always better, which has never been proven.

Would the American Medical Association support, before the Congress, legislation that would furnish adequate inspectors for the FDA so that they could sample, check the producers on a regular basis, so that we can have assurances that adequate quality control exists at each producing plant, so that once and for all we can say that these plants are inspected, they do meet USP or NF standards, so that the doctor can be assured that what he is buying meets these standards? Would the AMA support that?

Dr. ANNIS. I am under the impression that the FDA already has that authority. They need a little more money to implement it and to carry it out.

I would like to say, however, that I do not think either I or the American Medical Association can be put in a position that we have ever stated that the brand name is always preferable to the generic term. There are many excellent drugs available generically that come from responsible manufacturers who have built-in quality controls to put out good drugs. There are many generic drugs that actually come from these same manufacturers. Again, our point is that prescribing generically does not in itself assure that you are going to get what you expected.

It has been about 2½ or 3 years ago, Senator, that I read an article repeated in many of our medical journals about an instance that took place in the Province of Ontario. I am sure that is where it was, wherein

tolbutamide, a drug taken by mouth to control diabetes rather than injections of insulin, had been purchased in large quantities by virtue of its price. It was the low priced generic drug purchased. Subsequently many physicians who were using this drug in government hospitals and in that area began to have patients go into diabetic coma or show other evidences that their diabetes was not controlled. Subsequent investigation found and traced the trouble to the generically purchased drug, tolbutamide. Chemical examination proved that the tolbutamide was in fact what it was supposed to be; it was tolbutamide. However, in putting it together, the manufacturer who supplied it compressed it in such a way that it was not properly absorbed. It was not properly utilized.

Senator NELSON. We had testimony——

Dr. ANNIS. May I continue? I was waiting to see whom you were going to listen to, because this is an important point.

The drug was not absorbed. Many people passed it out of their intestinal tract in the same state they took it in. It was a good drug. They got what they bought. But it did not have the quality of absorption so the patient would get the result desired by the physician.

About a year and a half ago I had an opportunity to speak in Toronto before a drug trade meeting. On that occasion I raised this question: I said:

It is the first time I have been in Canada and I read this a year or two ago. I would like to know more about what really happened.

The president of the association said:

Gee whiz, I wish you hadn't asked me. I was the main supplier for the drug.

He went on to say that when they purchased it, it was purchased by virtue of its price from a supplier, and the chemical ingredient was exactly what it was supposed to be. It did not have the other built-in changes which would come from a quality product of those who had made longer examinations as to its ability to be absorbed and properly utilized.

I think this is why a number of physicians feel in prescribing many drugs that they will prescribe it with the brand name with reference to a particular manufacturer. I know this is true of many of my physician colleagues who treat diabetes. They will not just depend on one, but they will prescribe tolbutamide and then put two—either one or the other of two producers. What they want is to be certain that the pharmacist can supply it from whichever source is the cheaper of three or four sources.

The main thing the physician wants is that whatever the source that produces it generically, it comes from a source that also can assure a product that has the other necessary qualities which will make it absorbable and usable by the patient.

Senator NELSON. We had testimony on that exact case, and the record will speak for itself. I am simply going by memory. This case was discussed on pages 1340 and 1341 of part 4 of our hearings——

Dr. ANNIS. There were a number involved.

Senator NELSON (continuing). That is not valid to prove the particular point, because, as I recall it, it did not meet Canadian standards. Whether they use U.S.P. I am not sure.

Dr. ANNIS. It was generically equivalent. I would not say whether

it met any other standards, because I do not know where it was purchased.

Senator NELSON. We have a constant instance involving generic and brand names where somebody will testify that it proves that the generic is not as good, because here is a case in which it did not do such and such. Every single case we checked is the case of a drug that did not meet U.S.P. standards. Of course, when that happens, that is front page in all the medical press and the pharmaceutical manufacturers naturally say, "Here is another case that you cannot trust it."

We have cases in the files from the last hearing in which exactly the same thing happened to the brand names, so you might as well say you cannot trust brand names. In the cases I mentioned of the 4,600 drugs tested, with 8.8 percent of the brand name not being able to meet potency standards, that proves the case that you had bettter stick with generics, because generics meet it more often.

Dr. ANNIS. My point was just the opposite—that the mere generic equivalence in itself is not sufficient. If we were talking about building in additional safeguards, as I indicated earlier, many generic drugs prescribed come from satisfactory suppliers. We are not opposed to these. All we want is to be sure that when a physician prescribes a drug, he gets the drug that he prescribes and one that has the other qualities over and above its chemical constituency that are essential to its proper and expected action.

Senator NELSON. The point is made very frequently by USP, manufacturers and so on, that if the drug meets NF or USP standards, they are equivalent. Then the other side argues that they are not and they use chloramphenicol as one of their cases, in which there is no proof that there was any theraputic difference between the Chloromycetin and the other two in the marketplace. They just reached different blood levels in a different period of time, but the FDA decided that they would make them uniform. They could have made them uniform to the other drug as far as any clinical knowledge of the therapeutic efficacy of either one of them is concerned.

But the problem is that every time you find a generic that fails a test—and the brand names appear to fail them just as often—that is publicity to all the doctors, who then say, "Well, you cannot trust the generic."

Now, the thing that we have to resolve, it seems to me, is how do we get adequate testing to assure the medical profession, whether it is brand or generic, that it does meet the USP or NF standards.

It seems to me there are two things: One of them is to give enough personnel to FDA so that they can make adequate quality control inspections. You will not get this unless distinguished groups such as the AMA appear before Congress and say this is critical to America. Not just say this in the journal but appear before the Appropriations Committee and say that it is going to be critical to the health and pocketbook of the consumer, and, therefore, we think you ought to give FDA more inspectors.

Would the AMA appear before the Appropriations Committee when the issue arises in support of inspection?

Dr. ANNIS. Senator, we would be happy to appear before the Appropriations Committee or anybody else to assure increasing quality standards for all these products made for the benefit of the American people.

The Senator may be aware of the fact that the AMA is one of the three financial supporters of the Drug Standards Laboratory here in Washington, D.C. We pay one-third of the budget to supply specific research and standardization of these drugs. Few people realize that. But this is just one other area, that indicates our long desire for quality drugs. We will be very happy to testify.

We have long felt that the Food and Drug Administration—and the record will show it came into being many years ago with a strong continued support of the American Medical Association—we have no battle with these men who are trying to assure quality products. The only time that we come into conflict with anyone is when they say that by virtue of a chemical similarity the drugs are the same. These other standards are absolutely essential. We would support such a stand for more dollars to enable the FDA to do an ever-better job.

Senator NELSON. Are you saying that you disagree with the testimony of a representative of the USP and the NF that if a drug meets USP standards, it is therapeutically equivalent?

Dr. ANNIS. No; I did not say that, Senator.

Senator NELSON. Oh, I see.

Dr. ANNIS. I did not read their testimony, and if this is indeed their testimony, I would suspect that it would deserve serious consideration. I have not seen it.

My point is that the general continuing argument has been against brand as opposed to generic, with the assumption that if a drug is generically the same, it therefore has therapeutic equivalence. If the valuations referred to by USP and NF include these other standards, the absorbability in certain areas of the intestinal tract within a certain period of time, so that when I give a drug I know it is going to be absorbed within the person's body, I have no quarrel. But this is shown by clinical testing. This will not show up sometimes in the laboratory. What is true in a guinea pig, or a dog, a cat, or rabbit is not necessarily true in a human.

So in many cases the laboratory alone, the chemist, the pharmacologist cannot give the whole answer. So our position is that we must look at the drug in its whole spectrum—from the standpoint of how it is compounded, its basic purity and the rest, including its reaction within the body—so that we can assure a physician when he prescribes the drug generically, nothing will be supplied his patient that falls short of these desirable physiological reactions and he will know the end result, then I am sure we would be on common ground.

Senator NELSON. But the position of the USP is, and it has been the position of a number of witnesses, including distinguished pharmacologists and clinicians, that if a drug meets USP standards, then it is therapeutically equivalent to any other drug that meets that standard and that in the whole history of this debate there have been—there has been I think one proven case where that was not the situation. That would be a case when all the distinguished people who set the standard happen to have missed the point—the clinicians, the chemists, and so forth—in evaluating the drug have established the standard and missed some point. But in the whole history of drug testing, there has been a proof of one or maybe two cases. Therefore, if we are going to use any standard at all, it would seem to me the USP standard is the one that we should use. If clinical evidence is developed

that the two drugs with the same compound did not have the same clinical result and they discovered that some different excipient was used in one and that caused it and USP had missed that point, that would be an exception to the rule. But when we have never been able to find more than one or two such cases in history. It would seem to me that this is the standard to rely on.

Dr. ANNIS. Senator, here is an area I would like to ask Dr. Hayes about. He is much more knowledgeable in this area. Do they set up USP standards after the extensive basis of clinical testing?

Dr. HAYES. Of course, this is a problem which has engendered a great deal of discussion amongst interested parties. In fact, several learned bodies have spent considerable time studying it. Two come to mind, the Academy of Pharmaceutical Sciences and the Drug Research Board of the National Research Council. They have recently, as a result of their study of the problem, called for some improvement of the standards for assuring physiological availability or biological equivalence, as it were, of all drugs reaching the market. I believe that both the USP and NF at the present time are reevaluating their testing procedures in order to develop tests which will more properly evaluate the biological equivalence of all drugs reaching the market. So I do not think it is possible to say that the existing standards—although I know the people in the NF and the USP, that they are sincere, dedicated scientists, and the fact that they question their own testing procedures and look to improve them—that the matter can be settled as to whether, under existing standards of the USP and the NF, that they, in themselves, will assure biological equivalence. I think that more work has to be done. I think that work is being done.

Dr. ANNIS. Senator, may I add, too, that in this connection—I thought this was true, but I was not certain enough to testify. Recently the Drug Standards Laboratory had to come back to us; they needed more money. They are suffering from something known as inflation, too. The American Medical Association feels so strongly about this kind of testing that you are referring to that, without hesitation, when the Council recommended to the Board that additional appropriations be made, we did so.

This is an area where we are concerned. But we are even more concerned that it goes beyond what can be done in that chemical or pharmaceutical laboratory, because ultimately the laboratory of a drug for a person who is ill is in that patient's body. This is why that biological testing that Dr. Hayes refers to and other groups apparently feel must be upgraded, too, is so important. Here again is an area where we would want to be assured before testifying along that line.

Senator NELSON. I just want to say on this point that Dr. Miller of the USP and a representative of the NF have not testified that their standards were perfect. They have testified that they are the best standards existent in the world today and that they can be improved, and, of course, they will be. But the question arises, after accepting the USP standard or NF standard in some clinical testing we find out a year later that the standard omitted something, then they would correct it. But as of the date that standard is there, it is the best standard there is. Therefore, if a generic drug meets that standard and a brand name meets that standard, on what basis does an individual practitioner say or the PMA, in particular, say that one is better than another?

Dr. ANNIS. I would agree if standards are all the same they could

not say "Ours is better." As the Senator is well aware, about a year and a half ago I had requested, through Senator Smathers the opportunity to come to these hearings and speak as a private physician. At that time I did not realize that I was going to be elected to the Board of Trustees and have an opportunity to serve the American Medical Association.

When I went into the practice of medicine, we did not have all these drugs. When I talk to medical students today, I remind them that 90 percent of the drugs they learn about were not in existence when I went into medical school. I have two sons in medical school, and what they study, what they learn, was not known when I was there. I grew up knowing that I lost a young brother who died of an infectious disease because what he had could not be controlled. I lost a father at the age of 22 from a ruptured appendix. So I know as a clinician what these drugs mean. I have seen what they mean. I have seen people and children die of diseases that now we prevent and control. I am one of those who has grown up with great respect for the pharmaceutical industry.

Over this same period of time, with the constant addition of all these new drugs, naturally others have come in with the idea of producing. But, though I prescribe generically on occasion and I prescribe generically with the name of two or three producers following, I lean heavily on the reputable, responsible, long-term members of a great industry because I believe that, in most instances, I can depend upon their reliability.

There is a second reason. There are only, out of some 1,700 or 1,800 drug manufacturers—only about 130 or 140 do any significant amount of research. It is from this group that have come some 95 or 97 percent of all these drugs that I have seen produced in my 30 years as a physician. So, naturally, I feel obligated as a physician—as an individual practitioner, for what it has done for me and the tools that they have given—to support that segment of the pharmaceutical industry that is more than just a business, that segment which also does the research and has come up with one tool after another—first to control infection and diseases and then put into the hands of doctors in the field of anesthesiology, upon whom surgeons are dependent, some of the tools that have made possible modern surgery as we know it. So when I prescribe a drug—I do not care what it is—I generally will support that segment of this great industry that continues research, that continues to seek out other and better ways to solve the problems that we have not solved.

In my personal experience, it goes beyond just generic or trade mark drugs. It also goes to support that segment of the industry—I do not know what percentage it is, but I would guess 10 percent or less of the total industry—who are doing this great amount of research which I think is a boon to America and to medicine.

Senator NELSON. I have some more on this, but Senator Dole has a question.

Senator DOLE. First, I apologize for being late. I have been at another committee hearing.

I am a new member of this committee and I have not had the benefit of the extended hearings held in the past 2 years. I do not want to spend a lot of time covering old ground, but I have a question or two.

I am a great believer in drugs. I do not know whether they are

generic or brand name. Several years ago I was the recipient of streptomycin when it was in the guinea-pig stage, as a part of World War II, and also lived on streptomycin and Dicumarol for quite a while and became a great believer in drugs and the wonders they perform.

I had a letter last week asking me whether I was a generic or brand-name Senator, and I have not decided, yet, which; so I have not answered the letter. But it poses a problem with us, of course. There is a feeling, as you know, Dr. Annis, from your present and past capacity, among some members of the public that there is a sort of conspiracy or unholy alliance between the AMA and the pharmaceutical industry. This is a matter of concern to all of us. I do not know if you can answer that generally, but I would appreciate your comment. I know it is ground that has been gone over time and time again, but not in my presence. So if you could just comment on that, then I have two or three questions I would like to ask.

Dr. ANNIS. I know of no conspiracy. If you will look at the deliberations of our council on drugs, and their evaluation of drugs, and how they have spoken out against drugs that have had bad side effects, the abuse of drugs, the overuse of dangerous drugs, constantly reminding physicians, you would see no such conspiracy exists.

I have been raised in the school of therapeutic nihilism. I do not believe in drugs. The next moment, I say they are tremendous. I lean on them.

My point is that I refuse, and over the years have refused, to let my patients tell me when they should get a pill or a shot or something else. All drugs have a potential for harm. All drugs are dangerous. The medical profession as a whole has spoken out repeatedly on this. Drugs, whether they are aspirin or any of the other more potent drugs of today, all have a real potential for harm.

Aspirin has been a great boon. It is a great drug. But it still kills children every year.

Penicillin has changed the whole complexion of medical practice, since my early years of practice. Yet penicillin kills people every year.

There is no such thing as a truly safe drug. They all have potential danger. I think this is the message that the medical profession has continued to spread. We have no alliance with the industry.

If you think so, I would welcome you to come to some of the meetings of our house of delegates to hear physicians discuss these contributions to medicine, absolutely milestones in our progress, and yet, like so many great things, that also carries along with it built-in hazards that are very serious.

Had we such an alliance with the pharmaceutical industry, I am sure we would not have carried the thousands and thousands of pages of critical and analytical discussion on drugs that should be eliminated, drugs that are dangerous, drugs with a serious potential, and we would not have constantly advised physicians to carefully evaluate the therapeutic use and the necessity for their use before prescribing any drug.

Senator DOLE. Does a generic prescription automatically assure that the patient is going to save money?

Dr. ANNIS. No; there is no automatic assurance that that is the case. A generic prescription leaves to the pharmacist the decision as

to what drug he will prescribe. Assuming it is a neighborhood pharmacist with some good generic drugs from a good supplier, as opposed to a brand name, and he supplies it on a generic basis, knowing of the background—here, in this instance, a patient could conceivably save dollars.

If, on the other hand, a physician prescribed a certain drug without mentioning the name of the supplier, another kind of pharmacist, not of the neighborly, friendly variety, could supply him with the highest priced drug from a generic source. So it is not essentially so. It could be.

Senator DOLE. How much influence, in your opinion, does drug advertising have on a physician's decision to prescribe any particular drug? Do you have time to read the Journal of the American Medical Association—do you have time to read this monthly publication or just how much does advertising, whether it is written or verbal, influence your decision?

Dr. ANNIS. The journal I have an opportunity to review every week, the Archives of Surgery every month, and many other publications.

I have made it a practice for over a year to ask physicians, wherever I have gone, to what extent does advertising or the detail man determine their choice of a drug? You know what? I have yet to find one physician—and I have asked hundreds in medical schools, medical centers, in small cities and large cities—who makes his judgment on them. What they do is remind physicians of many drugs in the field.

I run into this frequently, where I will, having read in an ad about a new drug for a certain condition, or a drug that is supposed to be of value in, say, the field of orthopedics or medicine or in areas that I do not know anything about, I will ask doctors, what about this; I read about it in the last few days. Twice in the last week, I have phoned medical centers to find out, to be brought up to date on the medical use of Dopra, dihydroxyphenyl, something or other. I can't remember the long term hooked up with it. But it is being used now, experimentally, under limited circumstances in the research of Parkinson's disease. Now, as a surgeon, I have read about it. I knew that it was taken off the market for a while because of its dangerous side effects, but allowed back in for experimental use because it had been proven that despite its danger and toxicity, it also has a great potential for good in conditions where we do not have much in the way of treatment.

Now, what I read in the journals merely reminded me that there are drugs that are treating this. So when I had a personal request from a friend of mine because his mother is afflicted with this disease, I got on the telephone and called four of my good friends in different parts of the country in the field of neurology and neurosurgery and spoke to a man in one of our large research centers that is working on it. So the advertising in the journal often will remind me of advances in other fields.

But as far as having an ad ever determine for me to initiate and to use a drug without further checking it with—I often will write to, as many physicians do, the AMA. Our mail runs at the moment something like 15,000 or 18,000 letters a day. We get requests for information all the time.

I also would check it with medical men in my area who know men who deal with these things all of the time, as well as the pharmacist

and the pharmacologist. I know of no physicians with clinical experience and no physicians educated in the Nation's medical schools today who would prescribe a drug on the basis of what they read in an ad. Their attention might be called to it so that they look into it. But, gee whiz, you never think of prescribing it on that basis.

We have a number of copies of the journal if for any reason you would like to review some of them or some of their various ads.

This is a part of advertising. It is like Coca Cola. We have known about it for years, yet wherever we go in the world, you see a sign, Coca Cola. It is a sign that reminds you something is around if you need the pause that refreshes. Even a 5-year-old will tell you that. It is the way America has commercialized its products around the world.

But it would be dangerous if we bought drugs like we buy Coca Cola. They just remind you that they are there.

I do not know of any physician, and I have asked hundreds, who will prescribe a drug on the basis of what they have seen in ads of any kind. I have yet to know one.

Mr. GORDON. Dr. Annis, may I interrupt here?

According to the study which was done for the American Medical Association in the town of Fond du Lac, Wis.—are you acquainted with that particular study?

Dr. ANNIS. I am acquainted with the city but not with the study. I went to school with some men from Fond du Lac.

Mr. GORDON. That study showed that around 50 percent—that may not be the exact figure, but it is around 50 percent—of the doctors prescribed on the basis of advertising and detail men; as a matter of fact, it is mostly the detail men. With respect to certain individual items, like Achromycin, a trade name drug, and others, it went as high as 80 percent.

Dr. ANNIS. This is a different matter. Had you asked me to what extent the detail men or advertising has called my attention to drugs, that is a different matter. My first years, in my first 8 years in practice of medicine, I was in general practice in the capital city of Florida, Tallahassee. Those were days when transportation was not very good. We didn't have airplanes in and out. I think after a couple of years, Eastern went once a day north and south and National once a day east and west. Transportation was not good. We had no television in those days; radio certainly was not a medium for education. Only the publications of the American Medical Association, the medical journals, and the detail men kept me informed.

This was during the time that sulfanilamide, sulfamerazine, sulfasuxidine, sulfathiazine, right on down the line of the sulfas, that gave us control over gonorrhea, a previously uncontrollable disease, were developed. The sulfas gave us control of pneumonia and kept lives going. But they had side effects. People would be getting sick. They would be nauseated. Half of them would go down.

Now, the important point is the detail man or the ad would call my attention to the fact that he have a new derivative that eliminated the side effects, the nausea and vomiting. Very often it would be the detail man who would call it to my attention. You would not start off on a drug or prescribe on that basis initially. These people, however, kept us informed—in those days of a different kind of communications than we have today—as to what is new and reasons to look into these drugs and what they were doing. So their role was there as an initiator, as

a stimulus to look, but certainly they were not the deciding factors as to whether or not we prescribe the drug.[1]

Senator NELSON. I did not mean to or intend to open up this whole question at this moment involving the drug chloramphenicol, upon which I have some questions to ask later. But I might pose this question: We have had Dr. Goddard appear before the committee, and to quote him, he said, "I am at wits end on how to dissuade doctors from misprescribing chloramphenicol"—in this case, Parke, Davis' chloromycetin. We had Dr. Dameshek, Dr. Best, Dr. Lepper, and two others, all of these whom you know, estimating that between 90 and 99 percent of the patients receiving this drug were receiving it for nonindicated cases. This was their estimate. It has not been refuted by anybody. A week or so ago, Dr. Ley appeared before the committee and estimated that still 90 percent of the cases are receiving it for nonindicated cases.

The medical journal, the literature have all stated what the indicated cases are. If advertising and detail men are not important in determining what the doctor prescribes, how do you account for the fact that contrary to all the expertise and all the literature, including articles in the AMA, doctors continue to prescribe this drug for hangnails, upper respiratory diseases, sore throats, infected toes, infected gums, a whole miscellaneous list of cases for which it is not indicated?

Dr. ANNIS. Senator, I share with the distinguished array of scientists who have been before this committee their concern for the misuse of any drug. I am concerned about the use of a drug with great potential for harm when other drugs with less potential are available and about the use of a dangerous drug for minor conditions, especially when other drugs are available. We are in accord with this. This is a long record of the American Medical Association. I am sure that the Senator is aware that we have agreed and our council on drugs is happy to serve and work with Dr. Ley, and others to increase our efforts to further educate more physicians.

What I keep looking for in the records, and what I have yet to find and am hopeful of finding, is who is prescribing these drugs, where do they fall, for example, in age groups—not just age chronologically—and how long have they been practicing and where are they practicing?

Many physicians in the earlier days, before we knew the side effects of this and other drugs, leaned upon it as a drug that was found to be effiective in many conditions. It has been a number of years since the AMA testified that our clinicians, as well as our researchers and advertisers and teachers were finding some of the very serious side effects from the use of chloramphenicol.

I suspect two things, but I canot prove ether of them. One, if we could look and see a spectrum of physicians who prescribe the drug, I think we will find that they fall, I would expect, on the basis of my experience with the profession, into two areas. One, the physician in practice a number of years, as I have been, who has gotten into my habit, I have never been a great prescriber of new drugs. You learn six, eight, 10 or 12 well that serve your purposes and that is generally where you stay. I suspect that some of these, will be found in physi-

[1] See app. XII for excerpts of affidavits submitted to FDA by doctors who prescribed Thaliomide on basis of statements by detail men, pp. 4857–4862, infra.

cians as old as I am, 30 years in practice, who many years ago began to use this drug and because it did give good results. Even in the records presented to you, the fatality is one in 20,000, something of this kind. Too many. One in a hundred thousand is too many unnecessarily. That is not my point.

My point is a physician could have been using it for 15 or 20 years and never himself have had a fatality. So they are not persuaded against it. I would suspect that we find a great number in this category.

I doubt seriously if you will find many of the medical students of the past 10 years misusing it. I have already talked to my sons and some of those in school with them. They have all been forewarned.

The second group includes physicians who work in areas far removed from a medical center, physicians who are often far removed from a hospital where they could run sensitivity tests, where they do not have the chemist and the pharmacologist and the pathologist, to assist them, and where they are dealing with diseases often associated with poverty, with lack of nutrition and other factors. On high temperature diseases, sometimes of a gastrointestinal nature, where they are not quite sure what is the maatter with the youngster or with the patient, and knowing its broad spectrum applications and that it is readily absorbed, and again on the basis of experience, they will often lean on this drug.

Now, again, I am not citing this to justify it, because we share with your witnesses the very serious concern for the use of a good drug in too many instances. But I would not be at all surprised if this is where we are going to find them.

Now, we have to increase our efforts to educate these physicians that even though they have not gotten in trouble themselves, or they are not aware of it, the danger is there, the record is there, the potential is there, and that the use of this drug, like others of tremendous potential, should be limited to strict areas where it is the only drug of choice or where it is preferable because of other conditions of sensitivity or otherwise on the part of the patient. I have to admit to you frankly, Senator, I have never prescribed Chloromycetin. One reason, perhaps, was that Harry Beekman at Marquette, where I went to school, was one who educated me and my colleagues to be very wary of any kind of drugs. So I cannot speak from personal experience.

But I have talked to physicians around the country who use the drug. I talked to them especially this past year or so. In every instance, the physician who continues to insist on it has not been persuaded.

So I agree with you. This is why the American Medical Association is anxiously awaiting a meeting that had to be postponed twice in the last couple of weeks. Dr. Ley was tied up with other problems of the Food and Drug Administration. We are most anxious to expand our effort to bring the total message to all of our physicians.

We feel that the drug itself has proven in the minds and in the experience of every qualified clinician to have a very worthwhile and a very definite place in the armamentarium of drugs, but it is one that should be limited in its use to definite indications. We go along with this completely.

Senator NELSON. The issue that was raised, however, is the extent to which doctors base their prescribing upon advertising, promotion, and detail men vis-a-vis the literature——

Dr. ANNIS. I think the success of the advertising was 15 or 20 years ago, Senator. I do not think it has continued success today.

Senator NELSON. I do not think that is shown by the record. When it was taken off the market back in 1952 or 1953 it dropped way down in its usage. Then—Dr. Hayes can answer more accurately, but I think this is roughly correct—it was off the market. The indications for its use were drafted some 15 years ago, very limited for some disease, for limited use in other cases where no other drug was effective and where this drug was effective against the particular organism causing the problem. That has been the indicated use for, I think, 15 years and it came right back up again and continued to rise.

Now, that was against all the medical literature, against all the authorities. Yet it continued to rise and be widely misprescribed.

Now, once it dropped, but then people starting using it again—I do not think you can say that the advertising and promotion is not effective.

Here you have a case where, since 1954 or 1955, the indicated uses were very limited, and yet it is being widely misprescribed according to the testimony we have had. The AMA Journal carries ads. It used to have lots of reminder ads which simply said, "Chloromycetin, when it counts." In fact, the JAMA ad carried a picture of a bronchoscope. Now, the Drug Council and the AMA knew very well that it is not indicated for bronchial diseases, but the AMA allowed the ad to be run.

Now, I think the fact of the matter is that just from a commonsense viewpoint, contrary to all the education, contrary to all the articles in medical journals, contrary to all the expertise in this country, the drug company successfully promoted it and continued to get doctors to use this. I do not know how you explain it.

Dr. ANNIS. Senator, I presented to you two theoreticals from my own experience and guessing, because I do not use it. However, Wisconsin is known for its good physicians. I used to do a little fishing in Michigan, where I was born and reared. And for some time, your fine lures are off the market and you cannot use them because they are off the market. But if you hear they are on the market again, you go back to that fine lure with which you caught good bass and pike years back.

What I am saying is that the man who built his confidence earlier for whatever reason may be the area where we are going to have to concentrate our education. I do not believe it is being prescribed in these ways to which you referred. I doubt if this is prescribed by today's young generation of educated physicians.

I doubt if the advertising is educating new physicians to its use. I would have to give a point and indicate and admit to you that if I were a doctor who was persuaded some years ago that it was a good drug, and then it was taken away by what I might call an arbitrary decision of somebody and it upset me, the advertising might remind me that it is back again.

The advertising accepted by the AMA—and I have to absolve the Council of the bronchoscopic ad because the Council itself would not have seen this ad prior to its being published—I think it was a reflection back to the older days when it was used on children. I have heard pediatricians who used it extensively——

Senator NELSON. I do not think it was ever indicated for any bronchial infection.

Dr. ANNIS. One of the cases has been hemophilus influenza and there are still physicians today who still feel it is the drug of choice in hemophilus influenza or pneumonia.

Senator NELSON. That is contrary to the National Academy of Sciences-National Research Council, who said it is no longer "the" drug of choice for any reason.

Dr. HAYES. As far as respiratory infections are concerned, there are some who believe that treatment in specific instances of cystic fibrosis, involving the lungs, that chloramphenicol is effective in reducing the possibility or potentiality for serious respiratory infection. I certainly would agree that in any pneumonitis bacterially caused, there may well be other as effective antibacterial agents as chloramphenicol. It would be unlikely that you would prescribe chloramphenicol unless it became a life-threatening situation and for one reason or another other antibacterial agents could not be used, such as sensitivity of the bacteria itself or possibly in the matter of some reaction of the patient to other drugs that might be used. It would be a rare instance where it might be used.

Senator NELSON. Has it ever been indicated in general for upper respiratory diseases, bronchitis, or any other thing like that?

Dr. HAYES. Not that I know of as a general indication. However, you must take into account that irrespective of the hazards of chloramphenicol, and they are very real and I think that every physician is aware of them—I do not condone the misuse of the drug in the face of these hazards at all—it is a very effective broad spectrum antibiotic. In fact, at the institution where I do some volunteer teaching, they occasionally post a summary of the sensitivities as determined by their routine testing of bacterial sensitivities to a number of organisms. It is surprising that chloramphenicol in the vast majority of the organisms that they encounter will turn out to be most effective antibacterial agents in and under those tests. I do not say on the basis of those that you would use the drug, but I merely say that to emphasize that it is an effective antibacterial agent and in the face of a life-threatening situation, a physician might elect to use chloramphenicol if he was not certain of the offending organism or organisms. And that is the situation that he might encounter if he is remote from a medical center where all of the sophisticated facilities might be available to him.

Again, I would not condone the use of chloramphenicol or possibly any other antibacterial agent for a hangnail or some incidental infection.

Senator NELSON. I am sure you know better than I do that the indications have been stated as very, very, very limited. As I stated before, according to the National Academy of Sciences, it is not the drug choice for any disease.

Dr. ANNIS. I understand that has been very recent. I do not know how recent, but I heard it the first time 2 or 3 days ago.

Senator NELSON. It was last October. But for 15 years, correct me if I am wrong, it was indicated for ricketsial diseases, it was indicated when the disease was serious—it always had to be serious—when no other drug was effective against the organism and when chloramphenicol was effective against it.

So now on the question of advertising and promotion, if I understand the experts correctly here, it has never been generally usuable as a broad-spectrum antibiotic, at least since the first side effects were found in 1952 or 1953. It is not indicated for general upper respiratory diseases, as I understand it.

On the question of which is the most effective, the articles of the journals as to its indicated use or drug advertising promotion and detail men, it seems to me that the ad in the AMA Journal with the bronchoscope picture is not saying: "We are running this bronchoscope to indicate that you might use Chloromycetin if there is cystic fibrosis." What they are doing with the bronchoscope is saying, gentlemen, if there is anyhing in that area, use Chloromycetin when it counts. So obviously, that is an improper ad, making a claim on its face that I do not think any scientist who has testified here would defend.

It obviously must have had effect, because it is vastly and widely prescribed for upper respiratory problems. We have had letters of deaths in the files that it was used for that purpose.

So on the question of which is effective, just again using horse sense, I would say vis-a-vis the articles by Dr. Dameshek and others in the journal cautioning against it and vis-a-vis the effectiveness of the ad, I think the ad and the detail man run away with the case.

So I raise the question, one, I think it is effective, and, two, why would the AMA run an ad with a bronchoscope in it when they know very well it is not indicated for that use?

Dr. ANNIS. Mr. Chairman, I would not plead that we do not have human error in judgment. I suspect that in this particular instance, the evaluation of the bronchoscope and the rest, from the standpoint of its implied suggestion that it would alleviate the need for bronchoscopics and conditions of that kind, this undoubtedly was inappropriate. I would think so as I review the record and what is there.

But I still would like one of these days to have someone, if we can find out from the records, find out the age of the doctors prescribing it. Are we, in effect, getting new prescribers in the last 5 or 6 years, or, in essence, are we still getting prescriptions coming primarily from the same sources?

Or as indicated by Dr. Hayes, from those in medical centers where, on sensitivity tests, it is indicated?

These are some of the other perplexing areas that are involved in this drug and its advertising and we are seriously concerned about the effects of this or any other drugs that have similarly serious effects.

This is why I reiterate the welcome participation that we will receive from Dr. Ley in an effort to expand our efforts to inform those segments of the profession that still use this very dangerous drug that its limitations are even greater than they used to be by virtue of newer and more effective drugs to take care of conditions that in the past were treated by chloramphenicol.

Senator NELSON. But it seems to me the facts in the case scream rather loudly. They use the advertising device very widely. They have sophisticated advertising, a powerful group of creative minds involved.

Dr. ANNIS. It was cleverly done; no question about it.

Senator NELSON. And they have been able to get doctors to prescribe it. If I can use the expert testimony, they misprescribe it 90 to

95 percent of the time. Now, the best estimates are that this involves 4 million people who were receiving that drug in 1967, but anywhere from 90 to 95 percent were for nonindicated cases. Does it not indicate obviously that the precautions of the profession itself and all the experts have just not prevailed, and is that not an indictment on three counts—the doctors who are prescribing it, continuing to prescribe it, and the company who will continue to promote it, and the journals that accept the ads despite the fact that they know it is being widely misprescribed.

Dr. ANNIS. May I remind the Senator that today, under the rule of the law, the content of the ads has to meet the many and rather stringent requirements of the Food and Drug Administration. But here is a drug, as you indicated, that was taken off the market and a drug returned to the market. The content of what they say in their ads is relatively controlled by the Food and Drug Administration. So what you are suggesting is that we had better take a look at some of the regulations and controls there.

But again, I see no evidence—I will not argue, I can't, one way or the other—that the ads in today's journal are increasing the numbers of new prescribers of this drug.

Now, we do not take ads, for example, of the most dangerous drug in the United States, the drug that contributes toward more deaths than chloramphenicol and all the rest of them put together. And I cite alcohol.

Now, here again, we educate all of our public against the dangers of alcoholism and driving while under the influence. Yet the records of the National Safety Council indicates that it is involved in 50 or 60 percent or more of the accidents: 52,000 Americans last year were killed in automobile accidents. A million nine hundred thousand were injured sufficiently to require doctors.

Now, a drug was involved, the most dangerous drug we have. Education of the masses of the people has been inadequate and we have to step up our efforts.

Senator NELSON. It is not a prescription drug.

Dr. ANNIS. In the field of medicine, we have another drug, extremely dangerous, nowhere near as dangerous in its effect on the numbers of people, nor even in its lethal effect, but one, nevetheless, that poses a very serious and continuing problem. I would again reassure you of our desire to use every reasonable means to get the message to more physicians. Admittedly, this is an area where the message has not gotten through to everybody. What I question is an indictment on the basis of an ad or a particular drug company's ad about a certain drug when the content basically is controlled by the Food and Drug Administration. What I question is the effectiveness of this or any other ad to be the prime reason for a physician practicing medicine. This is what's not in accord. They have never persuaded me to prescribe it. But perhaps I have not had the indications of others.

My only point is that an ad alone is inadequate. I would like to know if the physicians who are prescribing it today are the same ones who were prescribing it 10 or 15 years ago, or with the rare exceptions Dr. Hayes has indicated by virtue of sensitivity tests. This is merely raising a question, Senator.

Senator NELSON. Well, I have no doubt about that, but the facts are there that the medical profession—the AMA is the leading organization——

Dr. ANNIS. What would you suggest that we do, Senator?

Senator NELSON. Well, I would not run an ad, if I were in control, with a bronchoscope in it. I think it was an outright fraud. I think it was intended to be a fraud; it was intended to mislead. We received letters about people who died from it. Therefore, why should the AMA Journal be a part——

Dr. ANNIS. I have indicated that human fallibility is a part of our structure, too. We build in as many filters as we possibly can. In this particular ad, I would agree with you. This was a good Madison Avenue effort that slipped through the screen.

Senator NELSON. It has been slipping through for 15 years.

Dr. ANNIS. Oh, no. I do not think this ad has been slipping through.

Senator NELSON. I think so. As a matter of fact, if we go back——

Mr. HARRISON. Senator, perhaps I can add just a little bit to place this in somewhat its proper perspective.

Senator NELSON. I thought I had.

Mr. HARRISON. I just want to add something that I think will be of interest to the committee.

Looking through our records, I find that in the past 5 years, AMA journals have carried a total of about 84 pages of chloramphenicol ads. Since we publish 52 issues a year, or a total of 260 issues in 5 years, we have had a total of about 65,000 pages of paper. I would say that the total advertising with respect to this drug is something like less than three-tenths of 1 percent. At least here, it is indicated that we are not speaking of an advertising campaign. We have only some 85 pages over a total of 5 years, out of a total of 260 issues, and perhaps somewhere in the neighborhood of 65,000 pages.

Senator NELSON. I do not really think that answers much. If it is 85 pages in 5 years, you are talking about what, 18 pages of advertising a year—19?

Mr. HARRISON. This publication, you know, is weekly. That is 52 issues per year, with approximately 250 pages in each issue. So it is a relatively small number and I have computed it to be about 0.3 percent.

Senator NELSON. But do you think the percentage is relevant? It is 19 times a year that the ad for Chloromycetin has been in the magazine during the whole period. Experts all over this country have been tearing their hair out about the misuse of this drug and the promotion, the company has won the battle against the AMA and the medical profession consistently and continuously until they were prescribing 42 or 43 million grams in 1967. It took these hearings and wide exposure to drop that in 1968 down to I think 18 million grams. As I said before, this committee is not the expert on it. Where was the medical profession? The public is entitled to say, my heavens, the AMA carried ads and promotion of it but very, very little about how bad it was.

We cannot find very much in the last 2 or 3 years. There was very little material on our hearings. We found two or three little notes, but it would seem to me it would call for a front-page editorial, just saying, Doctors, are you off your rocker? It seems to me it would

call for the AMA to say to all its people, call meetings in your State, right now, people are dying from this, have a public meeting, get to the doctors, get it on the front page, tell them they are misprescribing these drugs, and that the AMA would do the same. The great, responsible medical profession, did not. And it took these hearings to expose it.

Mr. HARRISON. We take strong objection to the statement on whether or not the AMA has been doing something in this regard. I think Dr. Hayes can respond with respect to what the Council on Drugs is doing. I have here some adverse drug comments taken from the Journal of AMA, very consistent and in great detail. The AMA News which is distributed free of charge to all physicians, members or not, just over a period of recent weeks, and even more so in prior months, has consistently included comments with respect to the discovery of adverse reaction on chloramphenicol, and the statements made by this committee or by others with respect to the dangers involved. The Association is very much concerned and very much aware.

Now, we have also accepted advertisements with respect to the drug—that is correct—recognizing that the Food and Drug Administration has not seen fit to take the drug off the market. The AMA has scrutinized these ads and, as Dr. Annis has suggested, it is possible that this one particular ad did carry some background of a picture which slipped by and, perhaps on reflection, should not have been included. But in the overall picture, Senator, I think it can be seen that the Association has been very much concerned, and I would ask Dr. Hayes, if he would, to add to this comment with respect to the activities of the Council on Drugs.

Senator NELSON. May I respond just a moment on that? We had the Library of Congress check every single edition of JAMA and of the AMA News since this issue was raised by the committee. As I look through the material, and we have photostats here, I consider it a pitiful effort in terms of notifying the profession about what was wrong. I raise this point again: the medical profession, the AMA has the health of America in its hands. We want to have confidence in it. One can examine these and see how pitifully small these articles are.

Dr. ANNIS. Senator, this is just one publication. We have county and State medical societies across the country. We have medical meetings where this is presented to physicians. I outlined to you we have 100 pages of medical programs to physicians where there is repeated by physician teachers. This is consistent with the medical profession. You have a drug which our own Food and Drug Administration of this country took off the market and they put it back on the market and allowed it again to be sold. If this is the case——

Senator NELSON. For limited application.

Dr. ANNIS. If this is the case, they have given tacit approval to the drug. We have always, in accepting advertising, repeatedly told the profession, this is a drug with ever-increasing evidence of its dangerous side effects and that it should be used on a limited scale. If further information is demanded by virtue of the facts, these then should come from the Food and Drug Administration.

Senator NELSON. Of course, it is interesting to note that the FDA is attacked time after time by various members of the medical profession——

Dr. ANNIS. Everybody is attacked. We are attacked, too, Senator,

Senator NELSON (continuing). For regulating too much. But I think, Doctor, in all fairness—we will look through these ads—the fact is that whatever the AMA did, it did not work. That is a fact. Now, what this committee did——

Dr. ANNIS. The facts are, Senator, that Moses brought 10 little messages down from Mount Sinai and that message has not gotten through yet. The fact that the message gets out does not mean that it is received on the other end. It takes two people to absorb a message, those that send it out—and we have put effort after effort to get it out—and those who are to receive it. I have admitted to you that there is a segment of the profession that has not gotten the message and does not understand it. This does not mean that we have failed to send it out. It has failed to fall on receptive ears. We are willing to meet with you, or with the Food and Drug Administrator, or anybody else in an effort to increase the receptivity of these ears that it has not fallen upon.

But do not accuse us of not trying. You can say what we have done has not been enough. We will do more. But this is in keeping with what we have been doing.

Senator NELSON. I look at the ads and we can examine them later. There is not much in them.

Dr. ANNIS. May we have Dr. Hayes give you at least a summary of what we know we have done?

Senator NELSON. Of course. The point I want to make is whatever you have done it is not effective, and then I suppose if you have done all that you think it is feasible to do, you ought to concede that a congressional subcommittee, with no experts on it, has been 100 times more effective in telling the doctors the story than the AMA, because we got it reduced in 1 year from 43 million grams to 18 million.

Dr. ANNIS. This is great. We are happy about it. But may I give you an example of what was even more effective than your drug hearings? That is the conquest of polio. But why? Here is an area of a serious disease.

Senator NELSON. What's the analogy?

Dr. ANNIS. The analogy is the mechanisms, the communications media, the overwhelming use of press, radio, television, civic clubs, everyone, to tell the story. We had everyone telling the story on this. And it was tremendous what we were able to do, not just because we had a drug that could solve the problem, but that the great pharmaceutical industry could manufacture it by the millions of doses. Then the story was told to everybody, come, not just with your doctor and your nurse, but with grandma, grandpa, mother and dad and everybody. Here is an example of an overwhelming approach with every communications media available. And it got to the American people.

In some instances where the education was poor, buses were sent out into the areas and the kids were given lollypops and balloons and physicians joined with volunteers all over the country in a massive effort to tell the story.

Now, these are the two extremes, one that is undoubtedly tremendously effective, and it was quickly so, and an effort through us to use every kind of medical communication, from publications, meetings at hospitals, medical centers, county and State societies. And we still

have not gotten the message through to some members of the profession. I still do not know whether it is the same ones that were using it because they were happy with it 10 or 15 years ago.

My point is we have to step up the means of communication. My analogy with the polio effort is merely what can happen when every medium of communication is concentrated and where what they are selling has merit, where the problem we are facing is a serious one, and where those who are the potential victims as well as those who are their protectors share a common interest.

And this, I am satisfied, is what you are seeking. That is better medical care, better drugs, safer drugs. And in the instance of a drug that may have to be kept available for its very limited use, what you want to do is to see to it that all physicians get this message, that they are motivated by it, having received it, and that in the future, they prescribe this drug only when it is needed. We are in total accord.

Now, the question is what's the best way to do it? But do not say what we have done wrong 5, 10, 15 years ago. Many of the drugs that are in here were not available 5, 10, 15 years ago. We are not carrying an ad today that has not carried the tacit approval of the Food and

Senator NELSON. I might say that in the past 2 years, you have carried 10 for which a remedial "Dear Doctor" letter was written. We will look at those later—the FDA forced the company which misrepresented the drug in your publication, as well as in others, to write a letter to every doctor in the country.

Dr. ANNIS. But you just admitted, Senator, that there is a contract by regulation between the FDA and the company. You admitted, to, that the ad that was carried was a violation of that contract on the part of the company. And if we carried it, and I willingly admitted that we have human error occasionally on matters of this kind, too, where things get through occasionally that we would not want to have gotten through had we had all of the facts—but I think you will have to admit that if there is an understanding between the Food and Drug Administration and any producer, this, in effect, establishes through that company and their advertising agency the basic principles that they should not violate.

Senator NELSON. The question was raised, and as you will recall, it was raised around the question of whether advertising or promotion is effective. Something is effective.

Dr. ANNIS. I do not think anybody in America can deny the important role of advertising in any area.

Senator NELSON. My committee counsel advises me—this does not have a date on it; we will recheck it to see if it is correct—but this is a 1968 ad.

Dr. ANNIS. I would not be surprised, and I have already indicated——

Senator NELSON. This was carried in 1968.

My point again is what you said in your articles did not work. It seemed to me that there should have been a meeting, a public meeting in every State in the Union saying that this company's drug is being misused.

Dr. ANNIS. Senator, I just asked Dr. Hayes how long we have carried the contraindications on chloramphenicol, and he said since 1952. What you and I agree on is that some doctors either do not read it or having read it, they do not comprehend it, or having comprehended

it, they do not believe it and do not accept it. But this is not the fault of a failure on the part of the AMA to attempt to properly inform its members.

Senator NELSON. Well, I think, Doctor, and I think you will agree with this, that the medical profession, the AMA, has a peculiar responsibility.

Dr. ANNIS. I would agree.

Senator NELSON. It is not like an ad for a piece of machinery or something else which may be deceptive. It may fall apart and it may do all kinds of things. The AMA is highly regarded by the medical profession and by the public. It seems to me they have to do much more in terms of their responsibility than just saying——

Dr. ANNIS. And we do——

Senator NELSON (continuing). Than just saying FDA approves.

Dr. ANNIS. I agree with you, and we do.

Senator NELSON. Let me ask you a question: The AMA Journal is still running the ad: "When it counts, Chloromycetin."?

Dr. ANNIS. That is still true. When it counts, it is the drug. When it is indicated, it is the drug.

Senator NELSON. But you and I know what they mean by that.

Dr. ANNIS. What do they mean, Senator? You read into it something that some of our doctors obviously do not. I agree with you, let's get the message to those who do not.

Senator NELSON. Let me ask you a question: The medical profession does have a peculiar, very important responsibility to the public. Why should they not insist that in big print, right here, it says "The National Academy of Sciences says this drug is not 'the' drug of choice for any disease"?

You might say, well, this drug passes the FDA. I do not think you can shift your responsibility to the FDA. If you are willing, I have some laws I would like to pass and have your support on. But it is serious enough and they are not reading fine print any more. If it is correct, as you say—and I have no information one way or another, but I doubt it—I think there are plenty of young doctors prescribing this.

Dr. ANNIS. I do not say there are not. I am asking you. I would love to know, too. I do not know any young ones that are.

Senator NELSON. I do not know, either. But if it is true that lots of of them, and I think that is correct, that lots of them are people who have been prescribing it for many, many years, therefore, they do not read the new contraindications——

Dr. ANNIS. It could be.

Senator NELSON. They see the reminder. That helps remind them. They have been using it. It is being widely misused, and because of the AMA's, the medical profession's peculiar responsibility, why do they not say, this just is not working and it is being overused and if you are going to run this ad in our Journal, I want to be sure that the doctor who reads it sees in big print, "Not indicated as the drug of choice for anything" and some other precautions, plus the editorials that are big and displayed prominently in the Journal.

Dr. ANNIS. The editorials and all these approaches there, our council on drugs and the ranking members of the elected representatives of the association share your concern. I have repeated this over and

over again. This is an area of real concern to us. When it comes to advertising, I have specifically raised this question with some of our people. We also have fair trade problems involved in discriminating against one company as opposed to another. If we are talking about broad spectrum antibiotics and we except three or four companies, when they comply to certain other requirements, then we are in this position, too. I do not attempt to know whether or not this applies in this instance by virtue of the other side effects of chloromycetin, chloramphenicol, its generic name. However, this is an area where we admit there is a real problem. It is one we have tried to solve. And again, I would like to ask Dr. Hayes if he can give a summary at least of what we have done in this area.

Senator NELSON. Of course.

Dr. HAYES. Well, the first statement on chloramphenicol that the council on drugs published was in 1951. That original statement indicates the peculiar and dangerous hazard of chloramphenicol. Since that time, in all of the statements of the council and its publications, the message has been very clear and consistent that there is a peculiar, dangerous hazard to the use of chloramphenicol as regards bone marrow depression, and that as time has gone on and other effective antibacterial agents have appeared for use by physicians, the indications for chloramphenicol have become fewer. Those statements have clearly indicated that.

In addition to those statements in the formal publications, the council has periodically published in JAMA statements firmly enunciating the proper perspective of chloramphenicol as regards its uses and its hazards.

Now, I might just say in addition that in JAMA itself over the past 20 years that chloramphenicol has been available, the Journal itself has published some 285 articles on chloramphenicol, of which, as I recall, 55 were directly related to its toxicity. In the specialty journals, there were some 30 articles published—that is, the 10 specialty journals—of which 20 or more related to its toxicity.

But most important, in 1953, recognizing the seriousness of the hazards of chloramphenicol as a cause of aplastic anemia, the council established a Committee on Blood Dyscrasia to look into the matter. They established a registry of blood dyscrasia which collected case reports on all drugs causing blood dyscrasia, but it was generated by the problem involving chloramphenicol.

In 1963, the council expanded that registry on blood dyscrasia to include the reporting of adverse reactions of all types on all drugs. And that activity continues to this day.

We recognize that in spite of this consistent effort which, when added up, is quite considerable, in my opinion, we need to get our message across in a more effective way.

In 1963, we approached the Joint Commission on Hospital Accreditation and asked the commission to include in their standards the reporting of adverse reactions to drugs. The commission at that time was not amenable to do that. They did agree to publish in their bulletin statements encouraging hospitals, through their hospital and pharmacy therapeutics committees if they did exist, to report adverse reactions. We have continued those conversations, and I am happy to say that it looks as though we are making a little bit of progress. The joint

commission is rewriting some of their standards and we are hopeful that they will actually get into it, into the standards, the need for drug usage surveillance programs.

Now, we recognize that there is a great limitation to the effectiveness of a registry which involves voluntary reporting of adverse reaction to drugs by physicians. A physician for some reason or another, and I am not prepared nor at any time would I be prepared to say why, is reluctant to report, but the sad fact is that they do not report readily. So now, and for the past year and a half, what we have been doing is developing a plan to establish drug usage surveillance programs in hospitals, so that those programs would develop the data, the firm data, reliable data, so we would have some indication of the overall usage of chloramphenicol and all other drugs used in a hospital and be able to get firm data on their adverse actions. We would know who is prescribing them—that is, the local hospital would know who is prescribing them, for what conditions and what the effects were. Out of that, we would have, instead of estimates, we would have firm reliable data.

At the same time, the governing body of the hospital, in situations where there was evidence of misuse or overusage of a drug, would be able to take some remedial action against those who might be misusing or overusing drugs.

So we recognize our deficiencies. We are trying to do something about it. I think that over the course of years, the posture of council has been one of progressive deliberation. We are not sticking our heads in the sand; we are trying to do something about it. I think that we enjoy a considerable amount of success.

Senator NELSON. I have some more questions on this, but it is 12:30. Let me ask you, Doctor, I have not covered but a fraction of the questions and areas I want to cover. How much time will you have this afternoon?

Dr. ANNIS. I made the whole day available to you, Senator, because I am just as anxious as you are to present our position and our willingness to cooperate toward the end of better drugs and better therapy.

Senator NELSON. If it is not possible to finish, can we set another date in the future to finish?

Dr. ANNIS. Yes, we could in the future. It would not be in the immediate future, but I imagine your schedule is just as tight as mine.

Senator NELSON. Yes. I ask you that because I do not think we can get to all the material today.

Dr. ANNIS. I would be very happy to come back.

Senator NELSON. Thank you. Why not come back at quarter to 2? That will be 1 hour. Is that all right?

Dr. ANNIS. Very good.

(Whereupon, at 12:35 p.m., the committee recessed, to reconvene at 1:45 p.m., this same day.)

AFTERNOON SESSION

Senator NELSON. I had not intended this morning, or at that moment, to get off on the chloramphenicol thing, but since we did it, I did have a couple of questions to ask just to finish what we had before we left.

On the continuing dialogue we had on the defectiveness of advertising, did JAMA or the AMA News carry the story, and to what extent, on the National Research Council of the National Academy of Sciences' recommending filing with the Federal Register that chloramphenicol was not the drug of choice for any disease?

STATEMENT OF DR. EDWARD R. ANNIS ET AL.—Resumed

Dr. ANNIS. Do you know, Tom, whether they did or not?

Dr. HAYES. No, I do not know whether they did or not.

Dr. ANNIS. Was it given general currency?

Senator NELSON. On October 19, 1968, the FDA published in the Federal Register the results of the National Academy of Sciences' study on chloramphenicol. Copies of the reports——

Dr. ANNIS. I must admit, I did not see it in the medical or the lay press. That is the reason I did not know about it until just recently.

Senator NELSON. Well, the drug council of the AMA is advised forthwith of whatever goes in on drugs, is it not?

Dr. HAYES. No, we ordinarily do not receive any special notification from the Food and Drug Administration of its publication. We do, of course, review its pronouncements as published in the Federal Register.

Senator NELSON. I assume you review them on a regular basis, do you not?

Dr. HAYES. Not entirely. It depends on the substance of the announcement; also, in relation to what is our immediate concern at the time. We have taken this into account, that we are reviewing the background information on chloramphenicol for this book that was mentioned, and we are aware of the announcement and are awaiting further developments on it.

Senator NELSON. Here is a drug which has been receiving lots of publicity for better than a year, and the National Research Council of the National Academy of Sciences states its indicated use which is filed in the Federal Register, and the AMA knows the publicity all this has had and all this took place 5 months ago.

Dr. ANNIS. This might be a good example, of better publicity from some of these findings, Senator. I understood this morning, you said December.

Senator NELSON. October 19, 1968.

Dr. ANNIS. When was it published, do you know?

Senator NELSON. It was published in the Federal Register on October 19, 1968, according to the information I have.

Dr. ANNIS. My only point is, this is another good example that we had better step up lines of communication, especially on matters that are vital. I was not aware of it.

Senator NELSON. I would assume that any filing with the Federal Register by the FDA on a drug would be of great interest to the AMA.

Mr. HARRISON. May we see the notice?

Mr. GORDON. We do not have the notice here.

Senator NELSON. We just have the date on which it was filed.

Is there any question about that?

Mr. GORDON. No, no question about that.

Mr. HARRISON. I thought if we had a copy of the notice, we could see the purpose of the notice itself. As you know, some are just pub-

lished as official notice to the manufacturer so they can submit comments with respect to the action that is proposed to be taken, or whatever would be involved. That is official notice.

I thought if we had a copy of it, we could look to see what is involved in this particular instance.

Dr. ANNIS. Merely as a citizen, I am a little surprised, Senator, that after all the publicity that has redounded from your investigation on this drug, a finding of this kind, if it were a final decision, would not have gained more currency if it were really put into the distribution channels.

In other words, here is an essential finding that is very important to the Food and Drug Administration. We find when they begin to investigate mixed drugs like Panalba and Mysteclin and others—this we found in the medical press as well as other press, so someone made it immediately available.

I must admit I may be derelict, but I read a great deal and it has only come to my attention in the last few days.

Senator NELSON. I think it was in the public press.

What I am curious about is when the National Academy of Sciences issues an evaluation of the drugs in some detail, and the FDA announces it in the Federal Register, does not the American Medical Association get these filings and look at them?

Dr. ANNIS. In this particular instance, without seeing it, I would not know.

Mr. HARRISON. If you are asking, Senator, whether we review the Federal Register as to items that are and should be of interest to medicine, the answer is "Yes," we review the Federal Register on a regular basis. I am inclined to believe that the notice you are speaking of, and I do not recall it, may have been notice to the manufacturer with respect to some finding and an opportunity for the manufacturer to provide some additional information. I do not know.

Senator NELSON. No, this was an evaluation, a new evaluation of the drug by the National Academy of Sciences, the National Research Council, Division of Medical Studies. It is a drug efficacy study. It was a formal study done on it. They reached their conclusion and this is an 11—a 10½-page evaluation of the drug. It is then made public by a filing in the Federal Register.

Mr. HARRISON. This is with respect to the changes agreement that may be required in labeling?

Mr. GORDON. Yes.

Senator NELSON. That would be part of it.

Mr. HARRISON. Most likely it was intended to provide notice to the manufacturer for the purpose of giving him an opportunity to comment.

Senator NELSON. But it evaluates the drug for all purposes. Staphylococcal infections—it makes a statement about that, evaluates it "possibly effective." It gives documentation; ricketsial diseases, and the evaluation is "effective, but * * *." Evaluation of typhoid fever, "effective, but * * *" and so on.

The NAS–NRC review of chloramphenicol is filed in the public record. AMA reviews it, you tell me. I would assume you would. The Federal Register is a public record, of public notice.

Mr. HARRISON. Yes, we review the Federal Register, no question about it.

Senator NELSON. Then my question is, since this has been an item of such importance and with so much discussion in the past year, and there is such a failure on the part of somebody to convince the doctors not to overprescribe, why did not the AMA Journal, which carries all the ads, give prominent play to the fact that the National Academy of Sciences says it is not the drug of choice for any disease?

Mr. HARRISON. I would have to review exactly what is stated there—what is stated in the Register. You do not happen to have a copy of the Register at the moment?

I would only say to you, Senator, that we would need to look again at the Register and see what action was taken by the AMA pursuant to it. It would be through the mill to effect the implementation.

I cannot respond at the moment, first, because I do not recall the specific situation, except to say as to what it likely must have been, and second, because we do not have a copy of the Federal Register on hand. If you would like further information on that, we shall be glad to supply it to you.

Senator NELSON. I would, but do you not agree that this raises a question. Here is a very important document on a very important issue, the leading medical organization of America is directly involved in this. It carries ads in the area, carries articles about the drug, is concerned about the misprescribing of the drug, and apparently, no prominent story is run—we could not find any.

Dr. ANNIS. Senator, could you get somebody to get a copy of the Register so that we could have some people review it. It might be a good idea for us to know what we are talking about.

Senator NELSON. We will see if we can get it upstairs. But I would have thought it was just routine for everybody——

Mr. HARRISON. Routine would not be sufficient, Senator. If it is of that importance, it should not be handled in a routine manner. We receive the Federal Register on a regular basis. We also receive copies of the Congressional Record on a regular basis and your daily calendar on a regular basis. There are a thousand bills of health interest that are introduced in every Congress we review on a regular basis.

I think in the last Congress there were 1,500 health bills. There are many things important to medicine, and the health of the Nation, that the AMA is interested in. On a routine basis, we take these matters and process them through the various councils and committees of the AMA directly concerned with these subjects, and again on a routine basis, give them an opportunity to comment and provide their expert opinion.

This may have been in the nature of a routine matter. If so, a copy of that article or a copy of that notice would have been sent to the Council on Drugs to be considered in its usual course of business—when they next meet again. If it was more than routine, perhaps other action would have been taken. At this moment, it appears that this was a notice to manufacturers with respect to changes in labeling. Until some further comment is made and the picture develops, we would be unable to provide further information.

Senator NELSON. Well, I did not mean that it is routine in the sense that it was unimportant. I meant that I would assume that it

would be routine to the American Medical Association in a matter as important as this, that it would be automatically acted upon.

Dr. ANNIS. It would have been, Senator, if it had come to attention of the right people. But we are talking about something that we do not even know what was printed in the Register.

Senator NELSON. I understood the witness to say that they did regularly review the Register.

Dr. ANNIS. They do.

Mr. HARRISON. Yes. I do not know the particular item at the moment. I do not know what it was about in the Register.

Senator NELSON. I beg your pardon?

Mr. HARRISON. I am saying that, as a routine matter, we do go through the Federal Register and a number of other publications that come from Washington and the Federal Government. I would assume then that as a routine matter, we would have seen this particular item. I am not familiar with the contents of the item at this moment.

Senator NELSON. I would be concerned about two things: one, if the drug evaluation efficacy study, and there is a big one going on as, of course, you are well aware in the medical profession ——

Dr. ANNIS. Many of them all over the country. We are very proud of it.

Senator NELSON. Yes, and it is being reported to the Food and Drug Administration. One, is the communication so bad between the National Academy of Sciences, the FDA, and the distinguished medical societies that 5 months would go by on an important issue like this without the societies knowing it? That would be the first question.

The second question is, if that is not the case, if attention were called—I mean, if the AMA reviews the Register, why was not the publicity given by AMA? That would be the second question.

Dr. ANNIS. I would be able to answer that question when we know what we are talking about.

Mr. GORDON. There is an official from the Food and Drug Administion present. I just asked him what was in the Federal Register.

Mr. Schneider would you step forward for just a moment, please?

What was in the labeling?

Mr. Schneider is with the Food and Drug Administration.

Senator NELSON. Would you identify yourself, please, and give your agency and title?

STATEMENT OF MORTON M. SCHNEIDER, CHIEF, CONGRESSIONAL SERVICES, FOOD AND DRUG ADMINISTRATION

Mr. SCHNEIDER. My name is Morton M. Schneider; I am Chief of Congressional Services for the Food and Drug Administration.

Mr. GORDON. What was in the Federal Register?

Mr. SCHNEIDER. The Federal Register announcement contained a statement to the effect that, based upon the NAS-NRC report, the following labeling is recommended for the drug. It then set forth the complete labeling for the drug.

Senator NELSON. The new labeling?

Mr. SCHNEIDER. Yes, sir.

Senator NELSON. Did it recite the National Academy of Sciences' efficacy study?

Mr. SCHNEIDER. The statement is based upon the report. It did not copy it.

Mr. GORDON. Did you say copies were available?

Mr. SCHNEIDER. Yes, that is true. Copies were available from our office, and the address where it could be obtained was given in the Federal Register announcement.

Senator NELSON. This was filed with the Federal Register?

Mr. SCHNEIDER. Yes, sir.

Senator NELSON. Did it give the reason for the revised labeling?

Mr. SCHNEIDER. Yes, based upon the NAS-NRC report.

Mr. HARRISON. Did that FDA publication, or the publication in the Federal Register, contain the statement that it is not the drug of choice?

Mr. SCHNEIDER. In the labeling you are talking about, are you talking about the disease typhoid?

Mr. HARRISON. I am talking about the presentation in the Register of which you are speaking.

Mr. SCHNEIDER. It gave the labeling as recommended.

Mr. HARRISON. Did it contain the statement that this is not the drug of choice?

Mr. SCHNEIDER. For typhoid?

Mr. HARRISON. Does the labeling state it is?

Mr. SCHNEIDER. The labeling states that the article is a drug of choice in typhoid.

Mr. HARRISON. It does not state that it is the drug of choice——

Mr. SCHNEIDER. It restricted its use for severe salmonellosis and typhoid.

Mr. HARRISON. This appears to be substantially different from what was just stated here.

Senator NELSON. What is substantially different?

Mr. HARRISON. There apparently is no statement—again without having the Federal Register available—that there is a labeling requirement for a statement that this is not the drug of choice.

Mr. SCHNEIDER. You see, the labeling was oriented not toward specific illnesses as much as it is designed or oriented toward specific organisms. You see, that is the difference.

Mr. HARRISON. I understand.

Dr. ANNIS. But am I correct that this basically is the information of the Food and Drug Administration on the basis of which regulations will be instituted to insist on change of labeling?

Mr. SCHNEIDER. This is the labeling that is required, based upon the NAS-NRC review.

Dr. ANNIS. And you give the manufacturer 30 days——

Mr. SCHNEIDER. I don't know if we gave 30 days to anyone that was adversely affected by the statement in this case.

Dr. ANNIS. This automatically would affect the subsequent advertising and labeling for us, because the company, in making up its advertising for our publication or any other publications would have to bring about the changes. Is this not correct?

Mr. SCHNEIDER. That is correct.

Dr. ANNIS. So it is an automatic thing as it pertains to their advertising to the profession. These are their changes that they would therefore institute and would come into subsequent ads submitted to the AMA or any other source.

Senator NELSON. Let me ask another question.

What kind of distribution is given to the studies made by the National Academy of Sciences?

Mr. SCHNEIDER. Once it becomes public, anyone who wants it can ask for it and receive it. We do not distribute it per se. Our press relations office has it available to anyone who is interested.

Senator NELSON. That was stated in the Federal Register?

Mr. SCHNEIDER. Yes, sir, that is correct.

Senator NELSON. Thank you.

What puzzles me about it is, here is a very important matter and apparently, there has been no report in JAMA, and 5 months have gone by. Now, I feel like this, where there is an independent press that is reporting to consumers on things all the time, the moment the Federal Trade Commission says something about the tire or about this or that, there are big stories about it in a number of magazines.

STATEMENT OF DR. EDWARD R. ANNIS ET AL.—Resumed

Dr. ANNIS. I am surprised they did not pick up this one.

Senator NELSON. They might have. What surprises me is that the medical journals did not. This brings up a question that people have raised, as you are well aware, over the years, regarding the tie-in between the drug industry and the medical profession—and the large amount of advertising.

Dr. ANNIS. Senator, this might be a good place to raise this question: Has anybody testified as to the percent of drug advertising that is spent with the American Medical Association and our fine professional journals? I think you will find, and this is prescription advertising, that we get approximately 13 percent of the total budget expended in this area.

Senator NELSON. Thirteen percent of whose budget?

Dr. ANNIS. Thirteen percent of the moneys expended for medical drug advertising is spent in our journal. This is where we get our professional readers.

Senator NELSON. You mean 13 percent of the total amount of money spent by the industry——

Dr. ANNIS. Right.

Senator NELSON (continuing). Is spent by the——

Dr. ANNIS. No, spent by the industry in advertising drugs. The rest of it is spent in other competitive publications.

Senator NELSON. I do not have that statistic.

Dr. ANNIS. My only point is that we are not alone in exposing the profession to this kind of advertising. And if, in truth, as you indicate, there has been advertising that has slipped through our screens, that in retrospect, at least, might better not have been accepted, we plead guilty of human frailty.

My point is that in this particular instance we are only—13 percent is a good percentage, but it is certainly not an overwhelming percentage of the recipients of drug advertising. So that if changes are to be made by the medical association alone and no change is instituted in other areas, you will not accomplish the desired objective.

Senator NELSON. Let me say, Doctor, that I intend to raise the question with all recipients of prescription drug advertising.

Dr. ANNIS. We are going to assist you in your efforts to zero in on those who unwisely use an admittedly double-edged sword as it pertains to particular drugs. We are not in disagreement on this.

Senator NELSON. Actually there is a very, very brief reference in the AMA News.

Dr. ANNIS. You mean we said something about it.

Senator NELSON. Yes, we expose everthing here.

On August 26, 1968, there is a very, very brief reference in an article on chloramphenicol with brief reference to this in which it said that, as you may recall, chloramphenicol was decertified and then, after examination and study, put back on the market, and those that did not meet the Chloromycetin blood level-time spectrum were required to meet it. This is about that.

It says that the Food and Drug Administration, as expected, announces that it will resume certification of chloramphenicol sodium succinate.

The National Research Council reported to the FDA, according to this, that the drug is effective only for the limited applications, and it lists them.

So there was that——

Dr. ANNIS. When was this published?

Senator NELSON. August 26.

Dr. ANNIS. This is even before it appeared in the Register?

Senator NELSON. Of course, there was publicity to the effect——

Mr. HARRISON. Which publication is that?

Senator NELSON. This is the AMA News.

Mr. HARRISON. Which is a publication that goes to every physician in the country.

Dr. ANNIS. Whether he is a member of the AMA or not.

Senator NELSON. This demonstrates my point that it did appear.

Dr. ANNIS. A few minutes ago you were being counseled that we did not have it.

Senator NELSON. Correct.

Dr. ANNIS. That was in August. That is when I was on vacation with my kids, up in camp in Michigan, enjoying fishing.

Senator NELSON. The National Academy of Sciences/National Research Council reported to the FDA that the drug is effective only for the limited indications in the drug's new labeling. It does not say what it is. It does not say what the National Academy of Sciences said about it. If that is all that is in here, the point I am making, I think, is still valid, considering what is going on in the drug misuse around the country, considering all the publicity about it, and considering that the AMA News and JAMA take a lot of advertising from the company. It would seem to me that those magazines ought to have a big headline to emphasize the fact that the National Academy says it is not the drug of choice for anything. This is my point.

Dr. ANNIS. Senator, when we discussed this particular drug with its limited use, and its side effects which—Dr. Dameshek indicated this—side effects and bad reactions are rare, but it is when they occur that they are so serious. We admit this. In this context, maybe we should have put it in the front page of the journal. But if we talk to the National Safety Council, they think we ought to put the overuse of alcohol and "Don't drive when you are drinking" on the front

page of the journal. It kills more people each year than chloramphenicol in its whole history.

I think your point is that we, in reviewing the Federal Register, have not given this information the circulation it deserves. May I ask Dr. Hayes how we handle such routine things—I do not want to say this is routine—how we handle such matters when they appear in the Federal Register, whether it is chloramphenicol or any other drug. Although I am not aware of it myself, I know that they have a regular way of handling reports of this kind. It may be helpful in clarifying the point that has been raised.

Senator NELSON. I shall be glad to have him respond to that, but let me say, you raise the question of alcohol. Alcohol is not advertised in JAMA. The point is that chloramphenicol is.

Dr. ANNIS. Correct.

Senator NELSON. And it is a——

Dr. ANNIS. I am talking about putting on the front page of JAMA the dangers inherent in a drug.

Senator NELSON. This is actually what puzzled me about the whole thing. I cannot find in journals, in the medical newspapers, big headlines emphasizing what has happened here. That is why I think Dr. Goddard had to say, "I am at wits' end on how to handle this."

But it raises the question then, one, is the medical association being effective in informing the doctors; and, two, what question does that raise about heavy advertising in these journals when there is a big criticism to be made of a drug which is advertised there? That question has been raised by distinguished doctors in this country. Dr. Console raised it in his statement to the committee this week.

Mr. HARRISON. Senator, the Register statement indicated that this drug had some limited uses and that some labeling changes would be required. That was the extent of it. It did not contain the other information that you speak of, except that perhaps it contained some information that other documents were available upon resquest.

From that, to draw any implication with respect to influence, or undue influence by advertisers would appear to me, at the very least, to be unwarranted. Nor could the public accept such an assumption. Earlier I stated that the amount of Chloromycetin ads—and if you are going to be influenced, there has to be a substantial amount—represents something like 0.3 of 1 percent. That was the figure over a period of 5 years.

Now, when we start looking for conflicts of interest, Senator, I think we have to recognize that they have to be of some merit or of some substance.

So, first, I do not believe that the implication is warranted at all, because all the Federal Register contained was some changes in labeling and we would examine the ads to see if they complied with our own requirements for advertising; secondly, we are talking about an ad that appeared in the Journal over 5 years at such infrequent times that perhaps to infer that the public would draw an inference of conflict, even with all other things not being known, would be totally unwarranted.

Senator NELSON. I do not say there is necessarily any intention about it. I just say it is, I think, recognized as implicit in the case, that newspapers are very reluctant to run critical attacks on their biggest advertisers. Everybody knows that.

Dr. ANNIS. They do not have any compunctions about the medical profession, because we are not very many.

Senator NELSON. Well, the medical profession does not advertise in newspapers, either.

Dr. ANNIS. That is right.

Senator NELSON. This is only one of a whole spectrum that we intend to explore, of the drug companies starting out with gifts to the students in medical school, the promotion of their drugs in various ways, and their advertising.

Dr. ANNIS. What would you suggest that we substitute? We have so many different avenues, Senator, whereby physicians are educated. I just indicated that only about 13 percent of the advertising dollars spent for advertising drugs is spent with the AMA for advertising in its journal.

Senator NELSON. But is that the question? The question is what percentage of that advertising comes in as a percentage of the total AMA income. That is a better question; 13 percent or 1 percent of somebody's advertising could be my total income.

Dr. ANNIS. On the contrary, your commenting on the advertising as carried in our journals as, in effect, carrying with it an implied endorsement whch affects the physicians that you are talking about, who continue to use chloramphenicol where it is not indicated. We have repeatedly indicated, and our publications show this, that we have, time and over again, in many publications attempted to reach physicians to let them know of the potential hazards of using a drug where other drugs, less toxic, equally effective, are certainly preferable. We admit we have not been successful in reaching all of our physicians, and we will put forth every effort to continue.

Mr. HARRISON. And as Dr. Annis indicated earlier, we have in the works, or we are attempting to work out at the present time, recognizing the problem, Senator, to meet with the Commissioner of the Food and Drug Administration for the purpose of providing further information through our communications media.

We anticipate, for example, an interview with Dr. Ley and a release in the AMA News on this subject as soon as it can be arranged. Then we will carry on beyond that.

Senator NELSON. An interview on what?

Mr. HARRISON. On the subject of chloramphenicol and its dangerous side effects and its proper use. In other words, we recognize the problem. There are more things that can be done and we are seeking means of getting that information out even more than it has been in the past.

So we are not trying to say that we are not interested in providing this kind of information or we are not seriously concerned about it. We plan more things. It is just that it appears to be unfair to warrant a conclusion on the part of anybody, and in the public's mind especially, that because some limited ads have appeared with respect to a drug that has been approved by the Food and Drug Administration, in our scientific journals as well as in many others, that because of the appearance of these ads, there is some kind of unholy alliance.

Senator NELSON. Well, I did not use the words "unholy alliance." But——

Dr. ANNIS. Senator, would you suggest that we deliberately suppressed this information? I hope this is not a part of the implication

of your questions. Assuming that the FDA announcement said more than it did, are you assuming that we deliberately suppressed dissemination of this information?

Senator NELSON. No; I have not said that, either. Although I will say that I think that most people would recognize that if somebody is a very good friend, you are unconsciously more considerate——

Dr. ANNIS. Why have we been so inconsiderate in our publications—where we have called attention to these side effects repeatedly in JAMA and the other publications, as pointed out by Dr. Hayes? There were several hundred occasions.

Senator NELSON. Yes; I am glad to get into others, but we are just on one that has been a big story.

For example, what kind of stories did JAMA run in the News; what kind of play did they give to the very dramatic statements of Dr. Dameshek, Dr. Lepper, Dr. Best, and the others who testified on this?

Dr. ANNIS. As I recall, they were given pretty good currency. This is where it was first brought to the attention of many physicians.

Senator NELSON. Could you send those to us?[1] We could not find many in the past year. We have xeroxed what we have found in the past year on chloramphenicol, and I went through it yesterday. I thought it was quite minor. We shall put it in the record and it shall speak for itself. But it certainly was not commensurate with the dramatic situation.

Now, I do not know how you fairly evaluate that, but I think you can certainly say that on a dramatic, important issue in which the responsible custodian of the public welfare, in terms of health, the medical profession failed dramatically in this case.

Dr. ANNIS. Senator, the profession deals with drama and death every single day, many times a day. If you deal with some of the more serious areas, some of your decisions, affecting life and death, occur many times in one day. In that context, all things have to fall into their proper perspective as they are presented to the public. This is the reason that I did ask if we may have Dr. Hayes indicate to you what happens, not just for this one drug, but how we handle matters that appear in the Federal Register that are of importance to the profession, and by virtue of drug connections, important to our council on drugs. It is through these methods that basic changes, as well as continuing education, are presented to the physician.

Senator NELSON. I shall be glad to hear from him. I am just raising one part of the iceberg. We shall have at a later date extensive testimony; we have had some from some distinguished pharmacologists and clinicians about how the drug industry has successfully overpromoted drugs so that one of our distinguished witnesses, Dr. Frederick Wolff, research director of the Washington Hospital Center and professor of medicine, George Washington University, said that he thought that 60 to 70 percent of the drugs taken by people were not indicated; they did not need them at all.

Dr. ANNIS. I have read some of those, Senator. There are other people who do not take the medicine that is prescribed, some of them made fearful of drugs by virtue of some public utterances, as reported.

[1] Material not received.

The drug not taken often results in a greater tragedy than the drug that is prescribed could cause.

Senator NELSON. There are statistics available that I do not have here on the number of patients in hospitals who are there for drug reactions——

Dr. ANNIS. No question about it.

Senator NELSON. (continuing). From drugs that were not indicated. They should not have had the drugs. This is what we are talking about as just one item in the whole picture. The reason I have taken chloramphenicol is that it is a very dramatic case that has persisted for 15 years without the medical profession successfully convincing the physicians, and there must be a lot of them, because estimates are that some 4 million people received the drug in 1967.

Dr. ANNIS. Its life history is very short alongside of morphine and other opiates. Neither the medical profession of the world nor the legal and law enforcement agencies of the world have been able to control them very well, either. This does not mean that they do not continue to try and continue their efforts.

Senator NELSON. I do not know whether that is overprescribed or not.

Dr. ANNIS. Let us say it is overused.

Senator NELSON. That is not the issue we are on here. We are on the issue that has lasted for 15 years.

Dr. ANNIS. Oh, yes, that is part of the issue. A lot of these drug reaction cases are drugs that are purchased over the counter. Probably 40 or 50 percent of all drugs are purchased over the counter. Reactions come from these just as much as from the prescribed drugs.

Senator NELSON. Some day we intend to have hearings on over-the-counter drugs. But we are at this moment on prescription drugs. What I am saying is, reviewing what we have had in testimony for over a year, this a dramatic case of the medical profession failing its responsibility over a 15-year period, and I am wondering how much longer it would have gone on if we had not had the dramatic testimony we had a year ago, before this committee.

Then that raises the question whether the profession is derelict in its responsibilty here. I would say yes. I do not know what you would say.

Dr. ANNIS. I would say that is a matter of opinion. What you are saying is that the educational efforts of the organized profession to use its regular channels of communication have been unsuccessful in dissuading some members of the profession from the use of a drug when other drugs could perhaps have been better and more safely used. This is a question of the failure of education.

Again I come back to alcohol and the failure of education. Here is another drug that has many good and profitable uses as a drug. It has uses in other areas in our social structure. Yet here again, although we have all been educated that it, like most other drugs, if abused, can result in troubles, we have failed to get that total story to physicians, to lawyers, to lawmakers, the people at home that vote for them, and to our patients. This does not indicate a failure on the part of someone to try to tell the story, but rather a failure, as I indicated this morning, on the part of the message recipient. What is true in one area is equally true in another as long as we continue to be humans and fallible.

We agree with you totally as far as the dangers of the misuse of any drug, and we are doing everything we can. We have made appointments with Dr. Ley; he has had to cancel them on a couple of occasions because of other, more pressing business. But we will continue our efforts.

And he has agreed, as quickly as possible, to meet with our council on drugs and our representatives toward this end of improving the effort of communication that you feel is so essential. We are in agreement.

Senator NELSON. Let me say I respectfully suggest that alcohol is not analogous. You say the recipient has to listen.

Dr. ANNIS. He has to be sold, too.

Senator NELSON. But the recipient in the chloramphenicol case does not know, has no option of his own.

Dr. ANNIS. The recipient of the message is the doctor who still overprescribes or unwisely prescribes. We are talking about getting a message to the physician who prescribes the drug.

In this instance we agree with you, we have to get more messages to more physicians who unwisely prescribe it.

Senator NELSON. The issue I am raising, Doctor, concerns promotion of drugs by the drug industry.

Dr. ANNIS. This is a part of education.

Senator NELSON. I think it appears clearer and clearer to me as I read the past hearings, as I read the testimony that comes here, that in fact, we have a case in which the drug industry, by its advertising promotion directly to the doctor and through the medical journals, is so persuasive and effective that it persuades doctors to use drugs for purposes that are not indicated. It seems to me this clearly demonstrates something wrong with the whole method of bringing drug information to doctors. Chloramphenicol is just one dramatic example of the total picture. I do not claim to know the answer.

I would think it ought to be a matter of such concern to the profession that it would reexamine the whole relationship with the drug industry and the whole relationship in terms of advertising, in terms of drug promotion, because it is pretty clear that the drug industry is outpacing the drug experts in the profession by a country mile day in and day out.

Dr. ANNIS. Senator, I would not agree with the premise. I have seen what drugs have done to change the whole face of medicine.

Senator NELSON. I am not arguing about that, Doctor. I am not objecting——

Dr. ANNIS. But I would object, I would object strenuously when you give the impression that doctors are dolts; that they do not know what they are doing—that they are persuaded by some advertising and the rest, and that this is the only basis on which doctors are acquainted with the drug and upon which they made a decision for a drug.

This is only one part of the overall educational process.

Senator NELSON. Nobody is saying that the drug industry has not made a great contribution. All I am saying is that there are distinguished people in the medical profession who have testified already, there will be more who will testify, who say that the influence of the drug industry on the medical profession is far greater than it ought to be.

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

Senator NELSON. Surely.

Dr. ANNIS. If this influence is so great, and I have not counted all the antibiotics that compete with chloramphenicol or even all of the broad-spectrum antibiotics, they are all advertised, too—why is this one particular product used in a relatively small, circumscribed area, even to the extent that it is used, in proportion——

Senator NELSON. Chloramphenicol, you mean?

Dr. ANNIS. We have 200 million people in this country, so even in the proportion that they are used, why are not all these other manufacturers of antibiotics equally persuasive in being able to persuade physicians that their product is better?

Senator NELSON. We have had testimony to that effect here and we shall have more. I think you, as a doctor, are quite aware of the fact that there are plenty of your distinguished colleagues who will tell you that doctors frequently prescribe a broad-spectrum antibiotic for sore throat and other such ills.

I have had them prescribed over the phone for my own family, for my kids. The doctor did not look to see if there was an organism involved, of any kind.

There are plenty of doctors who say: Well, a sore throat, this and that, takes a broad-spectrum antibiotic. This goes on extensively and the organism has not been identified, but it is very handy, a broad-spectrum antibiotic, and ready to go.

Dr. ANNIS. Yes; patients will call you up and say I want a shot of penicillin or thus and so. They read the publications that are non-medical oriented, that are not directed to physicians, but only to the consuming public, the women's magazines, the weekly magazines, the monthly magazines and all the rest, including feature articles by science writers and newspapers.

This is not only because of the drug advertising by the drug manufacturer.

Senator NELSON. Many of the articles you talk about are induced by the manufacturers themselves, time after time after time. Some of them are already in the record.[1] The manufactures get an article written on their drug to popularize it.

That is again part of the influence of the drug industry on the medical profession.

I do not draw any specific, direct conclusion.

Dr. ANNIS. Should we eliminate all advertising, Senator?

Senator NELSON. I think there is a serious question, under all the circumstances, whether the medical journals should accept advertising. I think there is a serious question. If they do, I think there is a very serious question about the kind of advertising they accept.

Dr. ANNIS. If we eliminate from medical journals advertising of drugs—there has been, for many years, a little joke among physicians that they have to buy the Reader's Digest in order to keep up on the latest drugs. Sure enough, a patient will walk in and ask him: How about getting me a prescription for thus and so?

Are you going to propose that such articles also be eliminated?

Senator NELSON. No; I do not think you could eliminate them. The advertising, as I read it and look at it in the journals, time after time,

[1] See article on Indocin (indomethacin) from Pageant magazine, pt. 8, pp. 3177–3181. See also app. V, "The MER–29 Case," pt. 10, pp. 4202–4296.

is cleverly slanted to promote it for a purpose for which it is not indicated. And it is accepted time after time.

Dr. ANNIS. Then you are suggesting that the advertising copy itself should be of a different kind?

Senator NELSON. I think that the journals in general—I am not just talking about JAMA—just default to the drug companies. When you consider the impact of advertising—doctors are not any different from lawyers and engineers. Public relations, promotion, advertising—clever people in promotion clearly have an impact on busy people.

I think that these chloromycetin ads are disgraceful, myself. I think it has been clear for a long time that if you run one bronchoscope and "when it counts" and then a whole bunch of fine print that you know is not going to be read, but you are required to print it, it has an impact that the journals do not have. You would not accept that stuff as an article in your magazine.

I think there is something wrong with what is accepted in the medical journals. I am just saying this as a layman. I have looked at a few hundred ads now, and I see that in 29 instances, better than once a month for the past 2 years, there has been a drug advertised in one of the medical journals in which the company made a claim which was absolutely not justified, and the company was forced to write letters to some 300,000 doctors, corrective "Dear Doctor" letters.

Now, as I said, there were 10 of those in your journal. The next time we have another journal, I shall just take that as an example.

But take the AMA Journal. In the 10 cases in 2 years, in which ads were carried in the JAMA which the FDA said were misleading, some of them grossly misleading, and in which they were required to send a letter to every doctor in the United States, we cannot find a single occasion where the journal said: This ad was misleading, we regret we ran it; they made claims for it that are not justified; we think that is bad advertising practice: we should not have done that. And emphasize it. After all, the doctor is looking at that ad.

Dr. ANNIS. You have indicated, Senator, that the drug company has been called to task by the FDA, and rightly so, because they violated that which has been spelled out by the FDA. We admit that the advertising, especially these past couple of years, basically is that which is in accord with the inserts demanded by rules and regulations of the FDA. We admit this. We admitted this earlier this morning as well.

Senator NELSON. The point I am making here is a little different. That is that in 10 cases where they made illegal claims, improper claims, they were required to spend a lot of money to send 300,000 letters to all the doctors in America, this ad was carried in JAMA and we cannot find any case—now, I shall stand corrected if there is—we cannot find any case where JAMA made a big point, because the ad is big, a big point of saying: This company was guilty of misleading the doctors in its ad.

Dr. ANNIS. Senator, this morning we indicated that the reason we stopped the seal of acceptance of the American Medical Association is because, in the minds of too many, it carried implied approval of the safety, efficacy, and reliability of the drugs accepted. One of the reasons we discontinued it was because of the absolute inability to

have an organization of sufficient strength—of sufficient scientists, chemists, pharmacologists, and the rest—to examine every drug to be certain as to its efficacy and safety that we could put a stamp of approval on. This was taken over by the Food and Drug Administration.

Admittedly, we also agreed that if the Food and Drug Administration, and we have testified to this repeatedly—has inadequate and insufficient funds to do so properly, they should say so.

But we cannot be in a position to evaluate every drug that is made available.

Now, when we have a department of our Government well financed, or at least it should be, to carry out a certain job, when they make out the rules and the regulations for information to be provided to a physician and when the essence of an ad is in accord with what has been spelled out by the FDA, we feel that as the ad pertains to safety and efficacy, which have been the main role of the FDA in recent years, we feel that they have the means, or should have; have the personnel, or should have; have the finances, or should have, to see that this job is accomplished.

There is no such ability on the part of any professional organization.

Senator NELSON. Yes, but Doctor, that does not, I think, address itself specifically to the question I raised, which is that 10 times in the last 2 years, ads have been run in JAMA which made false claims, 29 times in all publications.

Dr. ANNIS. Some part of which, as you indicated, has been not in accord with the facts; that is correct. The producer violated the regulations of the FDA.

Senator NELSON. This is the point, though. It made important claims, and if a doctor reads it and it is the official position of the AMA that the ads are educational, so the company makes a false claim, pays for the ad, puts it in JAMA——

Mr. HARRISON. Are there instances where we have continued to run these ads after the "Dear Doctor" has been sent, or after we have been notified that portion of the ad is unacceptable?

Senator NELSON. I shall give you another example. The point I am trying to get at—I thought I was making myself clear—is that you have a paid ad. A claim was made that was important for the drug. The AMA claims the ads are educational.

Dr. ANNIS. Which claim are you talking about?

Senator NELSON. The claim of the general counsel of the AMA before the Tax Committee in the House of Representatives.

Dr. ANNIS. No, you aren't talking about an ad containing claims that are in error.

Senator NELSON. We have a number here. I do not know whether this is the toughest one or not. But it makes my point clear that the claim was made and it is an important claim that is educational to the doctor. He reads it. The FDA says it is false and misleading and forces the company to send a "Dear Doctor" letter.

My question is: Why does not the AMA feel obligated to run a big story right then, saying, this company misled you? Maybe that doctor would be a little bit more cautious the next time about believing the claims of these brand-name companies that he stands on so firmly. Why does the AMA not do that?