and the testimony has been that from 10 to 20 times the normal dose is the amount causing these deaths.

Yesterday, Dr. Moertel of the Mayo Clinic and Sidney Wolfe, a physician, indicated, if I am correct, that two capsules of Darvon were lethal.

Dr. BEAVER. That is categorically not the case.

Senator HATCH. In other words, you are totally refuting what they say.

Dr. BEAVER. I do not believe they actually said that, but it is not the case.

Senator HATCH. Assuming they did, why would they say something like that?

Dr. BEAVER. Did you say that?

Dr. WOLFE. I was quoting the coroner in San Francisco who said people using it on a regular basis, twice the normal dosage, not two capsules we are talking about but two capsules every 4 hours instead of one.

Senator HATCH. I am glad you were here to correct that.

With regard to those who take propoxyphene regularly in recommended dosage over many years; some people have indicated they may be dying from a drug buildup.

What does the record show with regard to that, is there a buildup potential here?

Dr. BEAVER. There is a buildup when the drug is taken repeatedly at 4-hour intervals at the recommended dose of 65 milligrams.

Senator HATCH. I see.

Dr. BEAVER. At the recommended dose of 65 milligrams there is an accumulation of both propoxyphene and nor-propoxyphene. Both of these flatten out at some level because the more there is, the more rapidly both of these things are eliminated.

You get to the point here where the amount coming in equals the amount going out, at which time you get a plateau.

For the usual recommended therapeutic dose of propoxyphene there is no evidence that when you take 65 milligrams every 4 hours indefinitely you can build up a blood level of either or both of these materials which is fatal.

Senator HATCH. As a matter of fact, at the University of Utah, Dr. Finkel indicated that the record shows millions of patients who use it in the normally prescribed manner do not suffer any serious or fatal effects at all, is that correct?

Dr. BEAVER. That is correct.

Senator HATCH. And Dr. Finkel's findings affirmed that.

Dr. BEAVER. That is correct.

Senator HATCH. Do you know of any deaths which occurred from normal, prescribed use?

Dr. BEAVER. I have not been able to identify any, but you see, often with the literature on this subject even the medical examiner is not certain of what dose was taken. When you have somebody who is dead, it is sometimes not possible to determine how much of what they took, particularly until very recently when you had methods for measuring blood levels. I found no evidence that the usual therapeutic dose of propoxyphene can result in death, and, as I pointed out, it does not

even tend to result in much in the way of subjective side effects or even serious adverse effects.

Senator HATCH. Or even a buildup which could cause death?

Dr. BEAVER. Yes. Now, the matter which I think is a reasonable question here is what happens if someone crowds the dose a bit because they are not getting enough pain relief in taking 65 milligrams every 4 hours, so they decide to take twice that—130 milligrams every 4 hours. This will accumulate to a higher plateau level and there will also be more propoxyphene in the blood.

A lot of people in fact, take double the dose and they seem to get away with it, though you get more side effects. Then the question is, if on top of that situation somebody then takes a modest overdose, but not a massive overdose, whether you now have the stage set for a lethal occurrence, and I think some of these cases that were described by the coroner in Oregon may represent that kind of a situation.

That, sir, is my educated guess from looking at the data in the literature. Somebody has already gotten up to a blood level such that even a small overdose on top of that—in other words, it no longer takes 15 to 20 capsules to kill you, which is what McBay and Hudson would say is a single lethal dose, but now a lower single overdose will kill if the person has already been taking it for a long period of time.

Senator BOSCHWITZ. If the person is taking it as prescribed, it is not a problem. Is that your conclusion?

Dr. BEAVER. Yes; that is my conclusion, and I do not know if any of the people who testified here have argued that if it is taken as prescribed it constitutes a problem.

I think the problem, as I envision it, is that propoxyphene is a drug which is very commonly available and, in overdose, quite clearly can kill.

Senator HATCH. What you seem to be saying is that overdose is drug abuse and that overuse coupled with other drugs or alcohol can kill.

Dr. BEAVER. Yes.

Senator HATCH. But you do not think anybody would refute your statement that normal, prescribed use would not kill and would not be dangerous to the normal human being?

Dr. BEAVER. That is right, but you have to consider the issue as to the margin of safety and how far these two doses are away from each other in any given case. If they are close enough you can have a fairly risky situation.

It is obvious that if you have a drug which used in its appropriate way at a certain dose produces no serious side effects and it takes a hundred times that to kill you, that drug is safer than a drug which, if you only take ten times the usual therapeutic dose can kill you, because the likelihood of people dying from overdose is going to be inversely related to the size of the lethal overdose relative to the therapeutic dose they usually take.

With aspirin, it is hard to commit suicide because most adults cannot stomach enough aspirin to poison themselves.

Senator HATCH. With regard to Darvon—in the prescribed dose it is not a serious drug problem?

Dr. BEAVER. I would say that. I would like to continue my discussion briefly with the adverse effects of alternative mild analgesics

because any attempt to assess the benefit/risk ratio for propoxyphene must necessarily take into account the known adverse effects of alternative mild analgesics.

I am concerned that there is expressed or implicit in certain recent discussions of the usefulness of propoxyphene the assumption that alternative mild analgesics are more or less devoid of adverse effects and are in some general sense "safe." This is clearly not the case, and I can speak to this on the basis of having worked extensively in this field since about 1963.

Aspirin can be lethal, not only in overdose, but also at usual therapeutic dose levels in individuals who are hypersensitive to the drug or who experience massive gastrointestinal bleeding or other bleeding associated with aspirin's effects on blood coagulation.

Until recently, acetaminophen has been felt to be singularly free of adverse effects, and this is probably still true at conservative therapeutic doses. However, it is becoming increasingly apparent that overdose with acetaminophen can produce massive hepatic injury resulting in death, and in Great Britain, where the use of acetaminophen is even more widespread than in the United States, it has been estimated that acetaminophen poisoning is now a leading cause of acute hepatic failure.

Chronic use of phenacetin-containing analgesic mixtures has been associated with potentially fatal renal damage, and the Food and Drug Administration's Over-the-Counter Analgesic Review Panel has recommended removing phenacetin from the over-the-counter market for that reason.

The relative contribution of phenacetin as opposed to other mild analgesics in the development of this syndrome is a subject of debate, and it is unclear whether acetaminophen may not also produce serious renal injury when abused in combination products for prolonged periods of time.

The incidence of adverse reactions to codeine in usual therapeutic doses is low. The drug can produce a typical narcotic overdose syndrome and death, but the reported incidence of this appears low relative to codeine's extremely wide clinical use.

Codeine may be safer in this respect than equi-analgesic amounts of propoxyphene, although further study would have to be done to establish this. Codeine has narcotic-type dependence liability, although, like propoxyphene, the incidence of this problem is very low considering the wide therapeutic use of codeine-containing combinations.

Oral pentazocine is an effective mild analygesic more or less comparable to codeine in potency. Because the drug is a mixed agonist/antagonist rather than a classic narcotic, there is reason to believe that lethal overdose would be even less of a problem than with either propoxyphene or codeine. However, pentazocine seems to produce a somewhat higher incidence of unpleasant adverse effects at usual therapeutic doses than equi-effective doses of codeine, and pentazocine occasionally produces frank psychotomimetic reactions which may be very disturbing to the patient.

While pentazocine has less abuse liability than regular narcotics, deliberate self-administration of the drug for its mood effects undoubtedly occurs, and the Food and Drug Administration's Controlled

Substance Advisory Committee has recently recommended scheduling pentazocine in schedule IV.

The purpose of the above comments on alternative mild analgesics was not to denigrate the value of these drugs for the patient with pain, but rather to put the adverse effect liability of propoxyphene in some reasonable perspective.

Now, concerning the adverse effects of schedule II narcotics. The only currently available alternative oral analgesics to the mild analgesics discussed above are the schedule II narcotics. These include such drugs as morphine, hydromorphone, hydrocodone, oxycodone, levorphanol, anileridine, meperidine, and methadone.

While in substantial oral doses, these drugs are all capable of producing significantly greater pain relief than the mild analgesics noted above, they are all quite capable of producing lethal narcotic overdose, and all have a clearly higher dependence and abuse liability than propoxyphene, codeine or pentazocine.

In addition, doses of these schedule II narcotics which produce pain relief greater than the mild analgesics are also associated with a significantly higher incidence of disturbing gastrointestinal and central nervous system adverse effects. Therefore, their use would only seem to be indicated for those patients for whom conventional mild analgesics or combinations prove ineffective or not tolerated.

I will list, not necessarily in order of importance the number of factors which seem to me responsible for the popularity of propoxyphene products.

First, it has been claimed that the popularity of propoxyphene in the face of its less than impressive performance in controlled clinical trials is primarily due to the extensive and effective promotional efforts for Darvon by Eli Lilly & Co.

Indeed, the best ballpoint pen that I ever owned was given to me by a Lilly detail man and is emblazoned with the words "Darvocet N–100." However, many drug companies utilize the services of inventive advertising agencies and have dedicated swarms of detail men at their disposal and yet, much to their chagrin, these companies are unable to stir up the sustained high demand for their analgesic product which has been accorded the Darvon family. I think one must look further than promotional efforts alone to explain the success of propoxyphene over the past 20 years, which leads me to reason number two.

Physicians seem to need a mild analgesic which is as effective as aspirin, acetaminophen or APC but which is not available over-the-counter.

Many patients feel that these antipyretic-analgesics cannot be terribly effective because they are available over-the-counter and have a psychological need to receive an analgesic which is only available on prescription. Physicians recognize and respond to this need. Propoxyphene products are available in a variety of impressive colors, shapes and sizes and are only available through prescription. Furthermore, as noted above, over 80 percent of prescriptions for propoxyphene products are for combinations containing aspirin, acetaminophen or APC and these combinations are at the very least as effective as the antipyretic-analgesics which they contain. This must be coupled with the fact that at recommended doses propoxyphene produces an extremely

low incidence of any sort of adverse effects and a virtually zero incidence of serious adverse effects.

One must also consider the alternatives which the physician has available. When Darvon came on the market in 1957, the significant mild analgesics available as single entites and in combination included aspirin and other salicylates, acetaminophen, phenacetin, and codeine.

Today, over 20 years later, the only addition to this group has been oral pentazocine. When the patient with persistent pain tells his doctor that his current medication is either ineffective or poorly tolerated—a repetitive occurrence for many patients with chronic pain problems—the physician needs alternatives available. Useful alternative medications have simply not been forthcoming.

Number three, physicians in general are very sensitive to the issue of the dependence liability of narcotic drugs. In many situations, this concern has been far in excess of what was warranted by any realistic evaluation of the likelihood of producing iatrogenic narcotic dependence.

This anxiety extended to codeine, which in fact has extremely low abuse liability when used in any medically responsible way.

Propoxyphene was probably originally perceived by physicians as a non-narcotic substitute for codeine and propoxyphene-containing combinations were marketed which corresponded to all of the existing codeine-containing combinations.

Until the beginning of 1977, propoxyphene was an unscheduled drug, which implied that it was safer than codeine and its combinations in terms of dependence liability and also made for more convenient prescribing and dispensing.

Number four, although the most appropriate and, in fact, most popular use of both propoxyphene and codeine is in combination with the antipyretic-analgesics, there are occasional pain problems in which the physician can quite legitimately want to prescribe either propoxyphene or codeine alone. These include situations where there is an allergy or contraindication to the use of aspirin and acetaminophen. It would also include situations in which the practitioner wished to use a mild analgesic with no associated antipyretic effect.

Number five, there is, in fact, good evidence that combinations of narcotics with antipyretic analgesics produce more analgesic than the antipyretic-analgesic given alone, and this increment of analgesic effect may often make the difference between unsatisfactory and satisfactory pain relief for particular patients.

This increment of analgesic is often associated with very little increase in adverse effects and therefore, constitutes a very real benefit for the patient.

To my way of thinking, this constitutes the major acceptable rationale for the use of propoxyphene. It should be noted that this rationale does not apply if the prescribed dose of a combination contains substantially less than the usual full therapeutic dose of the antipyretic-analgesic constituent.

Senator NELSON. With regard to your fourth point, if the patient were allergic to aspirin, of course I assume the doctor then would not want to prescribe the compound of aspirin and propoxyphene.

Dr. BEAVER. Would not?

Senator NELSON. Would not.

Dr. BEAVER. That is correct. What I am saying here is that there are a few situations where you would want to give either codeine or propoxyphene alone.

To my view, the major use of either of these drugs is in combination with drugs such as aspirin or acetaminophen and actually the drugs aspirin and acetaminophen are the first line drugs among the mild analgesics, and then one can add narcotics to them.

Now, getting back to my sixth point, controlled clinical trials of analgesics invariably compare the *average* responses of *groups* of patients to the various treatments.

While the average relative performance of various analgesics is the best predicator of how the generality of patients with pain will respond, individual patients may, for reasons which we simply do not currently understand, derive a better analgesic effect from a drug which on the average is less effective than another.

Controlled clinical trials of analgesics are not currently designed to explore this phenomenon, and the determination of the optimal analgesic regimen for any given patient must ultimately be based on the empirical observation of the effect of various analgesics in that patient.

It is, therefore, in the patient's interest to have as wide a variety of effective analgesics available as possible, even though some of these may on the average be less efficacious than others.

Item No. 7—virtually all controlled clinical trials of analgesics, including propoxyphene, have involved comparison of single administrations of various analgesics; however, in the practice of medicine, most patients receive not a single dose but repetitive doses of analgesic drugs for the control of their pain.

While up to this time the results of single administration studies have seemed to constitute reasonably accurate predicators of the relative performance of analgesics when administered repetitively—if one keeps in mind the impact of the development of tolerance to narcotics—it is conceivable that repeated administration of some analgesics results in a higher level of efficacy than would be predicted on the basis of single-dose administration.

Propoxyphene has a substantially longer half-life in the blood than other mild analgesics such as codeine, acetaminophen or aspirin. When administered every 4 to 6 hours, as mild analgesics usually are, there will be a significantly greater cumulation of propoxyphene levels than with alternative mild analgesics.

We do not currently understand the relationship between the blood level of an analgesic and the analgesic effect experienced by the patient, but a plausible argument can be made on the basis of blood level data that one might expect greater analgesia after a few repeated doses of propoxyphene relative to alternative mild analgesics than is, in fact, seen in single administration studies.

Unfortunately, few analgesic studies of repeated dosing have been done to examine this hypothesis, and those that have been done are difficult to interpret. It is, therefore, possible that practitioners empirically find that propoxyphene products are more effective in regular

clinical use—that is, when administered in repeated doses—than would be predicted on the basis of the controlled clinical trials which involve single administrations of test medication.

Senator NELSON. When you say repeated doses, what do you mean by that, over a period of days or weeks?

Dr. BEAVER. Even three or four doses in the course of, say, 12 to 20 hours. The cumulation reaches about 90 percent at its maximum if propoxyphene is given, say, every 6 hours for about 6 doses or so.

Beyond that it does not go up any further.

Senator NELSON. In your testimony, my impression is you are carefully addressing the question of a patient who may not respond to aspirin or acetaminophen and therefore; if I understand your testimony, there may be circumstances in which the doctor then would prescribe something that had a narcotic in it, whether codeine or propoxyphene.

Let me ask you this: As a matter of good medical practice for a patient who the doctor had not evaluated as one whose pain problem was not controlled by the ordinary mild nonprescription analgesics, for that patient what is the drug of choice?

Dr. BEAVER. Oh, my feeling in this matter is very much the same as Dr. Moertel's. I do not know whether he said so yesterday, but he has written about this in a recent paper. I feel the basic mild analgesics of choice are aspirin and acetaminophen. That is where you start and then you start moving on, start adding certain other things to these drugs if they alone are not effective.

Now, the situation you have, though, with a practitioner is that very often the patient, when he arrives at the doctor's office, has already tried out aspirin or APC because they can be purchased over-the-counter. In other words, the patient says, "I have this problem with headache and I have tried aspirin and it does not help" or "I twisted my ankle and it hurts. I have taken some aspirin and it gives me some relief but not enough relief."

For the doctor to turn around and say, "take two aspirin every 4 hours" is perceived by the patient and the doctor as perhaps inappropriate.

You see, all of these reasons I am giving you are not equally defensible reasons for using propoxyphene. What I am trying to do is to get to the issue that repeatedly comes up and is never really grappled with: Why doctors are prescribing $80 million worth of this stuff a year when controlled clinical studies seem to indicate propoxyphene is sort of a mediocre drug.

What I am pointing out here is that there are a lot of considerations that go into the use of analgesics in the actual practice of medicine as it is practiced. They have not been stated and I am trying to define them. We can argue with some of these reasons, and I am not necessarily for all of those different reasons concluding they are good reasons for doing something. I am merely trying to get them on the table so we can consider them.

Suppose propoxyphene were to vanish from the market tomorrow. Puff, and its just gone. I can guarantee one thing that would not happen. The physicians who are now prescribing propoxyphene and its combinations would not tell their patients to go home and take two

aspirin or two acetaminophens. They are going to go to some other combination or product which is only available by prescription, because that is one of the reasons they are using propoxyphene now, so they will go to another prescription analgesic.

This brings up the issue of what other ones there are and what are the dangers of these materials.

Senator NELSON. Are you suggesting if you made all of these prescription drugs, which would increase the price, that that might be better?

Dr. BEAVER. Well, people need to have the ability to go to the drugstore and get something effective for pain relief for situations that they do not consider important enough to go to a physician.

I have said many times that if there were a green aspirin that nobody knew was an aspirin except the doctors, and you could prescribe it and it came in long green tablets or capsules or blue and green capsules and so on, this would be a very useful medication from the standpoint of the physician because it would allow the tangible therapeutic symbol of writing the prescription for the patient. The patient comes into the doctor with a self-limiting illness. The doctor does a history and physical and comes to the conclusion that if he can prevent the patient from doing something foolish within the next few days the patient will get better.

Now, the patient has some pain so the physician wants to do something about this, and it may very well be that an appropriate thing to do is to say, "go home and take two aspirin every 4 hours and stay in bed or get lots of fluid or take two Tylenol," but the patient may feel, "look, I have spent $25 and I have lost a half-day of my time and this boob tells me to go home and take two aspirin."

The doctor is sensitive to this possibility, so what happens is that the doctor wants to prescribe something that may be a little bit more effective than two aspirin and that can only be gotten by prescription so the patient will feel that he has been treated.

Well, the doctor writes a prescription for, say, a Darvon combination with aspirin, APC, or acetaminophen, or a small amount of codeine with aspirin or APC. These are slightly more effective than the aspirin and they fulfill this perceived need to give a prescription.

The reason I am bringing this out is that you are unlikely to change this aspect of medical practice, this need to give something by prescription, so if one were to ban propoxyphene, just flatly ban it, doctors would not just tell people to take over-the-counter drugs; they will use other combinations and other drugs available only by prescription.

Therefore, part of the implication of banning propoxyphene has to be a consideration of what are the risks of other kinds of preparations, prescription drugs that the patients might get instead.

Senator NELSON. That sounds as if you are really saying that if it were banned, many doctors for whatever reason would not engage in what would be the best medical practice in terms of treating a headache or something like that but, in fact, would look for something else.

You look at the studies and you know there is a rather frightening situation in the use of antibiotics, where you find for the common cold, 95 percent of the doctors give something, maybe aspirin,

and about half of that 95 percent give an antibiotic and there is no virus controlled by it.

Dr. BEAVER. And hopefully, they no longer give chloramphenicol. After your hearings it went down a long way. I think that was a very extremely valuable result of our hearings. It is true that from an objective standpoint, doctors often practice less than optimal medicine, but as I said, there are a lot of patients who come into the doctor's office and say they have already tried aspirin or acetaminophen and it has not helped, so the option the doctor has is to give this or something else.

Senator NELSON. Well, a little while back you said something about agreeing with Dr. Moertel, but let me read to you his last paragraph of his statement yesterday.

Dr. BEAVER. Well, this was not his statement yesterday. I was talking about a paper published in the Australian-New Zealand Medical Journal where he gave a hierarchy of how he would treat pain starting with aspirin and acetaminophen, and if that did not work, he would add codeine at certain dose levels, and if that did not work, he would go to larger doses of orally effective narcotics and if that did not work, he would go to injections. There is that hierarchy and we would not be that much at variance.

Can I just finish this statement?

Senator NELSON. Sure. Go ahead.

Dr. BEAVER. There are a larger number of unresolved issues here concerning the benefit/risk ratio of Darvon and its place as an analgesic, and these deserve further study.

Since a majority of fatal propoxyphene overdoses seem to result from mixed intoxication with propoxyphene and other central nervous system depressants, some effort should be directed at determining whether propoxyphene is simply adding to the depressant effects of other drugs or is producing a supra-additive interaction which is particularly hazardous.

Second, although the descriptions of fatal poisoning with propoxyphene which I have studied suggest that this drug is producing death in the same way as any classical narcotic overdose—albeit, the overdose syndrome is usually complicated by the presence of convulsions—studies should be done to determine whether propoxyphene has a direct cardiovascular toxicity in excess of other narcotics, and further studies should be done to elucidate the role of nor-propoxyphene in the toxicity produced by propoxyphene.

Three, since codeine-containing combinations are the logical alternative to existing Darvon combinations and are prescribed to an even greater extent than Darvon combinations it would appear logical to make a concerted effort to determine whether the apparent lower incidence of codeine-related deaths is a real phenomenon and, if so, why?

Four, controlled analgesic studies involving repeated dose administration of propoxyphene compared to other mild analgesics should be done to determine whether the predicted increase of efficacy of propoxyphene on repeated-dose administration really occurs.

Dr. McBay feels that codeine is very rarely related to overdose death. The DAWN data would indicate it is lower than propoxyphene. This needs to be clarified, because if codeine is truly extremely seldom

related to overdose death, then one has a very clear and perhaps preferable alternative that you can generally recommend.

On the other hand, if codeine is only a little less likely to produce overdose death than Darvon, you get into an "out of the frying pan into the fire" situation if you just flatly ban one drug and then everybody rushes to the other. That matter needs to be settled.

Another point in my statement is alternatives to the use of propoxyphene and other narcotics.

The number of oral analgesics which might be predicted to have advantages over propoxyphene and other currently available mild analgesics in terms of increased analgesic efficacy and/or decreased adverse effect liability are currently in various stages of clinical testing.

These include the nonsteroidal anti-inflammatory drugs such as indoprofen, suprofen, zomepirac, diflunisal and many others; narcotic antagonist analgesics such as butorphanol, nalbuphine, buprenorphine, propiram and others; and compounds of uncertain mechanism of action such as nefopam.

There are controlled clinical studies indicating that all of these compounds are effective oral analgesics and other studies indicating they may have certain real advantages over existing drugs. The public interest would be served by seeing that these drugs get on the market without undue delay.

I would point out that the average physician will very quickly start prescribing a drug which has real advantages for his patient if such a drug becomes available.

Since Darvon came on the market in the late 1950's, if there were a number of other drugs out there and studies showing they had something to offer, my suspicion is you would not have to push clinicians into moving away from Darvon, because they would perceive these other drugs had real advantages for their patients with less potential hazard.

Senator NELSON. Thank you, very much, Dr. Beaver. We may have some additional questions.

Dr. BEAVER. Senator, there are a number of references in my statement that I did not give orally and I would ask that the full text of the statement be printed in the record.

Senator NELSON. Without objection, your full statement will appear in the record at this point.

[The prepared statement of Dr. Beaver follows:]

STATEMENT ON THE EFFICACY AND SAFETY OF PROPOXYPHENE (DARVON) BY WILLIAM T. BEAVER, M.D., ASSOCIATE PROFESSOR OF PHARMACOLOGY AND ANESTHESIA, GEORGETOWN UNIVERSITY SCHOOLS OF MEDICINE AND DENTISTRY, WASHINGTON, D.C.

This statement is in response to the request of the Monopoly Subcommittee of the Senate Small Business Committee that I discuss what I consider to be the relative efficacy of Darvon as compared to other analgesics, the medical justification for its use and any other aspects of Darvon which I consider relevant to a critique of its safety and efficacy.

During the last 15 years, I have had repeated occasion to review the literature on propoxyphene. In 1965, I wrote a review of the clinical pharmacology of the mild analgesics, which included a substantial section on propoxyphene [Beaver, 1965 and 1966]. In 1966 and 1967, I served as a member of the Panel on Drugs for Relief of Pain, Drug Efficacy Study of the National Academy of Sciences-National Research Council and was the primary reviewer on propoxyphene and

its combinations for the Panel. On November 24, 1970, I appeared before this Subcommittee to discuss the relative merits of various mild analgesics in the relief of pain, and a portion of this testimony was devoted to a critique of propoxyphene (Darvon®). From 1969 to 1976, I served as a consultant for the Food and Drug Administration, primarily on matters related to analgesic drugs and the design and interpretation of controlled clinical trials for drug efficacy. While serving as a consultant for the FDA, I prepared a special critique of the efficacy of propoxyphene based on my review of the published literature and the New Drug Applications for various propoxyphene products. This critique, submitted to Henry E. Simmons, M.D., Director, Bureau of Drugs, plus recommendations for revision of the propoxyphene labeling served as the basis for the relabeling of propoxyphene products which occurred in 1972. In 1976, I assisted the FDA in revising the propoxyphene labeling to reflect increased medical awareness [Finkel *et al.*, 1976; McBay and Hudson, 1975] of the incidence of fatal overdose with propoxyphene alone and in combination with other central nervous system depressants. I subsequently served as a FDA consultant to their Controlled Substances Advisory Committee in the matter of the advisability of scheduling Darvon under the Controlled Substances Act. The Committee recommended placing propoxyphene products in Schedule IV. The Department on Health, Education, and Welfare concurred in this recommendation, and, in February 1977, the Drug Enforcement Administration issued an order to that effect. Since 1976, I have continued to follow the literature on propoxyphene, in part because I am Chairman, Advisory Panel on Analgesics, Sedatives and Anti-inflammatory Agents for the 1975–1980 revision of the United States *Pharmacopeia*.

In addition, for the purpose of this testimony, I have studied a letter dated November 21, 1978 from Dr. Sidney Wolfe of the Health Research Group to Joseph Califano, Secretary of the Department of Health, Education, and Welfare urging an immediate ban on the marketing of propoxyphene as an imminent hazard under the Food, Drug and Cosmetic Act, and a petition by the same group to the Attorney General of the United States and the Drug Enforcement Administration resquesting the transfer of propoxyphene from Schedule IV to Schedule II under the Controlled Substances Act. I have read those literature references cited in that petition with which I was not already familiar and have reviewed the response to the letter to Secretary Califano prepared by the Eli Lilly Company and submitted to the Food and Drug Administration on December 28, 1978. I have also reviewed those clinical trials relevant to the analgesic efficacy of propoxyphene products appearing in the archival literature since my review of this subject for the Food and Drug Administration dated May 18, 1971. The critique which follows represents my opinions derived from examination of the above cited data base, my general knowledge and experience as a clinical pharmacologist primarily concerned with the clinical evaluation of analgesic drugs and my experience as a clinician and consultant responsible for the use of analgesics in the management of patients with various acute and chronic painful states.

GENERAL PHARMACOLOGIC PROPERTIES OF PROPOXYPHENE

Propoxyhene or dextropoxyhene (Darvon®) is structurally related to the potent narcotic methadone and is itself a narcotic in all pharmacologic and toxicologic respects. It produces the full spectrum of pharmacologic effects in animals and man characteristic of the narcotics, and these effects are selectively reversed by the specific narcotic antagonist naloxone. Quantitatively, however, propoxyphene is substantially less potent on a milligram basis than narcotics such as morphine, hydromorphone (Dilaudid®) and methadone. In addition, high doses of propoxyphene have certain excitatory properties not noted with most other narcotics which, while they tend to discourage deliberate abuse of propoxyphene, make convulsions a common feature of propoxyphene overdose in addition to the usual narcotic overdose manifestations of respiratory depression and coma.

ANALGESIC EFFICACY

On reviewing reports of studies which have appeared in the interim, I find little necessity to modify my evaluation of the efficacy of dextropropoxyphene which appeared in 1966 [Beaver, 1966] and which I presented in my testimony before this Subcommittee on 24 November 1970.

Propoxyphene vs. placebo: In addition to the studies cited in my 1966 review, several additional controlled analgesic studies have confirmed that that 65 mg dose of propoxyphene hydrochloride or the equivalent 100 mg dose of propoxyphene napsylate is statistically significantly superior to placebo in relieving postoperative and trauma pain [Sunshine *et al.*, 1970; Sunshine *et al.*, 1971; Young, 1978], postpartum uterine cramping [Baptisti *et al.*, 1971; Gruber *et al.*, 1971], postpartum episiotomy pain [Berry *et al.*, 1975], pain subsequent to oral surgery in outpatients [Winter *et al.*, 1973] and chronic pain of mixed etiology [Wang, 1974].

A couple of studies have also succeeded in demonstrating a statistically significant difference between placebo and either 32 mg propoxyphene hydrochloride [Sunshine and Kantor, 1966] or the equivalent 50 mg dose of propoxyphene napsylate [Sunshine *et al.*, 1971] but these obviously represent threshold or marginally effective doses of propoxyphene, the analgesic effect of which doses can only very rarely be measured in even the most sensitive analgesic assays.

Propoxyphene dose-response curve: Several additional studies have also confirmed the existent of a significant positive slope for the dose-response curve of propoxyphene using various graded doses of the hydrochloride salt from 32 to 200 mg and/or the equivalent doses of the napsylate salt of 50 to 300 mg [Sunshine *et al.*, 1970; Sunshine *et al.*, 1971; Sunshine *et al.*, 1978; Baptisti *et al.*, 1971; Gruber *et al.*, 1971].

In my opinion, the above cited studies, alone and in conjunction with those I have previously reviewed [Beaver, 1966], prove beyond any doubt that propoxyphene hydrochloride in doses of 65 mg and higher or propoxyphene napsylate in doses of 100 mg and higher have some analgesic activity in patients with pain of a wide variety of etiologies. Indeed, since propoxyphene produces narcotic-like responses in all pharmacologic tests with which I am familiar, can produce drug dependence of the classic narcotic type and produces an overdose syndrome characteristic of narcotics, I would find it impossible to explain how the drug could possiblye *not* be an effective analgesic at some dose level.

Yet, several double-blind studies which ostensibly meet the minimum criteria for a controlled clinical trial of analgesic efficacy have not demonstrated a statistically significant difference between the analgesic effect of 65 mg of propoxyphene hydrochloride and a placebo treatment. There are a number of possible explanations for this state of affairs, and most of them hinge on an understanding of the concept of assay sensitivity as it applies to clinical trials of analgesics. Because of the multiplicity of known and unknown variables which affect the course of a patient's pain and its response to analgesics, and because there is no satisfactory measure of a patient's pain other than the patient's own subjective reports of this experience, analgesic clinical trials vary greatly in their ability to demonstrate the efficacy of even known effective analgesics: i.e., they vary widely in their assay sensitivity. Therefore, unless an analgesic clinical trial contains an internal measure of assay sensitivity that demonstrates that the trial is capable of measuring an analgesic effect of the magnitude anticipated to result from administration of the test drug (e.g., propoxyphene), a negative finding concerning the efficacy of the test drug has no meaning [Modell and Houde, 1958; Houde et al. 1965, 1966]. Most of the clinical trials which did not distinguish propoxyphene from placebo either did not contain a measure of assay sensitivity or were clearly insensitive in that they also could not distinguish known analgesics (e.g., codeine or aspirin) from placebo. Furthermore, since single doses of propoxyphene 65 mg are almost certainly less effective than the usually used doses of the mild analgesic standards, codeine 65 mg, aspirin 650 mg, acetaminophen 650 mg or 2 APC tablets, an oral mild analgesic study may have adequate assay sensitivity to demonstrate a statistically significant difference between one or more of these standards and the placebo, while still not being able to identify the less substantial analgesic effect of propoxyphene 68 mg as statistically significant [Moertle et al., 1972].

Other confounding factors in the interpretation of mild analgesic clinical trials include the fact that some types of pain may respond much more dramatically to peripherally-acting analgesics (e.g., aspirin and acetaminophen) than to centrally-acting narcotics (e.g., coreine and propoxyphene) [Cooper and Beaver, 1976; Bloomfield et al, 1976] and the fact that patients who have received narcotics develop tolerance to these drugs and will subsequently experience more pain relief from aspirin or acetaminophen relative to codeine or propoxyphene than narcotic-naive subjects [Houde et al., 1965, 1966].

Propoxyphene vs. codeine: Since propoxyphene is a "weak" narcotic, oral codeine is the most appropriate standard of comparison. My review of the literature in 1966 [Beaver, 1966] led me to the conclusion that propoxyphene hydrochloride was definitely less potent on a milligram basis than codeine, my best estimate of the relative potency of the two drugs being that propoxyphene is ½ to ⅔ as potent as codeine. In the interval, no definitive relative potency assay comparing graded doses of the two drugs has appeared, but the results of a few more recent clinical studies are generally consistent with the above estimate [Moertel et al., 1972; Sunshine and Kantor, 1960; Forrest, 1970]. Two other studies [Gruber, 1977; Young, 1978], designed to evaluate the analgesic effect of two consecutive doses of each of the study medications, suggest that propoxyphene napsylate 100 mg is approximately equianalgesic to codeine 60 mg, but deficiencies in data presentation make it impossible for me to judge the validity of this interpretation.

Propoxyphene vs. aspirin, acetaminophen or APC: The results of studies I reviewed in 1966 and a few more recent studies comparing propoxyphene hydrochloride 65 mg or propoxyphene napsylate 100 mg with aspirin 650 mg [Moertel et al., 1972], acetaminophen 650 mg or 1000 mg [Moertel et al., 1972; Hopkins et al., 1973; Berry et al., 1975] or APC 2 tablets are consistent with the evaluation which I presented to this Subcommittee in 1970; namely, that propoxyphene at recommended doses is certainly no more, and probably less, effective than usually used doses of aspirin, acetaminophen or APC.

Efficacy of propoxyphene as a constituent of drug combinations: Relatively little propoxyphene is used as a single-entity analgesic. Well over 80 percent of the prescriptions for propoxyphene products are for combinations of propoxyphene with acetaminophen, APC or aspirin. The rationale for these combinations is the same as that which underlies combinations of codeine and other yet more potent narcotics with these same antipyretic-analgesics; namely, production of more intense analgesia than can be provided by using a single agent and reduction of side effects by reducing the dose of any one analgesic. Although experimental evidence to substantiate these theoretical rationales is far from ideal or complete, there is a substantial body of evidence from well-controlled clinical analgesic trials to indicate that combinations of appropriately chosen doses of antipyretic-analgesics with narcotics do, in fact, achieve these objectives [Beaver, 1966; Beaver, 1975].

The slopes of the log dose-response curves of analgesic drugs are relatively flat, with the result that even successive doubling of the dose produces only modest increments of analgesic effect. Narcotics and antipyretic-analgesics such as aspirin are known to produce analgesia by different mechanisms, and the simple additive effect of a narcotic and an antipyretic-analgesic given together is often significantly greater than the analgesia achieved by doubling the dose of either drug administered alone. Furthermore, antipyretic-analgesics probably exhibit a ceiling of analgesic effect at about the usually used doses (650–1000 mg) and the usefulness of higher doses may also be limited by increased incidence of adverse effects and serious cumulative toxicity. Increasing doses of codeine, propoxyphene and other narcotics are associated with progressively increasing incidence and severity of gastrointestinal and central nervous system side effects and increased risk of drug dependence. The problem of providing adequate pain relief in the face of the above noted limitations of currently available analgesics may sometimes be circumvented by combining an optimal dose of an antipyretic-analgesic with an orally effective narcotic in a modest dose which is reasonably safe and well-tolerated.

Older relevant studies for both codeine and propoxyphene combinations are cited in my 1966 review. There are a few more recent studies which appear to demonstrate a significant increase in analgesic effect produced by the addition of propoxyphene to acetaminophen [Hopkinson et al., 1973], APC [Bauer et al., 1974] and aspirin [Wang and Sandoval, 1971]. Moertel and his associates showed a small increase in the effect of aspirin 650 mg produced by the addition of propoxyphene napsylate 100 mg, but the difference was not statistically significant.

ADVERSE EFFECTS OF PROPOXYPHENE

Adverse effects of propoxyphene at therapeutic dose level: At recommended dose levels (propoxyphene hydrochloride 65 mg or propoxyphene napsylate 100 mg Q4H, PRN for pain), propoxyphene produces an extremely low level of adverse effects. In fact, most studies are unable to demonstrate a significantly higher

incidence of adverse effects with these doses of propoxyphene than with a placebo [Baptisti et al., 1971; Gruber et al., 1971; Gruber, 1977; Moertel et al., 1972; Moertel et al., 1974; Sunshine et al., 1971, Wang, 1974]. When large enough groups of ambulatory patients are studied to demonstrate any difference in terms of adverse effects between therapeutic doses of propoxyphene and placebo, the adverse effects consist of a very low incidence of nausea and drowsiness [Winter et al., 1973]. Considering the extraordinarily large use of propoxyphene products, there is extremely little in the entire literature which indicates that the drug in recommended therapeutic doses can produce any serious adverse effects, and even minor adverse effects seem to occur only infrequently.

Toxicity of Propoxyphene in Overdose: As noted above and as is amply attested to by numerous individual case reports and several epidemiologic studies [McBay and Hudson, 1975; Finkle et al., 1976; Sturner and Garriott, 1973] propoxyphene, like any other narcotic, can be lethal in overdose. Unlike most other narcotics, the propoxyphene overdose syndrome is complicated by a high incidence of convulsions, which complicates its treatment.

Dependence Liability of Propoxyphene: Since propoxyphene is pharmacologically a narcotic, it has some ability to produce drug dependence of the narcotic type, and this has been recognized since before the drug was marketed [Fraser, 1960]. Propoxyphene can produce the classic triad of psychic dependence, physical dependence and tolerance, and, in those patients who are able to tolerate high enough doses to result in substantial physical dependence, a narcotic-type abstinence syndrome has been observed on withdrawal. "Street abuse" of the drug clearly occurs, as does dependence secondary to therapeutic use [Chambers et al., 1971; Maletzky, 1974]. However, in my opinion, relative to the extremely wide use of propoxyphene, the demonstrated incidence of serious deliberate abuse of the drug to experience its mood effects is not great and is certainly substantially less than is the case with potent narcotics.

ADVERSE EFFECTS OF ALTERNATIVE MILD ANALGESICS

Any attempt to assess the benefit/risk ratio for propoxyphene must necessarily take into account the known adverse effects of alternative mild analgesics. I am concerned that there is expressed or implicit in certain recent discussions of the usefulness of propoxyphene the assumption that alternative mild analgesics are more or less devoid of adverse effects and are in some general sense "safe". This is clearly not the case.

Aspirin can be lethal, not only in overdose, but also at usual therapeutic dose levels in individuals who are hypersensitive to the drug or who experience massive gastrointestinal bleeding or other bleeding associated with aspirin's effects on blood coagulation. Until recently, acetaminophen has been felt to be singularly free of adverse effects, and this is probably still true at conservative therapeutic doses. However, it is becoming increasingly apparent that overdose with acetaminophen can produce massive hepatic injury resulting in death, and in Great Britain, where the use of acetaminophen is even more widespread than in the United States, it has been estimated that acetaminophen poisoning is now a leading cause of acue hepatic failure.

Chronic use of phenacetin containing analgesic mixtures has been associated with potentially fatal renal damage, and the Food and Drug Administration's Over-the-Counter Analgesic Review Panel has recommended removing phenacetin from the over-the-counter market for that reason. The relative contribution of phenacetin as opposed to other mild analgesics in the development of this syndrome is a subject of debate, and it is unclear whether acetaminophen may not also produce serious renal injury when abused in combination products for prolonged periods of time.

The incidence of adverse reactions to codeine in usual therapeutic doses is low. The drug can produce a typical narcotic overdose syndrome and death, but the reported incidence of this appears low relative to codeine's extremely wide clinical use. Codeine may be safer in this respect than equi-analgesic amounts of propoxyphene, although further study would have to be done to establish this. Coedine has narcotic-type dependence liability, although, like propoxyphene, the incidence of this problem is very low considering the wide therapeutic use of codeine-containing combinations.

Oral pentazocine is an effective mild analgesic more or less comparable to Codeine in potency. Because the drug is a mixed agonist/antagonist rather than a classic narcotic, there is reason to believe that lethal overdose would be

even less of a problem than with either propoxyphene or codeine. However, pentazocine seems to produce a somewhat higher incidence of unpleasant adverse effects at usual therapeutic doses than equi-effective doses of codeine, and pentazocine occasionally produces frank psychotomimetic reactions which may be very disturbing to the patient. While pentazocine has less abuse liability than regular narcotics, deliberate self-administration of the drug for its mood effects undoubtedly occurs, and the Food and Drug Administration's Controlled Substance Advisory Committee has recently recommended scheduling pentazocine in Schedule IV.

The purpose of the above comments on alternative mild analgesics was not to denigrate the value of these drugs for the patient with pain, but rather to put the adverse effect liability of propoxyphene in some reasonable perspective.

ADVERSE EFFECTS OF SCHEDULE II NARCOTICS

The only currently available alternative oral analgesics to the mild analgesics discussed above are the Schedule II narcotics. These include such drugs as morphine, hydromorphone (Dilaudid®), hydrocodone (Diocodid®); oxycodone (constituent of Percodan®), levophanol (Levodromoran®), anileridine, meperidine (Demoral®) and methadone. While in substantial oral does, these drugs are all capable of producing significantly greater pain relief than the mild analgesics noted above [Moertel, 1976], they are all quite capable of producing lethal narcotic overdose, and all have a clearly higher dependence and abuse liability than propoxyphene, codeine or pentazocine. In addition, doses of these Schedule II narcotics which produce pain relief greater than the mild analgesics are also associated with a significantly higher incidence of disturbing gastrointestinal and central nervous system adverse effects. Therefore, their use would only seem to be indicated for those patients for whom conventional mild analgesics or combinations prove ineffective or not tolerated.

WHY DO DOCTORS PRESCRIBE PROPOXYPHENE?

I have listed below, not necessarily in order of importance, a number of factors which seem to me responsible for the popularity of propoxyphene products.

1. It has been claimed that the popularity of propoxyphene in the face of its less than impressive performance in controlled clinical trials is primarily due to the extensive and effective promotional efforts for Darvon® by Eli Lilly & Company. Indeed, the best ball point pen that I ever owned was given to me by a Lilly detail man and is emblazoned with the words, "Darvocet N–100". However, many drug companies utilize the services of inventive advertising agencies and have dedicated swarms of detail men at their disposal, and yet, much to their chagrin, these companies are unable to stir up the sustained high demand for their analgesic product which has been accorded the Darvon® family. I think one must look further than promotional efforts alone to explain the success of propoxyphene over the past 20 years.

2. Physicians seem to need a mild analgesic which is as effective as aspirin, acetaminophen or APC which is not available over-the-counter. Many patients feel that these antipyretic analgesics cannot be terribly effective because they are available over-the-counter and have a psychological need to receive an analgesic which is only available on prescription. Physicians recognize and respond to this need. Propoxyphene products are available in a variety of impressive colors, shapes and sizes and are only available through prescription. Furthermore, as noted above over 80% of prescriptions for propoxyphene products are for combinations containing aspirin, acetaminophen or APC and these combinations are at the very least as effective as the antipyretic-analgesics which they contain. This must be coupled with the fact at recommended doses propoxyphene produces an extremely low incidence of any sort of adverse effects and a virtually zero incidence of serious adverse effects.

One must also consider the alternatives which the physician has available. When Darvon® came on the market in 1957, the significant mild analgesics available as single entities and in combination included aspirin and other salicylates, acetaminophen, phenacetin and codeine. Today, over 20 years later, the only addition to this group has been oral pentazocine (Talwin®). When the patient with persistent pain tells his doctor that this current medication is either ineffective or poorly tolerated (a repetitive occurrence for many patients with chronic pain problems), the physician needs alternatives available. Useful alternative medications have simply not been forthcoming.

3. Physicians in general are very sensitive to the issue of the dependence liability of narcotic drugs. In many situations, this concern has been far in excess of what was warranted by any realistic evaluation of the likelihood of producing iatrogenic narcotic dependence. This anxiety extended to codeine, which in fact has extremely low abuse liability when used in any medically responsible way. Propoxyphene was probably originally perceived by physicians as a non-narcotic substitute for codeine and propoxyphene-containing combinations were marketed which correspond to all of the existing codeine-containing combinations. Until the beginning of 1977, propoxyphene was an unscheduled drug, which implied that it was safer than codeine and its combinations in terms of dependence liability and also made for more convenient prescribing and dispensing.

4. Although the most appropriate and, in fact, most popular use of both propoxyphene and codeine is in combination with the antipyretic-analgesics, there are occasional pain problems in which the physician can quite legitimately want to prescribe either poropxyphene or codeine alone. These include situations where there is an allergy or contraindication to the use of aspirin and acetaminophen. It would also include situations in which the practitioner wished to use a mild analgesic with no associated antipyretic effect.

5. There is, in fact, good evidence that combinations of narcotics with antipyretic-analgesics produce more analgesia than the antipyretic-analgesic given alone, and this increment of analgesic effect may often make the difference between unsatisfactory and satisfactory pain relief for particular patients. This increment of analgesia is often associated with very little increase in adverse effects and therefore constitutes a very real benefit for the patient. To my way of thinking, this constitutes the major acceptable rationale for the use of propoxyphene. It shoud be noted that this rationale does not apply if the prescribed dose of a combination contains substantially less than the usual full therapeutic dose of the antipyretic-analgesic constituent.

6. Controlled clinical trials of analgesics invariably compare the average responses of groups of patients to the various treatments. While the average relative performance of various analgesics is the best predictor of how the generality of patients with pain will respond, individual patients may, for reasons which we simply do not currently understand, derive a better analgesic effect from a drug which on the average is less effective than another. Controlled clinical trials of analgesics are not currently designed to explore this phenomenon, and the determination of the optimal analgesic regimen for any given patient must ultimately be based on the empirical observation of the effect of various analgesics in that patient. It is therefore in the patient's interest to have as wide a variety of effective analgesics available as possible, even though some of these may on the average be less efficacious than others.

7. Virtually all controlled clinical trials of analgesics, including propoxyphene, have involved comparison of single administrations of various analgesics; however, in the practice of medicine, most patients receive not a single dose but repetitive doses of analgesic drugs for the control of their pain. While up to this time, the results of single administration studies have seemed to constitute reasonably accurate predictors of the relative performance of analgesics when administered repetitively (if one keeps in mind the impact of the development of tolerance to narcotics), it is conceivable that repeated administration of some analgesics results in a higher level of efficacy than would be predicted on the basis of single-dose administration. Propoxyphene has a substantially longer half-life in the blood than other mild analgesics such as codeine, acetaminophen or aspirin. When administered every four to six hours, as mild analgesics usually are, there will be a significantly greater cumulation of propoxphene levels than with alternative mild analgesics [Waife et al., 1975]. We do not currently understand the relationship between the blood level of an analgesic and the analgesic effect experienced by the patient, but a plausible argument can be made on the basis of blood level data that one might expect greater analgesia after a few repeated doses of propoxyphene relative to alternative mild analgesics than is, in fact, seen in single administration studies. Unfortunately, few analgesic studies of repeated dosing have been done to examine this hypothesis, and those that have been done are difficult to interpret [Gruber, 1977: Young, 1978]. It is, therefore possible that practitioners empirically find that proproxyphene products are more effective in regular clinical use (i.e., when administered in repeated doses) than would be predicted on the basis of the controlled clinical trials which involve single administrations of test medication.

SOME UNRESOLVED ISSUES

In my mind, there are a number of unresolved issues relevant to the benefit/risk ratio of Darvon and its place as an analgesic which deserve further study.

1. Since a majority of fatal propoxyphene overdoses seem to result from mixed intoxication with propoxyphene and other central nervous system depressants [Finkle et al., 1976], some effort should be directed at determining whether propoxyphene is simply adding to the depressant effects of other drugs or is producing a supra-additive interaction which is particularly hazardous.

2. Although the descriptions of fatal poisoning with propoxyphene which I have studied suggest that this drug is producing death in the same way as any classical narcotic overdose (albeit, the overdose syndrome is usually complicated by the presence of convulsions), studies should be done to determine whether propoxyphene has a direct cardiovascular toxicity in excess of other narcotics, and further studies should be done to elucidate the role of norpropoxyphene in the toxicity produced by propoxyphene [Nickander et al., 1977].

3. Since codeine-containing combinations are the logical alternative to existing Darvon combinations and are prescribed to an ever greater extent than Darvon combinations, it would appear logical to make a concerted effort to determine whether the apparent lower incidence of codeine-related deaths is a real phenomenon and, if so, why?

4. Controlled analgesic studies involving repeated-dose administration of propoxyphene compared to other mild analgesics should be done to determine whether the predicted increase of efficacy of propoxyphene on repeated-dose administration really occurs.

ALTERNATIVES TO THE USE OF PROPOXYPHENE AND OTHER NARCOTICS

A number of oral analgesics which might be predicted to have advantages over propoxyphene and other currently available mild analgesics in terms of increased analgesic efficacy and/or decreased adverse effect liability are currently in various stages of clinical testing. These include the non-steroidal anti-inflammatory drugs such as indoprofen, suprofen, zomepirac, diflunisal and many others; narcotic antagonist analgesics such as butorphanol, nalbuphine, buprenorphine, propiram and others; and compounds of uncertain mechanism of action such as nefopam. There are controlled clinical studies indicating that all of these compounds are effective oral analgesics and other studies indicating they may have certain real advantages over existing drugs. The public interest would be served by seeing that these drugs get on the market without undue delay. I would point out that the average physician will very quickly start prescribing a drug which has real advantages for his patient if such a drug becomes available.

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Senator NELSON. I believe Dr. Newman wants to get out of here before noon and we will hear from him next.

Senator BOSCHWITZ. What do you, therefore, conclude? Do you conclude that the drug Darvon should be kept in schedule IV or put into schedule II?

Dr. BEAVER. I did not conclude this. This was not really the question that was addressed to me by Senator Nelson in the letter. It went to the place of Darvon in medical practice, and I said yes, it seems to have some place.

If I could answer those questions which I did not specifically speak to. I did compare propoxyphene to other drugs. I feel you can certainly practice good medicine without Darvon. It was practiced without Darvon before 1957. We have other drugs. On the other hand, losing Darvon means one less alternative in various situations.

Now, what should you do? There is the issue of just banning the drug as an imminent hazard. I am not terribly fond of that idea for a couple of reasons. One is, quite aside from the legal implications of this, there is nothing about Darvon that has come out recently which is fundamentally different than what we knew back in 1976 and 1977. It is not that there is some clear-cut, well-demonstrated new hazard that has appeared. It just seems to be more of the same, I do not think there has been an increase in Darvon deaths since the drug was put on schedule IV. Now, it is debatable whether or not there has been a decrease, but the problem about banning the thing as a hazard is, as I pointed out, doctors will use something else and the other things they may use may include combinations with sedatives and barbiturates which have higher abuse liability than Darvon.

Senator BOSCHWITZ. I thought you said they are reluctant to do that. What about codeine?

Dr. BEAVER. They may go to codeine. Some will go to codeine and I think that would be a perfectly appropriate movement.

Senator BOSCHWITZ. That does not have abuse liability?

Dr. BEAVER. It does have some; and it may in the sense of drug dependence be somewhat more than Darvon. It is more effective and you can take higher doses for mood effect without getting sick.

They may also go to potent schedule II narcotics, things such as Percodan, and these have a higher abuse liability than either codeine or Darvon.

Then the question is, "What about rescheduling?" There might be something said to this. One could, for example, treat the drug as codeine is currently treated. This would involve putting the entity itself on schedule II and the combinations on schedule III.

Now, seeing that the major perceived problem here is not the deliberate abuse of the drug for its mood effects, but rather suicidal or possibly accidental poisoning, I am not sure how much effect that would have, but what it would do is clearly alert physicians to a change in status of the drug and get them to thinking about it more seriously.

My feeling is that one of the problems with this drug is that physicians have taken it altogether too casually.

Senator BOSCHWITZ. When was it put under schedule IV?

Dr. BEAVER. 1977.

Senator BOSCHWITZ. Any changes in the prescription levels?

Dr. BEAVER. The prescriptions have gone down a little since then. If something like this were done and combined with a big black box up at the front end of the label and slapped into all the advertising pinpointing what the real risk of this drug was in terms of overdose and death, it might get physicians to use the drug in a bit more conservative way in terms of the amount prescribed, the kind of people they would prescribe it for and so on and it would generally alert them and this would be a useful option.

Senator BOSCHWITZ. Is the medical profession pretty much aware of the problems that have been discussed here?

Dr. BEAVER. I think perhaps the single, most important function a hearing such as this serves is to create a public awareness of this kind of problem; so it is all over television and things like that and people, including physicians, will be asking questions and trying to find out more about it.

Senator BOSCHWITZ. Senator, I do not want to hold up the doctor who wants to leave at noon. I would also like to leave at noon but I might ask Dr. Adriani one question.

Would you address yourself briefly to Dr. Beaver's point that when the patient goes to a doctor and that patient has already been taking aspirin—to identify with this, my doctor normally does not charge me $25, but then the only thing the doctor does is confirm that I should go home and take two aspirin; famous last words of medical advice—is what the doctor does important psychologically or should that not be a consideration?

Dr. ADRIANI. I do not think so. Here you have a drug inferior to aspirin. In prescribing, you want to prescribe the ideal medicine to a patient, and the best drug available for him irrespective of how he busy it, whether he buys it by prescription or over-the-counter.

Aspirin is bought over-the-counter. It is the best drug we have for arthritis. There are certain drugs like nitroglycerine and adrenalin which should be prescription for asthma and angina. The asthmatic can get adrenalin over-the-counter since he may need it in a hurry and not have time to get a prescription. The public is becoming more and more aware of what we do in the practice of medicine and the mistakes we make in medicine. They know aspirin is a good drug and do not object to buying it over-the-counter when told to do so by a doctor. Patients know what they are getting on prescription. The days are disappearing when a patient did not know what was being prescribed but now we have more and more full disclosure of everything.

Senator BOSCHWITZ. Sorry to hold up, Dr. Newman. I see your testimony is a little shorter.

Senator NELSON. Dr. Newman, you may go ahead. Your statement will be printed in full in the record and you may present it however you like.

STATEMENT OF MICHAEL A. NEWMAN, M.D.—Resumed

Dr. NEWMAN. Thank you.

My name is Michael A. Newman and I appreciate this opportunity to testify about the safety, efficacy, and usefulness of propoxyphene, or Darvon.

I am a doctor of medicine certified by the American Board of Internal Medicine. Testimony has been and will be presented by experts familiar with the pharmacology and epidemiology of propoxyphene. I testify as a physician engaged in the full-time practice of internal medicine in the District of Columbia who daily sees and cares for patients.

My opinion of propoxyphene is that it is a mild analgesic with pharmacological properties similar to narcotics although it is much less potent. It has not been shown to be of greater efficacy than either aspirin or codeine in relief of pain.

We are a heavily medicated society taking prescription, proprietary, licit, illicit, begged, borrowed, and stolen drugs. Why? Is it because physicians prescribe drugs too readily or inappropriately? Perhaps, but there are other factors involved. Drugs may be prescribed for reasons unrelated to disease or efficacy.

Propoxyphene illustrates the problem of prescribing drugs. Some drugs develop a public following—they become "pharmacological celebrities," their glamor and mystique unrelated to their efficacy, safety, or cost. Propoxyphene is such a drug.

Today, physicians seem to have a few misconceptions about the efficacy of propoxyphene. But many physicians are uninformed about the toxicity and abuse of the drug.

Consequently, unaware of its dangers, physicians too often prescribe it in an effort to provide comfort and relief or in response to a patient's expectations or request. These hearings will help inform physicians and patients about the toxicity and abuse of propoxyphene. Classification of propoxyphene under schedule II would further alert physicians and patients to its dangers and reduce its use.

Pain is perhaps the most frequent reason why patients come to see a physician. But pain is a symptom, not a diagnosis. Ideally, proper treatment of a patient depends on the correct diagnosis. But patients are not always interested in or appreciative of the thought, time, testing and expense entailed in establishing a diagnosis. Patients want relief as soon as possible. They often specify what medication they believe is necessary. Their belief being based on prior experience, hearsay, recommendations of relatives or friends, and articles in newspapers or magazines.

Physicians, like public servants, are influenced by their "constituents"—in this case, their patients. The public may be surprised, but many physicians want to act not only in the best interests of their patients, but to please them as well.

On occasion, sound clinical practice and good medical judgment may not satisfy patients seeking a specific treatment or drug. I and many other physicians have experienced such instances of dissatisfaction in response to sound medical recommendations, particularly when a drug is not prescribed.

I would disagree with Dr. Beaver's point that this means you need to go ahead and prescribe a drug. I have had experience both in a prepaid and in fee-for-service practice. Certainly, one of the things you are aware of is that patient satisfaction is important, but I still feel that physicians do not need to prescribe drugs on that basis. I do not prescribe drugs on that basis. I know patients may be disappointed and

I anticipate it by saying, "I can see you are a bit unhappy that you have not gotten a prescription." They acknowledge that and seem to leave satisfied. I think that is very simple. I do not think it is necessary to provide the prescription just to satisfy a patient.

Additionally, consider the fact that efficacy is elusive and subtle especially when we attempt to distinguish between biologic and nonbiologic or placebo effects. Often patients conclude, ipso facto, that because they felt better the drug was effective. This operant conditioning is a powerful factor and it is difficult to dissuade a patient of such persuasion or belief.

A physician in the midst of a busy day and unaware of the dangers of propoxyphene may find it easier to prescribe the drug rather than explain that aspirin is more effective and much safer. This is deplorable, but it happens. I think it is happening to a lesser extent because physicians are more cautious in what they prescribe and patients are asking tough questions when they get prescriptions, at least that is my view of practical practice here in Washington.

For many patients, a prescription for a drug like propoxyphene seems tangible proof that their illness was seriously considered and their visit to the physician worthwhile.

A prescription for aspirin has no such connotations and even suggests the opposite. Despite much merit in the recommendation, the jokes and cartoons are about the physician saying, "take two aspirin and call me in the morning." There are no similar jokes about Darvon. Drugs like propoxyphene give pseudolegitimacy to the complaint or illness for the patient, his family, friends and coworkers in a way that aspirin does not.

Also, patients seem happier paying the doctor when a presciption is written rather than paying for a visit after being told to take two aspirin or to follow a regimen of heat, rest, and exercise.

Thus, drugs are prescribed for many reasons not all of them valid. Clearly, the physician has the final responsibility in recommending how to proceed and what drug, if any is to be prescribed based on valid medical medications and knowledge of efficacy and safety. But unfortunately, this is not always what occurs.

What I am saying is it is possible to practice good medicine without prescribing propoxyphene and many other drugs and the indications for propoxyphene are very limited.

I would in no way feel constrained in my practice of medicine by having propoxyphene available only on an investigational basis or by having it scheduled as a class II narcotic. Unfortunately, despite efforts by this committee and others to inform physicians and the public about the lack of superiority, the toxicity and the potential for abuse of propoxyphene, it probably will remain a widely prescribed and used drug unless it is rescheduled as a class I narcotic. I strongly urge that this be done.

I thank you for this opportunity to present my views as a practicing physician before this committee. I would be glad to answer any questions.

I want to take a few moments for some additional comments. First of all, I support Dr. Charles Moertel's testimony 100 percent. I can see no reason why propoxyphene needs to be available.

I believe Senator Hatch was concerned if someone taking Darvon at the prescribed or recommended dose could conceivably experience a fatal or lethal overdose.

I am not a clinical pharmacologist, but I see the situations where people are taking medicine at the prescribed dose and then combine it with something else such as alcohol or tranquilizers or some other medication. The combination or interaction has the potential for being lethal even if both are within the prescribed recommended doses. That is a point that does concern me.

Another point in terms of prescribing drugs is that we have already had experience with DES with radiation to the head and neck and an increased incidence of cancer, with respect to the use of estrogens and increased instances of endometrial cancer and what we are going to find out about birth control pills in the future is unknown.

The same point pertains to Darvon. Just now as you heard it's been on the market for 20 years and only now are we learning more about its metabolites and potentially serious cardiotoxic effects that it has.

Who knows what we may find out in the future? I think it would be unfortunate to continue to have a drug such as Darvon widely and readily available without being aware of what its potential side effects are.

The most important point I want to make as a practicing physician is that I can practice medicine day in and day out and not be concerned about patients being disappointed, or be concerned about patients leaving me because I do not use it. I would not hesitate at all to say that I think it need never be prescribed.

Senator NELSON. Thank you very much, Dr. Newman.

We will now hear from Morris Boynoff, a pharmacist from Mendocino, Calif.

Senator BOSCHWITZ. Dr. Newman, how convincing did you find your explanations that aspirin is more effective and safer? Do your patients accept that?

Dr. Newman. My experience is that patients do accept it. Sometimes patients respond that they cannot take aspirin but they can take one of the buffered aspirin preparations. That is quite common.

There are some people who are legitimately allergic to aspirin. In those instances, acetaminophen is equally acceptable. If you talk to patients and explain why you are doing something or not doing something, they accept it.

Senator BOSCHWITZ. Therefore you do not prescribe Darvon?

Dr. NEWMAN. I use a type of prescription where I keep a carbon copy of all the prescriptions that I write. I went back and looked at the prescriptions for the past 6 months and found I had not prescribed Darvon in the past 6 months and I cannot really recall having prescribed it.

Senator BOSCHWITZ. What do you prescribe instead?

Dr. NEWMAN. As an alternative to aspirin or acetaminophen, I prescribed codeine. But, many times I do not prescribe anything. Sometimes people are going to hurt. I am a big prescriber of "time."

Senator BOSCHWITZ. And your patients accept that?

Dr. NEWMAN. The patients accept that; yes.

Senator BOSCHWITZ. Dr. Beaver, are you a practicing physician, or have you practiced?

Dr. BEAVER. I do not have a private practice of medicine. My practice or work is involved mainly in consulting on pain problems at the University Hospital. I am the analgesic consultant at the Washington Home Hospice where we are taking care of terminal cancer patients. I have done a little private practice.

Senator BOSCHWITZ. Do you consult with the patients or the doctors?

Dr. BEAVER. Both. We do not disagree at all on what is appropriate.

I was trying to describe my insights into why physicians do the things they do, which I think is what you have also said, Dr. Newman. I am not saying one should, therefore, prescribe whatever the patients ask for.

Dr. NEWMAN. As a physician, I would say there are types of pain, such as pain related to a specific acute episode.

The issue of chronic pain is a problem where I am not persuaded that drugs are the only modality. There are a variety of modalities of managing patients with chronic pain, and drugs are not the only modality to be used there.

I am sure Dr. Beaver would agree with that. In many instances people who have taken a large number of drugs for severe pain have been able to stop using those drugs entirely by using other modalities such as biofeedback, electrical stimulation, better control of the underlying process, hypnosis, and so forth.

Very often we think if the problem is pain, a pill is necessary. That simply is not the best approach.

Senator NELSON. Yesterday, Dr. Moertel from Mayo Clinic stated the following in his last paragraph; and I would ask you if you want to comment on it:

> To summarize, I will answer specifically the four questions addressed to me when I was invited to testify before this committee.
>
> The first question, from my knowledge and experience what is the relative efficacy of Darvon as compared to other analgesics?
>
> In my judgment Darvon is inferior to the commonly marketed aspirin, acetaminophen, or APC combinations.
>
> The second question, is it possible to treat patients for pain with analgesics other than Darvon? Absolutely. For patients with mild pain you can do just as good a job, if not better, with aspirin or APAP alone, and you can do it for about one-tenth of the price. With regard to the use of Darvon combinations for the treatment of moderate pain, you can achieve significantly superior pain relief using combinations of aspirin with codeine, aspirin with oxycodone, or aspirin with pentazocine or Talwin. For the treatment of severe pain, the use of Darvon either alone or in combination is grossly inadequate treatment and is really inhumane to the patient.
>
> The third question, is it possible to maintain good medical practice without the use of Darvon? Yes. I would seriously question whether the use of Darvon is good medical practice at all. And the last question, what is the medical justification for using Darvon? I know of none.

Dr. NEWMAN. I agree with Dr. Moertel's last paragraph entirely.

Senator NELSON. Dr. Adriani, would you agree or disagree?

Dr. ADRIANI. I agree with that. That summarizes my statement.

Senator NELSON. Dr. Beaver.

Dr. BEAVER. In terms of the comparative efficacy aspect of the thing, we are in reasonable agreement as I went to considerable pains to document in my prepared testimony which is part of the record.

With regard to the aspect of combinations, I agree that those of codeine and certainly oxycodeine are likely to be more effective. In the

treatment of severe pain, Darvon is certainly seldom going to be adequate even in combination with optimal doses of aspirin.

Is it possible to maintain good medical practice without the use of Darvon and what is the medical justification for using Darvon? I have gone into a number of possible ones in my testimony exploring to some degree both sides of the issue.

Senator BOSCHWITZ. Please excuse my ignorance, but Dr. Newman, could you just describe the side effects or other effects of codeine?

Dr. NEWMAN. The side effects of codeine?

Senator BOSCHWITZ. Is it addictive?

Dr. NEWMAN. Codeine is a narcotic. Codeine has addictive qualities.

Senator BOSCHWITZ. More addictive than Darvon?

Dr. NEWMAN. There are no studies I am aware of that comment on the addictive quality of codeine versus Darvon.

Darvon is the most closely related to methadone and there is no question about its addictive properties. I am not a clinical pharmacologist, but I have not seen any studies comparing whether propoxyphene or codeine are equivalent or not in terms of their addictive qualities. We are talking about narcotics, and a property of narcotics is that they are addictive. The most common side effect I see as a physician prescribing codeine is gastrointestinal problems. Codeine gives people anything from an upset stomach to severe cramps, nausea, and vomiting.

In terms of side effects of any of these compounds, I have not seen the data to compare the incidence or side effects.

Senator BOSCHWITZ. Dr. Beaver, would you comment briefly on the side effects of codeine?

Dr. BEAVER. Mainly what you see is some nausea, rarely vomiting, also drowsiness and dizziness. These are when the side effects occur, and these minor types of side effects are qualitatively very similar to the ones you see with Darvon.

Senator BOSCHWITZ. Thank you.

[The prepared statement of Dr. Newman follows:]

STATEMENT OF MICHAEL A. NEWMAN, M.D.

Mr. Chairman and members of the Senate Small Business Committee, my name is Michael A. Newman and I appreciate this opportunity to testify about the safety, efficacy and usefulness of propoxyphene (Darvon). I am a Doctor of Medicine certified by the American Board of Internal Medicine. Testimony has been and will be presented by experts familiar with the pharmacology and epidemiology of propoxyphene. I testify as a physician engaged in the full time practice of internal medicine in the District of Columbia who daily sees and cares for patients.

My opinion of propoxyphene is that it is a mild analgesic with pharmacological properties similar to narcotics although it is much less potent. It has not been shown to be of greater efficacy than either aspirin or codeine in relief of pain.

We are a heavily medicated society taking prescription, proprietary, licit, illicit, begged, borrowed, and stolen drugs. Why? Is it because physicians prescribe drugs too readily or inappropriately? Perhaps, but there are other factors involved. Drugs may be prescribed for reasons unrelated to disease or to efficacy.

Propoxyphene illustrates the problem of prescribing drugs. Some drugs develop a public following—they become "pharmacological celebrities", their glamor and mystique unrelated to their efficacy, safety, or cost. Propoxyphene is such a drug.

Today, physicians seem to have few misconceptions about the efficacy of propoxyphene. But many physicians are uninformed about the toxicity and abuse of this drug. Consequently, unaware of its dangers, physicians too often prescribe

it in an effort to provide comfort and relief or in response to a patient's expectations or request. These hearings will help inform physicians and patients about the toxicity and abuse of propoxyphene. Classification of propoxyphene under Schedule II would further alert physicians and patients to its dangers and reduce its use.

Pain is perhaps the most frequent reason why patients come to see a physician. But pain is a symptom, not a diagnosis. Ideally, proper treatment of a patient depends on the correct diagnosis. But patients are not always interested in or appreciative of the thought, time, testing and expense entailed in establishing a diagnosis. Patients want relief as soon as possible. They often specify what medication they believe is necessary. Their belief being based on prior experience, hearsay, recommendations of relatives or friends, and articles in newspapers or magazines.

Physicians, like public servants, are influenced by their "constituents"—in this case their patients. The public may be surprised, but many physicians want to act not only in the best interests of their patients, but to please them as well. On occasion, sound clinical practice and good medical judgment may not satisfy patients seeking a specific treatment or drug. I and many other physicians have experienced such instances of dissatisfaction in response to sound medical recommendations; particularly, when a drug is not prescribed.

Additionally, consider the fact that efficacy is elusive and subtle especially when we attempt to distinguish between biologic and non-biologic or placebo effects. Often patients conclude, ipso facto, that because they felt better the drug was effective. This operant conditioning is a powerful factor and it is difficult to dissuade a patient of such persuasion or belief. A physician in the midst of a busy day and unaware of the dangers of propoxyphene may find it easier to prescribe the drug rather than explain that aspirin is more effective and much safer. This is deplorable, but it happens.

For many patients, a prescription for a drug like propoxyphene seems tangible proof that their illness was seriously considered and their visit to the physician worthwhile. A prescription for aspirin has no such connotations and even suggests the opposite. Despite much merit in the recommendation, the jokes and cartoons are about the physician saying, "take two aspirin and call me in the morning". There are no similar jokes about Darvon. Drugs like propoxyphene give pseudo-legitimacy to the complaint or illness for the patient, his family, friends and co-workers in a way that aspirin does not.

Also, patients seem happier paying the doctor when a prescription is written rather than paying for a visit after being told to take two aspirin or to follow a regimen of heat, rest and exercise.

Thus, drugs are prescribed for many reasons not all of them valid. Clearly, the physician has the final responsibility in recommending how to proceed and what drugs, if any, are to be prescribed based on valid medical medications and knowledge of efficacy and safety. But unfortunately, this is not always what occurs.

It is possible to practice good medicine without prescribing propoxyphene and the indications for its use are very limited. I would in no way feel constrained in my practice of medicine by having propoxyphene available only on an investigational basis or by having it scheduled as a Class II narcotic. Unfortunately, despite efforts by this Committee and others to inform physicians and the public about the lack of superiority, the toxicity and the potential for abuse of propoxyphene, it probably will remain a widely prescribed and used drug unless it is rescheduled as a Class II narcotic. I strongly urge that this be done.

Thank you for this opportunity to present my views as a practicing physician before this Committee. I would be glad to answer any questions.

CURRICULUM VITAE

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Certification: American Board of Internal Medicine, June 18, 1975. No. 047786; National Board of Medical Examiners, July 1, 1970. No. 103449.

Medical Licensure: Maryland D 13352, issued 1971; District of Columbia 5496, issued 1971.

Military Obligation: U.S. Public Health Service, Surgeon (R) (T) PHS-33359, July 1, 1971 through June 30, 1973.

Professional Experience:

Assistant Clinical Professor of Medicine, Georgetown University School of Medicine, current.

Assistant Clinical Professor of Medicine, George Washington University School of Medicine, current.

Assistant Professor of Health Care Science and Medicine, George Washington University School of Medicine.

Associate Medical Director, George Washington University Health Plan, February, 1975–July, 1976.

Chief, Professional Resources Branch, Health Services Division, Health Maintenance Organization Service, Health Services and Mental Health Administration, Department of Health, Education and Welfare, December, 1971–July, 1973.

Special Assistant to the Director, Health Maintenance Organization Service, Health Services and Mental Health Administration, Department of Health, Education and Welfare. July, 1971–December, 1971.

Peace Corps Volunteer—Malaysia, 1963–65.

Fellowships:

1966—Summer Fellow in Epidemiology, California Department of Public Health, A Study in Epidemiological Status and of Health Beliefs and Practices in Two Communities in Bolivia.

1968—Health, Education and Welfare Fellowship (P.L. 480), A Study of Infant Diarrheal Diseases: Mohd. Ali Jinnah Post Graduate Institute, Karachi, Pakistan Seato Cholera Research Center, Dacca, Pakistan.

Honors: Outstanding Intern of the Year Award, 1970–71—University of North Carolina.

Publications:

Newman, Michael A. (Ed) The Medical Director in Prepaid Group Practice, American Group Practice Association, Alexandria, Virginia, 1973.

Raft, D., Newman, M., Spencer, R.: Suicide on L-Dopa, Southern Medical Journal, 65: 312.

Travel: Mexico, Japan, Hong Kong. Cambodia, Thailand, Malaysia, Singapore, Indonesia, Ceylon, India, Pakistan, Bangladesh, Kenya, Uganda, Liberia, Britain, Netherlands, France.

Senator NELSON. Mr. Boynoff, you may proceed. I am sorry to get to you so late.

STATEMENT OF MORRIS BOYNOFF—Resumed

Mr. BOYNOFF. In the interest of time, I will not read my prepared statement. I will submit it for the record and review a couple of comments that have come to mind.

Senator NELSON. Your statement will be printed in full in the record.

Mr. BOYNOFF. Thank you, Mr. Chairman.

One of the questions that has been central to what I have heard is what would happen if propoxyphene were not available to physicians?

We have that situation in California, in a practical sense, not legal, and we have had the situation under our medicaid program which operates on a closed formula basis.

Now, physicians as people involved in meeting human needs, as all of us are engaged in one health activity or another are also concerned with the costs that are inflicted by their decisions upon their patients

and since medicaid was devised to bring poor people into the main stream of medical care, that out-of-pocket cost to those specific patients is also important to the prescribing physician.

In 1967 when medicaid programs started in California we had a closed formulary and physicians then could not or would not prescribe propoxyphene for their medicaid patients.

Senator NELSON. What year was that?

Mr. BOYNOFF. 1967.

Senator NELSON. And the formulary did not list propoxyphene?

Mr. BOYNOFF. And does not as of this moment. So we have approximately 11 plus years of experience, of large numbers of patients presenting pain symptoms, treated without propoxyphene.

Now, the Medi-Cal formula does include narcotic pain relievers. It does not include the nonprescription pain relievers, although nonprescription drugs are included in the formulary and contraceptive devices and medical supplies.

Senator NELSON. But not nonprescription analgesics?

Mr. BOYNOFF. As a matter of fact, I believe our enabling act in California aspirin is specifically prohibited from being included so that the consultants that we call for authorization to supply nonformulary medications to patients and still be assured reimbursement and I have been told in the instance of a youngster with a disseminated juvenile arthritis who survives currently on aspirin, that even though it was clearly indicated as the drug of choice, the consultant was prohibited by regulations for payment of aspirin so that youngster's parents purchased the aspirin over-the-counter.

My point is that sometimes we are entrapped into dealing with images and codeine being an opiate has a poor reputation but it is unusual to receive a prescription, from a physician stipulating codeine alone.

Codeine alone is a schedule II narcotic complicated by the fact that in California, schedule II narcotics require the physician to write his prescription order on a State-supplied triplicate form and we have used that in California since 1938 or 1939 so that the kind of separate and unequal documentation required for schedule II narcotics almost assuredly guarantees that the prescriber will seek something more moderate in activity.

For these 11 years physicians have ordered codeine but always with aspirin and caffeine or with acetaminophen because that drops it down to schedule III and permits it to be a verbal telephone order.

Senator BOSCHWITZ. Schedule II is allowed under the verbal telephone order?

Mr. BOYNOFF. No; anything lower than schedule II.

Senator BOSCHWITZ. So codeine when mixed with aspirin is what?

Mr. BOYNOFF. When combined with a non-narcotic is schedule III.

Senator BOSCHWITZ. I thought you said it was a schedule II.

Mr. BOYNOFF. No; I have attained that age where I am now competent to look at some phenomenon from sort of a historic and retrospective standpoint and I think that the entire controversy regarding propoxyphene really relates first of all to the pharmacological question which is most difficult, if not impossible at this state-of-the-art to quantify. Is it a pain reliever?

Well, you pay your money and you take your answer. An item that was handed to me by a patient when I could not resist the ego satisfaction of saying I was going to Washington who brought me this ad and it is an ad stipulating that two 500 milligram tablets of acetaminophen are more effective than Darvon and in the area of attempting to measure pain relief, we are handicapped by the fact that we have not as yet devised a way of measuring pain. We measure it descriptively. We say "moderate," or "severe" or "intolerable." These are all adjectives. They are not measures, and even with a well-defined double-blind crossover study when push comes to shove, somebody has to ask the patient how do you feel.

I can think of no more totally subjective nonobjective measure so let us get back into historical perspective.

Eli Lilly & Co. had the great good fortune to come along at the legally opportune moment. It was during that era before the Kefauver-Harris amendments to the Food, Drug, and Cosmetics Act which meant a company proposing to market a product did not have to prove efficacy. They did not have to prove it was useful or it would, in fact, relieve pain. They merely had to demonstrate that if used as prescribed, it was safe. But there was an even more important coincidental factor and that is that the Comprehensive Drug Abuse Prevention and Control Act had not yet been enacted so the second factor was that under the older Harrison Narcotic Act, even Empirin compound with codeine could not be telephoned. The Department of the Treasury administering the Bureau of Narcotics had not yet, as yet, accepted the invention of the telephone. It had to be in writing and as a young pharmacist attempting to establish his own self-employed practice in an urban area—this was in the Berkeley, Calif. area—I spent a great deal of time nudging physicians to followup in writing their telephone prescriptions.

I hope that the statute of limitations has run out admittedly to an illegal activity but that is common practice and the patient presents himself to the pharmacy in pain. It is a continuing pain and the previous supply has been used up so I never felt that morally or in any way other than the literal interpretation of the law that I was doing wrong but just the need to assemble all these documents to justify my inventory in the event of an audit meant that physicians themselves, you see, were easily impressed and I am talking about multimillion dollar slick advertising. I am talking about facts taken out of context which remain fact so that Eli Lilly introduced Darvon and Darvon compound prior to the current laws relative to the introduction of new drugs and behold, Doctor, it can be telephoned. We are saving you time. Well, over the years there have been millions upon millions of what the advertising people call imprints or exposures but it is impossible to pick up a professional or scientific journal without a 50–50 chance of seeing an ad for Darvon in one form or another.

Now, the reason I am belaboring this is to show that all of us: Physicians, scientists, pharmacists, nurses, all kinds of people are human and the accumulative impact of the repetitive statement has its effect.

I would also like to point out that in the area of giant corporations, decisions are made on market possibilities rather than on human needs.

There is nothing intrinsically or inherently wrong with that. That is how our system works and we see in 1962 or 1963 collectively through the Congress of the United States who decided that it was, in fact, time for a change in the system and so the Kefauver-Harris laws were amended to the Food and Drug Act and we learn through misadventure and learn through our mistakes.

The point I am really trying to make is that there is this area in medical practice that requires some kind of response; that even though a physician can educate the patient to the fact that I am doing what is best for you, that even though you are disgruntled there is no document in your hand and I want you to go home and take two aspirin, put the ice pack on, give the injury a rest and it has greater merit.

In our cultural milieu we are so drug oriented that patient expectations become a very important factor in the pharmacy, in the medical office, in the radiology where the X-rays are taken because patients are more and more informed and ask more and more questions.

Now, I leave it to the clinical pharmacologist and the academic world to determine the exact degree of efficacy of propoxyphene but let me point out some of the economics of propoxyphene, that even though rescheduling it as a schedule IV product might have at corporate headquarters a discernible impact on sales.

Senator NELSON. You said even if you reschedule it.

Mr. BOYNOFF. I beg your pardon, even if it is taken out of the area of an unscheduled drug and put in schedule IV I have not in my practice seen any diminution of its use.

Part of that reason is I would find it very difficult to determine whether or not less propoxyphene were used because it has been so lit'le. I have the great good fortune of being in a geographically isolated community. I have close and daily contact with the 12 physicians, the two nurse practitioners and the two dentists and we share educational conferences at our local hospital and there is good rapport and good continuing day-to-day contact.

None of the prescribers feel diminished, offended, attacked if a pharmacist calls and says these two really should be given together or this drug should not be given every 4 hours. Its biological half-life recommends that it should only be given every 6 or 8 hours and I get thanked for this, that we all share a common concern for helping meet the needs of other people who have come in for help, so I could not see a diminution in the use of propoxyphene because the practitioners in my community sense very strongly and regard it as a kind of placebo that is indicated in those cases where they do not want to use opiates or do not want to send the patient out saying take two aspirin and call me in the morning. And because of the close geographic isolation the people who are chronic drug users are easily identified and with the kind of patient records I maintain for every patient for whom I dispense medication, by pulling a 5 by 8 card out of the drawer I can immediately scan that particular patient's drug profile, the frequency of use and if, for example, as was stated earlier a patient is doubling up on the dose, I pick up on that before the physician; frequently the physician who is authorizing the legal five number of refills and even under California law even though refills have been authorized, the pharmacy may not supply them except at chronological intervals

agreeing with the prescribed dosage and I say medically, if someone wants more before the appropriate term has elapsed, he does not get it.

In any event, even though it is a schedule IV drug from a practical standpoint as a community pharmacist it has increased the number of times I have to call the physicians to generate a new prescription.

The other impact I really cannot make a conjecture as to its cause outside of the fact that we are all trapped in the inflationary spiral, but the January 5 issue of Drug Topics, this happens to be a companion publication to Medical Economics, and it gets widely read, the two bits of literature are widely read, but the patent date has expired.

I was a member of the Pharmaceutical Reimbursement Committee to HEW's program of establishing maximum allowable costs for drug reimbursement under federally financed health care programs.

Well, propoxyphene was one of the drugs we discussed. It is a variable starting at the low end at a cost of under $15 per thousand all the way up to the January 5 price announcement from Lilly, the Darvon Compound 65 would now cost the pharmacies $80.52 per thousand.

In between there are other firms just as equally prestigeous as Eli Lilly, Parke, Davis, and Smith, Kline & French. Their products are supplied in the $24 to $25 range, not $80 and so as I perceive the problem we are talking about a drug that is not very useful and in the main since Darvon is much easier to remember I am talking about the national picture for all and Darvon is a much easier name to remember than propoxyphene—much easier.

In California legally for the past 18 months or so we have had what is euphemistically called a product selection law, even though the physician using the trade name on the prescription the pharmacist may substitute a different brand and we get into a nebulous area of the law as I understand it.

There are two messages implicit in the use of the trade name rather than the assigned name. When a physician writes Darvon, he is telling the pharmacist—or she as I do not mean to be sexist—the pharmacist is being told that the patient is to receive propoxyphene.

The second nonverbal message is that I should buy the propoxyphene from Eli Lilly & Co. That is the virtue of the trade name, but it has lost that virtue under the enactment of the product selection law.

We have another very interesting proviso in the California law since for medicaid patients, pharmacies receive reimbursement on the basis of the actual cost of the drug, plus a fee for their services. You see, there is no threat to the pharmacies.

Senator NELSON. It is a flat fee, not a percentage?

Mr. BOYNOFF. Indeed. Most of us use the same approach for the private patients and insurance patients, so there is no personal income involved in selecting a less expensive product.

The cheaper drugs are not a threat to the pharmacists' income. Historically, when it was illegal it did, and manufacturers generated a lot of antisubstitution support from pharmacists just on the basis of that, but the proviso of our law in California is that the difference in cost between the prescribed brand name drug and the nonbranded generic, if selected, must be passed through.

The difference in wholesale costs are the patients' money and I strongly feel is reasonable. So I must say those few patients receiving

propoxyphene in my pharmacy receive it at much less than Lilly's wholesale cost, let alone the addition of my fee.

I would like to conclude by stating that I do not really feel that toxicity, that suicides, that misuses are really that important to the entire argument surrounding propoxyphene. I just think it is no darn good.

Senator NELSON. Thank you very much for your very thoughtful testimony. I appreciate it. I do not need to ask you to comment on Dr. Moertel's statement because you just did.

Mr. BOYNOFF. I think I just agreed.

Senator NELSON. I want to thank you all very much for taking the time to come here and present your very useful testimony on the issue on which we are conducting the hearings.

We will continue these hearings on Monday, February 5 at 10 a.m., in this room, 5110 Dirksen Office Building.

Thank you very much.

[Whereupon at 12:30 p.m., the committee recessed, to reconvene at 10 a.m. Monday, February 5, 1979.]

[The prepared statement of Mr. Boynoff follows:]

Mr. Chairman, members of the committee; I am Morris Boynoff, a community pharmacist practicing in Mendocino, California. I shall attempt to convey to you observations on propoxyphene as seen from a pharmacist's frame of reference.

My practice is located in a small, isolated coastal village 175 miles north of San Francisco. The health care community consists of twelve physicians, three dentists and two nurse practitioners. I am the only pharmacist, and because I am unwilling to diffuse my time and energy into activities not related to health matters, my pharmacy is modeled in the pattern of an office, rather than a retail store.

In the nine years I have been in Mendocino, I have been repeatedly impressed by the time spent by all practitioners attending conferences, seminars and other educational meetings in their constant efforts to remain abreast of new developments. My day to day contacts with them, the information they seek from me concerning drug actions and interactions, and their obvious concerns involved inselecting safe, effective medications for their patients allows me to exercise more decision-making judgments than most community pharmacists.

On one point we are all agreed: Propoxyphene is not a significantly useful drug.

Recalling the enthusiasm with which it was greeted when introduced as "a non-narcotic effective analgesic," it received wide use. With more and more experience, however, its limitations were perceived by many prescribers, and I find that I dispense very few propoxyphene-containing products. It seems to to be viewed as a "probably ineffectual" drug, prescribed only when discomfor seems mild and use of opiates unwarranted. Its infrequent use suggests to me that it is chosen to fulfill patient expectations in conditions judged to be self-limiting. The fact that it is almost always ordered as a mixture containing other analgesics also conveys the silent message that little trust is put in the inherent capacity of propoxyphene alone.

Another clue to a commonly held view relative to the usefulness of the drug is the fact that it has never been admitted to our Medi-Cal (Medicaid) formulary. At first it seemed to be barred because of high cost. But even with propoxyphene products now available from multiple sources at greatly reduced prices, the Medi-Cal drug advisory committee has still not added it to the formulary.

As patents on drug molecules expire, my search for reliable sources of supply at competitive costs begins. The continuing allegations made by major manufacturers that less expensive brands are not therapeutically equivalent have encouraged FDA to require bioavailability studies for many products. When results of such studies are presented, the pharmacist can make reasonable choices. Published data, combined with experience in my practice have resulted in my exclusive use of non-branded propoxyphene products.

Basic to the entire controversy surrounding this drug is our inability to measure pain. In articles attempting to quantify results, descriptive terms, not measurements, are the norm. Even in double-blind crossover studies on pain relief, results must still be based on subjective observations such as asking patients how they feel. In the face of such a totally personal phenomenon as pain, the elements of imprecision are built into all studies. Complicating the problem is the matter of confusing advertisements and promotional materials.

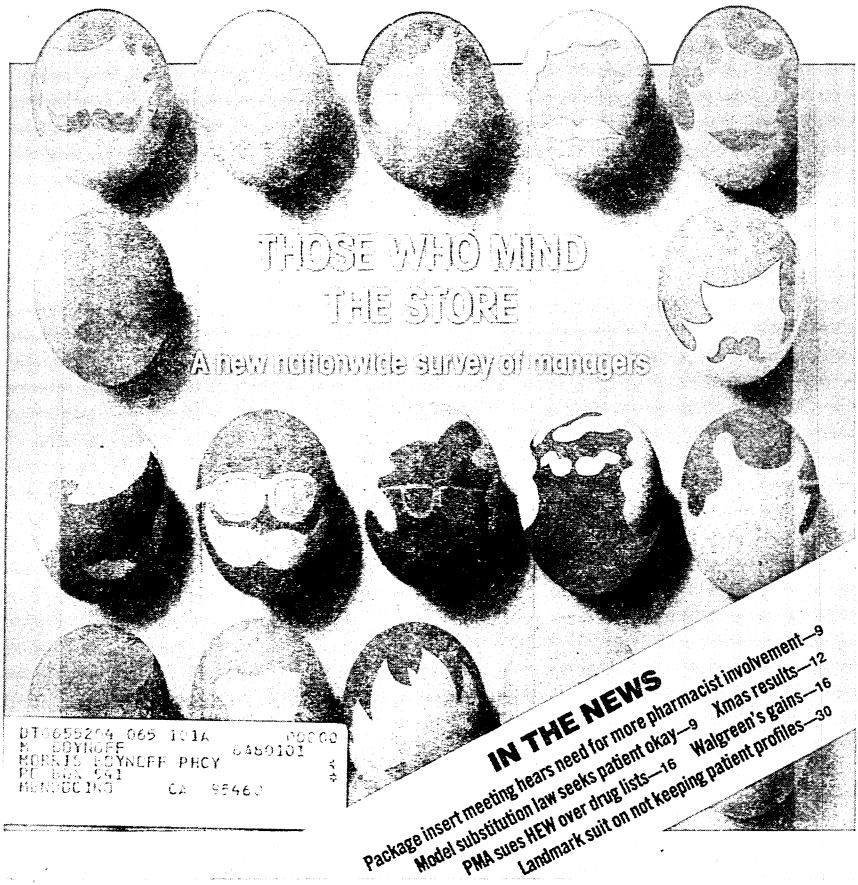
A prime example of such a tactic was a letter sent to physicians and pharmacists by Lilly following publication of a review article on analgesics in the New England Journal of Medicine. In their letter the drug firm objecting to the author of the article placing propoxyphene in the category of minor pain relievers along with aspirin and acetaminophen. This letter then cited other literature in which propoxyphene was described as an effective agent. A month or so later another letter was sent, stating that with the knowledge of FDA they were writing to call our attention to the fact that the articles cited in their previous letter really referred to propoxyphene compound rather than to plain propoxyphene!

Even though the drug was placed in Schedule IV of the Comprehensive Drug Abuse Prevention and Control Act of 1970, little effect has been noted on its frequency of use. To the pharmacist it has merely meant that after five authorized refills or after a six month period, a new prescription order must be generated. The net result has been an increase in the number of times a physician's office must be contacted and no visible diminution in the amount of propoxyphene used.

I cannot conceive of this controversy continuing for so prolonged a period were it not for the economics involved. Prices range from a low of under $15 per 1,000 capsules of propoxyphene compound 65mg. from Rugby Laboratories to a high of $80 for Darvon Compound-65, just increased from $76 this month. Between these two extremes, other prestigious firms such as Parke-Davis, Lederle and Smith-Kline price their offerings in the $24 to $30 range. To a large degree, I feel strongly that we are once again viewing the unwillingness of drug manufacturers to simply allow the merit of a product to determine its use.

I would like to conclude with a report of a "survey" I conducted among all the practitioners in my community. When informed of the petition asking the Food and Drug Administration to withdraw propoxyphene's certification as an analgesic, each respondent made the same observation: I can certainly get along without it.

Drug Topics
JANUARY 15 1979
the twice monthly news magazine





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*Hopkinson, J.H. et al: "Effective Pain Relief: Comparative Results With Acetaminophen In A New Dose Formulation, Propoxyphene Napsylate-Acetaminophen Combination, And Placebo." Curr Therap. Res. 19:622-630, 1976. Smith, M.T. et al: "Acetaminophen Extra Strength Capsules Versus Propoxyphene Compound-65 Versus Placebo: A Double-blind Study of Effectiveness And Safety." Curr. Therap. Res. 17:452-459, 1975. The kind and amount of analgesic (acetaminophen) employed in the tests are the same as that contained in two tablets of Datril 500.

Try Datril 500. From Bristol-Myers.

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

MONDAY, FEBRUARY 5, 1978

U.S. SENATE,
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The committee met, pursuant to call, at 10:05 a.m., in room 5110, Dirksen Senate Office Building, Hon. Gaylord Nelson, chairman, presiding.

Present: Senators Nelson, Baucus, Levin, Weicker, Hatch, Hayakawa, and Boschwitz.

Also present: Gerald D. Sturges, professional staff member; Stanley A. Twardy, Jr., minority counsel; and Judith K. Hillegonds, staff assistant.

Senator NELSON. Our first witness this morning will be Donald Kennedy, Commissioner of Food and Drugs accompanied by J. Richard Crout, Director, Bureau of Drugs and Richard Cooper, Chief Counsel, Food and Drug Administration.

Commissioner, we have your statement. You may proceed to present it as you desire.

STATEMENT OF HON. DONALD KENNEDY, PH. D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY RICHARD COOPER, CHIEF COUNSEL, FDA; AND J. RICHARD CROUT, DIRECTOR, BUREAU OF DRUGS, FDA

Commissioner KENNEDY. Thank you very much, Mr. Chairman. I am glad to have the opportunity to discuss our activity with respect to propoxyphene.

Although previous actions by both FDA and the Drug Enforcement Administration have had an important impact on the labeling and use of these drugs, the abuse and misuse of propoxyphene is nonetheless a genuine problem.

Senator NELSON. May I ask a question at this point? I have a copy marked "draft" and then you have another one. Are they significantly changed in any respect? I have marked up the copy marked "draft."

Commissioner KENNEDY. I would say that the changes are not extensive, Mr. Chairman, although I do not regard them as insignificant either. I think you will be able to follow just fine on your draft copy except for one or two places, but I would rather be held to the final version if that is all right.

Senator NELSON. I assume the changes were significant or you would not have bothered to make them.

Commissioner KENNEDY. Correct, sir. Thank you. Darvon, generically propoxyphene hydrochloride and combinations with aspirin, phenacetin, and caffeine, known as Darvon Compound, Darvon Compound 65, were first marketed in 1957 by the Eli Lilly & Co. after approval on the basis of safety alone.

After passage of the Drug Amendments of 1962, a panel of experts established by the National Academy of Sciences National Research Council reviewed propoxyphene products and concluded they were effective for the relief of pain. This group of drugs was then approved for effectiveness by FDA in 1969.

Senator NELSON. May I ask a question? You say "reviewed propoxyphene products." You are referring in that case to the combinations with acetaminophen and APC, as well as propoxyphene alone?

Commissioner KENNEDY. Only Darvon at that time and Darvon Compound and Darvon Compound 65. The new propoxyphene products containing the hapsylate salt of propoxyphene rather than the hydrochloride either alone or in combination with acetaminophen (Darvocet-N), (Darvon-N) or aspirin (Darvon-N with ASA) were approved and marketed in 1972. The term propoxyphene products, plural, refers to just propoxyphene in various dosages and terms.

Senator NELSON. Were these conclusions of the NRC based upon double-blind studies or review of the literature?

Commissioner KENNEDY. They were based entirely on review of the literature at the time. The NRC committees did no new studies of their own.

Senator NELSON. But they did review a good many of the drugs required to produce controlled studies to prove efficacy. You are saying they did not in this case?

Commissioner KENNEDY. That is right, they did not.

Senator NELSON. But in many drugs you have required that.

Commissioner KENNEDY. Yes; that is correct. For many years, propoxyphene-containing products have been among the most frequently prescribed prescription drugs in the United States.

I am putting up a chart for people who cannot see the chart in my statement so they can look at appendix A. Both the chart and the appendix show the number of outpatient prescriptions totaling over 39 million annually in those years, since 1964.

Products containing propoxyphene peaked in popularity from 1973 to 1975 with retail prescriptions totaling over 39 million annually in those years. While the total number of prescriptions has dropped to some 31 million for 1978, based on the projection of 9 months data, propoxyphene products are still very popular.

You will see that Darvocet-N, the napsylate compound ranked 12 and Darvon itself 93 and there is a point to be made about that just in passing. Something like 80 percent of the propoxyphene used out there is used in its various combination forms with aspirin, acetaminophen and whatever and when we are talking about use in the real world, we are talking primarily about combination use.

Senator NELSON. This is what I wanted to clarify for the record. Your chart shows the ranking of these four; three of them in combi-

nation and one of them propoxyphene alone, so they are ranked among the first 200 most widely prescribed drugs. Is that correct?

Commissioner KENNEDY. That is correct.

Senator NELSON. And the first on your chart, Darvocet-N 50 and Darvocet-N 100, are combinations of propoxyphene and acetaminophen. Is that correct?

Commissioner KENNEDY. Darvocet-N occurs in a couple of combinations. That is one of the places in which your draft testimony has to be adjusted.

The first two entries for Darvocet-N were confusing because neither one alone—they should have been combined in establishing a ranking for napsylate compound and so if you would consult the chart on page 2 of the final version of our testimony I think that will clarify your question. That chart has three entries instead of four. It combines the entries for the Darvocet-N product and shows that together they ranked 12th and that rank is established primarily by the company product.

Senator NELSON. The Darvocet-N 50 and Darvocet-N 100 are simply combinations of propoxyphene and acetaminophen in different amounts, is that correct?

In other words, the Darvocet-N 100 must be a different combination of acetaminophen and propoxyphene than Darvocet-N 50, is that not so?

Commissioner KENNEDY. Well, it certainly is a different amount of Darvon, but let us just straighten this out, Mr. Chairman, because it is confusing working from two sets of testimony.

Senator NELSON. But just so the record is clear, you combine them in your chart, subsequent chart, as just Darvocet-N, and that, I take it, is simply a combination product in which the only two active ingredients are propoxyphene and acetaminophen.

Commissioner KENNEDY. It is different amounts of propoxyphene but it is a combination product.

Senator NELSON. Then your other one, Darvon compound-65 is propoxyphene with APC—aspirin, plenacetin, and caffeine?

Commissioner KENNEDY. Yes.

Senator NELSON. Just one more thing for clarification because I did not see it in your original written statement, but I think you did testify to it. Do you say that 80 percent of all Darvon, or all propoxyphene sold, is in combination with either codeine, acetaminophen, or aspirin?

Commissioner KENNEDY. Not codeine.

Senator NELSON. No codeine combination at all? Some of the double-blind tests include it.

Commissioner KENNEDY. I do not believe there is any codeine combination at all.

Senator NELSON. Some of the double-blind tests had them in combination, I think.

Commissioner KENNEDY. That is correct, for the purpose of conducting studies there may have been combinations given but I do not know of a marketed combination.

Senator NELSON. In the marketplace, 80 percent of the propoxyphene sold is in combination with either aspirin or acetaminophen?

Commissioner KENNEDY. Yes; that is approximately correct with one reservation. Recall that we are talking here about patient prescriptions. The index we are reporting here is an index based on retail pharmacy sales. There obviously is an additional amount of use in hospitals. That use might tilt the statistics a little bit but I think not very much.

Now, as I mentioned NAS–NRC reviewed propoxyphene products for efficacy in the late 1960's. The chairman of the NAS–NRC Drug Efficacy Study Group Panel on Drugs for Relief of Pain was Louis Lasagna, an expert in the field of clinical pharmacology and analgesia.

A 1966 article review by William T. Beaver, another expert in the field of analgesia, concluded the following:

> In summary dextropropoxyphene is a mild oral analgesic which has proven superior to placebo in doses of 65 milligrams but which is of questionable efficacy in doses less than 65 milligrams. The drug is definitely less potent than codeine, the best availalbe estimates of the relative potency of the two drugs indicating that dextropropoxyphene is approximately one-half to two-thirds as potent as the latter drug. Likewise, dextropropoxyphene in 32-milligram to 65-milligram doses is certainly no more, and possibly less effective than the usually used doses of aspirin or APC.

FDA announced the results of the DESI review in 1969. The announcement described the indications for which the drugs were deemed effective—for the relief of mild to moderate pain.

Reservations about the efficacy of propoxyphene continued to be expressed during the 1970's. For example, R. R. Miller and associates in 1970 reviewed all available double-blind studies of propoxyphene and concluded that "* * * It is no more effective than aspirin or codeine and may even be inferior to these analgesics."

C. G. Moertel and associates in a 1972 double-blind study of single doses of propoxyphene, aspirin, and other oral analgesics in patients with cancer, were unable to show that even 65 milligrams of propoxyphene was significantly superior to placebo. In this study, aspirin was the most effective analgesic tested.

R. R. Miller in a second review in 1977 concluded that propoxyphene was no more effective than placebo in three studies, whereas in five others propoxyphene was not more effective than other analgesics.

On the other hand, Sunshine and others, in a 1978 study, found propoxyphene napsylate at 200 milligrams, twice the recommended dose, to be significantly better than placebo. The lowest dose used—50 milligrams—was only slightly better than placebo but the usual dose of 100 milligrams was not tested.

Mr. Chairman, in your letter of invitation you asked me to comment on the reasons for the sustained popularity of propoxyphene as an analgesic in view of its limited effectiveness. The answer to this question is complex and involves a number of factors.

First, I think it is important to point out a significant number of people—typically 30 to 35 percent—in clinical trials on analgesics obtain pain relief from placebo.

Recent research suggests that this placebo response is due to activation within the brain of the same neural receptors that are affected by narcotics. The pain relief obtained is just as real, and may be just as great in many instances, as that provided by drugs. The placebo response may be enhanced by encouragement from the prescribing physician. Thus, any prescription analgesic is likely to offer pain

relief to the many people who tend to be placebo responders—even if its inherent effectiveness is minimal.

I think Dr. Beaver in his testimony before you last week, at least as it was reported to us, gave a very thoughtful account of this part of the problem.

Senator BOSCHWITZ. Dr. Beaver in his testimony last week gave us a great deal of what you are giving us now. Perhaps, in the interest of time, you could summarize his conclusions and go on to new material. Many of us have other meetings to go to and time is of the essence.

Commissioner KENNEDY. Well, I understand that, Senator, and I will be glad to move through as quickly as I can. Perhaps then I will delete my attention to the questions that I was asked by your chairman about propoxyphene's popularity by saying that there were a number of reasons why physicians particularly at the time of its introduction chose to precribe it. It is of relatively short term effect; its utility in patients who for reasons of gastric problems, liability to liver damage, cannot take large amounts of aspirin or acetaminophen, and so forth. During the past 4 years, a number of prescriptions were written annually for the propoxyphene product has declined.

Senator NELSON. Where are you now?

Commissioner KENNEDY. I am sorry, I am at the bottom of page 6, Mr. Chairman.

Senator NELSON. I wish you would go back to your item 4 on page 6 starting, "propoxyphene * * *".

Commissioner KENNEDY. Yes; I was pointing out as Dr. Beaver had and did not want to bore you with it, that propoxyphene has been marketed in an array of dosage forms, combinations, and salts that offer physicians a wide variety of options for managing patients with painful disorders; combinations that do not work on one patient may be switched to another. One supposes that this is useful to the physician and to the patient, not only because the exploration may yield a compound that is more physiologically active, but also prospectively the patient feels more attended to and it is possible that placebo response is maybe mobilized by the switch.

Senator NELSON. Well, these comments, and your sentence on page 7 under "Safety of Propoxyphene," state that as compared with other prescription analgesics, the adverse reactions, the side effects, associated with propoxyphene are mild and infrequent.

Dr. Moertel did studies that you are familiar with and I would like to make some reference to his testimony, so that you may want to comment.

Dr. Moertel states in his testimony of the double-blind studies that he did at the Mayo Clinic:

> Darvon showed some advantage over sugar pills but this was small and not statistically significant—that is, the difference could easily have occurred by accident. Acetaminophen or APAP—commonly marketed as Tylenol or Datril—showed a much more substantial degree of relief; and surprisingly, leading the pack, two simple aspirin tablets. The superiority of aspirin over Darvon was statistically significant * * *

Now, in his double-blind studies he has the sentence on page 3 of his testimony:

> The addition of a full dose of Darvon to aspirin, however, provided essentially no improvement in pain relief.

So Darvon standing alone was, at best, a weak analgesic with some advantage over sugar pills. Aspirin with a full dose of Darvon in his double-blind studies provided essentially no improvement in pain relief.

Now, if the argument of those who advocate the use of Darvon or prescribe it is that they are prescribing it because their patient is allergic to aspirin or acetaminophen, I suppose it might be a justifiable reason. But about 80 percent of what they are prescribing is propoxyphene with aspirin anyway, so for all of those prescriptions the argument about allergy or gastrointestinal bleeding certainly makes no sense.

Commissioner KENNEDY. That is correct.

Senator NELSON. Now, if these studies by Dr. Moertel are correct that Darvon added to aspirin has no additional significant effect why does not the FDA prohibit the combination?

Moertel's studies indicate that adding Darvon to aspirin does not increase effectiveness. Why then permit the patient to be exposed to an additional drug with the side effects it has if, in fact, it is not additive or synergistic in combination?

Commissioner KENNEDY. Let me say two things in response to that, Mr. Chairman.

First, the Moertel study was the only one available, or if all studies on this point agreed, we would not be in difficulty but as I tried to indicate in my testimony the results of controlled clinical trial on the effect of analgesics are plagued with inconsistency between trial and it is a very difficult matter to decide.

Senator NELSON. There may very well be studies I have never heard of, but in the testimony and in the literature and in the references I have looked at from the hearings we had 8 years ago, and in the testimony thus far, I do not see any double-blind studies that show that Darvon added to aspirin is more effective than aspirin alone.

Have I missed any?

Commissioner KENNEDY. Well, we will review those studies. I do not know of any specifically, Senator Nelson. The point I was trying to make rather is that studies on Darvon compound alone and on Darvon in various combinations it comes out differently in terms of its relative efficacy in different people's hands.

Moertel's studies only covered cancer patients. For example, one might expect differences between that type of study done on patients with other sorts of pain.

My point is not that there is evidence that this particular compound is more effective than either ingredient alone, but that there is a lot of ambiguity in clinical trials in this whole area and I was going to go on and say that FDA is going to review the evidence on these products over the next year.

It may very well be that we will find that some of the combinations are not effective, but it will be a difficult business to sort out.

Senator NELSON. But the FDA has taken a very correct and strong stand on the 1962 amendments, which require proof of efficacy based on well-controlled scientific studies. Everybody who has testified and who is an expert in this field, of course, has said there is a great deal of subjectivity in judging pain relief.

Both you and Dr. Beaver have addressed the question of the placebo effect, which may be based on a physiological response because of encouragement from the doctor and the fact the patient got a pill. However, in order to allow this drug to be on the market or remain on the market, does not the law require you to come up with well-controlled studies that would show that, in combination, propoxyphene and aspirin are more effective than either one alone?

The law is fairly clear. It requires the positive proof of well-controlled studies to support the introduction of a drug in the marketplace. You have been very strong in that position on the combination antibiotics, requiring proof or ordering them off the market. Are they all off now?

Commissioner KENNEDY. Almost.

Senator NELSON. So my query is: How do you justify under the statute—which requires well-controlled studies—the presence in the marketplace of a combination of active ingredients for which there appears no scientifically controlled studies that prove it is more effective?

I may be wrong. Maybe there are studies out there. But in all the literature I have looked at, I have not noticed one well-controlled study that would prove that it is more effective in combination than standing alone.

Commissioner KENNEDY. Well, clearly at the time that the combination products were introduced and at the time that we did our review, the NAS–NRC Committee and our reviewers found the evidence at that time persuasive enough to allow the marketing of these compounds.

It often happens, Mr. Chairman, that as time goes on and evidence from clinical trials on already marketed drugs accumulate, that we have to change our minds and that is why I am telling you that there is going to be a careful review of the effectiveness as well as the safety of these products and that it might very well result both in large changes or in consideration of withdrawal of those of the combination product.

You are quite right in your assertions what our policy was.

Senator NELSON. I am sure you understand very well that once a drug is in the marketplace and being used by hundreds of thousands or millions of people, all kinds of reactions that were not anticipated, due to limited, controlled studies, are disclosed almost inevitably over a period of time. And I recognize this drug was in the marketplace in combination before the efficacy amendments of 1962, is that not correct?

Commissioner KENNEDY. Some of its combinations were.

Senator NELSON. However, if a new drug application (NDA) were before you now, would you require well-controlled studies demonstrating that in combination the drug was more effective than it was as a medicine administered alone before you would permit it to go into the marketplace?

Commissioner KENNEDY. Yes, sir.

Senator NELSON. Are you aware of any well-controlled studies as of this date that would support it going into the marketplace as a combination product if the application were currently pending?

Commissioner KENNEDY. Let me give you a very specific answer. I know of no studies that could be used for the justification of 65 milligrams of Darvon, plus 200 of aspirin; that is studies adequate to demonstrate controlled clinical trials, that that combination of ingredients is superior to either ingredient at that dosage level and that is what we would consider necessary to demonstrate, to allow the marketing of a combination.

Senator NELSON. Have there been any studies that identify a specific target population for propoxyphene alone?

Commissioner KENNEDY. That is a specific target population that cannot be benefited by other combinations of analgesics, or a single analgesic but needs propoxyphene alone?

Senator NELSON. Yes

Commissioner KENNEDY. No, there is no such study.

Senator NELSON. It is interesting to note the widespread use of Darvon, either as a single entity or in combination form, and then read the literature that argues in support of the idea of using it because some people have a reaction to aspirin or acetaminophen or codeine. Yet it would appear from talking with physicians and listening to people comment that it is very common to prescribe Darvon in combination as the drug of choice for mild analgesia without first identifying a patient for whom it would be preferred.

Is propoxyphene so far as you know the drug of first choice as a mild analgesic without previously identifying a specific indication for it?

Commissioner KENNEDY. Well Senator, that is a question about actual prescribing practice that I just do not feel equipped to answer. I will say this, if you just look at the prescribing behavior out there and note that 80 percent of it is for the drug in combination with one of those other two on the analgesic ingredient list you cannot make much of a case that it is being restricted to patients who cannot take aspirin or acetaminophen because most of the Darvon being prescribed is being prescribed in combination with those drugs.

As to the 20 percent of the Darvon being prescribed by itself, I have no idea in what proportion of those cases physicians seek first to ascertain whether the patient has a gastric ulcer, history of liver disease, or whatever would make that patient ineligible for receiving that medication. I just do not know.

Senator NELSON. Go ahead.

Commissioner KENNEDY. I had several points to make, Mr. Chairman, about safety and if it is satisfactory to you I will move through the material on pages 7 and 8, but not cover every paragraph.

Senator NELSON. Your statement submitted today will be printed in full in the record and you may present it in any way you desire.

Commissioner KENNEDY. Yes. We had some dialog a moment ago about the statement that compared with other prescriptions, the side effects of propoxyphene is mild and infrequent and that is quite independent from the problems we are going to be mentioning in a little while.

The drug abuse potential of propoxyphene was recognized as early as the late 1950's but was not a major public concern until the late 1960's and early 1970's.

Chronic propoxyphene use sometimes results in physical and psychological dependence of a type similar in nature but not degree, to that produced by morphine. Intravenous "street" use by drug addicts was popular in the late 1960's but waned, particularly because of its ability to cause vascular and other tissue destruction, and because of formulation changes in the product.

This pattern of abuse resulted in overdose deaths that resembled those seen with heroin and methadone, for example, respiratory depression and pulmonary edema.

As a result of these problems, DEA placed it under schedule IV of the Controlled Substances Act (CSA) in 1977.

Our analysis of the available data on propoxyphene fatalities shows that the majority of associated deaths occurred because of deliberate overuse or abuse, as shown in the two tables in appendix B. Propoxyphene is one of the most frequently used drugs in suicides and suicide gestures; in absolute incidents it follows only the barbiturates and nonbarbiturate sedative-hypnotics in associations with drug-induced suicide. However, when viewed in relation to the number of prescriptions issued, the relative number of deaths from propoxyphene is lower than that for a number of other drugs.

We know of no cases at present in which death was caused by propoxyphene products alone when taken in customary doses and in which neither alcohol nor tranquilizers were also involved.

There are, however, a number of "accidental" deaths which have apparently occurred as a result of the consumption of propoxyphene in quantities smaller than those used in suicide, yet still in excess of recommended therapeutic dosage and usually combined with alcohol and/or tranquilizers.

Mr. Chairman, let me emphasize that mentioned in this chart, combinations of agents are often involved in these deaths. There is no implication because propoxyphene is mentioned in a coroner's report or in an emergency room report that it is, in fact, the cause of death. It may be a participant in a combination death or might, indeed, have little or nothing to do with it.

Senator NELSON. In the testimony last week, one of the witnesses made the point that many laboratories across the country lack the ability to detect and measure the presence of propoxyphene in the blood with accuracy at either low or lethal concentrations. The witness said that means many cases of propoxyphene overdose are probably missed. Where the drug is established as a cause of death, there is the question of classifying the death as accidental or suicidal or, failing such judgments, as undetermined.

However, the forensic pathologist from Oregon took a view that was opposite from yours and several other witnesses who had said it was the intentional overdose that was causing deaths; people intending to commit suicide. He took an opposite view, that that was not the case. He thought well over 50 percent were accidental.

Are you familiar with his testimony on that point?

Commissioner KENNEDY. Yes; in a general way I am, Senator Nelson.

At the risk of responding at tedious length, let me begin by saying it is not an easy problem. First of all, the measurement of blood pro-

poxyphene is not one that everybody knows how to do very well and you find a good deal of laboratory inconsistency in that measurement.

Second, I recall all the data we have on associations with death comes from something called the Drug Abuse Warning Network (DAWN) which gets a coroner's report from 23 or 24 cities in the United States. It covers a significant portion of the United States population between one-third and one-half or I think it is 40 percent, but not all of it and you have to ask two different questions—first, are the DAWN reported deaths correct due to accident suicide and so on and do they reflect, albeit, what the pattern of national deaths really is, and that is not easy to tell either.

The testimony you have heard from Oregon and to a degree from San Francisco essentially proposes that there are deaths that go unrecorded in most places, hence are not a significant part of the DAWN data which result primarily from nonoverdose deaths, although they may be combination abuse deaths in some sense; a moderate number of Darvon pills combined with alcohol or perhaps with ordinary dosages of tranquilizers but not abusers in the sense that a grossly excessive dose was taken and so forth. That is a hypothesis that is difficult to evaluate. It has to be taken seriously.

You heard from Dr. Wolfe about nor-propoxyphene and its lifetime compared with propoxyphene and you heard him propose from some animal data he has shared with us that there is progressive heart block associated with the accumulated nor-propoxyphene that can be generated in the system as a consequence of ordinary repeated use, day-by-day, coupled perhaps with a slight overdose and with a few drinks, or whatever else.

That is a possibility, Senator, that is very difficult to evaluate at this time. I think the fairest thing we can say at the moment is that the DAWN deaths, the ones that are reported in generating these numbers are in overwhelming majority suicides or massive large accidental overdoses, but that there is still an unevaluated possibility that there is a large set of deaths out there in the world that we are not measuring that is much more accidental in character and that relates to this different action of propoxyphene on which the animal data are just beginning to give us an indication. That is something we are going to be looking at. We take it very seriously, but I think it is still difficult to evaluate at this time.

Senator NELSON. I raise it because it is a viewpoint not uncommonly expressed. As a forensic pathologist, he was looking at the end result and made the point that in many of these cases, if it were a suicide, you would expect to find a whole lot of propoxyphene in the stomach and it was not there. I would not want to go on further to say what he said, since the record speaks better for itself than I can, but I think it is worth looking at his conclusions. Having looked at people who died and have found propoxyphene involved one way or the other, he checked cities that had a good toxicology system and pathologist available to do appropriate studies and he did an extrapolation from that to reach his conclusion.

I have no qualification to judge his methodology or conclusions or anything else, but it did seem to me—since he was taking a position

different from the other witnesses and from most of what else I have read—that it would be worthwhile taking a look at his testimony and the methodology he used in reaching his conclusion.

Commissioner KENNEDY We certainly will examine that testimony when we obtain the transcript if only for the purpose of correcting the record on the point of his correspondence with the Food and Drug Administration Mr. Chairman, which hurt me a little because we were not really casual with his mail as he said we were.

Senator NELSON. Maybe the Post Office was at fault.

Commissioner KENNEDY No, no, he forgets the answers.

I would like to make one more point about the pattern of deaths, but first one thing that you said in your comments, Mr. Chairman.

There is something else about west coast data and that is although it pains me a bit to say so, suicide is more frequent on the west coast than it is on the east coast.

If you look at the large cities that report out DAWN data, the big leaders in suicides are all out there—San Francisco, Seattle, Portland, Los Angeles are all cities in which the suicide rates are higher than they are in eastern cities and the differences are significant—60 percent.

Anybody extrapolating accidental or intentional death data from there is going through an entire population, may be extrapolating from figures that are different from the ones that somebody on this coast would use.

Senator NELSON. But on that point, I do not know that he listed the cities he samples, but if in fact he was using west coast cities then that would support his testimony, since he concluded the largest percentage was accidental and not suicides.

Commissioner KENNEDY. Not arguing with his testimony. Mr. Chairman, just making a point that if one tries to go from DAWN data to estimates of death for the entire Nation which I took it he was doing, that is when he gave you the 3,000 or 4,000 figure, there is a reason quite independent of accidental deaths why somebody from the Pacific coast would give you 3,000 and somebody from the Atlantic coast would give you 1,600 or 2,000, that is all. It has to be factored in.

Senator NELSON. I do not know what cities he used, and I do not want to try to judge from his testimony anyway. He was, however, not coming up with statistics that supported the proposition that most of the deaths were intentional. He was coming up with statistics that argued otherwise.

Commissioner KENNEDY. I understand. There is another point about the distribution of deaths from the DAWN data and again, let me emphasize they are from the DAWN data and that has to do with an analysis by age groups and I think, Mr. Chairman, since we have covered most of the material before here in our colloquy I will move to the middle of page 9 and make two points about physicians and deaths.

Here, you have been given an age distribution both of which mention are note quite the same as prescriptions written but almost the same; that is, there are mentions by physicians of having arranged that a patient get a drug, whether they are actual prescriptions written or by the patient being told to refill or to take more, but they would be approximately proportional to the prescriptions.

As you can see from the chart, there are a large number of these products supplied to people over 60. Indeed, 33 percent of all the prescriptions written for Darvon and Darvon-containing products are written for the portion of our population over 60 years old.

Another third are written, you see there, that other high point is for another third or so of those prescriptions that are written for people in the age group 20 to 40.

Now, it is in the younger fraction of this age group that most of the deaths occur at a mean age of 25. Actually, that point represents the age intervals between 20 and 30 and there is another 22 percent or so of those deaths in that next point which represents the age range 30 to 40.

Now, you add those together so that you cover that 33⅓ percent of the prescriptions that are written for the entire age range 20 to 40 and you discover that over 52 percent of the deaths fall into that age group and yet, the people over 60 who account for an equal fraction of the prescriptions are only accounting for 8 percent of the deaths.

In other words, if I may be permitted a little liberty for the sake of description the young adults and people over 60 are equally likely to take a Darvon, but the people over 60 are only one-fifth as likely to do themselves damage as a consequence of that.

I would think that ultimately the public policy solution that we apply to this problem has to take account of the fact that the risks and benefits associated with the use of these products at least as we judge the risks (from the DAWN data) which are distributed very unevenly through our population.

Let me just summarize if I may, Mr. Chairman, the actions that FDA has taken over the past several years in response to problems associated with these issues regarding the efficacy and safety of propoxyphene products.

In 1972, because of misleading statements on the effectiveness of Darvon made to physicians in a letter from Eli Lilly & Co., we required the manufacturer to issue a "dear doctor" letter stating:

> There is no substantial evidence to demonstrate that 65 milligrams of Darvon is more effective than 650 milligrams of aspirin—two 5-grain tablets—and the preponderance of evidence indicates that it may be somewhat less effective.

In April 1976, FDA's Controlled Substances Advisory Committee recommended that propoxyphene and its salts and preparations be controlled in schedule IV of the CSA and as pointed out earlier, the DEA adopted that recommendation a year later.

Labeling for propoxyphene was further revised in 1978 to add a warning against the additive depressant effect of the products when used in conjunction with alcohol, tranquilizers, sedative hypnotics, and other central nervous system depressants, and to require additional information on adverse reactions, drug interactions, and management of overdosage. A warning against use of the products during pregnancy was also added because of the danger of causing addiction in the fetus and producing a neonatal withdrawal syndrome. That is a problem with any member of the narcotic family of drugs.

Now finally, I will just point out what you know very well that on November 22, 1978, the Secretary of the Department of Health, Education, and Welfare was petitioned by the Health Research Group to

suspend approval of the NDA's for propoxyphene-containing products under section 505(e) of the Federal Food, Drug, and Cosmetic Act on the grounds that the continued marketing of these drugs represents an imminent hazard to the public health.

HRG requested alternatively that if the Secretary did not suspend, he support HRG's petition to DEA that propoxyphene be rescheduled as a schedule II narcotic under the Controlled Substances Act.

FDA's Bureau of Drugs is conducting a new review of all data bearing on the safety and effectiveness of propoxyphene including those studies referenced in the HRG petition.

In summary, Mr. Chairman, the current status of propoxyphene presents us with an important and complex regulatory problem. The problems associated with its misuse are indeed troubling; but they must be weighed against significant benefits from the drug.

Propoxyphene is widely used; it provides pain relief for many people. Although it is not a powerful analgesic, it has advantages for persons who cannot tolerate aspirin or acetaminophen. It is prescribed and administered or dispensed in a special medical setting that provides significant psychological amplification of its effects. I am sorry that we cannot offer you a more definitive conclusion at this time. But we are still developing our analysis, Mr. Chairman. These hearings have helped materially in that regard, as well as drawing public attention to a disturbing abuse problem. We will continue to give the matter close scrutiny.

Senator NELSON. When you are saying propoxyphene, are you talking about propoxyphene alone?

Commissioner KENNEDY. Propoxyphene in the totality of its dosage forms and its pattern of distribution.

Senator NELSON. So that I do not forget it, I want to ask again—and you maybe are already reviewing the NRC studies of 1969, covered in your statement here: Is it your policy to continue to evaluate drugs, both prescription and over-the-counter, under the 1962 act? If so, will it be part of this review that you are now making to survey the literature to determine whether or not there is adequate proof of the efficacy—pursuant to the requirements of the statute—of combinations of propoxyphene and acetaminophen, propoxyphene and aspirin? If not, will you pursue the same course the FDA has pursued in the past of requiring companies to come up with controlled studies if, in fact, there is not adequate proof that the drug is effective? Will you require additional evidence to show that, in fact, it meets the statute?

Is that part of the procedure you are now going through?

Commissioner KENNEDY. Yes. We absolutely will review effectiveness information as well as safety information. The procedure for changing the marketing status of the drug is a little different for some of these combination products which are, in fact, post-1962 drugs and are not so-called drugs reviewed under the transitional provisions of the 1962 amendments, but that is a technical difference.

We can and will review the efficacy of the combination products as well as the single dosage.

Senator NELSON. But just a further question. If there are not adequate controlled studies to prove its efficacy in combination, are you or are you not required under the law to request that the studies be made?

Commissioner KENNEDY. Oh, yes, we could require studies.

Senator NELSON. I mean are you required or not?

Some combinations of this drug were on the market before 1962 and I have forgotten the grandfather clause provisions if, in fact, there are some as to efficacy. There were some as to safety.

As I recall it, when we had hearings maybe 3 years ago reviewing the progress of the FDA and the NRC under the requirements of the 1962 act, drugs were classified as effective, probably effective, and ineffective. Is that correct?

Commissioner KENNEDY. That is correct.

Senator NELSON. And if they were not identified as effective, the FDA was requiring evidence of effectiveness under the provisions of the statute. Is that correct?

Commissioner KENNEDY. Yes. Maybe I can help, Senator. I was not trying to put up any challenge to the requirement for adequate and well-controlled policy demonstrating effectiveness. It applies retroactively under the terms you describe under the efficacy statute and it applies to products afterward.

The only difference I was trying to call attention to was a technical difference—effective, probably effective, and not effective apply to those pre-1962 drugs that are treated under the transitional provisions of the law and drugs introduced post-1962, all have to meet that standard.

Some of the Darvon combination products are present and some are post-1962 but the central point is that they have to meet that standard on a continuing basis and if we approve a drug on a limited set of trials that appear to demonstrate effectiveness and then a much larger body of research comes in that challenges that initial conclusion and appears to put the weight of the evidence on the other side, we are obliged to take up the matter again and reevaluate that new drug application and begin withdrawal proceedings if the burden of the evidence shows they are not effective.

Senator NELSON. I guess that is what is confusing me and I apologize for not having relooked at the statute. It has been 2 or 3 years since we have had hearings on this.

What I am really saying is the literature that I have looked at, and it may not be all of it, of course, but, in Dr. Moertel's studies and others I can recall none that found propoxyphene in combination with aspirin was more effective than aspirin alone—that is, no adequate controlled studies to refute Moertel's studies or, more positively to demonstrate adequately that in combination they are more effective.

If that is the case, then is it not under the law the requirement of the FDA—based upon the simple evidence there is to the contrary—to say: It is not clear from adequately controlled studies that they are more effective in combination and therefore, we now request the company to produce the study to prove it and if they cannot, the combination should not be in the marketplace.

Am I stating that correctly?

Commissioner KENNEDY. You are absolutely correct.

Senator NELSON. And that is a procedure we will be following?

Commissioner KENNEDY. That is why we are doing the review. This review is being done to evaluate safety questions because that kind of

challenge to continued marketing could come either because we come to understand the risks are higher or because we come to understand that the benefits are lower and these questions have been raised on both sides with respect to these drugs and that is why we are examining them.

I only want to point out, Mr. Chairman, that an examination as far as efficacy is concerned is more difficult with these drug products than it is for most because of the confounding effect of the high rate of placebo response.

Everyone who has dealt with this kind of clinical trial knows it is a tough experiment to do and to interpret. That really makes our conclusion for us, Mr. Chairman. I think there is little more that I can say except that these hearings have helped materially, obviously, in bringing some of these problems to our attention.

We plan to use the record of the hearing as well as, of course, the reviews that we had underway in considering what to do next.

Senator NELSON. I have no more questions at the moment. I may have after reviewing the testimony, and if so, I will submit them and you can answer in writing for the record.

Commissioner KENNEDY. We will be delighted to do so.

Senator NELSON. Any questions?

Senator LEVIN. Thank you, Mr. Chairman.

I wonder if you could comment first of all on the several dozen effects of Darvon? Apparently, one of the offenses of its efficacy and now I am quoting the testimony is yet to come, but we had a similar bit of testimony last year about its great pain-relieving effects that come after several doses have been administered.

Can you comment on that, please?

Commissioner KENNEDY. I am not sure because I have not seen the testimony you are referring to, whether that means accumulative effect of several doses of a particular formulation or whether instead what is being referred to as its availability in a number of different dosage forms.

Senator LEVIN. Have you seen any studies involving either one of those two approaches where they are comparing several doses of Darvon and several doses of aspirin or codeine?

Commissioner KENNEDY. Not formally, although I believe that a number of physicians believe if they are able to use a number of dosage forms with a given patient that they have a higher probability of getting that patient on something that will work for him or her.

Senator LEVIN. Have you seen any studies comparing that?

Commissioner KENNEDY. No; no standardized studies.

Senator LEVIN. Pursuing the chairman's question for a minute, what were the efficacy standards in 1972 when the Darvon combination was marketed, the proof of efficacy when you added Darvon to aspirin and vice versa?

Commissioner KENNEDY. Adequate and well-controlled studies showing effectiveness.

Senator LEVIN. Of the combination over the single ingredient?

Commissioner KENNEDY. Well, I will have to take a moment for consultation. You see, the advantages over a single ingredient is not part of the law but its part of regulation as I understand it and I will have

to ask the Bureau whether at that time in history that standard was being applied to all combinations.

Senator LEVIN. I would like to pursue that line of questioning, Mr. Chairman, if I could.

Was that in the regulation?

Commissioner KENNEDY. Now, having refreshed my knowledge of history or rather gotten for the first time the information I can tell you.

In 1972 what happened, Senator, was that a new salt of Darvon, the napsylate was marketed. The Bureau's policy at the time was that a new salt, but with the same active ingredient all they needed to show is bio-availability. That is the same amount gets into the bloodstream in the same period of time so that as much active ingredient is mobilized and available to do what it is going to do. So the napsylate salt was approved in 1972 but without any new clinical trials.

The combinations of the napsylate salt with aspirin and acetaminophen were not new combinations; they were combinations of a new salt but they did not have to meet those clinical trials. In fact, the efficiency studies that supported the introduction of that new salt in 1972 were the same ones that had actually supported the efficacy review that had permitted the continued marketing of those combination products in 1969.

Senator LEVIN. In 1977 I understand that the propoxyphene was placed on schedule IV.

Commissioner KENNEDY. That is correct.

Senator LEVIN. Did the manufacturers in general, or the specific manufacturer of Darvon agree to that or opposed to the schedule?

Commissioner KENNEDY. They did not oppose it.

Senator LEVIN. Do you have the power to require the manufacturer of Darvon to put on the label the same thing that he was required to do in 1972 and that is to state in a letter to physicians at that time that there was no evidence to demonstrate that 65 milligrams is more effective than 650 milligrams of aspirin?

Commissioner KENNEDY. We probably could.

Senator LEVIN. Do you think it is appropriate to have that on the label?

Commissioner KENNEDY. We would have to support it convincingly and quite possibly convince a judge.

Senator LEVIN. Is that your standard proof, "convincingly"?

Commissioner KENNEDY. It is not our standard but quite frequently or not infrequently when we propose labeling changes that a drug's sponsor does not agree with us, or finds it unreasonable, we find ourselves litigating the matter.

Senator LEVIN. Is that the standard used by the courts have you found?

Commissioner KENNEDY. Well, I would think, in general, I think it has been our experience if we can show a court that the scientific evidence with regard to efficacy or safety is on the side of the statement that we are asking the manufacturer to make, that we win.

Senator LEVIN. In your opinion is that statement true that you require the manufacturer of Darvon to make?

Commissioner KENNEDY. The "Dear Doctor" letter, yes.

Senator LEVIN. You think you could carry that burden of proof in court?

Commissioner KENNEDY. I would suspect we could.

Senator LEVIN. Why do you not require it to be placed on the label in that event?

Commissioner KENNEDY. I would think that is something that would be considered as a part of the review that we are undertaking.

The labeling for doctors and its impact on what actually happens in the prescribing world is something else. It is not always clear that you have very much of an impact that way. I think that is sometimes why labeling changes are something that comes to mind is when effectiveness is at stake as opposed to safety. We find that box warnings with regard to safety labeling have some impact, although not as much as we would like.

Effectiveness, I think there is some doubt on our part there.

Senator LEVIN. Will you let us know the results of your consideration on that question?

Commissioner KENNEDY. We certainly will.[1]

Senator LEVIN. The last question I have has to do with your comments about significant benefits of the drug. We have not heard yet from the manufacturer, but based on your own testimony and based on the testimony of others, the reasons that you give for that conclusion is one that it was widely used.

I do not presume that leads to a conclusion that it has a significant benefit necessarily and the second part is that it provides pain relief for many people.

Do I understand you to say it has no greater pain relief than aspirin? Do you accept those studies or not?

Commissioner KENNEDY. Yes; I accept those studies but I think at the same time one has to be realistic. I think that a person who receives pain relief is experiencing the end point of a very complicated physiological process and I think the perception that a drug is helping is very often significant.

Senator LEVIN. That goes to your psychological implications, point four, but in terms of pain relief for many people you do accept the studies that say it is no greater, perhaps less than aspirin?

Commissioner KENNEDY. Yes.

Senator LEVIN. That does not lead to your conclusion does it, that it has a significant benefit?

Commissioner KENNEDY. Let me back off a minute and say that I think there might be a real difference in the real world situation there.

Remember, that what is really happening in the world is that Darvon and its combinations are being prescribed by a physician to somebody who is experiencing pain whereas the OTC analgesics are being pursued at the corner drug store or the physician is saying take two aspirin and call me in the morning.

There is a real difference between those two things and one cannot forget that this drug is not just a molecule; it is part of a therapeutic approach that is going on out there.

Senator LEVIN. That goes back to your physiological point again. That is point 4. Point 2 in terms it provides pain relief. You have stated you agree with the studies relative to aspirin.

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[1] See FDA drug bulletin of February-March 1979 following Commissioner Kennedy's prepared statement, page 16826.

Point 3, its advantages to people who cannot tolerate aspirin. There I presume at least 80 percent is used by people who cannot take aspirin.

Commissioner KENNEDY. That is correct.

Senator LEVIN. And you do not know whether the other 20 percent who take it alone can tolerate aspirin. Certainly, 20 percent take it for that purpose alone.

Commissioner KENNEDY. Very much less.

Senator LEVIN. Can you estimate what percent of the people who take Darvon get relief or can get relief from aspirin and can take aspirin?

Commissioner KENNEDY. You have moved us to the real world again and it is people who are taking Darvon in a particular therapy setting and asking them to change not only their drug but their behavior and I think that is a very difficult question to answer.

Senator LEVIN. From the studies, though, the objective studies putting aside the psychological implication questions, would you state it is over 80 percent putting aside the psychological aspects of having the prescribed drug instead of buying it at the supermarket counter?

Commissioner KENNEDY. Yes; if one were able to eliminate those entirely, perhaps over 90 percent.

Senator LEVIN. What it really comes down to is the biggest advantage of Darvon is that it is prescribed.

Commissioner KENNEDY. Well, there are some others. I mean compared with other things it really does, if used alone, have lower side effects and so forth, but I think if you take into account that 80 percent is prescribed in combination and so forth, then I would think a major advantage of it is that it is prescribed.

Senator LEVIN. Thank you.

Senator BAUCUS. No. 1, in listening to your testimony here the question arises in my mind is the degree to which you consider psychological amplification, I guess my point is—a drug which obviously does not safely test for some reasons has tremendous psychological implications. Do you weigh that or do you not weigh that?

Commissioner KENNEDY. I would be very unhappy to be in that position, Senator, but I fortunately think I never will be because the absolute essential property that the drug must have if it is to yield that kind of physiological amplification is if it is generally thought that the amplification is psychological instead of physiological. It is to be thought of as something else and I guess at the front end of an approval process, it would not occur to me I think to consider the psychological effect of a drug as an important part of the efficiency criteria given, however, that 35 million prescriptions a year are written for it and it is out there it seems to me that I would have to take that very much into account.

Senator BAUCUS. How do you measure psychological applications?

Commissioner KENNEDY. Well, you would experimentally get people to report their pain and to report their pain after having been given a physiological active analgesic and having been given something known not to contain any physiological active principal and then ask the question under circumstances where a certain percentage of people show placebo response, experience pain relief in response to placebo without some other kind of intervention and you then ask

the question, does a higher percentage of them show placebo responses when, for example, placebo is prescribed by a doctor, dispensed by a pharmacist, and so forth.

Specific studies to test that have not been done in this universe, but there is other evidence to suggest that the act of prescribing and the involvement of health professionals in the therapeutic setting do increase the probability that that response will occur.

We could supply the committee with studies to that effect.

Senator BAUCUS. If you would, please.[1]

My second general question has to do with the timing of your study. Will you give me some indication of your timetable, when you plan to complete the studies and make the studies known?

Commissioner KENNEDY. Well, this review will be completed within a few months I would say. There is a scheduled meeting of the Controlled Substances Advisory Committee on February 12 and 13 at which we will share with that advisory committee a number of the safety considerations and we will respond to the need to advise DEA on the petition to reschedule.

We will be continuing our review of the efficacy studies and should discuss those with another advisory committee later on in the spring.

I would estimate that 3 or 4 months would be required to complete what we have undertaken now.

Senator BAUCUS. Thank you.

Senator NELSON. Thank you, very much. We appreciate your taking the time to come and testify.

Commissioner KENNEDY. Thank you, Mr. Chairman.

Senator NELSON. Commissioner Kennedy's full statement will appear in the record at this point.

[The prepared statement and supplemental information of Commissioner Kennedy follows:]

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[1] See studies submitted by the Food and Drug Administration following Commissioner Kennedy's prepared statement, page 16826.

STATEMENT

BY

DONALD KENNEDY

COMMISSIONER

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

BEFORE THE

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

FEBRUARY 5, 1979

Mr. Chairman and Members of the Committee:

I appreciate the opportunity to discuss the activities of the Food and Drug Administration (FDA) with respect to propoxyphene.

Although previous actions by both FDA and the Drug Enforcement Administration (DEA) have had an important impact on the labeling and use of these drugs, the abuse and misuse of propoxyphene is nonetheless a genuine problem.

USE PATTERNS OF PROPOXYPHENE

Darvon (propoxyphene hydrochloride) and combinations with aspirin, phenacetin, and caffeine (Darvon Compound, Darvon Compound-65) were first marketed in 1957 by the Eli Lilly Company after approval on the basis of safety alone. After passage of the Drug Amendments of 1962, a panel of experts established by the National Academy of Sciences-National Research Council (NAS-NRC) reviewed propoxyphene products and concluded they were effective for the relief of pain. This group of drugs was then approved for effectiveness by FDA in 1969. New propoxyphene products containing the napsylate salt of propoxyphene rather than the hydrochloride, either alone (Darvon-N) or in combination with acetaminophen (Darvocet-N) or aspirin (Darvon-N with ASA), were approved and marketed in 1972.

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For many years propoxyphene-containing products have been among the most frequently prescribed prescription drugs in the United States. Appendix A (attached) shows the number of outpatient prescriptions written by year since 1964. Products containing propoxyphene peaked in popularity from 1973 to 1975 with retail prescriptions totaling over 39 million annually in those years. While the total number of prescriptions has dropped to some 31 million for 1978 (based on the projection of 9 months data), propoxyphene products are still very popular. The following table shows the rank of each among the 200 most prescribed drugs for the years 1972 through 1977:

Rank Among the Top 200 Most Prescribed Drugs

	1972	1973	1974	1975	1976	1977
Darvocet-N	-	87	24	20	18	12*
Darvon 32 mg & 65 mg	35	47	68	71	78	93
Darvon Compound-65 APC	2	3	3	6	15	20

*Darvocet-N was divided into two groups (50 and 100) for the year 1977 only. The 1977 rank for Darvocet-N 100 was 18; for Darvocet-N 50 was 169.

EFFICACY OF PROPOXYPHENE

As I have said, NAS-NRC reviewed propoxyphene products for efficacy in the late 60's. The chairman of the NAS-NRC Drug Efficacy Study Group Panel on Drugs for Relief of Pain was Louis Lasagna, M.D., an expert in the field of clinical pharmacology and analgesia. A 1966 article review by William T. Beaver, M.D., another expert in the field of analgesia, concluded as follows:

> "In summary, dextropropoxyphene is a mild oral analgesic which has proven superior to placebo in doses of 65 mg or more but which is of questionable efficacy in doses lower than 65 mg. The drug is definitely less potent than codeine, the best available estimates of the relative potency of the two drugs indicating that dextropropoxyphene is approximately 1/2 to 2/3 as potent as the latter drug. Likewise dextropropoxyphene in 32 mg to 65 mg doses is certainly no more, and possibly less effective than the usually used doses of aspirin or A.P.C."

FDA announced the results of the DESI review in 1969. The announcement described the indications for which the drugs were deemed effective--for the relief of mild to moderate pain.

Reservations about the efficacy of propoxyphene continued to be expressed during the 70's:

-- R. R. Miller et al. in 1970 reviewed all available double-blind studies of propoxyphene and concluded that it ". . . is no more effective than aspirin or codeine and may even be inferior to these analgesics."

-- C. G. Moertel et al. in a 1972 double-blind study of single doses of propoxyphene, aspirin, and other oral analgesics in patients with cancer, were unable to show that even 65 mg of propoxyphene was significantly superior to placebo. In this study, aspirin was the most effective analgesic tested.

-- R. R. Miller in a second review in 1977 concluded that propoxyphene was no more effective than placebo in three studies, whereas in five others propoxyphene was no more effective than other analgesics.

On the other hand, Sunshine et al., in a 1978 study, found propoxyphene napsylate at 200 mg (twice the recommended dose) to be significantly better than placebo. The lowest dose used (50 mg) was only slightly better than placebo but the usual dose (100 mg) was not tested.

POPULARITY OF PROPOXYPHENE

Mr. Chairman, in your letter of invitation you asked me to comment on the reasons for the sustained popularity of propoxyphene as an analgesic in view of its limited effectiveness. The answer to this question is complex and involves a number of factors.

First, I would point out that a significant number of people--typically 30-35 percent--in clinical trials on analgesics obtain pain relief from a placebo. Recent research suggests that this placebo response is due to activation within the brain of the same neural receptors that are affected by narcotics. The pain relief obtained is just as real, and may be just as great in many instances, as that provided by drugs. The placebo response may be enhanced by encouragement from the prescribing physician. Thus, any prescription analgesic is likely to offer pain relief to the many people who tend to be placebo responders--even if its inherent effectiveness is minimal.

Second, by far the most popular propoxyphene-containing products are those combinations containing aspirin, phenacetin or acetaminophen in addition to propoxyphene. They are thus clearly effective products even though the contribution of their propoxyphene component may be relatively small.

Third, until recently propoxyphene has been viewed by the medical profession as a relatively safe analgesic. It does not carry the risks of serious gastro-intestinal bleeding associated with aspirin, the liver damage associated with overdoses of acetaminophen, or the kidney damage associated with phenacetin.

Neither does propoxyphene cause drowsiness or constipation to the same extent as codeine. Addiction liability from propoxyphene is relatively low, compared to that from morphine and other Schedule II narcotics. This factor is the major reason it was placed in Schedule IV rather than Schedule II of the Controlled Substances Act (CSA) in 1977. The most prominent safety problem associated with propoxyphene is the risk of death due to overdosage--a problem whose extent has become apparent only in recent years.

Fourth, propoxyphene has been skillfully marketed in an array of dosage forms, combinations, and salts that offer physicians a wide variety of options for managing patients with painful disorders.

And finally, no other prescription analgesic possesses a combination of properties so attractive to the general physician for the management of patients with mild to moderate pain. Propoxyphene-containing products have been prescribed for nearly two decades on the assumption that they were safe, relatively low in addiction potential, and more effective than over-the-counter drugs. Codeine, which has been classified in Schedule II for some time because of its well-known dependence liability, is the only other prescription analgesic with similar usage.

In the past four years the number of prescriptions written annually for propoxyphene products has declined by about 15 percent. This drop-off parallels a similar but more moderate decrease in the rate of prescriptions for all drugs. We attribute this decline to a

combination of factors: an increasing awareness by physicians of abuse potential and the problem of deaths associated with propoxyphene, the placing of propoxyphene in Schedule IV of the Controlled Substances Act in 1977, and growing competition from certain newer drugs such as the non-steroid anti-inflammatory agents used for arthritis.

SAFETY OF PROPOXYPHENE

Propoxyphene is structurally related to the narcotic analgesic methadone. Although its general pharmacologic properties are those of the narcotics as a group, it does not compare with them in analgesic potency. Compared with other prescription analgesics, the adverse reactions (side effects) associated with propoxyphene are mild and infrequent.

The drug abuse potential of propoxyphene was recognized as early as the late 1950's but was not a major public concern until the late 1960's and early 1970's. Chronic propoxyphene use sometimes results in physical and psychological dependence of a type similar in nature but not degree to that produced by morphine. Intravenous "street" use by drug addicts was popular in the late 1960's but waned, particularly because of its ability to cause vascular and other tissue destruction, and because of formulation changes in the product. This pattern of abuse resulted in overdose deaths that resembled those seen with heroin and methadone (for example, respiratory depression and pulmonary edema). As a

result of these problems DEA placed it under Schedule IV of the CSA in 1977.

Our analysis of the available data on propoxyphene fatalities shows that the majority of associated deaths occurred because of deliberate overuse or abuse, as shown in the two tables in Appendix B. Propoxyphene is one of the most frequently used drugs in suicides and suicide gestures; in absolute incidents it follows only the barbiturates and non-barbiturate sedative-hypnotics in associations with drug-induced suicide. However, when viewed in relation to the number of prescriptions issued, the relative number of deaths from propoxyphene is lower than that for a number of other drugs.

We know of no cases at present in which death was caused by propoxyphene products alone when taken in customary doses and in which neither alcohol nor tranquilizers were also involved. There are, however, a number of "accidental" deaths which have apparently occurred as a result of the consumption of propoxyphene in quantities smaller than those used in suicide, yet still in excess of recommended therapeutic dosage and usually combined with alcohol and/or tranquilizers.

The mechanism of death in those cases is commonly attributed to respiratory depression, a typical action of narcotics, although cardiac toxicity must be considered with seriousness. In testimony

before the Subcommittee last week Dr. Sidney Wolfe stressed the cardiotoxicity of propoxyphene and its longer-lived metabolite norpropoxyphene in animals. We have examined the references cited by Dr. Wolfe and they do give cause for concern. The demonstration of dose-related progressive conduction block is clear in experimental animals and in some patients with acutely toxic doses there are similar electrocardiographic changes. What is still hypothetical is Dr. Wolfe's proposal that there may be significant numbers of deaths unrecorded by the DAWN system that are truly accidental (that is, not involving overdoses) and for which the cardiotoxic phenomenon is responsible.

When analyzed according to age groups, the various data sources reveal significant differences in levels of use, misuse and abuse, as shown in the two tables in Appendix C. Most notable is the marked discrepancy between the average age of suicide, death or emergency room visits and the actual population for which propoxyphene is prescribed. For example, whereas over 33 percent of propoxyphene prescriptions are written for the over 60 population (the group most subject to cardio-vascular, respiratory and central nervous system problems) only 8 percent of deaths occur in this group. Although the same percentage of prescriptions was written for the age 20-39 group, 57 percent of the deaths occurs in these groups.

REGULATORY ACTIONS

Over the years, in response to problems associated with efficacy and safety of propoxyphene products, FDA has taken a number of actions:

-- In 1972, because of misleading statements on the effectiveness of Darvon made to physicians in a letter from Eli Lilly and Company, we required the manufacturer to issue a "Dear Doctor" letter stating: "There is no substantial evidence to demonstrate that 65 mg of Darvon is more effective than 650 mg of aspirin (two 5-grain tablets), and the preponderance of evidence indicates that it may be somewhat less effective."

-- In April 1976, FDA's Controlled Substances Advisory Committee (CSAC) recommended that propoxyphene (and its salts and preparations) be controlled in Schedule IV of the CSA.

-- DEA, in March 1977, placed propoxyphene, its salts and preparations, in Schedule IV of the Controlled Substances Act.

-- Labeling for propoxyphene was further revised in 1978 to add a warning against the additive depressant effect of the products when used in conjunction with alcohol, tranquilizers, sedative hypnotics, and other central nervous system depressants, and to require additional

information on adverse reactions, drug interactions, and management of overdosage. A warning against use of the products during pregnancy was also added because of the danger of causing addiction in the fetus and producing a neonatal withdrawal syndrome.

RECENT DEVELOPMENTS AND ACTIONS

On November 22, 1978, the Secretary of the Department of Health, Education, and Welfare was petitioned by the Health Research Group (HRG) to suspend approval of the NDA's for propoxyphene-containing products under section 505(e) of the Federal Food, Drug, and Cosmetic Act on the grounds that the continued marketing of these drugs represent an imminent hazard to the public health. HRG requested alternatively that if the Secretary did not suspend, he support HRG's petition to DEA that propoxyphene be rescheduled as a Schedule II narcotic under the Controlled Substances Act.

FDA's Bureau of Drugs is conducting a new review of all data bearing on the safety and effectiveness of propoxyphene including those studies referenced in the HRG petition.

CONCLUSION

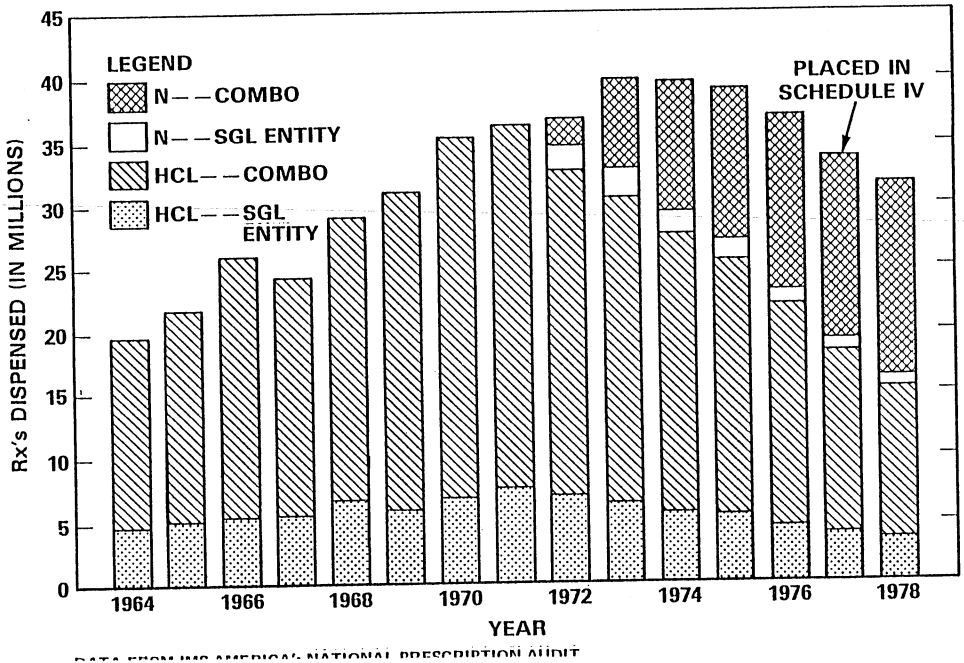
In summary, Mr. Chairman, the current status of propoxyphene presents us with an important and complex regulatory problem. The problems associated with its misuse are indeed troubling; but they must be weighed against significant benefits from the drug.

Propoxyphene is widely used; it provides pain relief for many people. Although it is not a powerful analgesic, it has advantages for persons who cannot tolerate aspirin or acetaminophen. It is prescribed and administered or dispensed in a special medical setting that provides significant psychological amplification of its affects. I am sorry that we cannot offer you a more definitive conclusion at this time, but we are still developing our analysis. These hearings have helped materially in that regard, as well as drawing public attention to a disturbing abuse problem. We will continue to give the matter close scrutiny.

Mr. Chairman, my staff and I will attempt to answer any questions you may have.

APPENDIX A

PROPOXYPHENE USE BY SALT AND FORMULATION TOTAL RETAIL Rx's DISPENSED YEARLY——1964 THROUGH 1978



DATA FROM IMS AMERICA'S NATIONAL PRESCRIPTION AUDIT

APPENDIX B
(TABLE I)

ASSOCIATIONS WITH DEATHS: 1977
(DAWN, NPA DATA)

Drug Group	Total Rx's	Coroner Mentions	Coroner Mention/ Million Rx's	Group Rank
I. Barbiturates* Secobarbital Pentabarbital Amobarbital Secolamobarbital	3.8	1071	282	1
II. Other Sedative-Hypnotics* Methaqualone Ethchlorvynol Glutethimide Chlor hydrate	6.5	326	50	2
III. Benzodiazepines Diazepam Flurazepam Chlordiazepoxide	80.2	552	7	5
IV. Major Tranquilizers Chlorpromazine Thioridazine Trifluoperzine Haloperidol	16.1	147	9	4
V. Other Common Prescription Analgesics Fiorinal +/- codeine Codeine +/- other analgesics Pentazozine +/- other analgesics	63.8	346	5	6
VI. Propoxyphenes Alone +/- other analgesics	33.5	607	18.1	3

*Phenobarbital and meprobamate were intentionally excluded since their prominant use, as anticonvulsant and "muscle relaxant," respectively differs from other drugs in the same pharmacologic category.

APPENDIX B
(TABLE II)

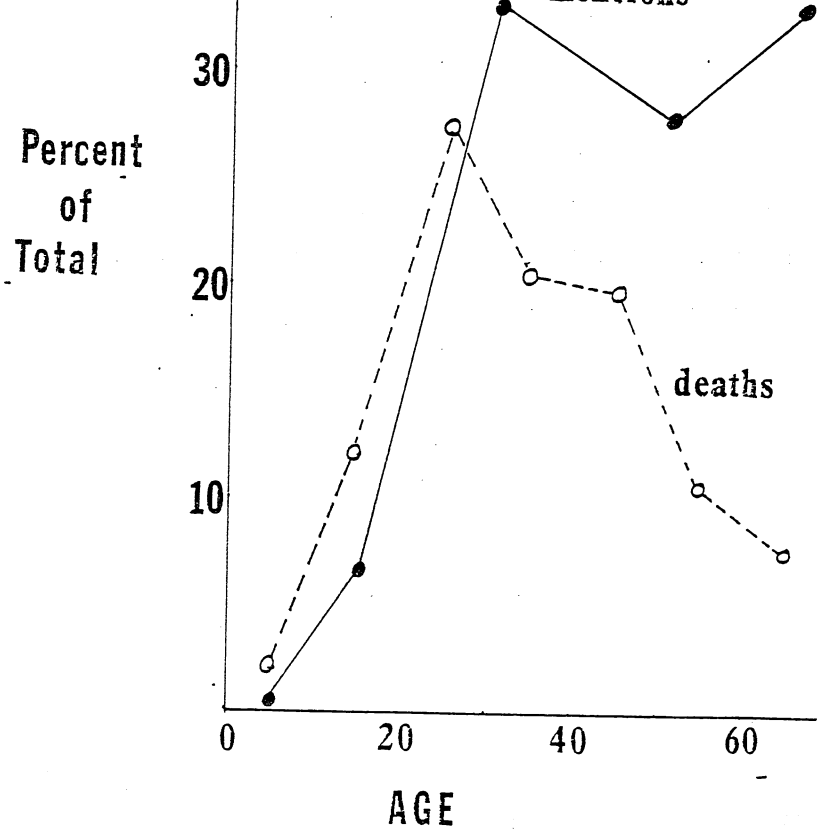
COMPARISON OF PROPOXYPHENE WITH OTHER DRUGS (NPA, DAWN DATA) - 1977

ALL REPORTERS

Drug	Total Rx's (in millions)	ER Mentions	Coroner Mentions	Coroner Mentions/ER Mentions	Coroner Mentions/Million Rx's	Relative Rank
BARBITURATES						
Secobarbital	1.2	2457	350	.14	292	3
Pentobarbital	1.3	946	272	.29	209	4
Secobarb/Amobarb	1.0	3093	326	.11	326	2
Amobarbital	0.3	130	123	.95	410	1
Phenobarbital	7.8	2989	254	.08	32.6	9
BENZODIAZEPINES						
Diazepam	53.6	21678	418	.02	7.8	18
Chlordiazepoxide	13.0	3411	54	.02	4.2	22
Flurazepam	13.6	4643	80	.02	5.9	19
OTHER SED/HYP						
Meprobamate	8.2	1238	95	.08	11.6	16
Methaqualone	1.0	2405	62	.03	62.0	6
Ethchlorvynol	1.7	2202	135	.06	79.4	5
Glutethimide	1.8	639	94	.15	52.2	7
Chloral hydrate	2.0	618	35	.06	17.5	14
TRANQUILIZERS						
Trifluoperazine	3.0	1072	6	.01	2.0	24
Thioridazine	6.8	2175	74	.03	10.9	17
Chlorpromazine	4.7	2404	64	.03	13.6	15
Amitriptyline	9.0	3281	386	.12	42.9	8
Imipramine	4.6	921	74	.08	16.1	14
Doxepin	4.1	1397	104	.07	25.4	10
Haloperidol	1.6	1058	3	<.01	1.9	25
ANALGESICS						
Morphine	0.6	134	0	-	-	
Codeine & Codeine compounds	49.8	3597	274	.08	5.5	20
Fiorinal	7.5	1204	0	<.01	-	25
Fiorinal w/codeine	2.3	130	1	<.01	.43	26
Pentazocine	3.5	1079	71	.07	20.3	11
Pentazocine comp.	.7	4	0	<.01	-	28
Aspirin	NA	7184	156	.02	-	-
Acetaminophen	NA	2559	77	.03	-	-
Propoxyphene	33.5	4179	607	.15	18.1	12
OTHER						
Diphenhydramine	10.8	1113	23	.02	2.1	23
Diphenylhydantoin	8.6	2271	41	.02	4.9	21
Methapyrilene/ scopolamine (OTC)	NA	1725	1	<.01	-	-

APPENDIX C
(TABLE I)

PHYSICIAN MENTIONS AND DEATHS ASSOCIATED WITH PROPOXYPHENE: AGE DISCREPANCY



APPENDIX C
(TABLE II)

OUTCOMES OF DARVON USE: SUICIDE ATTEMPTS AND GESTURES, PROPOXYPHENE DEATHS AND PRESCRIPTIONS: RELATION TO AGE

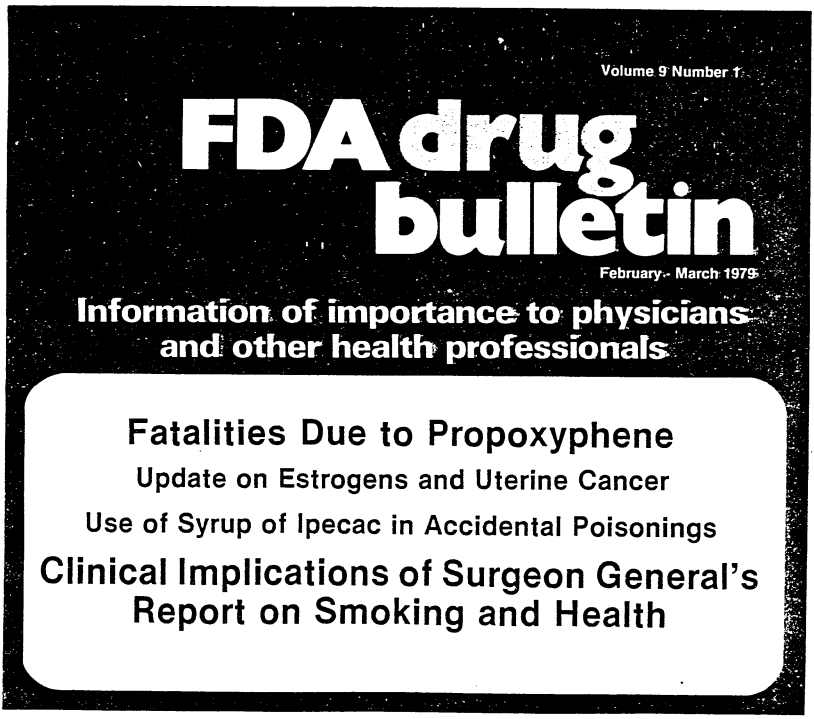
CATEGORY	DATE SOURCE	AGE GROUP 0-9	10-19	20-29	30-39	40-49	50-59	60+
I. Mentions for propoxyphene	NDTI	0.4%	6.5%	33%			28%	33%
IIa. ER Visits related to Propoxyphene n = 408	FDA Poison Center	23%	29%	31%	8%	4%	3%	1%
IIb. ER Visits for Suicide, Gestures (1% lethal)	FDA Poison Center		37%	40%	11%	6%	4%	1%
DEATHS								
III. FDA: Probable Suicides reported Total = 173 83M: 84F	FDA ADR Reports	0	22%	37%	20%	14%	8%	
IV. FDA: Probable "Accidental" Total = 48 19M: 28F	FDA ADR Reports	13%	13%	34%	17%	6%	2%	
V. Finkle data Propoxyphene Associated Deaths (all) n = 1022 45%M: 55%F	Finkle, et al, J. Forensic Sci 1976	2%	12%	27%	21%	20%	11%	8%
VI. DEA Data	DEA							
WM 20% BM 5% WF 44% BF 16%	ER Visits 1/75-8/78		24%	41%	19%	10%	6%	

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Food and Drug Administration
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FDA Drug Bulletin

February - March 1979

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CHANGE OF ADDRESS: Address changes for those labels marked with a "Q" should be sent to FDA *Drug Bulletin*/HFI-20, Rockville, Md. 20857. If your label is not identified with a "Q," send address changes to the professional association to which you belong, i.e.: American Medical Association, American Osteopathic Association, American Dental Association, American Nurses Association, American Pharmaceutical Association, American Podiatry Association, or the American Student Pharmaceutical Association. FDA *cannot* change any address taken from a professional association mailing list, so check your mailing label before requesting an address change.

Fatalities Due To Propoxyphene

FDA calls to the attention of physicians, dentists, pharmacists, and other health professionals several serious risks associated with the use of propoxyphene (sold as Darvon, Darvon Compound, Darvon-N, Darvocet-N, other brand names, and under the generic name).

Propoxyphene products are widely used prescription analgesics in hospitals, clinics, and out-patient settings. Darvon products are the most frequently prescribed brand name analgesics, with over 30 million prescriptions written in 1978.

The major hazards associated with propoxyphene use are:

- An estimated one to two thousand deaths a year are associated with propoxyphene alone or in combination with other drugs, FDA estimates. The majority of these appear to be suicides. Propoxyphene ranks second only to the barbiturates as the leading prescription drug associated with drug fatalities.
- The possibility of accidental death associated with propoxyphene has been recognized more recently and is of growing concern (see *FDA Drug Bulletin*, March-April 1978). Some of these deaths have occurred among drug abusers using propoxyphene in high doses with other drugs or alcohol to get a "high." Other deaths, however, appear to have occurred among people who are not habitual drug abusers and who apparently took propoxyphene in conjunction with tranquilizers, alcohol, or sedatives without understanding the danger.
- There is increasing concern that some of these accidental deaths with multiple drugs may have occurred at propoxyphene doses only slightly higher than the upper limits of the recommended dose.
- Propoxyphene, when taken for an extended period of time, produces physical and psychological dependence of the morphine type. This may occur with as little as 500 to 800 mg. per day of the propoxyphene hydrochloride or 800 to 1200 mg. per day of the napsylate salt of propoxyphene (or about 8 to 12 tablets/capsules per day). Because of this dependence liability, propoxyphene was placed in Schedule IV of the Controlled Substances Act in 1977.

The usual cause of death associated with propoxyphene overdosage appears to be respiratory depression, a typical action of narcotics. Some researchers have suggested that cardiac toxicity due to norpropoxyphene, the major metabolite, may also be a factor in some propoxyphene-related deaths, but this is not known to be a frequent mechanism in accidental deaths.

FDA is now reevaluating all propoxyphene products, including propoxyphene HCl, propoxyphene napsylate, and combinations of these with aspirin, acetaminophen, and APC. The purpose of the reevaluation is to determine whether there is a need for additional warnings in the labeling, for a change in the scheduling of the drug under the Controlled Substances Act, or for withdrawal of the drug from the market.

An additional issue to be addressed during the reevaluation is the effectiveness of propoxyphene. Propoxyphene is prescribed most often (about 80 percent of the time) in combinations also containing aspirin, acetaminophen, or APC. Several new studies suggest that the contribution to overall effectiveness of the propoxyphene component in these combinations is minimal. As a single ingredient, propoxyphene in doses of 32 mg to 65 mg is approximately two-thirds as potent as codeine and is no more effective—and may be less effective—than the usual doses of aspirin or acetaminophen.

One part of the FDA reevaluation of propoxyphene will be an open hearing on April 6 at which health professionals and other interested persons can present their views. The hearing will seek additional information on the effectiveness and risks of propoxyphene. Future issues of the *Drug Bulletin* will report on FDA's reevaluation.

Health professionals can do much to reduce the number of fatalities associated with propoxyphene.

- Doctors and dentists are advised before prescribing propoxyphene to consider whether the patient may be suicidal, abuse prone, or addiction prone.
- Health professionals are advised to discuss with patients the abuse potential of propoxyphene and the possibility of its being dangerous if taken with alcohol, tranquilizers, or sedatives.
- Pharmacists are advised to warn people orally and on prescription drug labels not to take propoxyphene drugs with alcohol, tranquilizers, or sedative-hypnotics.

Update on Estrogens and Uterine Cancer

FDA has reviewed three recent studies on estrogen use, and the Agency concludes the new research affirms that menopausal and postmenopausal women who take estrogens have an increased risk of endometrial cancer. Although one of the studies[1] criticizes research linking estrogen therapy and cancer on methodological grounds, others[3,4] have attempted to address the objections.

The new data also strongly support estrogen label

warnings advising health professionals and women patients that the risk is much reduced if estrogens are taken at the lowest possible dose and if chronic administration is avoided.[2,3]

Jick et al.'s[2] study of patients in a large prepaid group practice in the Seattle area found parallel sharp declines in both the incidence of uterine cancer and in the number of prescriptions for replacement estrogens. This recent report suggests that when patients discontinue taking estrogens, the risk of developing endometrial cancer decreases markedly within one year. A possible alternative explanation suggested by Jick is that the time of diagnosis is postponed when patients discontinue estrogens. Jick concluded the correct explanation will emerge as the population and nationwide statistics continue to be monitored.

A downward trend for estrogen use began in 1976 after announcements of epidemiological findings on the risk in late 1975. Nationwide, FDA data indicates that estrogen use declined by 18 percent from 1975 to 1976, and by another 10 percent from 1976 to 1977. According to Jick and others, the incidence of endometrial cancer fell about 27 percent nationwide from 1975 to 1977. In 1977 approximately 5 percent of women in the United States, or 4.1 million, were taking estrogen therapy.

The papers by Jick et al.[2] and Antunes et al.[3] agree on two issues important to physicians prescribing estrogens and to women taking these drugs:

- The increased risk of endometrial cancer in estrogen users is proportional to the duration of use and is particularly high with use of 5 years or longer. It should be noted, however, that Antunes, Stolley et al., and Ziel and Finkle[4] reported an increased risk even with use of estrogens for a period of 1 to 5 years. No definite evidence of increased risk of cancer from estrogen use less than 1 year has been reported.
- The use of cyclic therapy or progestins for 7 days each month does not meaningfully protect against the risk of endometrial cancer. Whether use of progestins for longer periods each month will provide protection has not been adequately studied.

The only established way to use estrogens with minimum risks in women with intact uteri is to prescribe low doses for relatively short periods—i.e., months, rather than years.

A recent study by Horwitz and Feinstein sparked controversy about certain aspects of estrogen therapy and cancer link. They maintained that the risk of endometrial cancer in estrogen users may be overestimated, because women who have uterine bleeding after estrogen therapy receive increased diagnostic attention, and, therefore, their cancer is detected earlier than in women not taking the drugs. Using a procedure different from that of previous researchers, these authors found only a slight increase in risk of uterine cancer in estrogen users.

Hutchison and Rothman challenge Horwitz and Feinstein's findings,[5] maintaining that although women who take estrogens may be diagnosed with endometrial cancer somewhat earlier, nearly all women with invasive endometrial cancer ultimately will have their disease diagnosed. These researchers conclude that even if screening advances that date of diagnosis, it will have little effect on the number of cases ultimately found.

Antunes, et al. used a methodology that compensates for the possible screening problem, and they still found a strong association between estrogen use and endometrial cancer.

FDA since 1977 has required estrogen patient labeling to carry the warning about the association between prolonged estrogen use and a 5-15-fold increase in risk for uterine cancer. The warning label and FDA's information campaign to medical professionals aim at reducing uses of estrogen in treating conditions for which it is neither effective nor medically justified, such as for treatment of simple nervousness and depression during menopause, or to help women feel younger.

Estrogens are effective, however, for vasomotor symptoms of the menopause and can be used with no known increase in risk for the treatment of this common problem if doses are kept low and the period of treatment is less than 1 year.

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Syrup of Ipecac

National Poison Prevention Week is March 18-24, 1979, and FDA believes this is an appropriate time for health professionals to discuss with their patients the use of ipecac syrup in cases of accidental poisonings.

With proper use, syrup of ipecac is a safe and effective emetic. The recommended labeling for ipecac syrup was published on September 8, 1978, as part of FDA's tentative final monograph on emetic drug products. Syrup of ipecac is indicated "only to cause vomiting in case of poisoning."

The labeling warns consumers *not* to use syrup of ipecac if strychnine or corrosives (such as lye and strong acids) have been ingested. Because consumers may not know if the poisonous substance is highly toxic, a corrosive, or a petroleum distillate, the labeling stresses that they should contact a physician, poison control center, or emergency room for advice *before* using ipecac syrup. The drug should not be used if the patient is convulsing, semiconscious, unconscious, or has lost the gag reflex.

If ipecac syrup and activated charcoal (which is often given to prevent poison absorption in the stomach) are used together, vomiting must be induced with the ipecac syrup before the patient takes the activated charcoal. Activated charcoal adsorbs ipecac syrup and may reduce its effectiveness.

If vomiting does not occur within 20 minutes, the dose may be repeated once. If vomiting doesn't occur within 20 minutes after a second dose is given, the physician, poison control center, or emergency room should be called again.

February - March 1979

Clinical Implications of Surgeon General's Report on Smoking and Health

The recently released Surgeon General's Report on Smoking and Health has important implications for physicians' routine diagnostic and prescribing practices.

The report contains an unprecedented compilation of information on the effects of smoking on health. One of its conclusions is that the widely recognized smoking-related medical problems, such as lung cancer, other respiratory problems, and cardiovascular disease, represent only some of the medical issues health professionals need to consider.

The report brings to attention four other important areas related to smoking:

1. **Prescribing practices:** Smokers may experience altered therapeutic effects from some drugs, and the toxicity of drugs may be affected by smoking habits. The report notes several drugs for which smokers require higher doses or more frequent doses than nonsmokers.
2. **Use of diagnostic tests:** There may be significant differences in normal values for smokers and nonsmokers in various routine biochemical clinical tests.
3. **Treating and preventing nutritional deficiencies:** Smoking alters the absorption and metabolism of important macronutrients and micronutrients, such as protein and vitamins — with clear implications for nutritional management of smokers, especially pregnant women.
4. **Smoking and estrogen use** : Smokers who take oral contraceptives have an increased risk of myocardial infarction.

The following discussion on smoking interactions with drug therapy, diagnostic tests, and nutrition summarizes one major section in the Surgeon General's Report. Complete scientific literature citations are available in the full text of the Report (which can be purchased from the Government Printing Office).

Prescribing Practices

Smoking has significant implications for the drug therapy of a wide variety of conditions.

- For certain drugs, smokers need different doses or a different frequency of administration than nonsmokers.
- When patients stop or reduce cigarette consumption, their drug regimen may need adjustment.
- Doctors should expect smokers sometimes to have more numerous adverse reactions and sometimes fewer, or even to have different reactions to certain drugs than nonsmoking patients.

Mechanisms of Tobacco-Drug Interaction

The dominant effect of smoking on drug pharmacology is the ability of nicotine and other tobacco constituents to enhance drug disposition by inducing microsomal enzyme systems responsible for the metabolism of many drugs and chemicals.[1] The clinical effects of inducing these systems in smokers can include accelerated rates of drug disposition, decreased intensity, and duration of effect, and therefore, decreased therapeutic efficacy of drugs.

Two drugs for which the metabolic interaction with smoking can be a critical factor in a patient's therapy are theophylline and pentazocine. Theophylline is an important bronchodilator for treating acute and chronic asthma or bronchitis. This drug has a narrow therapeutic index, and smokers on the average are reported to need one and one-half to two times as much of the drug as nonsmokers to achieve the same effects — either through larger doses or more frequent administration.[2] The half-life of theophylline is reduced to about 4 hours in smokers, from about 7 hours in nonsmokers.

Hunt et al. have also reported that in patients using theophylline who stopped smoking, it took more than 3 months for the effects of chronic tobacco use on theophylline disposition to dissipate.[3] Therefore, close monitoring for altered dosage needs of theophylline is required in patients who make any changes in their smoking habits.

Another significant factor in considering theophylline-tobacco metabolic interactions is the frequency of adverse reactions with the drug. Smokers frequently experience reduced toxicity from theophylline apparently because of the increased biotransformation rate, and the frequency of adverse reactions correlates negatively with the smoking habit.[4] However, the large maintenance doses heavy smokers require in comparison to nonsmokers could put them in jeopardy of toxicity if they discontinue smoking without adjusting their dosage regimen.

In a study of pentazocine dosage requirements for supplementing nitrous oxide general anesthesia, investigators found that smokers needed larger priming and maintenance doses, up to 50 percent higher than nonsmokers.[5] Other research has confirmed that smokers metabolize 40 percent more pentazocine than nonsmokers — therefore, often necessitating larger and more frequent doses for analgesia.[6]

Other examples of drug-tobacco pharmacokinetic interactions are less dramatic than theophylline and pentazocine but appear with widely used drug classes — tranquilizers, analgesics, and antidepressants.

The following tables on interactions between smoking and drugs summarize clinical pharmacological data in humans and clinical observational studies from the Boston Collaborative Drug Surveillance Program.[7,8]

Table 1. Interactions between Smoking and Drugs in which Biotransformation Is Not Affected by Smoking

Meperidine	Ethanol
Phenytoin	Chlordiazepoxide
Nortriptyline	Phenobarbital
Warfarin	

Table 2. Interactions Between Smoking and Drugs Presumably Based on Alterations in Drug Metabolism.

Analgesics
Propoxyphene—higher rates of "ineffective" responses
Antipyrene—increased hepatic metabolism
Phenacetin—lower plasma levels
Pentazocine—higher maintenance dose needed
Tricyclic Antidepressants
Imipramine—increased clearance rate
Xanthines
Theophylline—significantly accelerated metabolism
Tranquilizers
Diazepam—CNS depression less frequent (probably due to increased rate of metabolism)
Chlorpromazine—reduced drowsiness

Diagnostic Tests

A number of studies have established the importance of considering a patient's smoking status in interpreting reports of diagnostic tests. There are clear differences between smokers and nonsmokers in "normal" blood levels of several factors. Most of these differences relate directly to the amount of smoking and disappear after the person stops smoking. Interpreting test results without taking into account the patient's smoking history in some cases could lead to incorrect diagnoses or inappropriate therapy.

A dramatic example of differences between smokers and nonsmokers involves carcinoembryonic antigen (CEA), which in nonsmokers can be an important aid in the diagnosis of colon cancer.[9] Clinicians need to use particular care when interpreting assay results on smokers, however, because CEA levels in smokers may reach the same high levels observed in patients with proven colon cancer.[10]

A number of studies have found higher concentrations of circulating white blood cells in smokers than in nonsmokers, although all the subjects were healthy and completely free of any symptoms of infection or other disease conditions that tend to raise white blood cell counts. These differences between what is normal for smokers and nonsmokers holds true for all ages from 15 to 79, in both sexes, and in all races.[11]

In all groups studied, it also was clear that the heavier the smoking, the higher the white cell count. The quantity smoked, inhalation practices, and duration of smoking history all relate directly to the leukocyte count.[11] Smokers who inhale also have a greater average number of leukocytes than those who do not, regardless of the amount they smoke. The count also is higher in light smokers who inhale than in heavy smokers who do not.[12]

Other significant altered diagnostic values in smokers are increases in hemoglobin concentration, hematocrit, and mean corpuscular volume.[13] The high levels of carbon monoxide in cigarette smoke reduce the oxygen-carrying capacity of the blood, so that smokers apparently adapt by increasing the red cell mass and hemoglobin concentration. As with the changes smokers experience in their normal white blood cell level, the degree of increase in hemoglobin concentration in smokers is not sufficient by itself to lead to a false diagnosis that a healthy person is ill. But cigarette smoking should be appreciated as a factor in producing incremental differences in these diagnostic tests.

The scientific literature includes reports of several other tendencies for different normal values on clinical tests in smokers and nonsmokers, but there are inconsistencies in research results. For healthy, smoking individuals, these findings probably may not be significant, but physicians may find the data helpful in handling certain illnesses. For example, several studies suggest that smoking reduces clotting time by potentiating platelet aggregation. The coagulation time of smokers' whole blood during a nonsmoking period was significantly shorter than that of nonsmokers.[14] Although this effect may have little importance for most patients, it could provide significant incentive to stop smoking for a patient who already has had a thrombosis or other clotting problems.

Treating and Preventing Nutritional Deficiencies

Interactions between macro- and micronutrients and tobacco are significant for pregnant patients because of the fetal malnutrition associated with smoking. Studies in both the United States[15] and Britain[16] demonstrate that babies born to smoking mothers are smaller and have greater risk of perinatal mortality. Partially responsible for their babies' low birth weight may be the impairment of mothers' protein metabolism, as well as lower levels in maternal blood of amino acids, vitamins B_{12} and C, glucose, and fatty acids. In addition, it is postulated that the smoking mothers' higher levels of carboxyhemoglobin and nicotine may decrease to some extent oxygenation of the fetus.

Scientists have known since 1939 that smoking causes changes in blood levels of certain nutrients, which may help to explain certain adverse effects of smoking on health. Since there has not yet been research to identify clearly such cause and effect relationships, the Surgeon General's Report considered only those nutrients for which there is a clearly understood interaction with smoking.

On the macronutrient level, investigators have found alterations in both carbohydrate and protein metabolism frequently associated with smoking. Both epidemiological and clinical nutrition studies established the smoking-carbohydrate interaction: Smoking raised blood levels of somatotropic hormone and plasma catecholamine—changes with significant implications for carbohydrate metabolism.[17] Smoking also appears to impair protein metabolism, reducing smokers' efficiency in retaining nitrogen.[18]

Smokers may also have increased needs for micronutrients compared to nonsmokers, which include: vitamin C, vitamin B_{12}, vitamin B_6, and bone minerals. Decreased plasma levels in vitamin C due to smoking are well-established,[19] although the exact mechanism has not

been identified. Vitamin C is essential in the formation of adrenalin, collagen, the synthesis of neurotransmitters, and many other biochemical functions.

Some of the bone mineral losses smokers experience also may be a secondary effect of low vitamin C levels or other nutritional conditions. Two studies[20] found significantly more severe osteoporosis in smoking postmenopausal women than for their nonsmoking counterparts.

Some heavy smokers develop amblyopia which reverses after they either receive vitamin B_{12} supplements or quit smoking. Smoking-related losses of this vitamin appear to be due to reaction of B_{12} with cyanide in inhaled tobacco smoke.[21] Research on the possibility that smoking induces vitamin B_6 deficiencies suggests that the loss of this vitamin may involve a reaction with carbon monoxide in smoke.[22]

Smoking and Estrogen Use

An important adverse interaction between smoking and a drug is the well-established increased risk of myocardial infarction in smokers who take oral contraceptives. FDA has required since April 1978 that oral contraceptive labels and information leaflets for patients carry the boxed warning: "Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes a day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke."

FDA imposed this warning following Mann et al.'s[23] research reporting the association between cigarette smoking and oral contraceptives. Subsequent studies have confirmed the high risk of cigarette smoking for oral contraceptive users. Jain[24] determined that (1) the use of oral contraceptives among women aged 40 and over who are heavy smokers is substantially more hazardous than no fertility control; (2) the use of oral contraceptives among heavy smokers aged 30-39 may be slightly more hazardous than no fertility control, and is substantially more hazardous than any other method of birth control; and (3) the use of contraceptives among heavy smokers aged 15-29 may be more hazardous than any other method of birth control, but somewhat less hazardous than no fertility control.

A recent study by Sloane et al.[25] of women who suffered a myocardial infarction before age 50 found a dose-response relationship involving smoking. Demonstrating that smoking is a risk factor for myocardial infarction in healthy women, these investigators estimated that women who smoke 35 or more cigarettes a day have a rate of myocardial infarction 20 times higher than those who never smoked.

Jick et al.[26] have also shown that apparently healthy women aged 39 to 45 who were taking noncontraceptive estrogens have an estimated relative risk of 7.5 for nonfatal myocardial infarction compared to nonusers of estrogens. All but one of the nonfatal myocardial infarction patients were cigarette smokers, and about half (16/34) of the controls were smokers. It then appears that women aged 39-45 may have a substantial risk when they both smoke and take estrogens.

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THE COMPREHENSIVE APPROACH TO PATIENT CARE SECTION 5—THE PLACEBO RESPONSE

by

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Section 5

THE PLACEBO RESPONSE

Louis A. Morris and Arthur K. Shapiro

Psychologic factors have been recognized as important in the etiology of disease since the time of Hippocrates. Galen estimated that 60% of patients had symptoms which were emotional in origin. This figure is in close agreement with contemporary estimates of 50% to 80%. Despite Galen's and Hippocrates' acumen, none of the drugs they administered produced therapeutic effects by virtue of their pharmacologic actions (1).

Treatment was not only primitive, unscientific, and essentially ineffective: it was often shocking and dangerous. Patients were given almost every known organic and inorganic substance, including crocodile dung, teeth of swine, hooves of asses, spermatic fluid of frogs, eunuch fat, fly specks, lozenges of dried vipers, moss scraped from the skull of a victim of a violent death, oil of ants, and numerous other equally ineffective nostrums. Blood from almost every animal, prepared and administered in many ways, was used to treat every conceivable symptom and disease. Nearly all human and animal excretions were employed in some manner.

Although medicine has held a place in the finest scientific, religious, cultural, and ethical traditions throughout history, one wonders how physicians maintained their position of honor and respect. Useful drugs or procedures appeared infrequently and were usually forgotten by succeeding generations. For thousands of years, physicians prescribed what we know were useless and often dangerous medications. This would have been impossible were it not for the fact that physicians did help their patients.

Today, we know that the effectiveness of these procedures and medications was due to psychologic factors often referred to as the "placebo effect." Since almost all medications until recently were placebos, the history of medical treatment can be characterized largely as the history of the placebo effect (2).

Medicine no longer relies chiefly on placebo effects. Today there is an increasing number of specific and predictable therapies. However, the results of any treatment are due to both the specific actions of the treatment and its nonspecific, placebo effect, influences. The relative contribution of placebo and nonplacebo components vary, depending on factors such as the potency and specificity of treatment, psychologic and physical state of the patient, and methods of administering and evaluating treatment effects. Although psychologic factors may be minimized, they cannot be excluded. It is true that if the dosage of a drug is too high, all the patients will react with toxicity or even death, regardless of psychologic factors. However, this predictability is of little consequence because the majority of clinically useful drugs are prescribed in dosages which are far below the toxic level, ie, in a range in which placebo effects are important.

The incidence of placebo reactions approaches 100% in some studies. Placebos can mimic the effects of active drugs, have profound effects on organic illnesses, and can be more powerful than or reverse the action of potent active drugs. Drugs are reported effective four or five times more frequently in uncontrolled studies than in

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controlled studies. If placebo effects are not reported in controlled studies, the studies are considered unreliable. Appreciation of placebo effects is reflected in the speculation that historians will record as a major medical achievement of the 1960s the development of methods and controlled experiments to test the efficacy of treatment.

The importance of the placebo effect is often underestimated by clinicians. Physicians may attribute successful treatment to their knowledge and skills while failing to recognize their own shortcomings. Questionnaire studies reveal that physicians think that other physicians use placebos three times more often than they themselves use placebos. Practitioners tend to exclude their own methods of treatment from what they consider to be placebo treatment. Surgeons exclude surgery, internists exclude active medication, psychotherapists and psychoanalysts exclude psychotherapy and psychoanalysis. In research, placebos are commonly viewed as experimental artifacts that have to be controlled. Only rarely does the placebo effect undergo empiric scrutiny as a primary research topic.

DEFINITION OF PLACEBO

The word "placebo" is derived from the Latin verb *placere*, meaning "to please" (3). In the 14th century, the term was used to describe a servile flatterer, sycophant, toady, or parasite. This usage was derived from derogation of professional mourners who were paid to "sing placebos" at the bier of the deceased, a role originally reserved for the family.

Few people realize that medical dictionaries have limited their definition to inert or inactive drugs only during the past few decades. The original medical definition appeared in 1785 as "a commonplace method or medicine." This original definition was often misquoted as a "commonplace method of medicine." The distinction between "of" and "or" is important since the former limits its definition to medicines (ie, drugs) while the latter includes methods (eg, procedures, devices, talking therapies). As drugs became more important, the meaning became limited to medicines. With the advent of controlled clinical trials, the meaning became limited to inert drugs. However, recent medical dictionaries have expanded their definition so that the meaning of "placebo" is more like the original 1785 definition.

A definition which we believe fulfills historic and heuristic criteria is as follows:

> A placebo is any therapy or component of therapy that is deliberately used for its nonspecific, psychologic, or psychophysiologic effect, or that is used for its presumed specific effect but which is without specific activity for the condition being treated. A placebo, when used as a control in experimental studies, is a substance or procedure that is without specific activity for the condition being evaluated. The placebo effect is the nonspecific psychologic or psychophysiologic result produced by placebos.

There are several important features of this definition. Placebos may be knowingly or unknowingly prescribed. The criteria for separating placebo from nonplacebo is based on objective evaluation. Placebos may produce negative, positive, or no noticeable effects. Placebos may take the form of oral and parenteral medication, topical preparations, inhalants, and all mechanical, surgical, and psychotherapeutic devices, procedures, and techniques.

Although this definition may prove to be too inclusive, at present it would be premature to make any specific exclusions. It is likely that placebogenic factors will be reliably isolated as treatment regimens become more thoroughly investigated. Once isolated, placebogenic components may have the potential to become specific therapies in their own right. For example, operant conditioning, which contributes to the manifestation of placebo effects, has become a specific psychotherapeutic procedure.

MECHANISMS OF PLACEBO ACTION

A wide variety of mechanisms have been advanced to explain how placebos produce placebo effects. Unfortunately, no single process can account for the diversity of empiric results. It is likely that the placebo effect is a multidetermined phenomena and that multiple pathways exist by which the placebo effect may become manifest. Definition, explanation, and integration of

these mechanisms awaits many more years of study. At present, we can only describe some of the numerous processes that have been suggested as explanations of the placebo effect.

Three general themes can be used to group placebogenic processes. First, the placebo effect may be caused by the relationship between the patient and the physician. Secondly, the placebo effect may be due to the expectations patients have about their therapy and illness. Thirdly, placebo effects can be explained as artifacts or natural outgrowths of the process of therapeutic evaluation.

The Placebo Effect as a Result of the Patient-Physician Relationship

The physician's role in society is unique. He performs and combines functions that have always been important to mankind: healer, priest, and scientist. These attributes facilitate the tendency of patients to view the physician as a socially powerful individual. The physician is seen as both expert and trustworthy. The patient usually develops a special relationship with the physician, which has been discussed frequently in psychiatric literature as transference, classically defined as feelings of love, hatred, trust or distrust, which the patient attached to significant persons in the past and are expressed to the physician in the present. This special relationship between a patient and his physician gives rise to several placebogenic processes.

Suggestion

Several authors have viewed the placebo response as a manifestation of the patient's suggestibility. Since patients are apt to be highly anxious and uncertain about their symptoms and treatment, they are highly susceptible to the therapist's suggestions. The gullible patient that can be duped into believing that bogus therapy is real is viewed as a key component in the placebo effect.

Tests of suggestibility have frequently been used to study the placebo response. It was hoped that the presumed common component in the response to a test of suggestibility and the response to a placebo would result in positive intercorrelation. Unfortunately, this expectation has been generally unsupported. One explanation for this lack of association between tests of suggestibility and the placebo response is that they possess differing stimulus values. The placebo response usually involves a clinical procedure while tests of suggestibility are given in laboratory settings. When tests of suggestibility are administered in clinical situations, they are usually uncorrelated with placebo reactions.

Persuasion

The physician-patient relationship may be viewed as an influence-flowing situation. The high degree of social power possessed by the physician makes him highly persuasive. In this paradigm the patient is viewed as reacting to the information supplied by the physician.

The persuadability model views the patient as a rational processor of information; the potence of the physician's arguments, rather than the gullibility of the patient, is stressed.

Transference

Psychoanalytic theory generally views placebo effects as the patient's transference relationship to the therapist. Positive placebo effects are viewed as a result of positive transference relationships with the physician. They are seen 1) as an outgrowth of satisfactory childhood experiences with parents and surrogates or 2) in individuals who expect succor and comfort despite early dissatisfactory relationships. Negative placebo effects can result from the patient's unsatisfactory early relationship and the doctor's negative countertransference relationship with the patient. A patient's hostility may be expressed by the report of negative side effects. The concept of transference is too global to be useful as an adequate explanation for the placebo effect and requires explanatory details and the specification of the intervening variables to be useful.

Placebo Effect as a Result of Patient Expectations

In addition to establishing special relationships with their patients, physicians communicate, by intended and unintended means, their expectation about administered treatment to patients. If physicians furnish insufficient information, patients may infer expectations based on their knowledge or ideas derived from

what they have heard from friends or relatives.

Classic Conditioning

The expectation that a treatment can cause a psychologic change can, by itself, induce that change. An early experimental demonstration of the placebo effect was done by Pavlov. Dogs reacted with nausea, salivation, and emesis to the injection of morphine. On repeated injections, these reactions occurred as soon as the dogs were approached with a syringe. The finding that reactions to drugs can occur quicker than when induced by pharmacologic means has also been attributed to classic conditioning.

Classic conditioning may account for the occurrence of placebo reactions after patients have experienced the effects of active treatments. Cognitive dissonance may help explain how expectations can induce placebo responses in individuals who have never experienced the effects of an active treatment.

Internal Standards

Classic conditioning or another cognitive mechanism may help explain how expectations can result in physical responses to placebos. In addition, expectations can influence judgments of whether treatment is a success or failure. An individual who expects too much from a treatment may judge results to be unsuccessful. The same outcome may be viewed as a therapeutic success by patients who have lower expectations.

An interesting finding of placebo research is that unfulfilled promises of the therapist sometimes produce a "boomerang" effect (4). Patients may experience a worsening of their initial symptomatology if therapists tend to oversell treatments. This may be especially true for patients with accurate expectations because of prior experience with the treatment or the disease.

Hope

Anticipations about a therapy and the desire for improvement are essential components for the mobilization of hope. The importance of hope, closely associated with faith, is reflected by a major religious group in the United States disputing the efficacy of medicine and attributing therapeutic benefits to their own faith.

The Placebo Effect as a Result of Therapy Evaluation

The environment created by the evaluation of treatment may itself influence the reporting of placebo effects. Mistakes can be made in the measurement of placebo effects. They can be misrepresentations of reality. The measurement process itself can be a potent stimulus which distorts clinical evaluations made by patients. The general environment in which measurements are made may significantly influence the judgments of therapeutic effects by patients and physicians.

Response Artifacts

The reactive effects of measurement have always been a problem for researchers. Patient and staff behavior may change with evaluation of behavior. When filling out questionnaires, patients may distort responses by lying, faking illness or health, responding thoughtlessly and carelessly, or tending to give socially sanctioned responses. Since placebo effects are often assessed in uncontrolled studies, it is impossible to know the degree to which response-bias artifacts influence the assessment of placebo effects.

Labeling

It is sometimes assumed that the self-reported feelings or emotions are accurate reflections of psychologic states. However, an individual's response is often vague and interpretable only within the social context. The same psychologic reaction may be called "anger" or "euphoria" depending on the situation in which the response occurs (5). Patients may label their therapeutic reactions in terms of their expectations or the descriptions furnished by their physicians. Furthermore, there may be a tendency for patients to use somatic labels when describing response to physical treatments such as medication but to use more affective and cognitive labels when describing response to treatments such as psychotherapy.

Misattribution

Patients also judge the cause of an observed change. A powerful therapeutic variable is the knowledge that a therapy has been rendered. Slight changes in a patient's emotional or physical state, which might otherwise go unnoticed, may

be misattributed to the administered therapy. A multitude of environmental factors may cause changes which patients attribute to their treatment. Alleged side effects of medication may actually be symptoms of inadequately treated preexisting disease (6). The natural or self-limiting course of the disease or an environmental factor may result in improvement and may be attributed by the patient to the physician's intervention.

CORRELATES OF THE PLACEBO EFFECT

Multiple interacting and competing variables derived from the patient, physician, environment, and culture may influence the placebo effect differentially, depending on the type of therapy rendered and the method of assessment. It is not surprising that a survey of the literature fails to find consistent correlates of placebo reaction, although several trends are apparent.

Patient Factors

Demographic factors such as sex, age, and intelligence are inconsistently related to placebo reaction. For example, some studies find that males react more than females, others that females react more than males, while most studies find no relationship between patient's sex and placebo response.

Although many personality variables have been hypothesized or reported in retrospective studies of the placebo response, few have withstood the test of prospective empiric scrutiny. At best, emotionalism, anxiety, and some personality variables such as acquiesence, social desirability, introversion, and extroversion are weak correlates of placebo reaction. They are often conceptualized as general predisposing factors, which may predict placebo reactions when combined with a multitude of other factors.

Physician Factors

The physician's contribution to the placebo effect, referred to as "iatroplacebogenics," has been emphasized in recent years. Discussion centers around three factors: 1) the physician's interest in the patient, which refers to the therapist's warmth, friendliness, liking, sympathy, empathy, disinterest, rejection and hostility; 2) the physician's interest in the treatment, which refers to the physician's faith, belief, enthusiasm, conviction, commitment, optimism, positive and negative expectations, skepticism, disbelief and pessimism; and 3) the bias generated by interest in the results of a therapy or experiment, which causes data distortion. These three factors have been demonstrated in many studies to be associated with successful treatment in general and with placebo effects.

Indirect iatroplacebogenics is a more subtle method by which physicians' motivations can effect patients' responses to treatment. It occurs when a physician's interest in a theory or treatment is misinterpreted and displaced by the patient as a personal interest by the physician in himself. Medical history provides many examples of prestigious physicians with intense intellectual and emotional commitments to various therapeutic theories and practices which were frequently elaborate, fashionable, expensive, and dangerous. After a period of great success, the majority of them were later judged to be ineffective. A common factor in these therapies was the interest of the physician.

USE OF PLACEBOS IN TREATMENT

Before 1960, most nonpsychiatrists favored the use of placebos in treatment. Although psychiatrists were predominantly opposed to the use of placebos before 1960, since that time they have accepted their use in treatment. In the late 1940s, an English survey of drug use indicated almost one third of the medicines prescribed could be considered placebos. Medicine has advanced since that time, and there is an increasing number of specific and active treatments for many symptoms and diseases. However, physicians still accept the use of vitamin B_{12} injections as placebos, and antianxiety-sedative-hypnotic drugs (including minor tranquilizers) are often prescribed for their nonspecific effects.

Can placebos be ethically and properly used in treatment? At the present time, the knowing or unknowing use of placebos is inevitable, although indications or counterindications are not possible to specify. Risk-benefit decisions are apt to become confounded by the physician's own value system. Therefore, encouragement should

be given to the use of specific and rational therapy whenever possible.

Indications

Although acceptable indications for use of placebos are controversial, some of the suggestions from the literature include 1) patients with degenerative, malignant, or incurable diseases for which specific treatment is unavailable; 2) patients hospitalized for prolonged investigation who become impatient while undergoing tests; 3) patients with a confusing clinical course, as a substitute for drugs which may contribute obfuscating symptoms; 4) weaning postoperative patients from narcotics to prevent habituation; 5) elderly or chronic patients who have become accustomed to taking medication of questionable value; and 6) to differentiate psychologic from nonpsychologic side effects in psychochemotherapy. The least controversial use of placebos is as a control in research. However, some investigators question the ethics and legality of using placebos even here (9).

Precautions

The indications for the use of placebos should be carefully considered. The physician should be cautious about their use if he is aware of hostile, contemptuous, or other negative feelings toward demanding and difficult patients. They should be used cautiously when the physician can think of nothing else to give. Patients may sense the underlying attitude of the doctor, and their response to treatment may vary accordingly. Patient disappointment about therapy may be expressed as hostility, noncompliance with therapeutic regimens, and dropping out of treatment. The credability of physicians can be severely undermined when patients are aware that they have been deceived.

Inactive vs Active Placebos

Opinions differ about whether to use inert substances such as lactose (inactive placebos) or active drugs at subpharmacologic doses as placebos (active placebos). Active drugs sometimes cause serious consequences despite placebo dosages. If an impure placebo is used, it should always be a safe drug. However, one should avoid attributing favorable results to an active drug used as a placebo.

Evaluation of Therapies

Recognition and study of the placebo effect has contributed to improvement in the methodology of evaluating therapy. Although many of the difficulties about evaluation remain unsolved, major advances have been achieved.

Single-Blind Procedure

Methods of clinical evaluation have had a varied and checkered history. One of the earliest techniques has been referred to as the single-blind procedure. In this method, the physician or investigator knows that control substances are being used and which patients are receiving them. The patient alone is unaware. The control is usually a placebo.

Double-Blind Procedure

Single-blind studies frequently produce spurious results because of bias that occurs when physicians or investigators know whether patients have been assigned to placebo or drug groups. To avoid these problems, the double-blind procedure, in which neither the patient nor the physician (or others treating or evaluating patients) know which group of patients have been assigned to receive active or inactive medication, was evolved. Although the earliest use of this procedure dates back to the beginning of the 20th century, it became popular only recently. Since 1960, the double-blind procedure has been the norm for most well-designed studies.

Exact Placebos. It is important that a placebo control have all the physical characteristics of the experimental substance. Patients, physicians, or investigators may uncover the code if the placebo does not resemble the experimental drug or have the same taste or consistency. Capsules, rather than tablets, should be used so that the medication placebo can more closely resemble the active drug under investigation.

Active Placebos. The use of active placebos which mimic the telltale side effects of the experimental substance has been recommended when feasible. Without an active placebo, physician and staff may be able to distinguish between experimental and control groups, in which case the double-blind procedure then actually would become a single-blind procedure.

Although the concept of active placebos is appealing, its application is limited to the study of active drugs the side effects of which can be mimicked by the active placebo.

Limitations of the Double-Blind Procedure. The use of the double-blind procedure decreases the possibility of an erroneous conclusion that a drug is effective when it is, in fact, ineffective. However, the double-blind procedure may result in incorrect conclusions about the effectiveness of drugs. This comes about for statistical reasons such as using too small a sample or inappropriate randomization or matching procedures, psychometric reasons such as using measures which do not adequately differentiate responses, and methodologic reasons such as staff bias in evaluating results.

Some investigators believe that objective experiments do not exist. This has prompted the suggestion that every experiment should be done by an enthusiast and a skeptic and that the investigator's bias about expected results be specified in the paper. Various suggestions have been offered concerning how to make methodology more sound and foolproof. Certainly, there is room for improvement.

Triple-Blind Procedure

The triple-blind procedure (a term more euphemistic than descriptive) has been used in two ways. Some investigators have attempted to exclude or minimize placebo effects by conducting a preliminary study with placebos. Subjects who respond to placebo are then excluded from the definitive study which follows. Unfortunately, because placebo responses are inconsistent, nonplacebo reactors in the preliminary study may develop placebo responses in the definitive study. A second use of the term refers to the "blindness" in the assessment of study results. An independent assessment team, unaware of study design and procedures, administers tests of therapeutic efficacy.

IMPLICATIONS

Therapy will be impaired if physicians are unaware of placebo effects. Therapeutic effects will be attributed to specific procedures, which, unknown to the physician, are caused by placebo effects. The therapist's credulity about the efficacy and specificity of the procedure will be incorrectly augmented, and the therapist may be encouraged to use one technique for all patients. Therapists who rely on one technique may be unable to treat many patients, some patients may be harmed because of inappropriate treatment, and specific indications for a therapeutic procedure will be confused. Awareness of placebo effects will enable physicians to better evaluate the effects of therapy, contribute to the development of more flexible and appropriate procedures, and make therapy more comprehensive, resourceful, and effective. The recognition that these factors will contribute to the treatment process will improve studies by investigators and may help clarify unsolved problems of specificity in many therapies.

It is important to remember that despite the massive evidence supporting the concept of placebogenesis and iatroplacebogenesis, the evidence is based primarily on retrospective data. Careful prospective studies will be necessary for clarification of the processes and the relevancy and validity of the concepts.

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10

THE PLACEBO EFFECT IN MEDICAL AND PSYCHOLOGICAL THERAPIES

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INTRODUCTION

Placebo effect research provides both an historic and methodological perspective of psychotherapy and behavior change. Psychotherapy is commonly believed to be a modern treatment based on scientific principles while the placebo effect is believed to be a superstitious response to a sugar pill. Yet, the placebo effect may have greater implications for psychotherapy than any other form of treatment because both psychotherapy and the placebo effect function primarily through psychological mechanisms.

The concept of the placebo effect is generally not popular among therapists and researchers. Physicians tend to deny their own use of placebos and assume that other physicians use placebos more often than themselves (Hofling, 1955; Shapiro & Struening, 1974). In research, placebo effects are viewed as experimental artifacts (McGuire, 1969). These artifacts are ignored or are sought to be controlled or eliminated from ongoing research. Very rarely does the placebo effect undergo empirical scrutiny as a research topic in its own right.

However, the placebo effect is an important component and perhaps the entire basis for the existence, popularity, and effectiveness of numerous methods of psychotherapy. The thesis of this chapter is that much can be learned about psychotherapy from study of the placebo effect. Attention to the placebo effect may help differentiate the meaningful specific influences from the

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nonspecific factors in psychotherapy. A true understanding of the specific components of psychotherapy can only occur when the components of the placebo effect are also understood (Gliedman, Nash, Imber, Stone, & Frank, 1958).

These considerations led to the search for generalizations and hypotheses about all methods of therapy. Although various mechanisms and processes have been proposed as explanations of the placebo effect, empirical support for an adequate theory is absent. Hypotheses and conclusions about psychotherapy and the placebo effect will be derived from review of prescientific and modern treatment, and the placebogenic factors contributed by the patient, situation, physician, and their interrelationships. Selected theoretical concepts, drawn primarily from the social, clinical, and experimental psychological literature, will be utilized to explain placebo effects. Only those concepts that can be applied to psychotherapy and behavior change will be focused on in this review.

PRESCIENTIFIC MEDICINE

Psychological factors, always important in medicine, were recognized as early as the period of Hippocrates. Galen estimated that 60 percent of patients had symptoms of emotional rather than physical origin. This figure is close to the contemporary estimate of 50 to 80 percent. Despite Galen's and Hippocrates' acumen, few if any of the drugs used by the physicians of their day caused pharmacologically induced therapeutic change. Treatment was primitive, unscientific, largely ineffective, and often shocking and dangerous (Shapiro, 1959, 1960a).

Patients took almost every known organic and inorganic substance—crocodile dung, teeth of swine, hooves of asses, spermatic fluid of frogs, eunuch fat, fly specks, lozenges of dried vipers, powder of precious stones, bricks, furs, feathers, hair, human perspiration, oil of ants, earthworms, wolves, spiders, moss scraped from the skull of a victim of violent death, and so on. Blood from every animal was prepared and administered in every way, and was used to treat every conceivable symptom and disease. Almost all human and animal excretions were used.

Some famous treatments used for centuries include the Royal Touch, Egyptian mummy, unicorn horn, bezoar stone, and mandrake. Theriac contained 37 to 63 ingredients; mattioli contained 230 ingredients and required several months to concoct. Galen's elaborate pharmacopoeia, all worthless, contained 820 substances. Medical reasoning was primitive: Lung of fox, a long-winded animal, was given to consumptives. Fat of bear, a hirsute animal, was prescribed for baldness. Mistletoe, a plant that grows on the oak that cannot fall, was specific for the falling sickness (Lehmann & Knight, 1961). A wound was treated by sympathetic powder that was applied to the inflicting implement. Throughout medical history patients were purged, puked, poisoned, punctured, cut, cupped, blistered, bled, leached, heated, frozen, sweated, and shocked (Garrison, 1921; Haggard, 1929, 1933, 1934; Major, 1955; Shapiro, 1959, 1960a).

Although medicine has held a place in the finest scientific, religious, cultural, and ethical traditions throughout history, one may wonder how physicians maintained their position of honor and respect. Useful drugs or procedures were applied infrequently and were usually forgotten by succeeding generations. For thousands of years physicians prescribed what we now know were useless and often dangerous medications. This would have been impossible were it not for the fact that physicians did help their patients.

Today we know that the effectiveness of these procedures and medications was due to psychological factors often referred to as the placebo effect. Since almost all medications until recently were placebos, the history of medical treatment can be characterized largely as the history of the placebo effect.

The first major contribution to the end of Galenism and to the beginning of scientific medical treatment is often attributed to Sydenham in the seventeenth century. He is erroneously credited with demonstrating that cinchona bark (which contains quinine) was specific only for fevers of malarial origin, and not for all febrile infections (Duran-Reynals, 1946; Forrer, 1964a). Cinchona bark often has been thought of as the first drug that

was not a placebo, because previously there had been no way to distinguish between placebo and nonplacebo. But the placebo effect flourished as the norm of medical treatment even after the beginning of modern scientific medicine seven or eight decades ago (Shapiro, 1959, 1960a).

These considerations have led to the famous admonition: *Treat as many patients as possible with the new remedies while they still have the power to heal.*

DEFINITION OF PLACEBO

The history of the placebo begins with the Hebrew Bible. The first word of Psalm 166:9 is "Ethalech," which was translated into the Latin Bible as "placebo." The word "placebo" is derived from the verb "placere," meaning "to please" (Murray, 1933). "Placebo" entered the English language in the twelfth century by becoming the name commonly given to vespers for the dead, a custom that is no longer followed and whose meaning is now obscure (*The Catholic Encyclopedia*, 1911).

"Placebo" took on a secular meaning in the fourteenth century and its connotations gradually became derisive during the next several centuries. The word was used to describe a servile flatterer, sycophant, toady, and parasite. The usage derives from disparagement of the professional mourners who were paid to "sing placebos" at the bier of the deceased, a role originally assigned to the family.

Few people realize that medical dictionaries have limited their definitions of the placebo to inert or inactive drugs only during the last three decades (Blakiston's *New Gould Medical Dictionary*, 1949). The original that appeared in the 1785 edition of *Motherby's New Medical Dictionary* (1795) was: "A commonplace method or medicine."

This original definition was misquoted as a "commonplace method *of* medicine." This error in the etymology of placebo has influenced the meaning attributed to the word. The distinction between "of" or "or" is important, since the former limits the definition to medicine, whereas the latter includes methods *and* medicines. Although the original definition included all therapies, as drugs became more important in medical theory and practice, the term became limited to pharmacologic interventions. This continued until 1949 when medical dictionaries, partly owing to their perpetuation of early errors, began to limit the definition to inert substances. Such interpretation has influenced the thinking of many physicians and nonphysicians, who conceive of placebos only as inert drugs. Recently, as treatments have changed and psychotherapy has become more prominent, definitions of placebo have expanded and now are more like the original definition that appeared in 1785.

Our proposed definition, which we believe fulfills historic and heuristic criteria, follows:

A *placebo* is defined as any therapy or component of therapy that is deliberately used for its nonspecific, psychological, or psychophysiological effect, or that is used for its presumed specific effect, but is without specific activity for the condition being treated.

A *placebo*, when used as a control in experimental studies, is defined as a substance or procedure that is without specific activity for the condition being evaluated.

The *placebo effect* is defined as the psychological or psychophysiological effect produced by placebos.

There are several important features of this definition. There are no assumptions made about the intent of the therapist to issue placebo therapy. The therapist may knowingly give placebo treatment. Conversely, he or she may administer placebos in the belief that they are specific and active but by *objective evaluation* the therapy does not have specific activity for the condition under treatment. There are also no assumptions made about the effects of therapy. Placebos may have positive, negative, or no effect. Placebos may or may not induce side effects.

Implicit in this definition is the assumption that active treatments may contain placebo components. Even with specific therapies results are apt to be due to the combination of both placebo and nonplacebo effects. Treatments that are devoid of

active, specific components are known as pure placebos, whereas therapies that contain nonplacebo components are called impure placebos (Leslie, 1954). Treatments that have specific components but exert their effects primarily through nonspecific mechanisms are considered placebo therapies. The relative contribution of placebo components in any therapeutic process is likely to decrease as more becomes known about the cause and cure of the condition, and as therapies more directly and specifically affect the maladaptive or disease entity.

The key concept in defining placebo is that of "specific activity." In nonpsychological therapies, specific activity is often equated with nonpsychological mechanisms of action. When the specific activity of a treatment is psychological, this method of separating specific from nonspecific activity is no longer applicable. Therefore, a more general definition of specific activity is necessary. Specific activity is the therapeutic influence attributable solely to the contents or processes of the therapies rendered. The criterion for specific activity (and therefore the placebo effect) should be based on scientifically controlled studies. In behavior therapy, some investigators have utilized "active placebo" control groups whereby some aspects of the therapy affect behavior but those aspects differ from the theoretically relevant ingredients of concern to the investigator (Kazdin & Wilcoxon, 1976).

This definition does not mention the mechanism of placebo action, although it implies that psychological factors are important determinants. The placebo effect is a multidetermined phenomenon influenced by many different factors and processes. Some of these factors are considered in subsequent sections. However, the issue is left open in our current definition because placebogenic factors are not yet well understood or documented.

Although this definition may prove to be too inclusive, for heuristic reasons it would be premature to make specific exclusions at this time. It is likely that various placebogenic factors will be isolated in the future. When enough is known about the placebo effect so that its effects can be predicted, the definition will no longer be needed, except in lexicons of obsolete terms. This is something to consider for the future.

MODERN MEDICINE

Modern medicine no longer relies chiefly on placebo effects. Today, there are an increasing number of specific and predictable drugs, devices, and procedures. However, as long as individuals are aware that they are receiving treatment, psychological factors cannot be excluded. Of course, if the dosage of a drug is high enough all patients will react with toxicity and even death, regardless of psychological factors. However, the predictability of toxicity is of little consequence because toxic dosages are rarely prescribed. Normal dosages are within the range in which placebo effects are important.

Claims about the importance of placebo effect to modern medicine range from ". . . the most effective [drug] . . . to be developed by the pharmaceutical laboratories . . ." (Zimbardo, 1969) to ". . . they are small treatments for small illnesses . . ." (Hamilton, 1968). Although, placebo effects are more prominent with certain conditions and treatments than others, the placebo effect remains an important element in modern medicine. Placebo effects have been demonstrated in dentistry (Shipman, Greene, & Laskin, 1974; Valins, Adelson, Weiner, & Goldstein, 1971), podiatry (Morris, Shangold, & Greenberg, 1975), optometry (Carter & Allen, 1973) and in every aspect of modern medical treatment including biofeedback (Miller, 1974; Stroebel & Glueck, 1973), acupuncture (Chaves & Barber, 1973; Gaw, Chang, & Shaw, 1975; Kroger, 1973), cancer treatment (Klopfer, 1957), surgery (Diamond, Kittle, & Crockett, 1960), and electroconvulsive therapy (ECT) (Guido & Jones, 1961; Marshall & Izard, 1974). Placebos have been demonstrated to be addictive (Vinar, 1960), to mimic the effects of active drugs (Lasagna, Laties, & Dohan, 1958), to reverse the action of potent drugs (Hagens, Doering, Ashley, Clarke, & Wolf, 1957; Wolf, 1959), and to have direct effects on bodily organs (Sternbach, 1964; Wolf, 1950) and on organic illnesses (Shapiro, 1963).

Recent interest in the placebo effect of medical treatment has also fostered the development of clinical methodology to control placebo effects in therapeutic studies. General appreciation of the placebo influence is perhaps the main reason for

the growth and acceptance of controlled clinical studies. In psychotherapy research, the placebo has become synonymous with the search for the appropriate control group against which therapies are compared.[1]

PROBLEMS OF RESEARCH

In reviewing placebo effect research, one is struck by the conflicting findings and failure to replicate. These inconsistent results occur partly because of the diversity of subject populations (ranging from college students to clinic patients to subhuman species), testing environments (from experimental laboratories to hospital clinics), degree and types of illnesses (from normals to organically ill to maladjusted), range of treatments (from surgery to biofeedback) and methods of measurement (from subjective self report measures to objective indicies of physiological change).

However, replication is infrequent even when seemingly identical procedures are used on highly similar populations (Bootzin, Herman, & Nicassco, 1976; Storms & Nisbett, 1970; Kellogg & Baron, 1975; Lipman, 1966). When the same subjects are given identical placebo stimuli in different environments, the response is inconsistent (Wolf, Doering, Clark, & Hagans, 1957; Liberman, 1964; Frank, 1968). The inconsistency of reaction could lead to the conclusion that the placebo effect is a random factor. A more likely conclusion, however, is that the placebo effect is not caused by a unitary process. Placebo effects are probably the result of a complex combination of many different variables and modes of action.

Identification and integration of all the different variables and processes affecting placebo reaction will await many more years of investigation. However, as placebo processes become identified and explained, they also gain the potential to become nonplacebo therapies. For example, operant conditioning, which may be a basis of the placebo effect, is now itself used as a specific therapeutic tool.

Unfortunately, explanations for the placebo effect are more often the result of ex post facto theorizing than empirical study. It is noteworthy that the recent motivation prompting interest in the placebo effect is the desire to improve research methodology (Honigfeld, 1964a, 1964b). The main methodological tenet from placebo effect research is that comparisons cannot be made in a vacuum. The only "facts" are derived on a relative basis and valid judgments about the effectiveness of any therapy can be made only by comparison to the appropriate control group (Boring, 1968).

Much of the theorizing about the placebo effect is based on the responses of control groups that were retrospectively interpreted but rarely tested prospectively. Explanations are more often based on the theories of the investigator than on study results. However, empirical study has suggested different variables and processes of placebo action. The contribution of any single element will likely depend on a multitude of factors. Variables that have not received full empirical confirmation cannot be dismissed at the present time, because if they were, there would be little left to report.

PATIENT VARIABLES

The Placebo Reactor

Although retrospective analyses indicate that the placebo effect was the cause of the success of many medical treatments, it is only since the middle 1950s that the placebo effect has become a research topic in its own right (Shapiro, 1960a). The observation that some subjects reacted to placebos while others did not fostered the hypothesis that reaction to placebos was an enduring patient characteristic.

There are two important features of the placebo reactor hypothesis. First, to validate this assumption, there must be a consistency of reaction across several placebo administrations. This is necessary to demonstrate that some enduring trait of the individual receiving treatment, rather than a transient factor, causes the placebo reaction. Second, if placebo reaction is an enduring characteristic of the individual receiving therapy, demographic and

[1] Borkovec, 1973; Borkovec & Nau, 1972; Boudewyns & Borkovec, 1974; Cutela, Flannery, & Hanley, 1974; Foreyt & Hagen, 1973; Haynes, Woodward, Moran & Alexander, 1974; Marshall, Boutilier, & Minnes, 1974; McReynolds, Barnes, Brooks, & Rehagen, 1973; Nau, Caputo, & Borkovec, 1974; Tori & Worell, 1973; Young, Rimm, & Kennedy, 1973.

personality traits may be isolated to identify the placebo reactor. Once identified, placebo reactors could benefit from placebo therapies that do not have the adverse effects of active treatments (Evans, 1974); they could be systematically excluded from therapy evaluations, thereby increasing the sensitivity and power of these studies (Ainsle, Jones, & Stiefel, 1965; Lasagna, Mosteller, von Felsinger, & Beecher, 1954; Linn, 1959); and placebo reactions might serve as a diagnostic aid (Bush, 1974).

Early placebo researchers reported support for the consistency assumption. Beecher (1955) reviewed 15 studies of 1082 patients, which evaluated placebo effectivenesss in varying subject populations and conditions. He reported an average placebo effect of "35.2 ± 2.2 percent." Beecher's figures are often quoted[2] as an indication of the high degree of consistency of placebo reaction. However, almost totally overlooked is the fact that Beecher's measure of variability, "±2.2 percent," was not a range or standard deviation, but a standard error of the mean (the standard deviation divided by the square root of the summed number of items). More recent reviews have shown that placebo effects vary from 0 to almost 100 percent among different populations, disease and treatment conditions (Hass, Fink, & Hartfilder, 1963; Parkhouse, 1963; Shapiro, 1964a).

It is important to recognize that even if the percentage of individuals who react to placebos is consistent, the consistency assumption would remain unproven. The placebo reactor hypothesis predicts that the same individuals react to placebos over time and varying environmental conditions. Studies of placebo reactions over time (Frank, 1968; Wolf et al., 1957), and for various conditions (Liberman, 1964), find inconsistent placebo reactions. Even investigators, who previously favored the placebo reactor model, now reject it (Lasagna, 1972; Liberman, 1966).

These data do not support the model of a consistent placebo reactor. However, it is possible that there are enduring patient characteristics that, together with other factors, might predict placebo reaction. If individuals do not consistently react to placebos, traits cannot be considered strong correlates of placebo reaction. It is possible that no definitive traits exist. However, a more accepted view is that certain traits may predispose some individuals to react to placebos but that a multitude of other factors also determine placebo effect (Campbell & Rosenbaum, 1967; Fisher, 1967; Gelfand, Gelfand, & Randin, 1965; Honigfeld, 1964a; Lasagna, 1972; Liberman, 1964). Two types of predispositions have been hypothesized: general predispositions that exert their influence in various environments and specific predispositions that become associated with placebo reactivity only in certain situations (Fisher, Cole, Rickels, & Uhlenhuth, 1964; Liberman, 1961).

The difficulty of relating personality and demographic variables to the placebo effect is demonstrated by a study of Shapiro, Mike, Barton, & Shapiro (1973). Fifty-five variables, which previous literature indicated might predict placebo response, were analyzed for their relationship to the placebo effect. The placebo effect was measured by four different self-report indices; change in symptomatology, global rating of overall change, the occurrence of side effects, and total score based on a combination of these three measures. Stepwise discriminant analyses showed that for each method of scoring the placebo effect, 85 percent of the patients could be correctly classified as to the type of placebo reaction (positive, negative, or neutral) by utilizing all 55 variables as predictors. However, the relative importance of each variable as a predictor was highly dependent on the method of scoring placebo reaction. Only four predictor variables were common to the first (and therefore most important) 25 predictors chosen in each of the four discriminant analyses: the MMPI variables of depression, hypochrondriasis and repression, and the duration of current illness as measured by a demographic scale.

Demographic Variables

Some studies have reported that females have more placebo reactions than males (Abramson, Jarvik, Levine, Kaufman, & Hirsch, 1955;

[2] Benson & Epstein, 1975; Blackwell, Bloomfield, & Buncher, 1972; Bourne, 1971; Brodeur, 1965; Carter & Allen, 1973; Davidson, 1960; Evans, 1969; Gliedman, Gantt, & Teitelbaum, 1957; Kurland, 1957; Lehmann, 1964; Lesse, 1964.

Beecher, 1955; Gliedman et al., 1958; O'Brien, 1954; Rickels, 1965), some that males react more than females (Goldberg, Schooler, Davidson, & Kaye, 1966), while other studies have found no difference between the sexes (Batterman & Lower, 1968; Bishop & Gallant, 1966; Black, 1966, Lasagna, et al., 1954; Samuels & Edison, 1961; Tibbets & Hawkins, 1956). These conflicting results would seem to rule out patient sex as generally predisposing a placebo reaction. However, Aletky and Carlin (1975) have suggested that the method of measuring placebo reaction and pertinant sex role expectations may function as intervening variables that mitigate placebo effects. In some studies, young age correlated positively with placebo effects (Gliedman et al., 1958; Kurland, 1958; Shapiro, Wilensky, & Struening, 1968; Tibbets & Hawkins, 1956); in others it correlated negatively (Lasagna et al., 1954; O'Brien, 1954), or did not correlate either positively or negatively (Abramson et al., 1955; Black, 1966; Fischer & Dlin, 1956; Hankoff, Engelhardt, & Freedman, 1966; Isaacs, 1959; Knowles & Lucas, 1960; Roberts & Hamilton, 1958; Stukat, 1958).

Like the sex variable, it is unlikely that age is a general predisposing factor for placebo reaction. Even when sex and age are conjointly examined, additional factors regarding the context in which therapy is administered, must be taken into account to explain results (Raskin, 1974).

Placebo effect have been associated with lower verbal IQ in one study (Rickels & Downing, 1965) but not in two others (Grimes, 1948; Shapiro et al., 1968). One study found lower educational level to predict placebo response (Gliedman et al., 1958), one study found higher educational level associated with placebo response (Moertel, Taylor, Roth, & Tyce, 1976), and several others found no significant effect of education (Downing & Rickels, 1973; Isaacs, 1959; Rickels & Downing, 1962; Rickels, Downing, & Howard, 1971; Samuels & Edisen, 1961).

Blacks have been reported to have greater placebo effects than whites in four studies (Batterman & Lower, 1968; Goldberg et al., 1966; Rickels, Gordan, Jenkins, Perloff, Sachs, & Stepansky, 1970; Samuels & Edisen, 1961). However, in one published (Shapiro et al., 1973) and three unpublished studies (Shapiro, Struening, Shapiro, Morris, & Raab, in preparation) race was unrelated to placebo reaction. These latter studies differed from the former in that the clinics treated primarily middle-class rather than lower-class patients. Any conclusions relating race to placebo reaction must be considered as extremely tentative in light of the multitude of confounding factors such as differential diagnoses and limited sampling of social classes.

Personality Variables

Suggestibility

The most extensively investigated factor in the study of the placebo effect is the concept of suggestion. This approach is important because of the presummed common components in tests of suggestibility and the placebo effect. Over the years, the meaning of the term "suggestibility" has expanded to include many diverse phenomena, including the placebo effect (Beecher, 1968; Sturpp, Levenson, Manuck, Snell, Hinrichsen, & Boyd, 1974). Although the plausible expectation that tests of suggestibility would correlate with the placebo effect has received partial substantiation (Duke, 1964; Hornsby, Bishop, & Gallant, 1967; McGlashan, Evans, & Orne, 1969; Steinbook, Jones, & Ainsle, 1965), overall, it has not been consistency supported (Bentler, O'Hare, & Kransner, 1963; Butler, Gaines, & Lenox, 1976; Duke, 1962; Evans, 1967; Frank, Gliedman, Imber, Nash, & Stone, 1967; Gliedman et al., 1968; Grimes, 1948; Stukat, 1958).

One possible explanation for this inconsistant relationship is that the placebo stimulus is not the same as that of a test of suggestibility. Barber and Calvery (1964) have shown that responses to a suggestibility test vary greatly depending upon whether the suggestions are introduced as a test of "gullibility" or "imagination." Placebos are commonly associated with therapeutic stimuli whereas tests of suggestibility are associated with laboratory experiments. Patient motivations and their interpretation of stimuli may vary greatly depending whether tests are administered in the context of experiments or therapies (Shapiro, 1960, 1964, 1968). Therefore, the relationship of suggestibility to placebo reaction is moderated by variables such

as expectations and the meaning attributed to stimuli by patients (Wolf, 1959).

Acquiescence and Social Desirability

The basis of the placebo effect is often conceptualized as due to a response style characteristic. People who tend to comply with questionnaire items regardless of content, or who answer questions in a socially desirable manner, are considered likely positive placebo reactors.

Reports relating traits such as social desirability, response bias, acquiescence, and "yea saying" to placebo reaction have appeared in the literature (Fisher & Fisher, 1963; Gelfand et al., 1965; Pichot & Perse, 1968). However, this relationship has not been consistently substantiated (Bank, 1969; Fast & Fisher, 1971; Linton & Langs, 1962; McNair, Kahn, Droppleman, & Fisher, 1968; Shapiro et al., 1973; Raskin, Boothe, Schulterbrandt, Reatig, & Odle, 1973).

At best, traits such as social desirability and acquiescence can be considered weak correlates of placebo reaction. The influence of these traits might be more substantial when placebo effects are measured by self-report paper-and-pencil tests. It seems unlikely that a response can be totally dissociated from the content of the questionnaire material (Rogers, 1974; Rorer, 1965; Taylor, Carithers, & Coyne, 1976). Therefore, the importance of these personality variables in any particular study may be highly reliant on the specific questions used to measure the trait and the placebo effect.

Dependency

The concept of dependency involves both emotional and perceptual components. Clinical folklore suggests the association between emotional dependency and placebo reaction. However, the only measure of emotional dependency that has been related to the placebo effect is based upon projective techniques used in a study by Lasagna et al. (1954). This study cannot be considered as offering adequate support for the relationship between emotional dependency and placebo reaction because of the low reliability of projective techniques and other methodological shortcomings. Questionnaire measures of emotional dependency fail to indicate any significant relationship (Campbell & Rosenbaum, 1967; Sharp, 1965). The related concept of external locus of control is similiarly uncorrelated with the placebo effect (Bradsma, 1973).

The perceptual measure of field dependency, hypothesized as related to placebo reaction, has not been confirmed by empirical study (Bradsma, 1973; Dinnerstein & Halm, 1970; Freund, Krupp, Goodenough, & Preston, 1972; Shapiro et al., in preparation).

Introversion-Extraversion

Both introversion and extraversion have been related to placebo reaction. The rationale relating introversion to placebo response is based on learning theory. The placebo effect is viewed as a generalization from other situations. Introverts, having greater speed of conditioning, should acquire placebo responses more readily and lose them less readily than extraverts (Trouton, 1957). Although by no means unanimous (Shapiro et al., in press), some empirical data support this relationship (Luoto, 1964; Morison, Woodmansey, & Young, 1961; Thorn, 1962).

The postulated relationship between extraversion and the placebo effect is based on extraverts' greater reliance on external factors. Knowles and Lucas (1960) have suggested that extraverts may be more apt to attribute relatively normal changes in behavior or physiological state to the action of an external agent such as a placebo. Support for this relationship is found in several studies (Black, 1966; Campbell & Rosenbaum, 1967; Gartner, 1961; Knowles & Lucas, 1960), but again, unconfirmed in a study of Shapiro et al. (In preparation).

Research supporting the relationship between the placebo effect and both of these opposite traits highlights the complicated association between personality and the placebo effect. It suggests the possibility of different pathways for placebo effects. The inherent contradiction of both introversion and extraversion being related to placebo reaction also suggests that this relationship may be artifactual. These results warrant further study utilizing reliable and valid measures of introversion-extraversion and the placebo effect.

Psychopathology

Placebo reactions are common in patients diagnosed as normal, neurotic, or psychotic. Conflicting results have been reported for an association between placebo effects and a general trait of neuroticism (Gartner, 1961; Luoto, 1964; Knowles & Lucas, 1960). Different methods of measuring placebo reaction make it impossible to directly compare the susceptibility of normals, neurotics, and psychotics to placebo effects. However, the range of measurements suggest that the nature and intensity of placebo reactions are greater for the psychotic. Hysteria, prone to suggestion effects, would seem likely to be related to placebo reactivity. However, several studies have failed to support this relationship (Gartner, 1961; Kornetsky & Humphries, 1957; Muller, 1965; Shapiro et al., 1973).

Shapiro et al. (1968) reported that placebo effects range from 18 to 67 percent for various diagnostic categories. The most frequently cited symptoms associated with placebo reactions are emotionality, depression, and anxiety (Lasagna et al., 1954; Pichot & Perse, 1968; Rickels & Downing, 1967; Shapiro, 1959, 1960a, 1968; Shapiro et al., 1973; Shipman et al., 1974; Sharp, 1965; Thorn, 1962). Manifest, unelaborated anxiety is frequently associated with placebo reaction. Beecher (1960) in anesthiology, Castiglioni (1946) in history and Parsons (1951) in sociology believe that suggestibility increases with increased stress. In proper amounts, anxiety also facilitates learning and focuses attention. Anxiety is considered a favorable prognostic sign in psychotherapy, insulin treatment, and lobotomy. However, careful evaluation of the importance of anxiety in studies of the placebo effect reveal somewhat inconsistent effects and weak correlations (Shapiro et al., in preparation). More carefully conceived and executed studies are required to substantiate this relationship and possibly elucidate the type of anxiety that may be associated with placebo reactions.

SITUATIONAL VARIABLES

The situation in which therapy is administered is an important determinant of its effectiveness. Judgments about the need for therapy and interpretation of a therapy's effectiveness are both highly reliant on situational factors. For example, Beecher (1956) found that the same type of wound caused vastly different reports of pain depending on whether the patient received the wound from surgery or in a war. Soldiers reported much less pain and need for analgesia, presumedly because the wound was a signal to them that they might be sent home.

Situational factors are especially important when placebo effects are measured by subjective reports, such as mood change (Schachter & Singer, 1962; Lyerly, Ross, Krugman, & Clyde, 1964), pain threshold (Clark 1969; Feather, Chapman, & Fisher, 1972; Davison & Valins, 1969), and the achievement of a marijuana (placebo) "high" (Ademec, 1973; Becker, 1974; Carlin, Bakker, Halperin, & Post, 1972; Carlin, Post, Bakker, & Halperin, 1974; Lennard, Epstein, Bernstein, & Ranson, 1971). Situational factors are conceived as providing an integral component of any emotional response. According to Schachter and Singer's (1962) theory of emotion, individuals interpret their own reactions by means of situational cues. The rendering of therapy provides a potent environmental cue.

In addition to interacting with bodily state changes, situational cues can influence the "milieu" in which therapy is given. Some of the situational variables that affect placebo reactions are staff attitudes, type of population under study, the setting, the treatment procedure, and other miscellaneous factors. Therapist variables, which constiute a major set of situational factors, will be discussed in a separate section.

Staff

Staff attitudes, expectations, biases, conflicts, and harmony can influence placebo effects.[3] Negative staff attitudes can reduce the effectiveness of active medication (Sabshin & Ramot, 1956). The effect

[3]Baker & Thorpe, 1957; Eissen, Sabshin, & Heath, 1959; Goldstein, 1962; Hofling, 1955; Linn, 1959; Mezaros & Galagher, 1958, Rathod, 1958; Shapiro, 1960a; Stanton & Schwartz, 1954; Volgyesi, 1954; Von Mehring & King, 1957.

of a placebo can be reduced from 70 to 25 percent if the negative attitude toward placebo injections by a nurse are communicated to the patient (Volgyesi, 1954). In another study, patients treated with placebos improved more than those on tranquilizers, a result the authors attributed to the bias of the nurses against psychochemotherapy and for habit-training psychotherapy (Baker & Thorpe, 1957). Nurses were observed crushing, dissolving, and tasting the tablets in order to distinguish placebo from active agents. Such attempts to identify drugs in controlled research have been reported in other studies (Fischer & Dlin, 1956).

Staff attitudes and behavior, such as displaying interest and optimism can influence patient behavior—for example, the disturbed behavior of patients has been attributed to staff conflicts (Rathod, 1958; Linn, 1959; Shottstaedt, Pinsky, Mackler, & Wolf, 1959; Stanton & Schwartz, 1954).

Setting

The setting within which treatments are administered offers a multitude of potential therapeutic stimuli for patients (Gelfand, Ullmann, & Krasner, 1963; Nash, Frank, Imber, & Stone, 1964; Barber, 1960). Patients sometimes improve without therapy, simply because they are placed in a therapeutic milieu (Goldstein, 1960; Goldstein & Shipman, 1961). The importance of the milieu is demonstrated in a study by Park and Covi (1965) in which patients were given placebos and told that the administered drugs were sugar pills. Despite this disclosure, all of the 14 patients who took the placebos improved. Although some patients thought that the drug contained active medication, the majority believed that they were helped by the placebo, the doctor, or themselves.

Changes can occur in patients after institution of research, which are unrelated to the contents or type of research activity. This process is similiar to the "Hawthorne Effect" observed in industrial psychology in which workers increased productivity because of the heightened interest, increased attention, and social stimulation of the research atmosphere rather than because of the variables manipulated by the researchers. In therapeutic situations this "milieu effect" can produce improvement in 80 percent of patients (Rashkis & Smarr, 1957). The bias introduced by research can influence clinical and experimental results in any number of ways (Rosenthal & Rosnow, 1969; Grosz & Grossman, 1968; Rosnow & Aiken, 1973).

The setting, because of its inherent "therapeutic" stimulus value, is a potent placebo variable. Direct comparisons of placebo response in different settings leaves no doubt that the setting can induce placebo effects and affect treatment outcome in many ways (Rickels, Downing, & Downing, 1966; Rickels, Catell, Weiss, Gray, Yee, Mallin, & Aaronson, 1966).

Population

A change in study setting may also change the nature of the population being measured. Lipman (1966) reported that an identical research protocol yielded opposite results when medical clinic patients were compared to psychiatric clinic patients. Differences in placebo reaction between private patients and clinic patients have also been noted (Rickels & Macafee, 1966; Heshbacker, Rickels, Gordon, Gray, Meckelburg, Weise, & Vandervort, 1970; Downing & Rickels, 1973).

Clinical patients and experimental subjects display vastly different response to placebo analgesia. Beecher (1960) found that about 35 percent of patients reported substantial pain relief from placebos but that only about 3 percent of experimental subjects reported substantial relief. Evans (1969), in a review of 14 other experimental studies, found average placebo relief to be about 16 percent, still well below the figure reported by Beecher for clinic patients. It is likely that factors such as individual needs, motivations and anxiety levels (Davison & Valins, 1969; Buss & Portnoy, 1967), the role of the "patient" versus that of the "subject" (Rosnow & Aiken, 1973; Silverman, 1968), and the norms for each situation (Orne, 1970) contribute to these findings.

Subjects used for clinical or experimental studies of the placebo effect are often volunteers. The ability to generalize results to nonvolunteer subjects is questionable (Rosenthal & Rosnow, 1975).

Treatment Procedure

Although clinical folklore gives the impression that the best placebo treatments have an element of

mysticism and cause a bit of discomfort, the empirical evidence is scanty (Honigfeld, 1964b). Patients do not react uniformly to different treatment procedures (Wolf 1959). Morison et al. (1961) and Traut and Passarelli (1957) found placebo injections to have greater efficacy then oral drugs, but another study found no difference (Goldman, Witton, & Scherier, 1965). Reactions to size, color, and shape of tablets or capsules vary (*JAMA*, 1955; Leslie, 1954; Schapira, McClelland, Griffiths, & Newells, 1970).

The efficacy of various placebo treatments may ultimately depend on the treatment modality that serves as the appropriate stimulus for each patient. One group of individuals may react best to a drug stimulus, another to psychotherapy or psychoanalysis, and another to biofeedback, behavior modification, or acupuncture, for example. Four studies by the authors (Shapiro et al., in preparation) revealed a consistent relationship between the desire for psychochemotherapy and positive response to medication placebo.

Miscellaneous Factors

Factors external to the administered therapy may cause changes that are misattributed to the influence of the therapy. Some of these external factors are; preexisting symptoms (Bushfield, Sneller, & Capra 1962; Schulterbrandt, Raskin, & Reatig, 1974; Green, 1964), spontaneous remissions (Lesse, 1964, 1966), the influence of group pressures and reactions of other patients (Knowles & Lucas, 1960; Letemendia & Harris, 1959; Morrison & Walters, 1972; Schachter & Singer, 1962) significant life events (Lipman, Hammer, Bernades, Park, & Cole, 1965; Davidson, 1960) and the process of filling out questionnaires (Glaser & Whittow, 1954).

Placebo reactivity is related to type of referral (Hankoff, Engelhardt, Freedman, Mann, & Margolis, 1960). Untreated patients may be favorably influenced by treated patients (Craig & Coren, 1974; Meszaros & Gallagher, 1958). The taste of a pill can influence placebo reaction (Baker & Thorpe, 1957). The type of bodily or behavioral reaction, and whether it is expected or unexpected, can affect the degree of placebo response (Morris & O'Neal, 1975).

There are many other factors, not fully explored, that probably influence placebo effects. Some situational variables that may influence placebo response include the cost of treatment, type and size of practice, reputation of the therapist, atmosphere of the office (informal or intimate, busy or unhurried, supporting or rejecting, etc.), use of therapeutic adjuncts such as nurses or aids to administer treatments, reinforcing directions with written information sheets or audiovisual aids, and so on.

PHYSICIAN VARIABLES

Although the relationship between physician and patient has been recognized throughout history as an important determinant of response to medical treatment, the responsibility of the patient has always been emphasized. However, therapeutic evaluations indicate that physician characteristics constiute a crucial variable in therapy. The great bulk of evidence supporting the role of the physician in therapy is derived from studies completed in the 1950 and 1960s. Although reaffirmed in more modern evaluations (Luborsky, Singer, & Singer, 1975), this potentially fruitful area has not become a major research topic for prospective research.

The study of the physician's contribution to placebo and therapeutic effects is referred to as iatroplacebogenics—physician-caused placebo effects. Iatroplacebogenics can be direct or indirect. The former refers to placebo effects produced by the physician's attitude to the patient, to the treatment procedure, and to the treatment results. Indirect iatroplacebogenics, a much more subtle mechanism, occurs when the patient misinterprets the physician's intent, and experiences the physician's interest in a therapy or procedure as a personal interest.

Direct Iatroplacebogenics

Attitude to Patient

Attitude to patient refers to the therapist's interest, warmth, friendliness, liking, sympathy, empathy, neutrality, lack of interest, rejection, and hostility. Its general importance is indicated by a survey that cited the physician's personal interest—not his or her competence—as the main determinant of

whether patients like their doctors (Polansky & Kounin, 1956).

Psychotherapy. The most impressive evidence supporting iatroplacebogenics in psychotherapy is furnished by a recent critical review by Luborsky, Singer, and Luborsky (1975). Methodologically sound comparative studies of several types of psychotherapy were examined. The review indicated a "tie score effect"; a high percentage of patients receiving any of the psychotherapies tended to improve, but none of the psychotherapies emerged as clearly superior to the others. Luborsky et al. concluded that the most potent explanation for this tie score effect was that improvement was related to the existence of the patient-therapist relationship common to all forms of psychotherapy.

The psychotherapist's interest in the patient is associated with the likelihood of acceptance of treatment (Brill & Storrow, 1963; Lowinger & Dobie, 1963, 1964), fewer dropouts (Freedman, Engelhardt, Hankoff, Glick, Kaye, Buchwald, & Stark, 1958; Hiller, 1958; Lowinger & Dobie, 1964; McNair, Lorr, & Callahan, 1963; Nash, Frank, Gliedman, Imber, & Stone, 1957), fewer complaints by patients (Nash et al., 1964), and successful outcome of treatment.[4]

Extensive research by Goldstein on the importance of patient-physician expectations in therapy indicates that the therapist's favorable feelings to the patient are related to the therapist's expectation of improvement and the patient's attraction to the therapist (Heller & Goldstein, 1961; Garfield & Affleck, 1960) and influence the obtained improvement (Goldstein, 1962).

Strupp has demonstrated in many studies that the therapist's liking or disliking of the patient is associated with the therapist's evaluation of the patient's personality, motivation, maturity, insight, anxiety, clinical status, diagnosis, treatment goals, proposed techniques, improvement expected, and mutual beliefs of patient and therapist.[5]

The frequent observation, although inadequately studied, that therapists are often more successful when they begin their careers than when they have become more experienced, may be related to greater interest of the novice in the patient.[6] Liking or not liking of patients may be a better explanation for reported cases of countertransference cures (Barchilon, 1958; Kolb & Montgomery, 1958), for failures in therapy (Ends & Page, 1957), and for the suggestibility of patients in psychoanalysis (Fisher, 1953).

Support for the positive association between physician attitude toward the patient and patient's therapeutic improvement is offered by a recent study (Shapiro, Struening, Shapiro, & Barten, 1976). Physicians were asked to rate patients in terms of likability, attractiveness, and how good a patient for treatment they appeared to be. Each of these three variables was strongly correlated with physician's rating of patient improvement.

Psychochemotherapy. Interest in the patient is related to successful treatment with antidepressants (Sheard, 1963) and minor tranquilizers (Uhlenhuth, Canter, Neustadt, & Payson, 1959; Rickels, Baum, Taylor, & Raab, 1964), as well as to the type of LSD response (Malitz, 1963) and drug acceptance by patients (Raskin, 1961).

General. The interest of the investigator affects surgery in dogs (Wolf, 1962), gastric acid secretion (Engel, Reichsman, & Segal, 1956), metabolic changes (Schottstaedt et al., 1956), laboratory procedures (Kaplan, 1956), and galvanic skin responses (Dittes, 1957). It has been described as a crucial variable for successful psychotherapy in

[4] Heine, 1959; Seeman, 1954; Blaine & McArthur, 1958; Board, 1959; Snyder & Snyder, 1961; Parloff, 1961; Cartwright & Lerner, 1963; Stoler, 1963; Strupp et al, 1964; Battle, Imber, Hoehn-Sarac, Stone, Nash, & Frank, 1966; Gendlin, 1966; Truax & Wargo (1966) summarized 14 additional studies that attributed successful treatment largely to the warmth or empathy of the therapist.

[5] Strupp et al., 1964; Strupp, 1958a, 1958b, 1958c, 1959, 1960a, 1960b, Strupp & Williams, 1960; Wallach and Strupp, 1960; Strupp & Wallach, 1965.

[6] Lowinger & Dobie, 1964; Truax & Wargo, 1966; Strupp, 1958c; Strupp & Williams, 1960; Ginsburg & Arrington, 1948; Brill, Koegler, Epstein, & Forgy, 1964; Berman, 1949; Kubie, 1956; Glover, cited by Kubie, 1956; Grinker, 1958; Barchilon, 1959; Frank, 1961; Cole, Branch, & Allison, 1962; Karno, 1965.

summaries reported at national research conferences on psychotherapy (Parloff & Rubinstein, 1959; Strupp & Luborsky, 1962); as the cornerstone of Rogerian client-centered therapy (Rogers, 1951, 1957a, b, 1961); and as important in behavior therapy, psychotherapy and psychoanalysis,[7] the placebo effect,[8] hypnosis (Barber, 1962), the success of shamans (Frank, 1961; Kiev, 1964) and quacks (Masserman, 1963), and the saving of derelicts by the Salvation Army (Feldman, 1956).

Attitude to Treatment

Recent research has established that the physician's attitude toward treatment—such as faith, belief, enthusiasm, conviction, commitment, optimism, positive and negative expectations, skepticism, disbelief, and pessimism—is a nonspecific factor in most therapies.

Psychochemotherapy. Feldman (1956) was the first to present data supporting the idea that the success of drug therapy varied with the enthusiasm of the doctor. He reported similar findings in a follow-up study, and observed that unsuccessful therapists had a greater commitment to psychoanalysis than to psychochemotherapy (Feldman, 1963).

These findings were confirmed in a study by Uhlenhuth et al. (1959), which indicated that only the interested and enthusiastic physician obtained significant improvement with active drugs compared with placebos, while the uninterested and unenthusiastic physician showed no differences in improvement, whether active or inactive drugs were used. An important implication of this study is that the therapist's interest may be a necessary prerequisite for the success of some treatments. These results have been confirmed in subsequent studies (Fisher et al., 1964; Rickels et al., 1964a; Rickels, Boren, & Stuart, 1964; Rickels & Catell, 1969; Uhlenhuth, Rickels, Fisher, Park, Lipman, & Mock, 1966).

Interest in drug treatment has been associated with successful treatment of depressed patients (Haefner, Sacks, & Mason, 1960; Sheard, 1963), schizophrenics and hospitalized patients (Honigfeld, 1962; Pearlin, 1962; Tuma & May, 1969), and depressed patients on placebo (Honigfeld, 1963). Negative attitudes toward drug treatment are associated with less favorable results.[9] Similar finding have been reported in the treatment of patients with bleeding ulcers (Volgyesi, 1954), as well as those treated by hypnosis (Orne, 1959; Troffer & Tart, 1964).

Psychotherapy. A relationship between the psychotherapist's interest in treatment and successful outcome has been described in studies of brief psychotherapy (Frank, 1965) and in studies of psychiatrists (Board, 1959; Frank, 1965) or medical students (Frank, 1961; Ginsburg & Arrington, 1948; Goldstein & Shipman, 1961). The psychotherapist's interest in the treatment has also been associated with the likelihood of patients remaining in psychotherapy (Heine & Trossman, 1960; McNair et al., 1963) and was cited as important in the summary report of the first Research Conference on Psychotherapy (Rubinstein & Parloff, 1959). Optimistic therapists rate their patients more improved than do pessimistic therapists (Rickels et al., 1964b; Rubinstein & Parloff, 1959).

Indirect evidence of a relationship between the therapist's interest in psychotherapy and success of treatment appears in the work of Strupp and Goldstein. Their work indicates that the therapist's

[7]Parloff, 1961; Strupp, 1960a, 1960b; Strupp & Williams 1960; Snyder, 1946; Fiedler, 1950; Ginsburg & Arrington, 1948; Barchilon, 1958; Frank, 1961; Cole, Branch, & Allison, 1962; Karno, 1965; Krasner, Ullman, & Fisher, 1964; Snyder, 1958; Greenachre, 1953; Ferenczi, cited by Greenachre, 1953; Fenichel, 1954; Braaty, 1954; Ellis, 1955; Breuer & Freud, 1957; Frank, Gliedman, Imber, Nash, & Stone, 1957; Frank, 1958, Frank, cited in Rubenstein & Parloff, 1959; Masserman, 1957, 1963; Meerloo, 1963; Berman, 1949; Heine & Trossman, 1960; White, 1961; Hobbs, 1962; Lesse, 1962, 1964, Voth, Herbert, & Orth, 1962; Luborsky, 1962, Hammett, 1965; Paul, 1963, Jaspers, 1965.

[8]Honigfeld, 1963; Lesse, 1964; Rickels et al., 1964a; Shapiro, A.P., 1959; Shapiro, A.K., 1959, 1960a, 1963, 1964a, 1964c, 1964f, 1968; Wolf, 1962.

[9]Baker & Thorpe, 1957; Eissen, Sabshin & Heath, 1959; Fisher et al., 1964; Feldman, 1963; Haefner et al., 1960; Honigfeld, 1962; Pearlin, 1962; Rickels et al., 1964b, Sabshin & Ramot, 1956; Uhlenhuth et al., 1959, Uhlenhuth et al, 1966.

evaluation of the patient's suitability for psychotherapy determines the therapist's interest in treatment (Strupp, 1960a). This correlates with the mutual attraction of therapist and patient and with the positive evaluation of the patient and the patient's success in therapy (Goldstein, 1962; Strupp, 1960a, b; Strupp, Wallach, & Wogan, 1964; Wallach & Strupp, 1960).

Unfortunately, in all of the studies cited, it is difficult to differentiate between the therapist's interest in the patient and the therapist's interest in treatment. Several studies suggest, however, that interest in treatment is primary and leads to a secondary interest in the patient. For example: a patient's motivation for therapy influences the therapist's estimation of prognosis and capacity to like the patient (Strupp, 1969a, b; Strupp & Wallach, 1965; Strupp & Williams, 1960). Some therapists dislike patients solely on technical grounds (Strupp, 1960b) or because they are more severely disturbed (Wallach & Strupp, 1960). Patients who complete studies are liked more than dropouts (Rickels et al., 1964a). The therapist's prognostic expectations relate to patient's attraction to the therapist (Heller & Goldstein, 1961). The therapist's evaluation of prognosis, capacity for insight, liking, empathizing, and eagerness to accept the patient vary with the patient's motivation for therapy (Wallach & Strupp, 1960). Retaining patients for psychotherapy appears to be more directly associated with the therapist's interest in treatment than with his or her interest in the patient (McNair et al., 1963). Experimenters may become more likable, personal, and interested in subjects if early data returns are favorable (Rosenthal, 1963a).

The observation about the success of younger therapists was previously related to their having more positive feelings toward patients than do older therapists. Neophytes may also be excessively enthusiastic (Frank, 1961) and optimistic (Strupp, 1960b) about the effectiveness of treatment because of their need for reassurance (Strupp, 1960b; Frank, 1961; Lesse, 1964), whereas the needs of experienced therapists shift from curing to understanding (Barchilon, 1958). The observation that some therapists are more successful with certain patients may be related to the therapist's interest in particular problems or types of patients.[10]

The profit motive has been conspicuously unexplored and may be a significant determinant of the therapist's interest in the treatment, patient, and results (Chodoff, 1964; Davids, 1964; Foreman, 1964; Kubie, 1964; Lesse, 1962; Mowrer, 1963; Ubell, 1964).

General. Finally, the therapist's interest in treatment is frequently cited as important in placebogensis,[11] general medical treatment (Honigfeld, 1964b; Houston, 1938; Janet, 1924; Lord, 1950; Shapiro, A. P., 1955, 1959; Shapiro, A. P., Myers, Reiser, & Ferris, 1954), insulin coma treatment (Shapiro, 1960a), hypnosis (Orne, 1959, 1962, 1970; Troffer & Tart, 1964), and the success of shamans (Eliode, 1964; Ellenberger, 1956; Kiev, 1962, 1964).

Attitude to Results

Attitude toward results refers to data distortion caused by random observer effects and by intentional or unintentional observer bias (Rosenthal, 1966; Rosenthal & Halas, 1962). Data distortion or unintended observer bias are probably more extensive than frauds and intended effects (Humphrey, 1963; Rosenthal, 1966, 1969).

Rosenthal's technique of demonstrating that "experimenters obtain the results they want or expect" is illustrated in a study of rat learning (Rosenthal, 1966; Rosenthal & Fode, 1963). Experimenters were told that their rats had been specially bred for either brightness or dullness, al-

[10] McNair et al., 1963; Snyder & Snyder, 1961; Goldstein, 1962; Strupp, 1960b; Heine & Trossman, 1960; Jaspers, 1965, Fenichel, 1945; Karpman, 1949; Oberndorf, Greenachre, & Kubie, 1953; Wolberg, 1954; Thompson, 1956; Alexander, 1958; Frank, 1959; Engel et al., 1956; Kubie, 1964.

[11] Frank 1961; Lesse, 1962, 1964; Weatherall, 1962, Shapiro, 1959, 1960a, 1960b, 1963, 1964c, 1964d, 1964f, 1968; Baker & Thorpe, 1957; Frank, 1959, Janet, 1924, 1925; Tibbetts & Hawkins, 1956; Wolf, 1959; British Medican Journal, 1961; Kelly, 1962; Liberman, 1961; Honigfeld, 1964b.

though rats in both groups were from the same genetically pure strain. The results indicated that experimenters obtained significantly better learning from rats they considered bright than did experimenters who believed that their rats were dull.

This is not an isolated study. Similar results have been obtained in more than 90 experiments involving rat, planaria, and human subjects (Rosenthal, 1963a, 1964, 1966, 1969; Rosenthal & Halas, 1962; Rosenthal, Persinger, Mulry, Vikan-Kline, & Grothe, 1964; Rosenthal, Persinger, Vikan-Kline, & Fode 1963a).

Sources of experimenter bias include the experimenter's hypotheses (Rosenthal, 1963a), expectation (Rosenthal, 1964; Shuller & McNamara, 1976), motivation (Rosenthal et al., 1964), and prestige (Rosenthal et al., 1963a; Rosenthal et al., 1964). Other factors are instances of cheating (Rosenthal, 1966; Rosenthal, Friedman, Johnson, Fode, Shill, White, & Vikan-Kline, 1964), early data returns (Rosenthal, Kohn, Greenfield, & Carota, 1965; Rosenthal, Persinger, Vikan-Kline, & Fode, 1963b), nonspecific factors in pre-data-gathering interaction (greeting, seating and instructing), (Rosenthal, Fode, Vikan-Kline, & Persinger, 1964), verbal conditioning (Rosenthal et al., 1963a; Rosenthal et al., 1964), visual and verbal cues (Rosenthal et al., 1964c), experimenter and subject physical, demographic and personality characteristics (Chapman, Chapman, & Brelje, 1969; Eisman & Huber, 1970; Rosenthal & Fode, 1963; Rosenthal & Lawson, 1963, Rosenthal et al., 1963a; Schultz & Hartup, 1967).

Rosenthal concluded that human beings engage in highly effective and influencial unintended communication with one another. This communication is so subtle that casual observation is unlikely to reveal the nature of the process (Heine, 1950; Rosenthal, 1963, 1966, 1969; Rosenthal et al., 1964).

Similar findings have been reported both in clinical psychology (Kent, O'Leary, Diament, & Dietz, 1974; Masling, 1959, 1960, 1965; Rosenthal, 1964) and experimental psychology (Friedlander, 1964; Krasner, Knowles, & Ullmann, 1965; Krasner, Ullmann, & Fisher, 1964; McGuigan, 1963; Orne, 1962, 1970; Rosenthal, 1966, 1969); the placebo effect,[12] psychochemotherapy;[13] psychotherapy;[14] psychoanalysis;[15] clinical and experimental hypnosis (Barber, 1962, 1965a, 1965b; Orne, 1959, 1962; Troffer & Tart, 1964); and clinical medicine (Friedman, Kurland, & Rosenthal, 1965; Garland, 1960; Shapiro, A. P., 1955, 1959; Williams, & McGee, 1962).

The prestige of the investigator, physician, or healer influences clinical and experimental results,[16] and has always been one of the common denominators in "bandwagon effects" in science (Kety, 1961), the success of quacks (Frank, 1961) and shamans (Eliode, 1964; Kiev, 1962; Shapiro, 1964d), the placebo effect (Lesse, 1962; Liberman, 1961; Shapiro, 1959, 1960a, 1960b, 1963, 1964c, 1964d, 1964f), and other healing techniques (Greenachre, 1953; Jaspers, 1965).

During the last decade, physicians and investigators have become increasingly aware of their bias. Bias is so pervasive that some investigators have suggested that clinical judgments may be less informative about patients than the therapists who make them (Grosz & Grossman, 1964). Bias explains why uncontrolled studies report success more frequently than controlled studies (Foulds, 1958; Fox, 1961). Attempts to minimize bias have led to increased use of statistics, placebos, double-blind procedures, independent assessment teams (Guy, Gross, & Dennis, 1967), and other controls.

[12]Shapiro, 1959, 1960a, 1960b, 1963, 1964d, 1964f, 1964c, 1968; Baker & Thorpe, 1957; Kelley, 1962; Letermendia & Harris, 1959; Wilson & Huby, 1961; Wilson, 1962a, 1962b; Joyce, 1962.

[13]Shapiro, 1959, 1964d, 1964f; Feldman, 1956, 1963; Sabshin & Ramot, 1956; Baker & Thorpe, 1957, Eissen et al., 1959; Letermendia & Harris, 1959; Wilson & Huby, 1961; Wilson, 1962a, 1962b; Uhr & Miller, 1960; Foreman, 1964.

[14]Garfield & Alleck, 1960; Strupp, 1960b; Wallach & Strupp, 1960; Shapiro, 1964c, 1968; Ward, 1964, Rezikoff & Toomey, 1959. Cutler, 1958; Endicott, 1962; Grosz & Grossman, 1964; Gill & Brenman, 1948.

[15]Krasner, 1962; Greenachre, 1953; Ward, 1964; Rosenthal, 1963b; Gill & Brenman, 1948; Burrow, 1927; Schmidberg, 1958; Glover, 1952; Kubie, 1953; Ehrenwald, 1958; Marmor, 1962; Sullivan, 1936–37.

[16]Kahn, 1957; Karno, 1965; Ullman & McFarland, 1957; Friedman, Kurland, & Rosenthal, 1965; Masserman, 1957; Meerloo, 1963; Rosenthal, Persinger, Mulry, Vikan-Kline, & Groth, 1964; Krasner, Knowles & Ullmann, 1965; Reiser, Reeves, & Armington.

Whereas controlled studies appeared infrequently in the medical literature before 1950, today they are the norm (Karch & Lasagna, 1974; Shapiro, 1960a, 1963, 1968; Waife & Shapiro, A.P., 1959).

Recognition of the subtlety and omnipresence of these effects has led some investigators to believe that objective experiments are illusory (Feldman, 1963; Grenier, 1962; Kelly, 1962; Kety, 1961; Rosenthal, 1966; Rosenthal et al., 1964). It has prompted suggestions that every experiment be done by an enthusiast and skeptic and that the investigator's bias about expected results be specified in the paper. Various suggestions have been made about how to make methodology more rigorous and foolproof.[17] Consistant with these conclusions is the recent demonstration by Barber and Silver (1968) of a Rosenthal "effect" on Rosenthal's procedures.

Observer bias may be related to the therapist's need for results. Therapeutic failure would be cognitively dissonant (Board, 1959; Davids, 1964; Lesse, 1962; Sullivan, 1936–1937; Ubell, 1964; Wolens, 1962). For example, unsuccessful cases may not be remembered and failures may be forgotten. Patients who are expected to be failures may be disliked and their treatment potentials may be negatively evaluated. In addition, investigators tend to be selective in their review of pertinent literature and they may assimilate and misrepresent their summary of the literature while omitting important details that are inconsistent with their views (Berkowitz, 1971). This latter effect, plus the tendency of journals to publish only positive results, tends to perpetuate the popularity of ineffective therapies (Russell, 1974).

Therapists may subtlely and unknowingly communicate information to patients, such as hypotheses, expectations, attitudes, cultural values, and so on.[18] The returned communication is then regarded as an independent confirmation of the therapist's theory (Frank, 1961; Gendlin, 1966). This increases the credulity and suggestibility of both. Bias influences the selection of patients, prognostic expectations, evaluation of insight potentiality, likability, warmth, the obtainment, perception, and remembering of raw data, and the interpretation and presentation of results.

Interest in results stimulates the need and activity to achieve them. It changes the therapist's behavior and interacts with his or her interest in the treatment and patient (Goldstein, 1966). The therapist is more interested in the treatment and the patient, gives more time and help, and shows more warmth and concern. The patient responds to the therapist with warmth and improvement. This relationship is reinforcing and circular. All these factors, and various interactions and secondary effects, result in real or imagined treatment success.

An inescapable conclusion is that the therapist's interest in the patient, treatment, and results is related to success in treatment and placebo effects. Research clearly supports the generality of the phenomena. The evidence includes many clinical studies of many patients with varying diagnoses and backgrounds, and treated with different methods by many therapists with diverse orientations and experience. The generality of the evidence is supported by similar findings in clinical and experimental psychology, psychiatry, and medicine.

A second conclusion is that there is complex interaction among the variables of therapists' interest in the patient, the treatment, and the ultimate results. The explanation of how those factors influence results is not clear. It is also not clear which factors are primary or secondary, or how these factors interrelate, and cause and effect one another.

[17]Goldstein, 1962; Rosenthal, 1963b, 1964; Rosenthal, Persinger, Mulry, Viken-Kline, & Grothe, 1964; Masling, 1959, 1960; Friedman, Kurland, & Rosenthal, 1965; Masserman, 1957; Barber, 1962, 1965b; Feldman, 1963; Troffer & Tart, 1964; Orne, 1962; Ward, 1964; Reznikoff & Toomey, 1959; McGuigan, 1963; Greiner, 1962; Endicott, 1962; Barber & Calvery, 1964; Kety, 1961; Shapiro, 1960a, 1961, 1963, 1964a, 1964b, 1968.

[18]Strupp, 1959, 1960b; Strupp & Wallach 1965; Strupp, Wallach & Wogan, 1964; Goldstein, 1962; Snyder, 1946; Kamo, 1965; Rosenthal, 1963b; Rosenthal, Persinger, Mulry, Vikan-Kline, & Grothe, 1964; Krasner, 1962; Lesse, 1964; Alexander, 1958, 1963; Gill & Brenman, 1948; Marmor, 1962; Sheard, 1963; Snow & Rickels, 1965; Frank, 1961; Rosenthal, 1966.

For example, a therapist may be interested in the treatment of a patient, expect success, and then like the patient. The patient may react to the therapist with similar feelings and stimulate the therapist with more interest in the patient, greater enthusiasm for treatment, and increased expectation of favorable results. All these factors may contribute to the final success of therapy.

Understanding of the complex interactions of the therapist's interest in the patient, treatment, and results requires more than retrospective speculation. Careful prospective studies are necessary to determine the relevance and primacy of these factors for placebogenesis and therapeutic effects.

Indirect Iatroplacebogenics

The physician's interest in his or her treatment and patient is a necessary component of almost every specific therapy, has a synergistic effect with most therapies, and often produces psychological or placebo effects in and of itself. Although the concept of direct iatroplacebogenesis has been demonstrated in many studies, another probably more subtle and extensive process, indirect iatroplacebogenesis, has not been considered adequately in the literature (Berman, 1949; Board, 1959; Frank, 1961; Glover, 1931; Greenachre, 1953; Honigfeld, 1964b; Rosenthal, 1963b).

Medical History

Medical history is characterized by a succession of prestigious physicians with compelling intellectual and emotional investments in various therapeutic theories and practices. These are frequently elaborate, detailed, expensive, time consuming, fashionable, esoteric, and dangerous. The majority were later judged to be ineffective (Shapiro, 1959, 1960a). A common factor in these therapies is the interest of the physicians.

The greater a physician's interest in a theory of therapy, particularly if he or she has innovated it, or if he or she is a recent convert, the more effective that therapy will be. This may occur because the patient displaces the interest from the therapy to himself or herself and experiences the physician's interest in treatment as a personal one. Many psychological factors arise in the patient-physician relationship. Hopes, expectations, fantasies, fears, feelings of guilt and inadequacy, and so on, become involved in the relationship and treatment. For example, if a patient has ego-alien impulses and fantasies, an interest on the part of the physician, to whom transference has developed, can decrease superego pressures, conflicts, and eventually symptoms. The patient may simply feel that if a physicain is interested, then he or she is not worthless.

The physician may be neutral or minimally interested in the patient. However, the physician's commitment to a treatment modality may produce an intense interest in the results of therapy. The patient may experience the physician's interest as an interest in himself or herself. In addition, the physician's interest in his or her treatment may enable the physician to tolerate or be unaffected by the personal idiosyncracies of the patient. The patient may expect criticism or rejection and be surprised or reassured when the physician responds with interest. In other words, some treatments, although ostensibly directed at the patient, may unknowingly affect the physician, and then mediate psychological change in the patient. The effectiveness of these treatments would be primarily due to the process of indirect iatroplacebogenesis.

Pharmacotherapy

Once fashionable insulin coma treatment is increasingly thought of as a complex placebo treatment (Shapiro, 1960a). The interest of the staff, necessitated by the dangers during treatment, may provide part of the explanation for its effectiveness. Patients were selectively chosen for this treatment and were a therapeutic elite. The treatment was expensive, fashionable, elaborate, time consuming, esoteric, dangerous, and patients required considerable attention during and after treatment.

A physician with an interest in psychochemotherapy usually has considerable knowledge about such treatment. He or she will be interested in the symptoms and the differential response of the patient to various drugs and will be careful to observe side effects, especially those that may be dangerous. The physician may encourage the patient to call at any time if side effects develop.

A new therapy whose indications, contraindications, and side effects are not fully evaluated will elicit even more interest and promote a greater intellectual and emotional investment of the physician. This may partially explain the reports of almost universal effectiveness accompanying the introduction of new therapies (Shapiro, 1959, 1960a, 1960b, 1963, 1964c, 1964d, 1964f, 1968).

Indirect iatroplacebogeneics can be illustrated by the following clinical case:

A 31-year-old married woman with a chronic borderline condition was referred to a psychiatrist for psychochemotherapy because of her inability to awaken in time for psychotherapy sessions. The underlying reason was probably that she could not be tolerated by whomever served as her therapist. She was the source of constant irritation, with excessive oral and dependent needs, and her behavior caused everyone to reject her. She had almost always reacted adversely to medication. The psychiatrist knew that he would have no greater success than others in changing the patient's masochistic pattern of thwarting attempts to help her. The psychiatrist decided to use a treatment he had never dared to try before, since there was no alternative. In addition, he wanted first to reassure himself that she was not highly sensitive to the effects of medicine.

She was put on an elaborate schedule of three different placebos totaling 12 tablets. Two hours after the patient left, she called stating that all the tablets had fallen out of their boxes and were mixed up in her handbag.

She returned the following week, and in a rash of words described her horrendous experience. She cautiously took only half the dosage at bedtime and on awakening. Immediately after the morning dosage she was nauseated, dizzy, groggy, experienced feelings of unreality, became markedly depressed, sleepy, and began to cry. This lasted six days. Needless to say, the patient discontinued the medication. The doctor followed her associations carefully, recorded much of the interview, and at an appropriate moment told her that she had taken placebos. At first she had no idea what a placebo was. Then she insisted that it was impossible for placebos to have caused her symptoms. Only after the doctor offered to swallow the remaining tablets was she convinced.

Somewhat anxious about using this procedure, the physician became even more so when the patient exclaimed that if medicine didn't work, she had no alternative but to kill herself. Reassuring her that this was not necessary, the therapist told the patient that the procedure was used to determine that her symptoms were caused by powerful psychological factors, not by the medication. The doctor acknowledged that the side effects were not imaginary, but insisted that they could not be serious. It was emphasized that the subtle beneficial effects of the medication could not possibly compete with her overwhelming psychological reaction. For treatment to be successful she must take the prescribed dosage of medication despite the development of side effects. If these did occur, she could always call her doctor. Although serious side effects were unlikely, should any develop, he would be able to differentiate between the serious and nonserious.

The patient seemed to accept the explanation, but needed time to get over the effects of the previous week.

Several months later, she called for an appointment. Treatment was begun with antidepressant medication. No calls were received during that week. At the next session that patient was improved, reporting only reliable side effects of the medication. One week later she said that she did not know if she had received placebos or not, but had no side effects. The nurse checked and found that the patient had been given placebos by mistake. The active medication was then resumed.

Many explanations for the patient's remarkable response are possible: that the physician was strong, authoritative, and could not be manipulated; the patient felt safe, with less need to discharge anxiety through masochistic development of side effects; the confrontation improved reality testing; and so on.

Although many explanations are possible, indirect iatroplacebogenesis is probably the best explanation. The psychiatrist was intellectually and emotionally interested in the placebo phenomenon, negative placebo responses, and the innovation of a treatment procedure. Management was

elaborative, detailed, time consuming, esoteric, dangerous, fashionable, and potentially expensive.

In other words, interest in the phenomenon was responsible for the doctor's not reacting to the patient's masochism with distance, lack of interest, hopelessness, and rejection. This experience was unique for the patient who was a specialist at courting rejection. Under the usual circumstances of the patient-physician relationship, the doctor might have reacted to the patient's masochism with anxiety, guilt, distance, lack of interest, hopelessness, and possible rejection.

To view the method that was used as having an effect only on the patient would be misleading. Its effect on the doctor probably had an effect on the patient. The underlying mechanism is the indirect interest of the physician in the patient. The mechanism of indirect iatroplacebogenesis is formulated as treatment directed at the patient, but unknowingly having effects on the physician which, in turn, mediates psychological change in the patient.

This formualtion was confirmed in an interview three years later. The patient, markedly improved, was asked about the effect of the placebo procedure and what helped her get well. She said that the effect of those "clever" placebos made her feel that the doctor was really "trying to help . . . really interested and concerned," whereas physicians previously "were too busy . . . uninterested" and "would only give her boxes of pills." The patient said she was "able to have faith in the clinic and the doctors," which enabled her to take medication and finally improve.

Psychotherapy and Psychoanalysis

How would this formulation apply to intensive psychotherapy? Psychotherapy shares with other therapies many placebogenic factors (Shapiro, 1964a, 1964b, 1968). It is a new method with considerable emotional, intellectual, and financial investment by prestigious practitioners. It is elaborate, fashionable, esoteric, and sometimes dangerous.

Many clinicials agree with this formulation, but might limit its applicability to therapies other than their own. For example, insight-oriented psychotherapists might say that the goal of other therapies was limited to reduction of symptoms through nonspecific factors or unresolved transference. The goal of psychotherapy is a reorganization of character; it is achieved through insight into unconscious processes, defense mechanisms, character traits, and a resolution of the transference neurosis. The therapist is characterized as a mirrorlike, objective, uninvolved technican with minimum direct interest in the patient and results (Hammet, 1965; Loenwald, 1960; Murphy, 1958; Strupp, 1960b). Although the concept of the mirrorlike therapist is a formulation of the naive past and increasingly regarded as fiction rather than fact,[19] nevertheless the insight-oriented psychotherapist communicates less old-fashioned, naive, and simple interest in the patient than does the nonsight-oriented therapist. Direct interest in the treatment or technique, however, may be greater than in other therapies and lead to indirect iatroplacebogenesis.

Classical psychoanalysis, a good example of a therapy with minimal direct interest in the patient and maximal interest in the treatment, can illustrate the mechanism of indirect iatroplacebogenesis, as well as clarify the problem of suggestion in psychoanalysis that was referred to by Freud as inadequately understood (Freud, 1948).

Acceptance for treatment by a prestigious physician has long been regarded as reassuring to patients. Because of the technical emphasis on suitability for psychoanalysis, many patients interpret acceptance for such treatment as evidence of intellectual capacity, insight potentiality, favorable prognosis, and not being seriously ill (Bergman, 1958; Boring, 1964; Scharaf & Levinson, 1964; Schmideberg, 1958).

The careful selection of patients for psychoanalysis involves many criteria that maximize response to therapy (Eyesenck, 1965;

[19] Lowinger & Dobie, 1963, 1964; Snyder & Snyder, 1961; Strupp, 1961; Strupp, 1958c, 1959, 1960b; Strupp & Williams, 1960; Wallach & Strupp, 1960; Berman, 1949; Frank, 1961; Krasner, 1962; Meerloo, 1963; Hobbs, 1962; Hammett, 1965; Karpman, 1949; Oberndorf, Greenachre & Kubie, 1953; Wolberg, 1954; Alexander, 1958; Schmideberg, 1939; Gill & Brenman, 1948, Hatterer, 1965; Glover, 1955; Wolff, 1956; Miller, 1949; Szasz & Nemiroff, 1963; Alexander, 1963; Jackson & Haley, 1963; Stein, 1966.

Glover, 1952; Hatterer, 1965). The criteria for selection has changed since Freud first treated patients who were diagnosed as hysteric, and recently rediagnosed as psychotic or having severe character disorders (Zetzel, 1965). Patients are now the least ill of any group, and have comparatively favorable prognoses even without therapy. The criteria for selection may have evolved during the past 60 years into an empirical recognition of those patients most likely to respond to psychoanalytic treatment and perhaps to any appropriate treatment (Burrow, 1927; Eysenck, 1965; Frank, Gliedman, Imber, Nash, & Stone, 1957; Hatterer, 1965; Hobbs, 1962; Luborsky, 1962; Meehl, 1965; Zetzel, 1965).

Patients who meet the criteria for psychotherapy or psychoanalysis frequently have sociocultural expectations, backgrounds and interests that are similar to their therapists.[20] Cultural mutuality, as noted previously, is related to the therapist's interest in the patient, treatment results and the success of treatment (Cole, Branch, & Allison, 1962; Frank, 1961; Goldstein, 1962; Gumpert, 1963, Heine & Trossman, 1960; Lesse, 1964). The patient's ability to pay a large fee for a long time is a prerequisite for treatment and the therapist's interest (Chodoff, 1964; Hatterer, 1965; Kubie, 1964; Mowrer, 1963).

Patients may be more educated, creative, intelligent, informed, accomplished, successful, and wealthier than the treating psychiatrist. Such patients would reject simple reassurance, persuasion, reeducation, support, and other culturally inappropriate placebo techniques. Only an unapproachable and prestigious physician, who was a master of esoteric dynamic theory, which was not easily understood by the uninitiated, would be able to engender the magic and mystery (one-upmanship) (Haley, 1953) necessary for placebo responses. As Schmideberg (1939), put it, drugs are a placebo for some patients; psychoanalysis for others (Fenichel, 1954; Jaspers, 1965; Kiev, 1962; Levenson, 1958). In the previous version of this chapter (Shapiro, 1971) a psychoanalytic case history was discussed to demonstrate that psychoanalysis is potentially susceptible to many placebogenic and iatroplacebogenic effects.

Many psychoanalysts believe that analytic treatment is differentiated from other therapies because it has specific, nonplacebo, and nonsuggestive effects. This review suggests the contrary position that it may have extensive, potent, and subtle placebo effects on patients for whom the treatment is appropriate (Bailey, 1965; Frank, 1961; Glover, 1955; Goldstein, 1966; Hatterer, 1965; Kiev, 1964; Rachman, 1963; Schmideberg, 1939).

The concept of iatroplacebogenesis is supported by its general applicability to many therapies. Iatroplacebogenesis is more important in some forms of therapy than others. It does not preclude concomitant specific effects, such as insights in psychotherapy or pharmaceutical effects in drug therapy. It may function as a prerequisite or catalyst for therapies that involve psychological factors or interpersonal relationships; see, for example, the evidence that specific effects occur in psychochemotherapy when the iatroplacebogenic atmosphere is favorable.

Many of these placebogenic and iatroplacebogenic influences are major but unacknowledged factors in the clinical practice and therapeutic claims of behaviorally oriented therapists (Russell, 1974; Shapiro, 1976; Shapiro, Bruun, & Sweet, in press). The existence of these same placebogenic factors and themes in disparate therapies such as psychoanalysis and behavior therapy (as well as biofeedback, megavitamin, acupuncture treatment, and innumerable other newly introduced and to-be-introduced therapies) is testimony to the inevitability, reoccurrence, and power of the placebo effect in the past, present, and the future history of clinical therapies.

NEGATIVE PLACEBO EFFECTS

An early, curious finding of placebo effect research was that placebos caused negative as well as desired or positive therapeutic reactions. Negative placebo effects are defined as the occurrence of

[20] Lowinger & Dobie, 1963, 1964; Snyder & Snyder, 1961; Strupp, 1960a; Frank, 1961; Cole, Branch, & Allison, 1962; Rickels, Baum, Taylor, & Raab, 1964; Frank, Gliedman, Imber, Nash, & Stone, 1957; Heine & Trossman, 1960; Hobbs, 1962; Lesse, 1962; Luorsky, 1962; Burrow, 1927; Goldstein, 1966; Eysenck, 1965; Hatterer, 1965; Zetzel, 1965; Meehl, 1955; Schaffer & Myers, 1954; Hollingshead & Redlich, 1958; Wood, Rokusin, & Morse, 1965.

side effects or as the worsening of symptomatology following placebo administration. It is important to separate these two definitions since the origin and significance of negative placebo effects may differ depending on the definition utilized.

Placebo-Induced Side Effects

The findings that side effects often followed ingestion of placebos has contributed to the mystique and potency attributed to placebos (Beecher, 1955). Early studies reported placebo side effects such as vomiting, headaches, dizziness, dry mouth, drowsiness, and nervousness (Brown, 1948; Diehl, 1933). Recent studies have confirmed the frequency of these placebo-induced side effects (Dhune, Agshikart, & Dimiz, 1975; Gowdery, Hamilton, & Philip, 1967; Hass, Fink, & Hartleider, 1963; Pogge, 1963).

The frequency and types of placebo side effects varies among studies. Pogge (1963) tabulated the results of 67 studies and found that 817 of 3549 patients (23 percent) reported at least one side effect following placebo treatment. The type of side effect was related to the type of active medication or disease entity under study. For example, nausea was more frequently reported with antispasmodic placebos and drowsiness with tranquilizer placebos. Many other studies have described the variety and extensiveness of placebo-induced side effects.

Placebo-induced side effects can occur in several ways. Some placebo side effects may be symptoms of the original disease. Even with active medications there may be a misinterpretation of the cause of a side effect. Many of the side effects of antidepressant medication are also symptoms of depression (Busfield, Schneller, & Capra, 1962; Schulterbrandt, Raskin, & Reatig, 1974).

Some placebo-induced side effects may be the result of becoming more sensitive to and aware of bodily reactions. Reidenberg and Lowenthal (1968), in a survey of healthy subjects not taking medication, found that only 19 percent did not experience any of the 25 symptoms inquired about in the last two days. Had they been taking medication, these symptoms would have likely been called side effects.

In two studies, the number of side effects was similar in subjects taking placebos and control subjects not given a placebo (Glaser & Whittow, 1954; Shapiro, Chassen, Morris, & Frick, 1974). However, the type of side effects were different. Patients on placebos tended to report somatic side effects (e.g., headache) while those not on placebo tended to report cognitive or affective side effects (e.g., inability to concentrate) (Linton & Langs, 1962; Shapiro et al., 1974). The environmental set induced by taking medication may, therefore, influence patients to interpret and "label" their bodily reactions in somatic terms (e.g., headache) rather than cognitive-affective terms (e.g., tension).

Some placebo-induced side effects may be considered a patient's indirect communication of dissatisfaction with treatment. High scores on a scale measuring indirect hostility positively correlated with placebo side effects (Downing & Rickels, 1967). Placebo side effects are more frequently reported by clinic patients compared to private practice patients (Rickels et al., 1964b). Two studies found that placebo-induced side effects were correlated with increased clinical symptomatology (Keup, 1971; Rickels, 1964). However, another study found that placebo side effects were common for improved patients as well as those reporting a worsening of symptoms (Shapiro et al., 1973). Thus, side effects may facilitate improvement in some patients, possibly by the communication that a treatment is working (Kast & Loesch, 1961).

Placebos and the Worsening of Symptoms

Eight to 48 percent of patients given placebos in various studies report their condition to be worsened (Keup, 1971; Morison et al., 1961; Shapiro, et al., 1968; Wolf & Pinsky, 1954). Although several mechanisms have been proposed to explain this type of negative placebo effect, the most frequently cited explanation is the "violation of expectation."

Therapist instructions lead patients to have expectations about the effects of their therapy (Knapp & Knapp, 1973; Morris & O'Neal, 1975). Patients may interpret unfulfilled expectations about therapy as an indication that their symptoms were worse than originally thought. For conditions like insomnia, worry may cause an exacerbation of symptoms (Mitler, Guilleminault, Orem, Zarcone, & Dement, 1975; Storms & Nisbett, 1970). This

type of "boomerang" in which the suggestion of improvement leads to worsening of an illness may be associated with factors such as "overselling" the efficacy of treatment (Valins, Adelson, Goldstein, & Weiner, 1971; Uhlenhuth et al., 1966) and patient inexperience with the treatment or the disease (Rickels, Baum, Raab, Taylor, & Moore, 1965; Rickels, Lipman, & Raab, 1966).

These considerations suggest that overall there are three types of placebo effects: a positive placebo effect defined as therapeutic improvement, a neutral placebo effect defined as the absence of change, and a negative placebo effect defined as a worsening of presenting symptomatology. Placebo-induced side effects are associated with both positive and negative placebo reactions (Shapiro et al., 1968). Therefore, placebo-induced side effects should not necessarily be labeled as negative placebo reactions. They should be considered as another aspect of placebo phenomenology and studied as a separate but related area (Struening, Shapiro, & Shapiro, in preparation).

CONCEPTS OF PLACEBOGENESIS

The method(s) by which placebos cause placebo effects is unknown. However, many processes have been advanced to explain placebo effects. Although there is little empirical verification for these processes, it is important to hypothesize processes of placebogenesis to organize and integrate the various relationships and predisposing factors associated with the placebo effect.

Three general themes serve to group the various placebogenic processes or mechanisms: social influence effects, expectancy effects, and evaluation effects.

Social Influence Effects

The role of the physician in society is unique. He or she performs and combines functions that have always been important to people—those of healer, priest, and scientist. These attributes facilitate the tendency of patients to view the physician as a socially powerful individual. Similarly, the experimenter's social power has been dramatically documented by Milgram's studies in which subjects were pressured into delivering potentially dangerous electric shocks to unseen victims (Milgram, 1963). Thus, therapists and investigators may contribute placebogenic influences by means of rewards and punishments or by their ability to deliver persuasive arguments. Placebo effects may also be attributable to normative role demands or the patients' and subjects' own suggestibility.

The patient-physician relationship gives rise to special transference and countertransference interactions. Several investigators have conceived of the placebo effect as due to this transference-countertransference relationship. Finally, the interest of the therapist in a patient may have a primary effect on reducing patient guilt thereby contributing to patients' improvement.

Suggestion

Suggestibility is the most often cited mechanism of placebo action. Several investigators have assumed that the placebo effect is merely a variation of the suggestibility response (Beecher, 1968; Strupp, Levenson, Manuck, Snell, Hinrichsen, & Boyd, 1974; Trouton, 1957). Although the process of suggestibility has not been well defined, factor analytic studies have demonstrated two major components. Primary suggestibility involves bodily responses to direct suggestions while secondary suggestibility is heavily loaded on items stressing the gullibility of subjects (Eyesenck & Furneaux, 1945; Evans, 1967). Both of these components are applicable to placebo effects. However, Trouton (1957) and Tibbetts and Hawkins (1956) considered secondary suggestibility more important in the genesis of placebo effects becuase both secondary suggestibility and the placebo effect involved "attitudes" whereas primary suggestibility involved "aptitudes."

Tests of suggestibility have been used as successful predictors of hypnosis. Unfortunately the hope that tests of suggestibility would predict response to placebo has not received empirical support.

Evans (1967) has suggested that a "therapeutic element" is necessary for suggestibility to correlate with the placebo effect. Shapiro (1964c) has hypothesized that differences in stimulus value of a test of suggestibility (which involves laboratory

procedures) and a placebo test (which utilizes a clinical setting) may account for the lack of association. In a study by Frank et al. (1957) tests of suggestibility administered in a clinical setting were positively correlated with placebo reaction. It seems likely that if both placebo and suggestibility procedures are viewed as therapy, rather than one as a treatment and the other as a gullibility test, results would have greater concordance (Barber & Calvery, 1964).

Persuasion

Following the general model advanced by Hovland, Janis, and Kelley (1953), Liberman (1961) conceptualized the placebo effect as a function of the persuasive influence of a therapist who is perceived by the patient as expert and trustworthy. In addition, certain personality characteristics may predispose patients to placebo reactions. Some of the characteristics are related to placebo reaction only under certain circumstances while other traits are not situation bound. Finally, the observed placebo effect is measured both as a "true" response reflecting actual therapeutic change and as an "artifactual" response such as a faked or spontaneous change.

Both suggestibility and persuasion are general models of social influence. The persuasibility model views the placebo reactor as a rational individual rather than a gulliable patient. The power of the physician's arguments, rather than the yielding of the patient, is stressed.

Transference

In the suggestion and persuasion paradigms, no distinction is made between the therapeutic and nontherapeutic environments. In the transference model, the placebo response is viewed as an outgrowth of the patient-therapist relationship. Although transference-type relationships may occur in experiments, they are apt to be qualitatively different from ones that could occur with a therapist. A classical definition of transference is that feelings, such as love, hatred, trust, and distrust, which the patient attached to significant persons in the past, are unknowingly displaced onto the therapist. Positive placebo effects stem from a positive transference caused by satisfactory early experiences with parents or parent surrogates, or by individuals who expect succor and comfort from the therapist despite unsatisfactory early relationships. A patient's dependent relationship on the therapist may be made acceptable by the placebo, which presents a socially permissible vehicle for patient's regressions (Kast & Loesch, 1959). Negative placebo effects can result from a patient's unsatisfactory transference relationship with the therapist, and the doctor's countertransference relationship with the patient. Patients' hostility may be manifested by the report of negative side effects (Downing & Rickels, 1967). Dramatic symptom relief may be the manifestation of a positive transference relationship.

The transference paradigm views the patient as an active communicator who has established a special relationship with the therapist. Placebo effects are patient communications that have symbolic meaning and may predict ultimate treatment response.

Role Demands

Pressures to behave in certain prescribed manners are inherent in the role of a patient or experimental subject. In a clinical situation, positive placebo reactions may reflect the role of a "good patient." A patient who reacts positively would justify the therapist's initial concern and subsequent interest, care, and attention (Goldstein, Rosnow, Goodstadt, & Suls, 1972).

The subject may pick up subtle cues in an experimental trial (Rosenthal & Rosnow, 1969), integrate hints from the experimental procedure to guess the true nature of the experimental hypothesis (Orne, 1970), or model his or her behavior after the experimenter (Chaves, & Barber, 1974). Subjects may then behave in a fashion that will confirm the hypothesis. Even under postexperimental questioning, subjects may not divulge their awareness of the true hypothesis in an attempt to satisfy the experimenter.

Mutual or congruent therapist-patient role expectations can have a positive effect on treatment outcome, whereas discrepant role expectancies can lead to the failure of treatment (Goldstein, 1962). In addition to the therapist, other patients may communicate normative influences about

proper behavior in particular situations (Schachter & Singer, 1962; Craig & Coren, 1975).

Operant Conditioning

High esteem for both the experimenter and therapist characterizes the experimental and therapeutic atmosphere and increases the potential of the therapist or experimenter to deliver rewards and punishments. Therefore, by both intended and unintended means, operant conditioning principles may shape subject and patient responses (Bourne, 1971; Frank, 1968; Gelfand, Ullmann, & Krasner, 1963; Kurland, 1957).

Buckalew (1972) demonstrated that reinforcements may increase placebo responding, independent of and in addition to the effects of suggestion. Conditioning by experimenters and therapists influences and reinforces simple behaviors as well as attitudes and complicated behaviors (Krasner, Ullmann, & Fisher, 1964). Operant conditioning may directly influence physiological responding (Byerly, 1976; Miller, 1974) or indirectly by cultivating arousal states that heighten patient's influenceability (Gliedman, Gantt, & Teitelbaum, 1957).

Guilt Reduction

The primary and direct effect of the therapist's interest in the patient is probably on guilt. Guilt is universal, and has been an important part of religion, philosophy, literature, and psychology throughout recorded history (Black, 1966; London, Schulman, & Black, 1966). It is involved in every system of psychopathology, clinically apparent in all patients with psychological and physical illness, and detected in nonpatients as well.[21] Guilt is manifested by or associated with many common feelings such as worthlessness, inadequacy, inferiority, impotence, depression, conflict between inner and outer behavior and shame about inner impulses and past behavior. Fantasies are often perceived as ego-alien experiences, not shared by other people. Inner sensitivity to irrationality stimulates fear and defense against insanity and loss of control, which cannot be fully examined without help from another person.

The prestigious heritage of the priest, scientist, and physician is represented in our culture by the psychotherapist (Frank, 1959, 1961; Jaspers, 1965; Kiev, 1964). To the physician are attributed omniscience, onmipotence, integrity, dedication, and esoteric knowledge (Schmideberg, 1939). Society's sanction of this role makes the physician an even more pretigious figure.[22]

Illness is usually stressful (Kiev, 1964). Familiar cues for integration decrease; ambiguity and stimulus hunger increase (Heine, 1950; Frank, 1969, 1961; Krasner, 1962, Kiev, 1964; Ward, 1964; Schmideberg, 1939); and regressive fantasies (Fisher, 1953), guilt (Frank, 1961; Glover, 1931), anxiety,[23] depression (Frank, 1961; Shapiro, 1963, 1964c, d, f, 1968), and dependency (Frank, 1961; Zuckerman & Grosz, 1958; Jakubszak & Walter, 1959) are stimulated: all these factors that have been cited as correlates of suggestibility and the placebo effect.[24]

The favorable feelings of the therapist have been associated with the increased expression of affect by patients (Fiedler, 1953; Frank, 1961), which may further decrease guilt through catharsis. It is also related to increased suggestibility, conditioning, and learning in patients. Patients become suggestible and are inordinately reassured by the interest of the prestigious therapist (Strupp et al., 1964; Frank, 1961; Brown, 1929; Schmideberg, 1939; Sargant, 1957; Estes, 1948; Sherif & Haney, 1952). Powerful therapeutic forces have now been set into motion. Guilt, anxiety, and discomfort are reduced, hope is mobilized and previ-

[21]Strupp, 1960b; Kahn, 1957; Fenichel, 1954; Hobbs, 1962; Kiev, 1962, 1964; Mowrer, 1963; Elliode, 1964; De Grazia, 1952; Rogers, 1956; Ripley & Jackson, 1959; Jersild & Lazard, 1962; Haley, 1963; Sargant, 1957; Mowrer, 1961; Murphy, 1964; La Barre, 1964.

[22]Heine, 1950; Frank, 1961; Fenichel, 1954; Lesse, 1964; Jaspers, 1965; Kiev, 1962, 1964; Ellenberger, 1956; Gumpert, 1963; Scharaf & Lerinson, 1964.

[23]Goldstein, 1962; Krasner, 1962; Kiev, 1962, 1964; Ellenberger, 1956; Estes, 1948; Sherif & Haney, 1952; Dibner, 1958; Walters, Marshall, & Shooter, 1960; Walters & Ray, 1960; Walters & Quinn, 1960; Walters & Parke, 1964.

[24]Strupp, Wallach, & Wogan, 1964; Goldstein, 1962; Barchilon, 1958; Frank, 1959, 1961; Krasner, 1962; Brown, 1929; Schmideberg, 1939; Kiev, 1962; Eliode, 1964; Sargant, 1957; Dibner, 1958; Walters, Marshall, & Shooter, 1960; Walters & Ray, 1960; Walters & Quinn, 1960; Borodin, 1955.

ously impaired assets can better be utilized (Frank, 1961; Estes, 1948). Spontaneous remission, as well as favorable environmental and other changes, have a greater chance of occurring, and are more easily stimulated, integrated, and utilized because of the favorable psychological state of the patient. These changes may be attributed to therapy, increasing the suggestibility of therapist and patient. At the same time, the therapist's interest is associated with increased understanding of the patient's behavior. These nonspecific therapeutic factors may now interact with the specific effects of various therapies.

Another possible mechanism is that interest in the patient leads to or coexists with an interest in the treatment.

An intense interest in treatment by a prestigious therapist mobilizes the patient's hope and optimism. The patient can depend on the therapist's integrity and competence, and be supported by the belief that he or she will be helped. The more intense the belief of the therapist in the patient's treatment, the more impressed will be the patient and the greater his or her belief. The patient may translate the therapist's belief: if the doctor is sure he or she can help me, I can rely on him or her to be helped (Frank, 1961; Kiev, 1964; Bergman, 1958; Menninger, 1959).

The therapist's interest in the patient's treatment also has an effect on guilt. A patient is reassured when problems are treated as symptoms of illness and not shameful character traits (Strupp et al., 1964; Snyder, 1946; Frank, 1961), or when or she learns that fears of losing control, insanity, and pathological uniqueness are unrealistic fantasies. Reassurance may occur in treatment with drugs and psychotherapy, in uncovering and repressive therapies, and whether or not direct reassurance is given.

The patient is in a highly suggestible state, as previously described, and may react to the therapist's interest with more hope and optimism than is warranted or realistic. Guilt and anxiety decrease and may interact with other therapeutic factors such as spontaneous remission, environmental changes, better utilization of resources, and other previously described factors. Finally, the therapist's interest in treatment may interact with his or her interest in the patient and in the results of treatment, and all of these factors may now interact with the potential specific effect of many therapies.

Support for the generation of guilt reduction from these factors and processes as well as the importance of guilt reduction to therapeutic and placebo effects requires empirical verification. Similiarly, concepts such as operant conditioning, transference, suggestion, and persuasion are only hypothetically related to placebo reaction.

Expectancy Effects

Along with establishing special relationships with their patients, experimenters and therapists, by both intended and unintended means, communicate expectations about the effects of administered treatments. If the therapist does not explicitly supply these expectations, the patients may search for "cues" or rely on their own ideas and values (Morris & O'Neal, 1975; Sternbach, 1966).

Patients and subjects may also enter therapy or an experiment with preconceived notions derived from past experience or what has been learned from others. Although there is some research indicating that patients' general attitudes about chemotherapy may predict improvement on medication (Honigfeld, 1963; Sheard, 1964), this finding is inconsistent (Glick, 1968; Gorham & Sherman, 1961). Patients' attitudes may contribute to the therapeutic milieu. The more favorable the patient and staff attitudes in the milieu, the greater the "therapeutic potential" (Honigfeld, 1963).

Although general attitudes are weak correlates of placebo response, "specific attitudes" (i.e., expectations) seem to be better predictors of the placebo effect (Goldstein, 1960; Goldstein & Shipman, 1961; Hill, Belleville, & Wikler, 1957; Morris & O'Neal, 1974; Uhlenhuth et al., 1966). Attitudes and expectancies are thought to be important, nonspecific aspects of psychotherapy (Nash et al., 1964).

Expectations are formed and modified by patients' or subjects' previous experience with a specific treatment. Studies of the nonspecific effects of marijuana intoxication indicate that familiarity with the active drug increases subsequent placebo response (Carlin et al., 1974; Jones, 1971). Other studies suggest that previous experience may tend

to decrease placebo reaction (Rickels, Lipman, & Raab, 1966; Snyder, Schultz, & Jones, 1974; Valins et al., 1971). The finding that previous experience with a treatment can both increase or decrease placebo reaction supports the contention that placebo effects can occur through any number of pathways. Differences in procedures, populations studied, or any number of variables could possibly account for these conflicting results.

There are at least four ways expectations contribute to placebogenesis: by classical conditioning, by "cognitive dissonance," by influencing the internal standard against which therapeutic effects are evaluated, and by affecting the hope and faith of an individual about the therapist and therapy.

The importance of expectations in drug therapy is highlighted by the findings that normal behavioral responses to active drugs are not found when patients are not told the nature of the drug they are administered (Lyerly et al., 1964; Penick & Hinkle, 1964) and physiological responses are decreased by inappropriate expectations (Penick & Fisher, 1965).

Classical Conditioning

When expectations are produced by prior temporal association, classical conditioning is believed to be a prime determinant of the placebo effect. The earliest demonstration of classically conditioned placebo effects was by Pavlov himself (Pavlov, 1927). Dogs who were initially injected with morphine reacted with salivation, nausea, and emesis. After repeated injections, the dogs displayed the same reactions to being prepared for the injection as they did to the initial injection. This conditioned placebo response was more complete and less dependent on the organism's motivational state than other forms of classical conditioning (Grant, 1964).

Classical conditioned reactions to drugs have been demonstrated in animals (Hernstein, 1962; Pickins & Crowder, 1967; Altman, 1971) and humans (Knowles, 1963). The finding that physiological reactions to drugs may occur quicker than when induced by a pharmacological mechanism has also been attributed to classical conditioning (Petrie, 1960; Stanley & Schrosberg, 1953).

Cognitive Dissonance

The anticipation that a therapy will produce a physiological effect can lead to the occurrence of that effect (Wolf, 1950). Cognitive dissonance has been advanced as a motivational mechanism that can account for psychologically caused changes in bodily states (Totman, 1976; Zimbardo, 1969).

When two beliefs are in a dissonant relationship (i.e., they are the logical converse of one another), there is believed to be a generalized (arousing) drive state within the individual to resolve this dissonance (Festinger, 1957; Pallak & Pittman, 1972; Waterman 1969; Zana & Cooper 1974). To resolve the aversive qualities of dissonance, individuals may be forced to change the attitude or belief that offers the "least resistance" to change. If attitutes or beliefs are strongly held, physiological functioning may be changed to achieve a state of cognitive consonance. Although the experimental demonstrations of dissonance produced physiological changes have been limited to pain endurance (Zimbardo, 1969), it is possible to envision more generalized application. An individual's belief in a prestigious therapist's dictum that certain events will occur ("my doctor said this therapy will make me feel better") or in the power of a therapy ("only very sick people fail to improve with psychotherapy") may be strongly entrenched. If the individual does not start to feel better, a state of dissonance will evolve. Beliefs that restore consonance such as "the doctor lied" or "the doctor did not know what he was talking about" may not be acceptable in the individual's value system. To achieve consonance, a dissonance caused placebo effect may be induced.

Internal Standards

Evaluation of a therapy is relative since an identical therapeutic outcome could be judged a success or a failure based solely on the criterion utilized. Therapies are evaluated in experiments by comparison with appropriate control groups. The criterion for the individual receiving treatment, however, is based on an internal standard. Expectations play a role in determining both the level and strength of this standard.

The placebo effect can be affected by instructions given by therapists that are conveyed by different therapists' attitudes (Uhlenhuth et al., 1959), or by explicity assigned roles (Uhlenhuth et al., 1966). An interesting finding is that unfilled therapeutic promises may backfire and lead to clin-

ical worsening (Valins et al., 1971; Storms & Nisbett, 1970). Similiarly, if patients' expectations about treatment are highly discrepant with the initial perceptions, they may prematurely drop out of treatment (Rickels & Anderson, 1967).

A second factor that influences the strength of an internal standard is the previous experience of the patient with the disease or therapy. Patients highly familiar with a therapy or a disease are apt to have more realistic expectations and, therefore, better standards of comparison. Rickels, Lipman, & Raab (1966) reviewed data indicating that a longer duration of illness and history of taking medication were both negatively correlated with placebo reaction. Data from studies utilizing the same patients in multiple treatments support the conclusion that once having experienced a satisfactory response, patients develop and employ this frame of reference to evaluate subsequent treatments (Adam, Adamson, Brezinova, & Oswald, 1976; Haertzen, 1969; Galanter, Stillman, Wyatt, Vaughn, Weingartner, & Numberg, 1974; Rickels, Lipman, & Raab, 1966). Accurate expectations, supplied by giving greater detail about the physical sensations one will experience can reduce the distress of painful stimuli (Johnson, 1973).

Hope

Expectations combined with desire are the essential ingredients of hope. Frank (1961) has argued persuasively for the importance of hope in psychotherapy and placebo effects. Hope is viewed as an integration of physiological arousal with certain cognitions. The cognitive component of hope involves envisioning a favorable change in one's life situation, usually in relation to one's actions or an anticipated environmental event.

Anticipations about therapy begin before the individual labels himself or herself a patient and are reformulated at the initial and subsequent stages of therapy (Goldstein, 1962). Hope is an essential element in the motivation of goals (Stotland, 1969). Frank (1963) views hope as directly related to the reduction of anxiety, depression, and other symptoms.

The importance of faith is reflected in the fact that one of the major, best-educated religious groups in the United States denies the rational efficacy of any treatment or medicine, and attributes all therapeutic benefits to faith. Faith, frequently denoted by terms such as trust, confidence, and the strength of a belief, might augment the influence of expectations on the placebo effect.

Evaluation Effects

A third process that influences placebo effects is derived from attempts to evaluate the placebo response. Patients may modify subjective reports or change their behavior because of the knowledge that they are being monitored. A more subtle mechanism occurs when patients are asked to report an emotion or attitude, and they rely on salient cues to "label" their response. Bodily states or behavioral responses may be interpreted in the context of the measurement situation. Misattribution is another process that influences placebo responses. The knowledge that therapy has been rendered constiutes a major environmental cue to both the patient and the therapist. A change in a patient's status may be misattributed to the therapy when it is actually caused by some other situational factor.

Response Artifacts

The assessment of therapeutic effects can distort the data (Webb, Campbell, Schwartz, & Sechrest, 1966; Nelson, Lipinski, & Black, 1975; Roberts & Renzaglia, 1965). Since there is so much variance in tests used to estimate the placebo effect (Shapiro et al., 1973), the reliability and validity of placebo effect measures is generally unknown. What investigators call placebo effects may actually be patients' response bias.

Response bias may be caused by inherent design problems of self-rating scales. In filling out questionnaires, patients may lie, fake, or tend to present themselves in a favorable light (Dahlstrom & Welsh, 1960). They may be thoughtless, overly generous, or tend to consistantly give themselves the benefit of the doubt (Jones & Sigall, 1971). They may consistently rate all aspects of a stimulus "good or "bad" without proper discrimination (O'Neal & Mills, 1969). They may generally tend to give socially desirable responses (Marlowe & Crowne, 1964; Edwards, 1957). Apprehension by patients about being evaluated can prompt a biased response (Rosenberg, 1969) or response bias can be stimulated by a desire to please or impress therapists (Tedeschi, Schlenker, & Bonoma, 1970).

Labeling

It is assumed that emotions can be validly measured by asking patients to reflect on their inner state. However, Schachter and Singer (1962) have hypothesized that an emotion is the result of a bodily state change that is "labeled" by means of appropriate environmental cues. The same change in bodily state can result in an angry or euphoric emotion, depending on the context in which the change occurs.

When a patient is asked to rate "how he or she feels," he or she may be uncertain about the nature and extent of his or her feelings. A most potent environmental cue is the fact that a therapy has recently been adminstered. The therapeutic milieu may lead the patient to "label" an ambiguous bodily state with "positive" words that reflect a therapeutic outcome.

The particular labels an individual chooses are apt to be dependent on the type of therapy rendered. Shapiro et al., (1974) administered drug-placebo and control-placebo therapies to psychiatric outpatients. The control placebo was conveyed by asking patients to sit in a quiet room for an hour and rate how their symptoms spontaneously varied. The number of side effects reported by patients did not differ between the two groups. However, patients who received the drug placebos tended to describe their side effects as somatic, such as "headache" and "stomach pain," whereas the control-placebo patients tended to use cognitive-affective labels such as "upset" or "feeling sorry for self."

In addition to environmental factors, previous experience with the particular therapy or similar therapies may supply appropriate labels in ambiguous situations (Linn, 1959). Becker (1953), has theorized that the experience of a marijuana induced "high" is dependent on an individual learning to label the bodily reactions that consitute this reaction.

An interesting phenomenon related to the labeling process is that any change in bodily arousal stimulates the need to explain the cause of the arousal. Individuals search the environmental for appropriate explanations (Barefoot & Straub, 1971; Girodo, 1973; Goldstein, Fink, & Mettee, 1972; Valins, 1966). If an adequate explanation does not exist, perceptions may be distorted to account for the arousal (Wilkins, 1971). The arousal associated with the uncertainty of the initial aspects of therapy may be "labeled" with terms that denote therapeutic success.

Misattribution

The basic premise of attribution theory is that people seek to know the causes of behavior, even their own behavior. However, sometimes mistakes are made and people misattribute the causes of behavior. (Jones, Kanouse, Kelley, Nisbett, Valins, & Weiner, 1972). Positive placebo effects may occur when the cause of a change in bodily state or behavioral response is erroneously attributed to the therapy rather than the actual cause such as some other environmental factor (Morris & O'Neal, 1974; Valins & Nisbett, 1971). The explanatory potential for misattribution as a mechanism for placebo effects is highlighted by a study by Schorer, Lowinger, Sullivan, and Hartlaub (1968). Sixty-four percent of a group of patients awaiting psychotherapy stated that their status had improved, even though they had not received treatment. Had these patients received psychotherapy it is likely that they would have attributed the improvement to their treatment.

According to attribution theory, individuals seek not only to assign reasons for observed changes, but also seek to fully explain why these changes occurred (Kruganski, 1975). If expected bodily state or behavioral changes do not occur, patients may experience a negative placebo effect. The negative placebo effect can occur when patient expectations about therapeutic results are overly optmistic (Hoenh-Saric, Liberman, Imber, Stone, Frank, & Ribich, 1974; Valins et al., 1971) or when patients assume that the cause of a therapy's failure is the severity of their illness (Storms & Nisbett, 1970).

Medication placebos have been used to manipulate the perceived cause for a reaction. By inducing people to falsely ascribe autonomic changes to the action of a placebo, fear of impending shocks can be diminished (Nisbett & Schachter, 1966), snake phobia can be reduced (Valins & Ray, 1967) discomfort from cigarette withdrawal can be reduced (Barefoot & Girodo, 1972), insomniacs may fall

asleep sooner (Storms & Nisbett, 1970), cognitive dissonance can be decreased (Zanna & Cooper, 1974), and anxiety from watching an upsetting film can be lessened (Girodo, 1973).

More recent studies have shown that the misattribution process may have severe limitations in therapeutic situations (Bootzin, Herman, & Nicassio, 1976; Calvert-Boyanowski & Leventhal, in press; Kellogg & Baron, 1975; Hoehn-Saric et al., 1974; Singerman, Borkovec & Baron, 1976). Further study of the applicability of attribution theory to the placebo reaction is warrented.

CONCLUSION

Therapy is impaired if physicians are unaware of placebo effects. Therapeutic effects are attributed to specific procedures that, unknown to the physician, are caused by nonspecific or placebo effects. The therapist's credulity about the efficacy and specificity of the procedure are exaggerated, and it encourages the use of one procedure or technique for all patients. Therapists who rely on one technique are unable to treat many patients; some may be hurt because of inappropriate treatment (Jasper, 1965; Ward, 1964), and specific indications for a therapeutic procedure are obfuscated. Awareness of placebo effects enable clinicians to better evaluate the effects of therapy, contribute to the development of more flexible and appropriate procedures, and make therapy more comprehensive, resourceful, and effective.

The recognition that these factors contribute to the treatment process improve studies by investigators and may help clarify unsolved problems of the specificity of many therapies.

It is important to remember that much of this chapter is based on review of retrospective data. Careful prospective studies are necessary for clarification of the primacy, relevancy and validity of these concepts.

The history of both physiologic and psychologic treatment is largely the history of the placebo effect; those who forget the past are destined to repeat it. Garrison observed that "whenever many different remedies are used for a disease, it usually means that we know little about treating the disease, which is also true of a [remedy] when it is vaunted as a panacea or cure-all for many diseases" (Garrison, 1921).

If we keep those thoughts in mind, we may avoid the problem that the complier of the Paris Pharmacologia insightfully observed a century ago: "What pledge can be afforded that the boasted remedies of the present day will not be like their predecessors, fall into disrepute, and in their turn serve only as a humiliating memorial of the credulity and infatuation of the physicians who recommended and prescribed them" (Haggard, 1934).

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Senator NELSON. Our next witness is Dr. Robert H. Furman, vice president, corporate medical affairs, Eli Lilly & Co., who will be accompanied by Edgar G. Davis, vice president, corporate affairs, and John Holt, secretary and general counsel, pharmaceutical division.

Dr. Furman, would you identify your associates for our reporter so any comments they may have would be accurately reported in the record?

STATEMENT OF ROBERT H. FURMAN, M.D., VICE PRESIDENT, CORPORATE MEDICAL AFFAIRS, ELI LILLY & CO., ACCOMPANIED BY EDGAR G. DAVIS, VICE PRESIDENT, CORPORATE AFFAIRS; AND JOHN M. HOLT, SECRETARY AND GENERAL COUNSEL, PHARMACEUTICAL DIVISION

Dr. FURMAN. I am Robert H. Furman, M.D., vice president, corporate medical affairs, Eli Lilly & Co.; and with me, next to me, is Mr. John Holt. To his left is Mr. Edgar G. Davis, vice president, corporate affairs.

Senator NELSON. You may submit your statement or proceed in any way you desire.

Does anyone other than you have a prepared statement?

Dr. FURMAN. No, sir, I am the spokesman.

Senator NELSON. If they have comments they wish to make, they may do so.

Before I forget it, let me say that the record will be open for 2 weeks, so that anyone who desires may submit additional material.

Dr. FURMAN. Thank you, sir. On behalf of myself and my associates, I want to express our appreciation for the opportunity to appear and state our views.

Lilly has been engaged in the manufacture of pharmaceuticals for the health professions since 1876. The company maintains one of the largest private pharmaceutical research programs in the world. There are 67 full-time physicians—M.D.'s, that is—exclusive of industrial health physicians.

Lilly provides a broad range of products for human medical needs and backs them up with extensive programs of medical and technical support. Lilly was the discoverer and developer of propoxyphene products, which it markets under its Darvon® trademark.

Extensive experience and study have demonstrated that propoxyphene products are safe when used as directed and that they are effective pain-relievers. Lilly knows of no death that has occurred when propoxyphene was properly used, and no previous witness has testified to the contrary. This point deserves emphasis because problems associated with the safety of other drugs have occurred with the use of the drug in recommended dosage.

Like any drug, propoxyphene can be abused. The vast majority of patients who receive Darvon use it properly. But there are some people who take Darvon in excessive doses and who take many drugs at one time—often along with alcohol. Frequently, their motives are suicidal. This kind of drug abuse is a medical and social problem that transcends

the abuse of any one drug. If Darvon suddenly were to become unavailable, the problem would remain the same.

Lilly is deeply concerned about this problem of drug abuse. The company believes that further study and educational efforts are needed to understand the problem and to help correct it. Available information indicates that the extent of propoxyphene abuse has, in fact, declined as physicians have become better informed about its abuse potential and since the drug was placed in schedule IV under the Controlled Substances Act in 1977. However, the larger societal problem—of which propoxyphene abuse is only a part—remains, and Lilly is committed to work with the Government and the medical profession in further efforts to ameliorate the problem.

The facts do not, however, support the health research group's contention that propoxyphene products should be subjected to the more stringent controls of schedule II, much less that they should be banned as an imminent hazard to the public health.

Propoxyphene is an analgesic for the relief of mild to moderate pain. Physicians prescribe it, either alone or in combination with other analgesics, such as aspirin, for pain of the kind and severity that follows surgery and tooth extractions and that accompanies lower back injuries, cramps following childbirth, and many other medical conditions.

It must be kept in mind that before Darvon was developed there was perceived a need for it. Lilly developed propoxyphene as the result of a national program of research, instituted in 1948, to find a synthetic substitute for the opium-derived analgesics—such as codeine—that would offer the therapeutically desirable properties of those drugs without causing addiction of drug dependence.

After extensive study, including clear-cut demonstration of pain relief in laboratory animals, Lilly introduced Darvon in 1957. Since then, the company has continued to improve its propoxyphene products, study their effects, monitor their use, and disseminate information concerning them to physicians and pharmacists.

Over the past 21 years propoxyphene has been extensively studied. More than 865 scientific papers concerning the drug have been published.

Clinical research, as well as long experience in actual medical practice, has shown that propoxyphene products are safe when used as directed. Therapeutic doses of propoxyphene provide a wide margin of safety to the patient. Lilly has sold more than 20 billion doses of propoxyphene over the last 21 years, and the company does not know of a single instance in which the use of its propoxyphene products in accordance with their labeling has caused death or serious injury. Propoxyphene's dependence liability is less than that of codeine.

Senator NELSON. How is a dose of propoxyphene described? Is that one tablet, one prescription?

Dr. FURMAN. It means its use, either single or multiple doses, in accordance with proper medical use.

Senator NELSON. You say 20 billion doses in the last 21 years. How would you define that?

Dr. FURMAN. That would represent several millions of patients using it.

Senator NELSON. No, what I meant was, what is a dose of propoxyphene—1 tablet of 65 milligrams?

Dr. FURMAN. Sixty-five of hydrochloride or 100 of napsylate.

Senator NELSON. So you are talking about in the case then of 20 billion tablets?

Dr. FURMAN. Or capsules, yes.

Senator NELSON. All right.

Dr. FURMAN. Propoxyphene is an effective pain reliever. Its efficacy has been demonstrated in controlled, double-blind clinical studies conducted in accordance with rigorous scientific standards. The Food an Drug Administration has repeatedly confirmed the efficacy of propoxyphene products, as has an expert panel of the National Academy of Sciences-National Research Council.

Several dozen companies have received new drug approval from the FDA to manufacture or market propoxyphene.

The efficacy of propoxyphene has also been demonstrated through its long history of successful use by medical practitioners in the relief of pain.

Mr. Chairman, I might point out that university-affiliated teaching hospitals generally have a formal pharmacy and therapeutics committee made up of faculty members who carefully review products for inclusion in their hospitals' formulary. These "P. & T." committees generally adopt only those drugs they consider appropriate for their institution's use. In a recent survey, we found that more than 90 percent of 466 university-affiliated teaching hospitals contacted have propoxyphene available in their formularies for their patient's use. We feel this is a good indicator of the acceptance of propoxyphene in such institutions.

Some studies have failed to demonstrate the efficacy of propoxyphene. Others have failed to show that it is any more effective as a pain reliever than aspirin. The same may be said, however, of other well-established pain-relief medications, including codeine.

Even Dr. Moertel's study mentioned in his testimony last week indicated that a 650-milligram dose of aspirin—two aspirin tablets—was superior to 65 milligrams of codeine; and in ranking analgesia according to patients' achieving more than 50 percent pain relief, propoxyphene 65 mg. was ahead of codeine 65 mg. (Moertel et al., NEJM, *286*: 813, 1972, fig. 1).

It is often very difficult to demons'rate the efficacy of a pain reliever in a clinicial study. This is so in part because the nature and cause of pain may vary and because the perception of pain involves an important, yet variable psychological component, the effects of which are difficult to measure or control in clinical studies.

For example, Beecher and his associates were unable to demonstrate the superiority of codeine, 60 milligrams, over placebo. (Beecher et al., J. Pharm. Exp. Ther., *109*: 393, 1953).

It is important to recall that studies using laboratory animals are not complicated by these psychological factors and that, in such studies, the pain-relieving properties of propoxyphene are consistently confirmed. In addition, many of the studies referred to earlier in these hearings compared propoxyphene with other pain relievers on the basis of a single dose. Our knowledge of the pharmacology of propoxyphene

indicates that it achieves its greatest pain-relieving effects after several doses have been administered. This is, in fact, the way the drug is used.

Let me depart once again if I may from the prepared text and say in two recent studies utilizing a two-dose sequence in over 300 patients hospitalized with postsurgical wound pain clearly indicate that propoxyphene and codeine provide equal pain relief. (Gruber, JAMA, *237*: 2734, 1977; Young, Curr. Ther. Res., *24*: 495, 1978).

In his testimony last week, Dr. Moertel challenged the statement that multiple-dose studies better demonstrate the efficacy of certain analgesics such as propoxyphene. Nevertheless, Dr. Moertel in his single dose study of 1974 reported in the *Journal of the American Medical Association* (JAMA, *229*: 55, July 1, 1974), had this to say about his results, and I quote:

> They cannot be interpreted as representative of the analgesic response that may be obtained for pain problems of different etiology nor can they be assumed to have any direct application to the long term response to analgesic agents.

In the final analysis, the true measure of the therapeutic usefulness of a drug is determined in the field of clinical practice. Here propoxyphene products have become well established. In practice, the physician's choice of an analgesic for mild-to-moderate pain is limited to: (1) The familiar nonprescription drugs like aspirin and acetaminophen, which in many cases of chronic or recurring pain have already been tried by the patient and found wanting; (2) to meperidine or opium derivatives like codeine—which carry a risk of dependence—and (3) to other analgesics such as propoxyphene or pentazocine—Talwin. There are always people who will respond better to one drug than another. Propoxyphene alone will work remarkably well in some patients whose pain is not well controlled by analgesics that some might regard on average as superior. In short, propoxyphene is a useful and well-established part of the physician's armamentarium for the control of pain.

Over the past 20 years, Lilly has promoted its Darvon products ethically and responsibly. The company has provided the medical profession with the most current information concerning propoxyphene through advertising, labeling, and the efforts of its pharmaceutical representatives. These persons are well trained. All of them are college graduates—at the moment there is one exception. Most are pharmacists.

Studies conducted before the drug was introduced into the market—including an evaluation carried out at the U.S. Public Health Service Addiction Research Center in Lexington, Ky.—showed, contrary to Dr. Wolfe's allegation, that its potential for abuse was limited and that its dependence—or addiction—liability was less than that of codeine. Experience has confirmed these findings.

You have heard testimony in these hearings about the pharmacology and toxicology of propoxyphene. Much of that information was developed in studies that were sponsored by Lilly, shared with FDA and DEA, and disseminated widely to the medical profession.

In 1975, the North Carolina State toxicologist, Dr. McBay, reported that deaths associated with the use of propoxyphene were increasing in that State. Lilly promptly investigated the report and subsequently sponsored a nationwide study by a respected toxicologist,

Dr. Bryan Finkle, of the University of Utah. Dr. Finkle reviewed medical examiner reports and files in 18 geographic areas in the United States and Canada which represented a total population of over 50 million persons. He concluded that most of the deaths associated with propoxyphene involved use of the drug at doses far in excess of therapeutic amounts and in combination with alcohol and other drugs, especially tranquilizers and other central nervous system depressants. A majority of the persons had a history of suicidal tendencies, emotional instability, or drug or alcohol abuse.

In April 1976, Lilly published the results of Dr. Finkle's study in a letter to the editor of the Journal of the American Medical Association. In cooperation with the Food and Drug Administration, the company revised the labeling for its Darvon products to reflect the new findings. A brochure containing the new labeling and Lilly's letter to the editor of JAMA was personally delivered to 114,000 physicians by Lilly pharmaceutical representatives, and copies were mailed to other physicians.

In February 1977, acting on the recommendation of the Department of Health, Education, and Welfare, the Drug Enforcement Administration issued an order placing propoxyphene products in schedule IV. In the petition submitted to the Attorney General, Dr. Wolfe asserted that the Drug Enforcement Administration's action had no effect and that the number of propoxyphene-related deaths had actually increased since the drug was placed in schedule IV. His petition characterized the DAWN figures for 1977 as representing a "crescendo of abuse." However, in his testimony to this subcommittee last week, Dr. Wolfe did not repeat this allegation—and for good reason—because the increase to which his petition referred did not, in fact, occur.

Mr. Durrin, the DEA witness who also appeared last week, testified that the deaths in 1977 appeared to be at a constant level and that the reports from emergency rooms participating in the DAWN system showed a statistically significant decrease in propoxyphene abuse. Lilly's own analysis of reports from medical examiners in the DAWN system indicates that the number of propoxyphene-related deaths has been decreasing since the first quarter of 1977.

Lilly recognizes that the DAWN system has limitations—some of which have been pointed out by other witnesses in these hearings. But the decrease in propoxyphene abuse which the DAWN reports show is consistent with information from other sources. Drs. Hudson and McBay, for example, have reported that propoxyphene-related fatalities have decreased in North Carolina. A partial update of Dr. Finkle's 1975 18-site study, carried out over the past 2 months, also indicates that the number of propoxyphene-related deaths has been diminished.

Now, the reason for this downward trend in medical examiner and emergency room reports that mention propoxyphene is not yet clear. One may reason, however, that the DEA's action placing propoxyphene products in schedule IV, and the attendant publicity, played a role. Increased physician awareness of the information from medical examiners' offices—including that which was based on the Lilly-sponsored study—probably also contributed to the decline. In his testimony on Wednesday, Dr. Lewman stated his belief that the re-

cent decline in propoxyphene-related deaths in Oregon was due to educational efforts and to what he called a "media blitz." A recent survey, conducted by IMS at Lilly's request, shows that 88 percent of physicians are aware of the warnings regarding the additive effects of alcohol and other central nervous system depressants when taken with propoxyphene.

Lilly has examined the results of Dr. Finkle's study and the data from DAWN in an effort to determine the reasons for propoxyphene abuse. This examination indicates, contrary to the assertions that have been made in these hearings, that propoxyphene-related deaths seldom result from accidents, abuse for psychic effects, "experimentation," or similar misuse. Instead, they are the consequence in the great majority of cases, of deliberate, suicidal motivation. There is widespread agreement that suicides are under-reported.

The DAWN medical examiner reports officially classify about 42 percent of propoxyphene-related deaths as suicides. Several factors indicate that these reports substantially understate the actual incidence of suicides. For example, on a city-by-city basis, the incidence of all propoxyphene-related deaths (whether officially attributed to suicide, accident, or other causes) is significantly correlated with overall suicide rates in those cities.

An evaluation of laboratory data from DAWN reports shows that, in a large proportion of cases not officially described as suicides, blood, or tissue concentrations of propoxyphene were detected that represent a quantity of drugs that could not reasonably have been ingested by accident. Dr. Finkle's study shows that the great majority of propoxyphene-related deaths involve persons with a history of alcoholism, emotional problems, psychiatric treatment, or a record of self-destructive behavior. Dr. Hudson's conclusion, reported to the subcommittee on Wednesday, is consistent with this information. He believes that as many as 80 percent of the propoxyphene-related deaths in North Carolina are suicides. In short, the facts do not support the contention that a significant number of propoxyphene-related deaths are accidents.

Nor do the facts support the contention that the deaths result from the accumulation of the metabolic product nor-propoxyphene in patients who take normal doses of propoxyphene over a period of time.

Lilly has conducted extensive studies of the manner in which the body metabolizes propoxyphene and the effects that the drug's metabolic byproducts can have. Those studies are summarized in detail in a memorandum we have submitted to the chairman of this committee.

The nor-propoxyphene metabolite has little of the central nervous system depressant action of propoxyphene, 1/20th to 1/40th, depending on the assay method used, and there is no reason to believe that nor-propoxyphene significantly increases any additive central nervous system depressant effects of alcohol or other drugs.

Nor-propoxyphene has local anesthetic properties which have effects on electroconduction in the heart muscles of laboratory animals that can be detected using extremely sensitive test methods. Many other drugs share these properties. Clinical observations of humans receiving propoxyphene in recommended doses—and in some cases, doses far in excess of the recommended dose—have shown no change in heart action, or in the electrocardiogram.

Thus, there is no reason to believe that the nor-propoxyphene metabolite is a significant factor in the propoxyphene-related deaths that have been reported, nor does the evidence concerning it call into question the conclusion drawn by forensic toxicologists like Dr. Hudson and Dr. Finkle that the great majority of propoxyphene-related deaths are suicides.

Lilly is deeply concerned about the societal problem of suicide, especially when it involves any of the company's products. There is no reason to believe, however, that the availability of propoxyphene has any relation to the incidence of suicide, either suicide in general or drug-related suicide, in particular. A comparison of the distribution data for Darvon products with medical examiner reports from various cities shows that there is no relationship between the quantity of propoxyphene available and the number of propoxyphene-related deaths. The trend in propoxyphene-related deaths has paralleled that for suicide in general.

In these circumstances, further controls on the distribution or dispensing of propoxyphene products will not solve the overall problem of abuse, or the specific problem of suicide. Their only effect would be to restrict the availability of useful medications to patients who need them. If propoxyphene products were placed in schedule II, they could not be dispensed by oral prescriptions, and prescriptions could not be renewed without additional visits to the physician. The result would be a waste of patients' time and money without countervailing benefit.

Mr. Chairman, I have pointed out that the great preponderance of medical evidence and more than two decades of practical experience by patients and their physicians confirm that propoxyphene—alone or in combination—is an effective analgesic agent for the relief of mild-to-moderate pain.

For more than 20 years individual medical investigators, official committees of the World Health Organization, expert panels of the National Academy of Sciences-National Research Council, agencies of the Federal Government, such as DEA and FDA, and advisory committees to those bodies have carefully and critically reviewed all available evidence and have concluded that propoxyphene is both safe and effective and is not subject to widespread street abuse.

As knowledge has been accumulated, the FDA and Eli Lilly & Co. have periodically modified the labeling of propoxyphene in order to fully inform physicians how to use propoxyphene effectively and safely for the relief of pain.

Dr. Kennedy has suggested that future steps are to be taken by the Food and Drug Administration to review the status of propoxyphene. Eli Lilly & Co. has asked to be on the agenda of the FDA Drug Abuse Advisory Committee, which will meet next week. We stand ready to participate in any other meetings or reviews called by the FDA or other agencies of the Government.

Thank you.

Senator NELSON. Does that complete your statement?

Dr. FURMAN. Yes, Mr. Chairman.

Senator NELSON. Your full statement will be printed in the record at this point.

[The prepared statement of Dr. Furman follows:]

STATEMENT OF ROBERT H. FURMAN, M.D., VICE PRESIDENT, CORPORATE MEDICAL AFFAIRS, ELI LILLY & CO.

I am Robert H. Furman, M.D., Vice President, Corporate Medical Affairs, Eli Lilly and Company. With me are Edgar G. Davis, Vice President, Corporate Affairs, and John M. Holt, Secretary and General Counsel of the Company's Pharmaceutical Division. On behalf of the Company and my associates, I wish to express our appreciation for the opportunity to appear and state our views.

Lilly has been engaged in the manufacture of pharmaceuticals for the health professions since 1876. The Company maintains one of the largest private pharmaceutical research programs in the world. Lilly provides a broad range of products for human medical needs and backs them up with extensive programs of medical and technical support. Lilly was the discoverer and developer of propoxyphene products, which it markets under its Darvon trademark.

Extensive experience and study have demonstrated that propoxyphene products are safe when used as directed and that they are effective pain relievers. Lilly knows of no death that has occurred when propoxyphene was properly used, and no previous witness has testified to the contrary.

Like any drug, propoxyphene can be abused. The vast majority of patients who receive Darvon use it properly. But there are some people who take Darvon in excessive doses, and who take many drugs at one time—often along with alcohol. Frequently, their motives are suicidal. This kind of drug abuse is a medical and social problem that transcends the abuse of any one drug. If Darvon suddenly were to become unavailable, the problem would remain the same.

Lilly is deeply concerned about this problem of drug abuse. The Company believes that further study and educational efforts are needed to understand the problem and to help correct it. Available information indicates that the extent of propoxyphene abuse has in fact declined as physicians have become better informed about its abuse potential and since the drug was placed in Schedule IV under the Controlled Substances Act in 1977. The larger societal problem—of which propoxyphene abuse is only a part—remains, and Lilly is committed to work with the government and the medical profession in further efforts to ameliorate the problem.

The facts do not, however, support the Health Research Group's contention that propoxyphene products should be subjected to the more stringent controls of Schedule II, much less that they should be banned as an imminent hazard to the public health.

Propoxyphene is an analgesic for the relief of mild-to-moderate pain. Physicians precsribe it, alone and in combination with other analgesics, such as aspirin, for pain of the kind and severity that follows surgery and tooth extractions and that accompanies lower-back injuries, cramps following childbirth, and many other medical conditions.

It must be kept in mind that before Darvon was developed there was perceived a need for it. Lilly developed propoxyphene as the result of a national program of research, instituted in 1948, to find a synthetic substitute for the opium-derived analgesics (such as codeine) that would offer the therapeutically desirable properties of those drugs without causing addiction or drug-dependence. After extensive study, including clear-cut demonstration of pain relief in laboratory animals, Lilly introduced Darvon in 1957. Since then, the Company has continued to improve its propoxyphene products, study their effects, monitor their use, and disseminate information concerning them to physicians and pharmacists.

Over the past 21 years propoxyphene has been extensively studied. More than 865 scientific papers concerning the drug have been published.

Clinical research, as well as long experience in actual medical practice, have shown that propoxyphene products are safe when used as directed. Therapeutic doses of propoxyphene provide a wide margin of safety to the patient. Lilly has sold more than 20 billion doses of propoxyphene over the last 21 years, and the Company does not know of a single instance in which the use of its propoxyphene products in accordance with their labeling has caused death or serious injury. Propoxyphene's dependence liability is less than that of codeine.

Propoxyphene is an effective pain reliever. Its efficacy has been demonstrated in controlled, double-blind clinical studies conducted in accordance with rigorous scientific standards. The Food and Drug Administration has repeatedly confirmed the efficacy of propoxyphene products, as has an expert panel of the National Academy of Sciences-National Research Council. The efficacy of

propoxyphene has also been demonstrated through its long history of successful use by medical practitioners in the relief of pain.

Some studies have failed to demonstrate the efficacy of propoxyphene. Others have failed to show that it is any more effective as a pain reliver than aspirin. The same may be said, however, of other well-established pain relief medications, including codeine. The simple fact is that it is often very difficult to demonstrate the efficacy of a pain reliever in a clinical study. This is so in part because the nature and causes of pain may vary, and in part because the perception of pain involves an important, yet variable, psychological component, the effects of which are difficult to measure or control in clinical studies.

It is important to recall that studies using laboratory animals are not complicated by these psychological factors and that, in such studies, the pain relieving properties of propoxyphene are consistently confirmed. In addition, many of the studies referred to earlier in these hearings compared propoxyphene with other pain relievers on the basis of a single dose. Our knowledge of the pharmacology of propoxyphene indicates that it achieves its greatest pain relieving effects after several doses have been administered. This is in fact the way the drug is used.

In the final analysis, the true measure of the therapeutic usefulness of a drug is determined in the field of clinical practice. Here propoxyphene products have become well established. In practice, the physician's choice of an analgesic for mild-to-moderate pain is limited to: (1) the familiar nonprescription drugs like aspirin and acetaminophen, which in many cases of chronic or recurring pain have already been tried by the patient and found wanting; (2) to meperidine or opium derivatives like codeine (which carry a risk of dependence); and (3) to other analgesics, such as propoxyphene or pentazocine (Talwin). There are always people who will respond better to one drug than another. Propoxyphene alone will work remarkably well in some patients whose pain is not well controlled by analgesics that some might regard as superior on the average. In short propoxyphene is a useful and well-established part of the physician's armamentarium for the control of pain.

Over the past 20 years, Lilly has promoted its Darvon products ethically and responsibly. The Company has provided the medical profession with the most current information concerning propoxyphene through advertising, labeling, and the efforts of its pharmaceutical representatives. These persons are well-trained. All of them are college graduates. More are pharmacists.

Studies conducted before the drug was introduced into the market—including an evaluation carried out at the U.S. Public Health Service, Addiction Research Center in Lexington, Kentucky—showed, contrary to Dr. Wolfe's allegation, that its potential for abuse was limited and that its dependence (or addiction) liability was less than that of codeine. Experience has confirmed these findings.

You have heard testimony in these hearings about the pharmacology and toxicology of propoxyphene. Much of that information was developed in studies that were sponsored by Lilly, shared with FDA and DEA, and disseminated widely to the medical profession.

In 1975, the North Carolina state toxicologist (Dr. McBay) reported that deaths associated with the use of propoxyphene were increasing in that state. Lilly promptly investigated the report and subsequently sponsored a nationwide study by a respected toxicologist, Dr. Bryan Finkle of the University of Utah. Dr. Finkle reviewed medical examiner reports and files in 18 geographic areas in the United States and Canada which represented a total population of over 50 million persons. He concluded that most of the deaths associated with propoxyphene involved use of the drug at doses far in excess of therapeutic amounts and in combination with alcohol and other drugs, especially tranquilizers and other central nervous system depressants. A majority of the persons had a history of suicidal tendencies, emotional instability, or drug or alcohol abuse.

In April 1976 Lilly published the results of Dr. Finkle's study in a letter to the editor of the *Journal of the American Medical Association*. In cooperation with the Food and Drug Administration, the Company revised the labeling for its propoxyphene products to reflect the new findings. A brochure containing the new labeling and Lilly's letter to the editor of *JAMA* was personally delivered to 114,000 physicians by Lilly pharmaceutical representatives, and copies were mailed to other physicians.

In February 1977, acting on the recommendation of the Department of Health, Education, and Welfare, the Drug Enforcement Administration issued an order

placing propoxyphene products in Schedule IV. In the petition which he submitted to the Attorney General, Dr. Wolfe asserted that the Drug Enforcement Administration's action had no effect and that the number of propoxyphene-related deaths had actually increase since the drug was placed in Schedule IV. His petition characterized the DAWN figures for 1977 as representing a "crescendo of abuse." But, in his testimony to this Subcommittee, Dr. Wolfe did not repeat this allegation—and for good reason, because the increase to which his petition referred has not, in fact, occurred.

Mr. Durrin, the DEA witness who appeared on Wednesday, testified that the deaths in 1977 appeared to be at a constant level and that the reports from emergency rooms participating in the DAWN system showed a statistically significant decrease in propoxyphene abuse. Lilly's own analysis of reports from medical examiners in the DAWN system indicates that the number of propoxyphene-related deaths has been decreasing since the first quarter of 1977.

Lilly recognizes that the DAWN system has limitations—some of which have been pointed out by other witnesses in these hearings. But the decrease in propoxyphene abuse which the DAWN reports show is consistent with information from other sources. Drs. Hudson and McBay, for example, have reported that propoxyphene-related fatalities have decreased in North Carolina, and a partial update of Dr. Finkle's 1975, 18-site study, carried out over the past two months, indicates that the number of propoxyphene-related deaths has been decreasing.

The reason for this downward trend in medical examiner and emergency room reports that mention propoxyphene is not yet clear. One may reason, however, that the DEA's action placing propoxyphene products in Schedule IV, and the attendant publicity, played a role. Increased physician awareness of the information from medical examiners' offices—including that which was based on the Lilly-sponsored study—probably also contributed to the decline. In his testimony on Wednesday, Dr. Lewman stated his belief that the recent decline in propoxyphene-related deaths in Oregon was due to educational efforts.

Lilly has examined the results of Dr. Finkle's study and the data from DAWN in an effort to determine the reasons for propoxyphene abuse. This examination indicates, contrary to the assertions that have been made in these hearings, that propoxyphene-related deaths seldom result from accidents, abuse for psychic effects, "experimentation," or similar misuse. Instead, they are the consequences, in the great majority of cases, of deliberate, suicidal motivations. There is widespread agreement that suicides are under-reported. The DAWN medical examiner reports officially classify about 42 percent of propoxyphene-related deaths as suicides. Several factors indicate that these reports substantially understate the actual incidence of suicides. For example, on a city-by-city basis, the incidence of *all* propoxyphene-related deaths (whether officially attributed to suicide, accident, tor other causes) is significantly correlated with *overall* suicide rates in those cities.

An evaluation of laboratory data from DAWN reports shows that, in a large proportion of cases not officially described as suicides, blood or tissues concentrations of propoxyphene were detected that represent a quantity of drugs that could not reasonably have been ingested by accident. Dr. Finkle's study shows that the great majority of propoxyphene-related deaths involve persons with a history of alcoholism, emotional problems, psychiatric treatment, or a record of self-destructive behavior. Dr. Hudson's conclusion, reported to the Subcommittee on Wednesday, is consistent with this information. He believes that as many as 80 percent of the propoxyphene-related deaths in North Carolina are suicides. In short, the facts do not support the contention that a significant number of propoxyphene-related deaths are accidents.

Nor do the facts support the contention that the deaths result from the accumulation of the metabolic product norpropoxyphene in patients who take normal doses of propoxyphene over a period of time. Lilly has conducted extensive studies of the manner in which the body metabolizes propoxyphene and the effects that the drug's metabolic by-products can have. Those studies are summarized in detail in a memorandum we have submitted to the Chairman of this Committee.

The nor-propoxyphene metabolite has little of the central nervous system depressant action of propoxyphene, one twentieth to one fortieth, depending on the assay method used, and there is no reason to believe that nor-propoxyphene significantly increases any additive central nervous system depressant effects of alcohol or other drugs.

Nor-propoxyphene has local anesthetic properties which have effects on electroconduction in the heart muscles of laboratory animals that can be detected using extremely sensitive test methods. Many oher drugs share these properties. Clinical observations of humans receiving propoxyphene in recommended doses—and in some cases, doses far in excess of the recommended dose—have shown no change in heart action.

There is no reason to believe that the nor-propoxyphene metabolite is a significant factor in the propoxyphene-related deaths that have been reported, nor does the evidence concerning it call into question the conclusion drawn by forensic toxicologists like Drs. Hudson and Finkle that the great majority of propoxyphene-related deaths are suicides.

Lilly is deeply concerned about the societal problem of suicide, especially when it involves any of the Company's products. There is no reason to believe, however, that the availability of propoxyphene has any relation to the incidence of suicides in general or drug-related suicides in particular. A comparison of distribution data for Darvon products with medical examiner reports from various cities shows that there is no relationship between the quantity of propoxyphene available and the number of propoxyphene-related deaths. The trend in propoxyphene-related deaths has paralleled that for suicides in general.

In these circumstances, further controls on the distribution or dispensing of propoxyphene products will not solve the overall problem of abuse, or the specific problem of suicide. Their only effect would be to restrict the availability of useful medications to patients who need them. If propoxyphene products were placed in Schedule II, they could not be dispensed by oral prescriptions, and prescriptions could not be renewed without additional visits to the physician. The result would be a waste of patients' time and money without countervailing benefit.

CURRICULUM VITAE—ROBERT HOWARD FURMAN

Born.—October 23, 1918, Schenectady, N.Y.

Parents.—Howard Blackall Furman; Jane Blessing MacChesney.

Wife.—Mary Frances Kilpatrick.

Children.—Carol Kilpatrick Furman, born November 4, 1947; Jane Christine Furman, born December 18, 1948; Robert Howard Furman, Jr., born September 19, 1950; Hugh Patrick Furman, born September 7, 1955.

Primary school education in the public schools of Schenectady, N.Y. Graduate, with honor, Nott Terrace High School, Schenectady, N.Y., 1936.

Undergraduate and graduate schools—Awards and Honors:

Union College, Schenectady, N.Y., 1936–40. Degree: A.B. Allison Prize (Debate), Junior Year.

Yale University School of Medicine, 1940–43 (Dec.). Degree: M.D., Alpha Omega Alpha, junior year.

Internship and Residency:

Intern, Medical Service, New Haven Hospital. Jan.–Sept. 1944.

Assistant Resident Physician, New Haven Hospital, Oct. 1944–July 1945.

Assistant Resident Physician, Vanderbilt University Hospital, July, 1948–June, 1949.

Resident Physician, Vanderbilt University Hospital, July, 1949–June, 1950.

Academic Appointments:

Assistant in Medicine, Yale University, School of Medicine, Jan. 1944–July, 1945.

Research Assistant, Dept. of Medicine, Vanderbilt Univ. School of Medicine, Oct. 1946–July, 1948.

Instructor, Dept. of Physiology, Vanderbilt University, March, 1947–July, 1948.

Assistant in Medicine, Vanderbilt Univ. Sch. Med., July, 1949–June, 1950.

Assistant Professor of Medicine, Vanderbilt University School of Medicine, July, 1950–March, 1952.

Associate Professor of Research Medicine, University of Oklahoma School of Medicine, March, 1952–July, 1966.

Professor of Research Medicine, University of Oklahoma School of Medicine, July 1, 1966–June, 1970.

Professor of Medicine, Indiana University Sch. Med., July 1970.

Other Appointments:
Head, Cardiovascular Section, Oklahoma Medical Research Foundation and Hospital, Oklahoma City, 1952–1970.
Associate Director, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, 1957–1970.
Executive Director, Clinical Research, Eli Lilly and Company, June 1970–1973.
Vice President, Lilly Research Laboratories, December 1973–November 1976.
Vice President, Corporate Medical Affairs, Eli Lilly and Company, December 1976.
Fellowships:
Eli Lilly Fellow in Medicine, Vanderbilt University School of Medicine, October 1946–September 1947.
National Research Council Fellow in the Medical Sciences, Department of Medicine, Vanderbilt University School of Medicine, October 1947–September 1948.
Hospital Appointments:
Assistant Visiting Physician, Out Patient Service, Vanderbilt University Hospital, July 1947–June 1948.
Associate Visiting Physician, Out Patient Service, Vanderbilt University Hospital, July 1950.
Assistant Visiting Physician, Vanderbilt University Hospital, July 1950–March 1952.
Attending Cardiologist, Veterans Administration Hospital, Oklahoma City, 1953.
Visiting Staff, Wishard Memorial Hospital, Indianapolis, October 1971.
Military Service:
U.S. Naval Hospital, Portsmouth, New Hampshire, July 1945.
U.S.N. Advance Base Personnel Training Depot, San Bruno, California, August 1945.
U.S.N. Separation Center, Puget Sound Navy Yard, Bremerton, Washington, October 1945–February 1946.
Senior Medical Officer, U.S.S. Yellowstone, AD27, February–August 1946.
Recalled to Active Duty for the period September 30, 1955–March 29, 1957.
Present Rank: CMDR, MC, USNR.
Society Memberships:
Alpha Omega Alpha (Honor Medical Society).
American Association for the Advancement of Science.
American Clinical and Climatological Association.
American College of Cardiology (Fellow).
American College of Chest Physicians (Fellow).
American College of Physicians (Fellow).
American Federation for Clinical Research.
American Heart Association.
American Physiological Society.
American Society for Clinical Pharmacology & Therapeutics.
American Society of Internal Medicine.
Association of Yale in Medicine.
Central Society for Clinical Research.
Club International.
Cosmos Club.
Delta Upsilon (College Fraternity).
Endocrine Society.
Indiana Heart Association—Board of Directors.
Indiana State Medical Association.
Marion County Heart Association.
Marion County Medical Society.
New York Academy of Science (Fellow).
Oklahoma Heart Association.
Sigma Xi.
Society for Experimental Biology and Medicine.
Southern Society for Clinical Research.
Southwestern Association of Naturalists.
The Royal Society of Medicine (Fellow).
Wilson Ornithological Society.

Board Certification: American Board of Internal Medicine, February 30, 1950.
State Licensure:
Connecticut—Medicine and Surgery, February 1945 No. 4994.
Indiana—Medicine, Surgery and Obstetrics, June 1971, No. 23551.
New York—Medicine and Surgery, June 1945, No. 43171.
Oklahoma—Medicine and Surgery, December, 1952, No. 6365.
Tennessee—Medicine and Surgery, 1946.
Committee Memberships and Other Appointments:
Section on Cardiovascular Physiology, Committee on Cardiovascular Disease, American College of Chest Physicians, 1957–60.
Board of Directors, American Society for the Study of Arteriosclerosis, 1956–59.
American Heart Association.
Fellow, Council on Arteriosclerosis.
Credentials Committee, 1958–60.
Program Committee, 1959–64.
Publications Committee, 1960–70.
Research Committee, 1960.
Secretary-Treasurer, 1962–63.
Vice Chairman, 1963–64.
Chairman, 1964–65.
Medical Education, 1966–
Cerebrovascular Disease, 1966–
Subcommittee to Revise Rules and Regulations, 1968.
Cardiovascular C Research Study Committee, 1971–74.
Council on Thrombosis, 1971.
Board of Directors, A.H.A.
Member, Executive Committee.
Member, Central Committee.
Research Committee of the Oklahoma Heart Association, 1957–68.
Board of Directors, Oklahoma Heart Association, 1959–70.
Executive Committee, Oklahoma Heart Association, 1963–70.
President, Oklahoma Heart Association, 1967–68.
Chairman, Committee for U.S.P.H.S. Area Cardiovascular Grant (H–1889), University of Oklahoma Medical Center, 1957–64.
General Advisory and Supervisory Committee for Special Procedures Laboratory, Mercy Hospital, Oklahoma City, 1959–60.
Cardiovascular Study Section, National Heart Institute, N.I.H., 1960–63.
Council Member, Central Society for Clinical Research, 1963–66.
Heart Special Projects Committee, National Heart Institute, N.I.H., 1963–66.
Board of Editors, Journal of Laboratory and Clinical Medicine, 1958–65.
Board of Editors, Circulation, 1966–70.
Board of Editors, Journal of Chronic Diseases, 1966–
Board of Editors, Stroke, 1969–1974.
Board of Managers, Wistar Institute, 1972—Scientific Advisory Committee, 1972.
Scientific Advisory Committee, The Hormel Institute, Austin, Minnesota, 1973–
Council for the Institute of Administration and Management, Union College, Chairman, Curriculum Committee.
Associate Trustee, University of Pensylvania.
National Research Council, Clinical Sciences Panel.

Lilly Testifies Darvon Is Safe and Effective

WASHINGTON, D.C.—Eli Lilly and Company's Vice President of Corporate Medical Affairs told a Senate subcommittee today that more than 20 billion doses of the pain killer Darvon have been prescribed over the last 21 years without "a single instance in which the use of propoxyphene products (Darvon's generic name) in accordance with their labeling has caused death or serious injury."

Dr. Robert H. Furman, M.D., the company's representative testified in detail before Senator Gaylord Nelson's Senate Subcommittee on Monopoly and Anticompetitive Activities, and refuted allegations that propoxyphene products such as Darvon were ineffective as analgesics but could cause death.

Dr. Furman pointed out that, contrary to assertions by the Health Research Group, the "findings of several medical authorities, including some who testified

earlier in the hearings, confirm that propoxyphene-related deaths are due to misuse and even such deaths are decreasing."

As Dr. Furman testified, company spokesmen called attention to a national survey, released last week, which showed that nine out of ten physicians said they regarded propoxyphene to be safe when used as recommended. The doctors also said they were aware of the dangers of the drug when used in excessive amounts and in combination with alcohol and other drugs.

"Like any drug, propoxyphene can be abused," Dr. Furman told the Senate subcommittee. "The vast majority of patients who receive Darvon use it properly. But there are some people who take Darvon in excessive doses and who take many drugs at one time—often along with alcohol. Frequently, their motives are suicidal. This kind of drug abuse is a medical and social problem that transcends the abuse of any one drug. If Darvon suddenly were to become unavailable, the problem would remain the same."

Dr. Furman stressed that "Lilly is deeply concerned about this problem of drug abuse. The company believes that further study and educational efforts are needed to understand the problem and to help correct it. The larger societal problem—of which propoxyphene abuse is only a part—remains, and Lilly is committed to work with the government and the medical profession in further efforts in resolving any questions regarding the safety and effectiveness of Darvon."

Senator NELSON. I raised this question with Commissioner Kennedy and I would ask you the same. As you noted from the testimony last week of Dr. Moertel, in his double-blind studies the conclusion he reached was that adding a full dose of propoxyphene to aspirin did not increase its effectiveness. I also raised this question with Mr. Kennedy.

Do you know of any well-controlled studies that meet the requirements of the 1962 act that would indicate that, in combination, propoxyphene added to aspirin is more effective than aspirin alone?

Dr. FURMAN. Well, one comes to mind right away, Mr. Chairman. It is a study by a physician, Dr. Bauer, in some 600 postoperative patients with wound or incisional pain. This study demonstrated that the combination of propoxyphene—I believe this was napsylate—with aspirin produced a greater analgesic effect than aspirin alone.

Senator NELSON. I was asking for references to any studies. Please submit that to us.

Dr. FURMAN. I will be glad to.

[Subsequent information was received and follows:]

ELI LILLY AND COMPANY,
Indianapolis, Ind., February 16, 1979.

HON. GAYLORD NELSON,
Chairman, Select Committee on Small Business,
U.S. Senate,
Washington, D.C.

DEAR SENATOR NELSON: I am pleased to respond to your request, made during the recent hearings you conducted on propoxyphene, that I submit the reference to the study by Bauer comparing aspirin with aspirin-propoxyphene combinations.

The reference is as follows:

Robert O. Bauer, Arthur Baptisti, Jr., and Charles M. Gruber, Jr., Evaluation of Propoxyphene Napsylate Compound in *post partum* Uterine Cramping, J. Med., *5*:317-318, 1974

Enclosed is a Xerox copy of the Bauer publication.

During the hearing Senator Levin also requested information on comparative studies. Enclosed are these references, listed under the following headings:

Clinical Studies Showing a Superiority of Propoxyphene Compound over APC.

Clinical Evaluation of Propoxyphene: Compared to Codeine.

Clinical Evaluation of Propoxyphene: Compared to Aspirin.

Clinical Studies Showing a Superiority of Propoxyphene with A.S.A. Over A.S.A.

Clinical Studies Showing a Superiority of Propoxyphene with Acetaminophen Over Acetaminophen.

Clinical Evaluation of Propoxyphene: Superior to Placebo.

I am also providing a bibliography of studies of propoxyphene analgesia in laboratory animals. This is entitled:

Pharmacological Evaluation of Propoxyphene: Analgesic Effect.

We are also submitting for the hearing record a copy of our February 13, 1979, presentation to the Food and Drug Administration Drug Abuse Advisory Committee.

Let me again express our sincere appreciation for the opportunity to appear before you and the other members of your Committee. I hope you found our testimony both interesting and useful.

Respectfully and appreciatively,

ROBERT H. FURMAN.

Enclosures.

ELI LILLY AND CO.,
Indianapolis, Ind., February 16, 1979.

Hon. CARL LEVIN,
Select Committee on Small Business,
U.S. Senate,
Washington, D.C.

DEAR SENATOR LEVIN: As the enclosed copy of my letter to Senator Nelson indicates, I have submitted to the Committee a list of references in response to your request made during the recent hearings on propoxyphene.

These references are enclosed herewith.

If you wish copies of any or all of these articles I shall be glad to obtain them and forward them to you.

My associates and I very much appreciated the opportunity to appear before you and other members of the Committee and I hope that our testimony was of assistance.

Respectfully yours,

ROBERT H. FURMAN.

Enclosures.

CLINICAL STUDIES SHOWING A SUPERIORITY OF PROPOXYPHENE COMPOUND OVER APC

1. Bauer, R. O., *et al.*: Evaluation of Propoxyphene Napsylate Compound in *post partum* Uterine Cramping, J. Med., *5*:317–328, 1974.

2. Brooke, J. W., and Brooke, R. D.: The Anti-Rheumatic Effect of Darvon, Western Medicine, *7*:133–134, 1966.

3. Lehrman, M. L., *et al.*: Analgesic Tests in Oral Surgical Practice, Journal of the Indiana State Dental Association, *39*:338–342, 1960.

4, Marrs, J. W., *et al.*: Report of an Investigation of D-Propoxyphene Hydrochloride, Am. J. Pharm., *131*:271–276, 1959.

CLINICAL EVALUATION OF PROPOXYPHENE: COMPARED TO CODEINE

1. Cass, L. J., and Frederik, W. S.: Clinical Comparison of the Analgesic Effects of Dextro-Propoxyphene and Other Analgesics, Antibiotic Medicine & Clinical Therapy, *6*(6):362–370, 1959.

2. Gruber, C. M., Jr.: Codeine Phosphate, Propoxyphene Hydrochloride, and Placebo, J.A.M.A., *164*(9):966–969, 1957.

3. Gruber, C. M., Jr.: Codeine and Propoxyphene in Post-episiotomy Pain, A Two-Dose Evaluation, J.A.M.A., *237*(25):2734–2735 (June), 1977.

4. Gruber, C. M., Jr., *et al.*: Clinical Bio-Assay of Oral Analgesic Activity of Propoxyphene (Lilly), Acetylsalicylic Acid, and Codeine Phosphate, and Observations on Placebo Reactions, Arch. Int. Pharmacodyn. Ther., *104*(2):156–166, 1955.

5. Gruber, C. M., Jr., *et al.*: The Effectiveness of d-Propoxyphene Hydrochloride and Codeine Phosphate as Determined by Two Methods of Clinical Testing for Relief of Chronic Pain, J. Pharmacol. Exp. Ther., *118*(3):280–285, 1950.

6. Howard, G. M., *et al.*: Clinical Evaluation of Analgesic Potency of Dextro Propoxyphene Hydrochloride on Orthopedic Patients, N.Y. State J. Med., *61*(19): 3285–3288, 1961.

7. Koslin, A. J.: Clinical Analgesic Study. A Single-Blind Comparison of Codeine Phosphate and Dextro Propoxyphene Hydrochloride, Oral Surg., *12*(10): 1203–1206, 1959.

8. Magee, K. R., and DeJong, R. N.: An Evaluation of Dextro Propoxyphene Hydrochloride in the Treatment of Headache, University of Michigan Medical Bulletin, *25* 74–78, 1959.
9. Sadove, M. S., *et al.*: A Controlled Study of Codeine, Dextro Propoxyphene and RO 4–1778/1, Am. J. Med. Sci., *241*:103–108, 1961.
10. Valentine, G., and Martin, S. J.: Evaluation of a New Analgesic Agent, D-Propoxyphene Hydrochloride (Darvon) in Preanesthetic and Postanesthetic Mangement, Anesth. Analg., 38(1) :50–55, 1959.
11. Van Bergen, W. S., *et al.*: Effect of Dextro Propoxyphene, Meperidine, and Codeine on Postoperative Pain, J.A.M.A., *172*(13) :1372–1375, 1960.
12. Wagner, W. A., and Hubbell, A. O.: Pain Control with a Mixture Containing Dextro Propoxyphene Hydrochloride, a Mixture Containing Codeine Phosphate and a Placebo, J. Oral Surg., *17*:14–18, 1959.
13. Wilson, W. L., *et al.*: A Comparison of the Effectiveness of Codein Phosphate and Dextro-Propoxyphene Hydrochloride, Pennsylvania Medical Journal, *62*:186–187, 1959.
14. Young, R. E. S.: A Two-Dose Evaluation of Propoxyphene Napsylate and Codeine in Postoperative Pain, Curr. Therap. Res., *24*(5) :495–501, 1978.

CLINICAL EVALUATION OF PROPOXYPHENE: COMPARED TO ASPIRIN

1. Boyle R. W., *et al.*; Analgesic Effect of Dextropropoxyphene Hydrochloride in Elderly Patients with Chronic Pain Syndromes, Ann. Intern. Med., *52*:195, 1960.
2. Lipton, S., *et al.*: A Comparison of a New Analgesic, Floctafenine, with Dextropropoxyphene and Aspirin Post-Operative Pain, Curr. Med. Res. Opin., *3*(3) :175–180, 1975.
3. Magee, K. R., and DeJong, R. N.: An Evaluation of Dextro Propoxyphene Hydrochloride in the Treatment of Headache, University of Michigan Medical Bulletin, *25*:74–78, 1959.
4. Sunshine, A., *et al.*: A Comparative Analgesic Study of Propoxyphene Fenoprofen, the Combination of Propoxyphene and Fenoprofen, Aspirin, and Placebo, J. Clin. Pharmacol., *18*:556–563, 1978.
5. Valentine, G., and Martin, S. J.: Evaluation of a New Analgesic Agent, D-Propoxyphene Hydrochloride (Darvon) in Preanesthetic and Postanesthetic Management, Anesth. Analg., *38*(1) :50–55, 1959.

CLINICAL STUDIES SHOWING A SUPERIORITY OF PROPOXYPHENE WITH A.S.A. OVER A.S.A.

1. Bedi, S. S.: Comparison of Aspirin and Dextropropoxyphene with Aspirin as Analgesics in Rheumatoid Arthritis, Br. J. Clin. Pract., *23*:413–417, 1969.
2. Gruber, C. M., Jr., *et al.*: Relief of Postpartum Uterine Cramping with Propoxyphene and Aspirin, Toxicol. Appl. Pharmacol., *19*:546–553, 1971.
3. Settel, E.: A Controlled Clinical Evaluation of Dextropropoxyphene Hydrochloride Plus Acetylsalicylic Acid, J. Am. Geriatr. Soc. *6*:818–821, 1958.
4. Wang, R. I. H.: Analgesic Effectiveness of New Propoxyphene Preparations, Journal of New Drugs, *5*:171–176, 1965.
5. Wang, R. I. H., and Sandoval, R. G.: The Analgesic Activity of Propoxyphene Napsylate With and Without Aspirin, J. Clin. Pharmacol., *11*:310–317, 1971.

CLINICAL STUDIES SHOWING A SUPERIORITY OF PROPOXYPHENE WITH ACETAMINOPHEN OVER ACETAMINOPHEN

1. Gruber, C. M., *et al.*: A Multicenter Analgesic Study Using Single Doses of Placebo, Propoxyphene and Acetaminophen, J. Med., *8*:35–51, 1977.
2. Huskisson, E. C.: Simple Analgesics for Arthritis, Br. Med. J., *4*:196–200, 1974.
3. Johnson, W.: Efficacy of Darvocet™ in Postpartum Patients. Darvocet Episiotomy Study, Submitted to NDA 16–844, *2.1* (E.3) :319–355, December 17, 1971.
4. Johnson, W.: Efficiency of Darvocet™ in Postpartum Patients. Darvocet Uterine Cramping Study, Submitted to NDA 16–844, 2.1 (E.3) :356–392, December 17, 1971.
5. Lash, A. F.: Darvocet-N Episiotomy Study, Submitted to NDA 17–122, *1.1*(3.3) :065–104d, December 17, 1971.

6. Messick, R. T.: Evaluation of Acetaminophen, Propoxyphene, and Their Combination in Office Practice, Submitted to IND 5727, Annual Report, pp. 384–396, April 29, 1976.

CLINICAL EVALUATION OF PROPOXYPHENE: SUPERIOR TO PLACEBO

1. Baptisti, A. Jr., *et al.*: The Effectiveness and Side-Effect Liability of Propoxyphene Hydrochloride and Propoxyphene Napsylate in Patients with Postpartum Uterine Cramping, Toxicol. Appl. Pharmacol., *19*:519–527, 1971.
2. Benson, R. C.: Double Blind Evaluation of Analgesic Agents in the Postpartum Patient, West. J. Surg., Obst. & Gynec., *71*: 167, 1963.
3. Boyle, R. W., *et al.*: Analgesic Effect of Dextropropoxyphene Hydrochloride in Elderly Patients with Chronic Pain Syndromes, Ann. Intern. Med., *52*:195, 1960.
4. Cass, L. J., and Frederik, W. S.: Clinical Comparison of the Analgesic Effects of Dextro-Propoxyphene and Other Analgesics, Antibiotic Medicine & Clinical Therapy, *6*(6) :362–370, 1959.
5. Gruber, C. M., Jr.: Evaluating Interactions Between Fenoprofen and Propoxyphene: Analgesia and Adverse Reports by Postepisiotomy Patients, J. Clin. Pharmacol., *16*:407, 1976.
6. Gruber, C. M., Jr.: Codeine and Propoxyphene in Postepisiotomy Pain, A Two-Dose Evaluation, J.A.M.A., *237*(25) : 2734–2735 (June), 1977.
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Evaluation of Propoxyphene Napsylate Compound in *post partum* Uterine Cramping

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Abstract. Two independent investigators, using identical protocols, evaluated the analgesic and adverse effects of aspirin and phenacetin alone and in combination. The result of adding caffeine and propoxyphene napsylate to the combination was included. *Post partum* uterine cramping was not altered to a significant extent when doses other than those of propoxyphene napsylate were doubled. Reports of adverse reactions were increased where the larger doses were given.

Key Words
Propoxyphene napsylate
Aspirin
Analgesia
Uterine cramping
Phenacetin
Caffeine

Subjects
Female patients with *post partum* pain

The issues concerning the drugs under test impose the design of each pharmacologic experiment on the investigators. A factorial study is the basic, and probably most efficient, method which is used to determine the clinical effects of analgesic drugs in combination [HOUDE *et al.*, 1965]. Orthogonal treatment contrasts allow evaluations of each drug alone and the effects of various combinations. Control with a blank or dummy medication is important. If an inactive medication is excluded, a secondary device – the dose response – may test the method for sensitivity to drug effects. Although there are several published reports of dose response to aspirin or aspirin compound [BEAVER, 1966], such responses occur inconsistently and, therefore, the dose response is a poor substitute for placebo in bioassays for clinical effects with these medications.

This report concerns a factorial study with propoxyphene and aspirin compound, a method of assay established in one institution [GRUBER and BAPTISTI, 1963] and extended to a second, and a protocol modified at the

request of a peer review group to omit the inactive control medication, and an attempt to evaluate the resulting data.

Method

Post partum patients with uterine pain following normal deliveries, with no language or intelligence barriers, participated in the study. They were questioned prior to the study and were informed about the medications and procedures to be used. All willingly signed informed consent forms. Patients were not given more than 1 experimental medication; if they experienced pain on more than 1 day of hospitalization, a 2nd dose of coded medication was not administered.

Each morning before breakfast, the subjects were questioned as to the intensity of uterine cramps. Equal numbers of patients were administered each of the experimental medications at each initial pain intensity level ('stratum') (table I). All of the experimental medications were identical in appearance. The dose was 2 capsules per subject, given on a double-blind basis, and each dose was individually identified by code number. Within each pain intensity stratum, the location of the patients on the ward determined the order in which they were interrogated and given medication. The interplay between the location of the patients and the rotation of the drugs determined the medication each patient received. For each initial pain intensity, successive groups of 10 medications included each dose. The order of medication in the groups was varied. Patients who awakened after 3.00 a.m. and requested medication for pain were asked to wait until 7.00 a.m. Those reporting pain earlier in the night were treated. The medications administered were prescribed by the patient care physician and were the same or similar to the drugs under study. All other analgesics were withheld for at least 4 h before the test drugs were given and for 8 h afterward, or until pain intensity had returned to pretreatment level for at least 2 interviews.

Observations were made before drug treatment and at 1, 2, 3, 4, 6, and 8 h after treatment. Before medication, the patients quantified the intensity of their pain from uterine cramping according to the empirical scale, 'a little', 'some', 'a lot', and 'terrible'. The pain intensity was stratified into these 4 levels, and the patients were assigned to the 'stratum' of their initial pain intensity. At each posttreatment observation, the subjects evaluated pain intensity and also estimated their relief (degree of pain alleviation), scored according to a similar scale which substituted the term 'complete' for 'terrible' as category 4. The pain intensity difference was calculated by subtracting the intensity at each subsequent point in time from the intensity reported at the time the medication was administered. The analgesia score is the sum of the pain intensity difference (SPID) and the relief score at each interval. The total analgesia score [GRUBER and BAPTISTI, 1963] for each patient was calculated by summing the analgesia scores for the 6 observations after treatment.

At the end of the 8th h of observation, the subjects were asked whether they had experienced any of the following symptoms: nausea, constipation, abdominal discomfort, headache, dizziness, drowsiness, nervousness, tremor, weakness, blurred vision, dry mouth, sweating, itching, or others. If any were reported, the patient

graded the intensity of the symptom according to the same empirical scale as that used for pain intensity, and also indicated whether she thought the symptom was caused by the medication. Special other symptoms are those with larger scores when the double dosage was administered. Sleeping patients were awakened in order to obtain the data which were recorded on a report form by a trained observer and assembled into tables for evaluation. The statistical methods (means, variance analysis, and orthogonal contrasts) are presented in standard textbooks [COCHRAN and COX, 1950; DIXON and MASSEY, 1951].

Results

320 patients in hospital I (UCLAH, BAUER) and 290 in hospital II (MCGH, BAPTISTI) participated in the study. The number of patients given each medication was the same in each institution strata (table I). Thus, the bias associated with institutions and pain strata should be distributed equally among the medications.

Each of the 610 patients supplied 18 sets of data for estimating efficacy and 14 for reporting adverse experiences. These 19,510 entries are not presented individually. Variance analyses for effectiveness are presented in table II. The main effects – hospitals, pain intensity, and medications – were expected to have significant variance. The unexpected findings were significant hospital intensity strata and hospital medication interaction variances. These findings indicate that the data obtained at the 2 institutions differ significantly and possibly should not be pooled. However, use of the primary interaction variance as the error term for main effects lends credence to the significance of the differences reported for hospitals, strata, and medications.

The upper graphs in figure 1 present the interactions between hospitals and pain intensity strata. The strong correlation present for the mean values at the 2 hospitals appears in the linear placement of the values. The interaction appears primarily as the minor displacement of the mean scores for stratum 3. The usual increase in SPID and decrease in relief scores with increasing intensity of initial pain is evident.

The lower graphs in figure 1 present the interactions between hospitals and medications. The differences among medications are not consistent for the 2 hospitals; therefore, the correlation is not pronounced. To a large degree, the correlation present is in response to medication H, the higher dose of propoxyphene and aspirin compound. However, even medication H apparently contributes to the significance of the hospital by medication interaction.

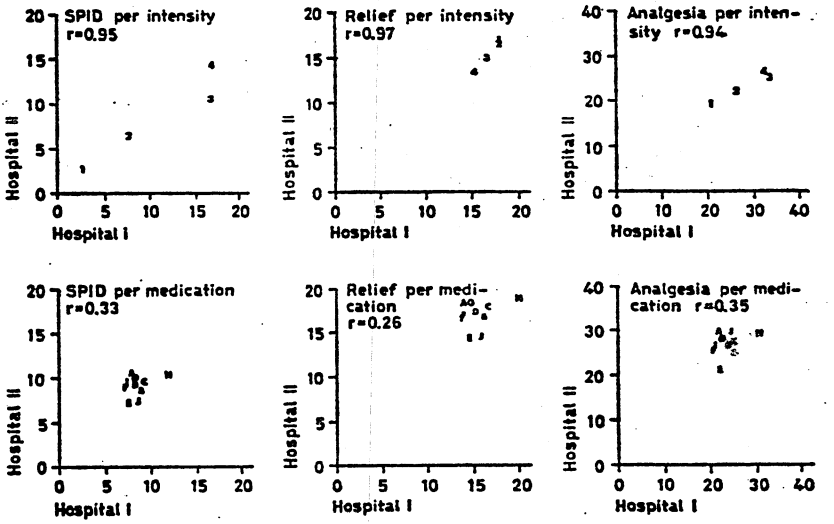


Fig. 1. Variance analyses of SPID, relief and analgesia score data (table II) indicate the presence of significant primary interactions between the institutions and pain intensity effects and between the institutions and medication effects. These relationships which exist between the interacting main effects are presented for each of the measures of effectiveness. The medications are identified in table III. The relative positions of the pain intensity strata and of the treatment groups indicate the degree of agreement between the 2 institutions.

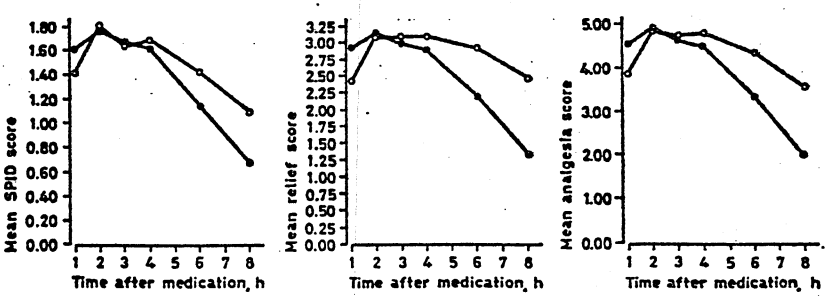


Fig. 2. The response time curves of the overall SPID, relief, and analgesia score data are presented for each institution. ● = Hospital I; □ hospital II.

Table I. Number of subjects in each subgroup. Each of the 10 medications was administered to this number of patients within these institution strata cells

Pain intensity stratum	Hospital		
	I	II	both
1 (a little)	6	7	13
2 (some)	10	10	20
3 (a lot)	10	8	18
4 (terrible)	6	4	10

Table II. Variance analyses of effectiveness data from both hospitals

Source of variance	df	SPID		Relief		Analgesia	
		MS	p <	MS	p <	MS	p <
H	1	58	0.200	454	0.001	837	0.008
I	3	3,558	0.001	260	0.001	1,956	0.001
M	9	65	0.040	66	0.050	339	0.006
Interaction H x I	3	117	0.001	55	0.200	231	0.050
Interaction H x M	9	32	0.050	66	0.040	189	0.030
Interaction I x M	27	17	0.500	17		63	
Interaction H x I x M	27	11		3		42	
Within blocks	530	17		34		92	
Error for primary interactions	557	17		32		89	
Error for main effects	39	28		31		105	

df = Degrees of freedom; MS = mean square; h = hospital; I = intensity of pain; M = medication.

The response time curves for each measure of effectiveness are presented in figure 2. The variance analyses presented above are based on the sum of the responses of each patient over this time period. The response time curves as well as the analyses suggest that the data from the hospitals should not be pooled. Therefore, further evaluation included analyses of the data from each hospital as well as the pooled data.

Table III includes (1) the code to the medications, (2) the analgesia scores for each hospital, (3) the orthogonal polynomials, (4) the numer-

Table III. Orthogonal contrasts for medications

	Medication									
	A	B	C	D	E	F	G	H	I	J
Dose of drugs, mg										
Aspirin	227	227	227	454		454	454	454	908	
Phenacetin	160	160	160		320	320	320	320		640
Caffeine		30	30				60	60		
Propoxyphene napsylate			100					200		
Total analgesia scores										
Hospital I (n = 32)	696	792	813	749	704	671	729	1,017	673	776
Hospital II (n = 29)	849	732	793	779	627	748	819	839	763	637
Orthogonal polynomials										
Contrast										
1	−1	−1	−1	−1	−1	+1	+1	+1	+1	+1
2				−1	+1				−1	+1
3	−1	+1				−1	+1			
4	+1	+1		−1	−1	+1	+1		−1	−1
5	−1	−1	+4	−1	−1	−1	−1	+4	−1	−1
6				+1	−1				−1	+1
7	+1	−1				−1	+1			
8	−1	−1		+1	+1	+1	+1		−1	−1
9	+1	+1	−4	+1	+1	−1	−1	+4	−1	−1

Contrast	Hospital I			Hospital II			Combined data		
	N	D	P <	N	D	P <	N	D	P <
1	112	320		26	290		138	610	
2	58	128		−278	116	0.002	−220	244	
3	154	128		−46	116		108	244	
4	−14	256		342	232	0.007	328	488	
5	1,530	1,280	0.001	574	1,160	0.050	2,104	2,440	0.001
6	148	128		26	116		174	244	
7	−38	128		188	116	0.020	150	244	
8	−84	256		−8	232		−92	488	
9	908	1,280	0.020	204	1,160		1,112	2,440	0.030
Error mean square	107.04			67.10			91.59		

N = Numerator; D = denominator; $(N)^2/D$ = mean square.

Table IV. The frequency of the scores for other symptoms reported by the patients

Score	All other symptoms		Special other symptoms	
	hospital I	hospital II	hospital I	hospital II
0	254	46	280	144
1	53	58	34	72
2	11	49	6	34
3	2	37		20
4		35		9
5		17		5
6		17		2
7		9		2
8		5		2
9		7		
10		2		
11		1		
12		2		
13		2		
14		1		
15		1		
16		1		

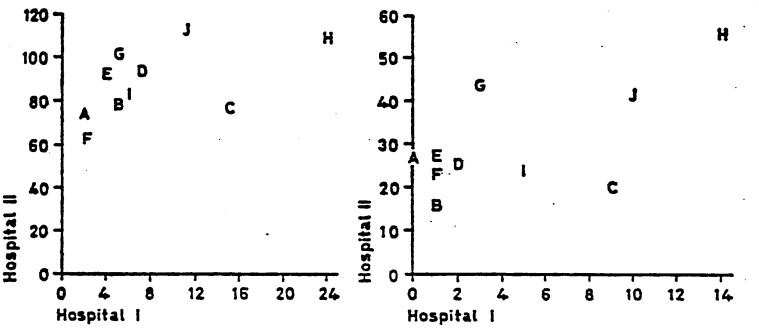


Fig. 3. The magnitude of the difference in the other symptom scores reported at the 2 hospitals is represented by the difference in the scales used on the abscissa and ordinate (approximately fivefold). The positions of the code letters for medications indicate the degree of agreement between the hospitals. The medications are identified in table III. Left: all other symptoms (r = 0.54); right: special other symptoms (r = 0.64).

ators and denominators for determining the variance of each contrast, (5) estimates of each significant p value, and (6) the error mean square for main effects used to determine these p values. This is the minimum data which allows at least partial reconstruction of the statistical procedure and permits evaluation of the results. The results of this drug study are presented in the following contrasts (table III):

Contrast 1 compares the results with the lower doses to those with the higher doses. The positive numerator indicates a trend toward a dose response, but this was not statistically significant.

Contrast 2 compares phenacetin to aspirin. A positive numerator indicates that phenacetin may be more effective than aspirin. In hospital II, aspirin was significantly more effective than phenacetin.

Contrast 3 examines the effect of the addition of caffeine to the aspirin-phenacetin combination. No significant effect was observed.

Contrast 4 compares the combination of phenacetin and aspirin with and without caffeine to phenacetin and aspirin given as separate medications. The positive numerator (hospital II) indicates the combination to be more effective than aspirin and phenacetin as single entities.

The positive numerator for contrast 5 indicates a significant increase in analgesia when propoxyphene napsylate was added to the medications. This was the only contrast which was significant for both institutions.

Contrasts 6–9 examine the interactions between dose (contrast 1) and contrasts 2–5, respectively. The positive numerators for contrast 9 at both institutions indicate a trend toward a greater difference between the treatments (with versus without propoxyphene) when the higher doses are compared. This trend was statistically significant at hospital I and supports the presence of a dose response for propoxyphene.

The differences between the 2 institutions were even more obvious when the adverse reports were examined. The distribution of these data is presented in table IV. The special other symptoms – nausea, abdominal discomfort, dizziness, blurred vision, and sweating – were selected on the basis of higher total scores with the heavier doses of medication. Both the total and the special other symptoms had a scewed distribution and were reported to be more frequent and more severe at hospital II than at hospital I.

Figure 3 indicates an increase in other symptom scores with the higher doses, especially with medications H and J, the higher doses of propoxyphene with aspirin compound and of aspirin, respectively. Patients may pay in adverse effects for greater analgesia.

Discussion

Initial contact with hospital I considered a study comparing placebo, propoxyphene napsylate, aspirin compound, propoxyphene napsylate plus aspirin compound, and propoxyphene hydrochloride plus aspirin compound. The peer group at the hospital considered the inclusion of a placebo an unjustifiable treatment. The protocol was, therefore, modified to include the dose response as a measure of the sensitivity of the method to medication differences.

BEAVER [1965, 1966] reports a personal communication from KANTOR and his co-workers as follows: '... patients with postoperative pain or pain secondary to acute trauma, have also demonstrated a significant difference in the response to placebo and 300 mg of aspirin, and comparison of 300 mg and 600 mg doses of this drug yielded a significant dose-effect slope. On the other hand, these same investigators were unable to demonstrate a significant difference in the response of patients with postpartum pain (lumping together uterine cramps or episiotomy pain, or both) to the 300 mg and 600 mg aspirin doses. They observed, however, that if the whole population of pastpartum patients was divided into sub-populations of those complaining of uterine cramps and those complaining of pain associated with episiotomies, the latter group was able to discriminate between the graded aspirin doses, while the former was not. In subsequent studies, this pattern of differential response has been repeated consistently.'

The subjects in our study were *post partum* with uterine cramping and, as would then be expected, failed to demonstrate a dose response to aspirin, phenacetin, or the combination of these 2 analgesics.

BEAVER also provides the following comment: 'In contrast to the considerable number of reports favorably comparing aspirin with placebo, it seems few workers have attempted to explore the aspirin dose-response curve using graded drug doses. Such experiments are especially significant, because, while aspirin is the single most widely used mild analgesic and the most often used standard of comparison for drugs in this category, true relative potency estimates require graded dose comparisons of test drug and standard ... knowing whether a "ceiling" exists for drug effect constitutes an important aspect of that drug's pharmacologic profile, and this information can only be obtained by the use of graded doses. When comparing two drugs, the relation of their ceiling effects or "relative potential" is often as significant and valuable as an estimate of their relative potency. In the case of aspirin, this is particularly true, because

if the off-stated clinical impression that a rather low ceiling exists for the analgesic action of this drug should prove correct, then a mild analgesic or combination thereof which could be demonstrated to have a greater potential (that is, a higher ceiling of analgesic effect) than aspirin would present a real therapeutic advantage.'

In our study, the dose levels of the anti-inflammatory analgesics did not differentiate. Failure to differentiate indicates either a very flat slope to the dose response or a 'ceiling'. When propoxyphene was added, a significant increase in analgesia was observerd justifying the use of the combination. However, an increase in adverse effects was also present suggesting that greater analgesia without increased side effects was not observed. Aspirin-containing preparations are unstable when exposed to heat and humidity. These preparations were packaged in paper envelopes and therefore, not stored in ideal containers. However, evidence for pharmaceutical instability was not evidenced by increasing adverse reports over the course of the experiment. Chemical analysis of the products at the end of the study was not done. Data suggesting that analysis should be done had not been compiled or evaluated at that time.

In pharmacological studies such as these, the differences among medications are less manifest than in clinical practice. Although we failed to demonstrate a significant dose response to the medications (contrast 1), we do not imply that the lesser dose is equivalent to the greater dose in therapeutics.

For similar reasons, this study does not answer the question 'Is there a preference between aspirin and phenacetin?' It appears, in our data, that these doses of phenacetin may be less effective than aspirin (contrast 2, hospital II) and produce significantly fewer and/or less severe minor adverse responses. However, since we did not demonstrate a dose response with aspirin or phenacetin, we have not established the ability of this method in this study to measure the effectiveness of these drugs. Therefore, a conclusion that phenacetin is less effective than aspirin is not justified. Furthermore, although the other symptoms following single doses of aspirin were greater than after phenacetin, we have no data, from this test, to establish long-term effects or the occurrence of serious side effects. Therefore, any claim for superiority of one drug over another is not tenable.

We do believe that pharmaceutical combinations which provide additive efficacy, but less than additive adverse effects, are advantageous therapeutic agents. In this regard, the addition of propoxyphene to the

combination promoted greater analgesia, but this occurred with a measurable increase in reports of other symptoms. We are not aware of any method by which these 2 responses may be integrated so as to demonstrate therapeutic gain or loss. Past clinical and therapeutic experience seems to justify these combinations.

There is no assurance that the original protocol by including placebo would provide more important information than the method used. However, the selection of the dose response control was expected to fail, but was necessitated by peer review. Similar situations must occur when peer groups review the protocols of experienced investigators.

Conclusions

(1) A twofold increase in aspirin, phenacetin, and the combination of aspirin and phenacetin failed to demonstrate a statistically significant increase in analgesia when single oral doses were given to *post partum* patients professing pain from uterine cramping. An increase in the number and severity of adverse reports was observed when the higher doses were given.

(2) Both an increase in analgesia and in adverse reports was observed when the dose of propoxyphene napsylate was increased. Thus, with this medication, the patients obtained measurably more analgesia but 'paid' in increased side effects.

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PRESENTATION OF ROBERT H. FURMAN, M.D.

VICE PRESIDENT, CORPORATE MEDICAL AFFAIRS

ELI LILLY AND COMPANY

TO MEMBERS OF THE FDA DRUG ABUSE ADVISORY COMMITTEE

TUESDAY, FEBRUARY 13, 1979

Mr. Chairman and Members of the Committee:

I am Robert H. Furman, Vice President of Corporate Medical Affairs for Eli Lilly and Company. Also present today is Dr. Bryan Finkle, Director of the Center for Human Toxicology, University of Utah, who will supplement these remarks later.

Last month we provided each member of the Advisory Committee and the FDA and DEA staff members with a document, a "Blue Book," containing information on propoxyphene. Should any member not have received that document, we will be glad to provide you with a copy at this time. We hope that the information we provided will be of assistance to this Committee.

We understand that today's agenda involves a preliminary discussion of the proposal to place propoxyphene in Schedule II of the Controlled Substances Act. We appreciate the opportunity to provide comments to the Committee today and will cooperate with and assist the Committee in its future deliberations.

In my comments, I will not attempt to cover all the material in Lilly's Blue Book. However, I would like to review a few items briefly before addressing the issues raised by the petition submitted by the Health Research Group to the Attorney General.

Background

The discovery and development of propoxyphene by Lilly resulted from a national effort following World War II to develop analgesic agents with a lower potential for dependence than the opium derivatives and synthetic narcotics available at that time. As part of this national effort, Lilly synthesized propoxyphene in the early 1950s. Although there are four stereoisomers of this compound, only one, the alpha-dextro isomer, has significant analgesic activity.

The anagesic effect of propoxyphene was demonstrated in animals and man. Dependence liability was evaluated in primates by the late Dr. Maurice Seevers at the University of Michigan. At the Public Health Service Hospital at Lexington, Kentucky, the degree to which propoxyphene would substitute for other narcotic agents was determined in humans. The consensus was that "its overall addiction liability is estimated to be no greater, and is probably less, that that of codeine."

The new drug application for Darvon was approved in 1957. Then-applicable law required only an evaluation for safety, although data demonstrating analgesic effectiveness in animals an man were also submitted to the FDA at that time.

From the standpoint of abuse control, the World Health Organization classified propoxyphene as a dependence-producing substance in early 1956. Subsequently, in 1964, WHO withdrew its initial classification, and later reviews by WHO reaffirmed that controls on propoxyphene were unnecessary. The Bureau of Narcotics proposed the classification of propoxyphene as an opiate in 1956. It did not act on this proposal, and in 1962 the Bureau found propoxyphene not be an opiate.

The Bureau of Narcotics and Dangerous Drugs (now the Drug Enforcement Administration) proposed that propoxyphene products be placed in Schedule IV of the Controlled Substances Act in 1973. This proposal was thoroughly reviewed by the FDA Controlled Substances Advisory Committee in 1974, and the Committee did not concur in the Schedule IV recommendation of DEA at that time.

In 1975 Dr. McBay, North Carolina state toxicologist, reported an increasing incidence of deaths, primarily suicides, attributable to propoxyphene alone or in combination with other drugs (Tab A). Following Dr. McBay's report in the Journal of the American Medical Association, Dr. Ivan F. Bennett, of Lilly, met with Dr. McBay and Dr. Page Hudson, chief medical examiner of North Carolina. Dr. Bennett was provided complete access to the information on propoxyphene cases in the files of the state medical examiner's office. Dr. McBay's observations were unique in that they were based on a systematic analysis of specimens on all drug deaths from all the coroners' offices in the state.

Following Dr. McBay's report, and in consultation with the Food and Drug Administration, Lilly requested Dr. Bryan Finkle to undertake an evaluation of medical examiner case records at various sites throughout the country. Medical

examiner files of deaths involving propoxyphene alone and propoxyphene in combination with other substances were reviewed at eighteen selected sites representing both urban and rural areas. Examiners were selected because of their high level of technical competence and the quality of their record systems.

Analyses of 1,022 medical examiner cases involving propoxyphene alone and in combination with other drugs were shared with FDA and DEA. In cooperation with the FDA, Lilly revised the labeling of its Darvon products in 1976. Lilly notified the medical profession through distribution of revised labeling, a special brochure presented to approximately 114,000 physicians, and publication of the results of Dr. Finkle's study in the Journal of the American Medical Association.

Complete information on Dr. Finkle's study was provided the FDA Controlled Substances Advisory Committee in April of 1976. After a full and careful evaluation of information relevant to the incidence of deaths, dependence liability, and abuse potential of propoxyphene, the Controlled Substances Advisory Committee concurred in the recommendation of DEA to place propoxyphene in Schedule IV.

Subsequently, DEA, with FDA's and HEW's medical and scientific evaluation, issued a proposed regulation in the Fall of 1976. Lilly did not oppose that regulatory change, and the drug went on control March 14, 1977.

Scheduling Criteria

The provisions of the Controlled Substances Act that govern the scheduling of drugs are described in detail in Tab B of the Lilly Blue Book. However, we might note several points regarding the Health Research Group proposal to place propoxyphene in Schedule II. First, we want to review the findings of the Drug Enforcement Administration, made with the advice of HEW and this Committee's predecessor, placing propoxyphene products in Schedule IV. Second, we would like to discuss briefly the statutory criteria for placing a drug in Schedule II. Thus, based on the materials provided you and on information presented in last week's Senate hearings, we submit that propoxyphene does not meet the criteria for Schedule II.

When the DEA placed propoxyphene in Schedule IV, it did so on the basis of the following conclusions:

> "1. Based on information now available, dextropropoxyphene has a low potential for abuse relative to the drugs or other substances currently listed in Schedule III.

> "2. Dextropropoxyphene has a currently accepted medical use in treatment in the United States.
>
> "3. Abuse of dextropropoxyphene may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III."

Those conclusions were, in turn, based on advice that DEA had received from the Department of HEW, from the FDA, and from the Controlled Substances Advisory Committee. The full text of the HEW recommendation is included at the end of Tab I of the Blue Book.

A decision to place propoxyphene products in Schedule II would require findings that propoxyphene is a drug:

> "(1) that has a 'high potential for abuse,'
>
> "(2) that has 'a currently accepted medical use in treatment in the United States, or a currently accepted medical use with severe restrictions,' and
>
> "(3) for which abuse may lead to 'severe psychological or physical dependence.'"

For propoxyphene products to be placed in Schedule II, conclusions substantially different from those made previously by DEA, HEW, FDA, and the Controlled Substances Advisory Committee would be necessary. We believe that no evidence has been presented that would invalidate these earlier conclusions.

When it placed propoxyphene products in Schedule IV, DEA determined that their potential for abuse was less than that of drugs in Schedule III. To revise that decision and place propoxyphene in Schedule II would be to determine that it is one of those drugs with the highest potential for abuse of any drugs with a currently accepted medical use. In fact, the best available evidence, which is described later in this presentation, indicates that the number of propoxyphene-related fatalities and emergency room reports has declined since the drug was placed in Schedule IV.

As to dependence, there exists no new information that would warrant changing the conclusions reached earlier. In its recommendation to DEA, the Department of HEW said at that time that "[p]ropoxyphene can produce a psychological and physical dependence which is qualitatively similar to that produced by 'classical' opiates (e.g. morphine or codeine) but which is quantitatively much less." Based on that advice, DEA reached the conclusion that abuse of propoxyphene may lead to "limited" physical or psychological dependence relative to the drugs in Schedule III (the schedule that includes, among other things, most codeine-combination preparations).

There has been no substantial evidence presented that propoxyphene products have the potential for producing the

severe physical or psychological dependence required to place a drug in Schedule II. In fact, the HRG petition itself does not seriously contend that propoxyphene meets this requirement for inclusion in Schedule II. The petition states, for example (at page 17), that "case reports tend to substantiate the claim that the physical dependence produced by DPX is generally moderate; however, psychological dependence can be significant." Even taken at face value, this characterization of the dependence liability of propoxyphene would place the drug in Schedule III, which provides that abuse of the drug "may lead to moderate or low physical dependence or high psychological dependence."

HRG's statement, however, cannot be taken at face value. Extensive experience and clinical studies, which are described in detail in Tab J of the Blue Book, show that the incidence of physical and psychological dependence resulting from propoxyphene abuse is so low that it is not of significant medical concern.

Aside from the technical statutory criteria for including a drug in Schedule II, one must also consider the practical effects of doing so. The controls that apply to Schedule II drugs differ from those for drugs in lower schedules in two important respects: first, DEA is authorized to establish manufacturing quotas for Schedule II drugs, which it is not

authorized to do for drugs in other schedules; and second, prescriptions for Schedule II drugs must be in writing and cannot be refilled.

Both of these forms of control are applicable to drugs with high potential for abuse, such as cocaine, morphine, methadone, the amphetamines, and the short-acting barbiturates, all of which have significant "street abuse" potential. Schedule II sanctions are intended to prevent the diversion of drugs from legitimate to illegitimate channels and to limit the quantity of drugs manufactured to the minimum amounts necessary to meet medical needs. The best evidence, however, indicates that propoxyphene abuse is not a "street abuse" problem. Mr. Kenneth Durrin, Director of the Office of Compliance and Regulatory Affairs of the DEA, acknowledged this in his testimony before Senator Nelson's subcommittee on January 31. Our analysis of the data from DAWN, together with reports from Dr. Finkle and others, indicates that the great majority of propoxyphene-related fatalities (as well as emergency room admissions) result from suicidal motivations. The incidence of propoxyphene-related fatalities appears to parallel that of suicide in general, and the evidence indicates that those fatalities are a part of the larger social problem of suicide. In these circumstances, the only effect of Schedule II controls would be to impose an unnecessary burden on patients who wish to obtain propoxyphene for legitimate medical needs.

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The proposal to place propoxyphene in Schedule II invites reconsideration of all drugs with frequent medical examiner and emergency room DAWN mentions. In other words, a large number of tranquilizers, sedatives, and antidepressants become candidates for Schedule II on this basis. In his recent Senate testimony Commissioner Kennedy addressed the frequency with which various drugs are associated with deaths and the frequency with which various drugs occur in the DAWN system as emergency room mentions (Exhibits A and B, attached).

A further observation might be made: The short-acting barbiturates have been in Schedule II for several years and yet remain among the leading drugs in coroner mentions, as noted in Exhibit A.

Effectiveness

Commissioner Kennedy's testimony during the recent Senate hearings indicated that the FDA will again review the effectiveness of propoxyphene. Although this Committee may not be charged with the responsibility for an effectiveness review, we would like to advise you that Lilly will cooperate fully with the FDA in any review the agency undertakes. Propoxyphene was evaluated for its analgesic efficacy in both animals and man prior to its introduction in 1957. An

expert panel of the National Academy of Sciences/National Research Council reevaluated propoxyphene in the late 1960s and found it effective for the relief of mild-to-moderate pain, and the weight of scientific evidence as presented both by individual investigators and those who have reviewed the literature sustains the view of the expert committee. The conclusions from well-designed trials have been confirmed by physicians and patients alike through the use of propoxyphene products over the last twenty years. Information on the effectiveness of the products is provided in the Blue Book, Tab C.

The Incidence of Misuse of Propoxyphene

The HRG petition states that deaths and abuse associated with propoxyphene are increasing. Information in the Blue Book with which you have been provided responds to these assertions. Since that material was developed additional information has been obtained from a variety of sources, including testimony in the recent Senate hearings and DAWN data. Information from the DAWN system is presented, not because it is regarded as complete or infallible, but because it is the most available of a limited selection of retrospective data sources. DAWN's sponsors acknowledge the system's insufficiency to serve as the sole basis for regulatory decision-making. What follows is a brief summary of evidence

bearing on the magnitude, trend, and character of propoxyphene abuse.

We obtained the basic data tapes from which the published DAWN reports are derived and, after consultations with DEA and NIDA and the system's operational intermediary, IMS America, Ltd., we prepared independent analyses of the data (see Blue Book, Tab D).

As will be described in more detail shortly, our independent analyses compare closely with comparable data in the last two DAWN quarterlies.

Magnitude of Propoxyphene Abuse

Although propoxyphene is third (after alcohol in combination with other drugs and heroin/morphine) in absolute numbers of medical examiner mentions in DAWN-VI, covering the period May, 1977-April, 1978, it ranks sixth in absolute numbers of emergency room mentions in the same report. Diazepam, alcohol in combination, heroin/morphine, aspirin, and flurazepam precede propoxyphene in the descending-order list of emergency room mentions.

Scaled in proportion to the number of people exposed to the drug, propoxyphene ranks eleventh or twelfth, depending

on the year, in descending order of medical examiner mentions and twenty-first in emergency room mentions. Examining the "mentions per new prescription" estimate for propoxyphene in relation to the figure for heroin/morphine*/ yields the conclusion that propoxyphene is about 2 percent as likely as heroin to produce a medical examiner mention.

Perhaps a word is in order about the use of prescription statistics as a proxy for affected population. We have used only new prescriptions in estimating, even though the average course of propoxyphene therapy involves 1.8 prescriptions, on the assumption that a refill, by definition, still subjects the same individual to risk. Since some of the drugs with which we compare propoxyphene do not qualify for refills or, if qualified, have low refill rates this assumption puts our case at an analytical disadvantage, but we feel it is important to be conservative in these analyses.

Trends in Propoxyphene Abuse

Propoxyphene abuse is declining. Our analysis of the DAWN medical examiner reports is presented in Exhibit C, attached (Blue Book, Tab D, Figure 2). The data plotted in Exhibit C were derived from our independent analysis of the

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*/ Blue Book, Tab D, Tables 1 through 4, pages 19-22.

consistent reporters' records on the DAWN data tape. Since our Blue Book was sent to you, DEA has published the newest DAWN Quarterly (April/June, 1978); an analysis of its relevant contents is presented in Exhibits D and E, attached. Our analysis (Blue Book, Tab D) very closely matches these newly published data. Both sources confirm the downward trend in propoxyphene medical examiner mentions beginning in the first quarter of 1977.

The number of medical examiner mentions for all drugs combined also appears to be trending downward. This downward trend in total mentions is due to the remarkable decrease in heroin and methadone mentions more than to any other single factor. There was a decrease of 692 total medical examiner mentions in the period from the first quarter of 1976 through the first quarter of 1978. Heroin and methadone alone accounted for a decrease of 461, i.e., two-thirds of the decrease.

There is a lag in the filing of medical examiner reports because of the time required for their preparation. To resolve any question regarding the reliability of the 1978 DAWN medical examiner data used in these analyses, we checked medical examiner reports to DAWN (both the date of death and the date reported to DAWN are shown in the computer records) for all drugs, all periods back to the beginning of DAWN.

The results for all drugs closely matched the results for propoxyphene alone, in a parallel analysis. Medical examiner reports were 93 percent complete within six months of the date of death and 95 percent complete within nine months. Since it is now ten months after the end of the first quarter of 1978 and seven months after the end of the second quarter, we feel it is appropriate to use first-quarter, 1978, data in these trending studies--as does DEA in its latest quarterly report. We have included second-quarter data with the understanding that the downward trend may not prove to be as steep as it now appears.

Emergency room trends are detailed in Exhibit E. Propoxyphene mentions exhibit a downward trend that is relatively greater than that for all nonnarcotic analgesics or for all drugs combined.

The downward trend in propoxyphene abuse is confirmed by data from other sources. Doctors Hudson and McBay, chief medical examiner and toxicologist, respectively, state of North Carolina, reconfirmed the downward trend in North Carolina in their testimony during the recent Senate hearings. (For the North Carolina figures see the Blue Book, Tab F, Table 1.) These figures indicate nearly a 40-percent decline in propoxyphene deaths since 1975.

A nine-site update of his 1975 eighteen-site study by Dr. Finkle indicates decreasing propoxyphene-associated deaths since 1975.

The Character of Propoxyphene Abuse

Our analysis of available information has led us to conclude that the great majority of propoxyphene-associated deaths result from suicidal intent.

During the recent Senate hearings, Dr. Page Hudson, the North Carolina chief medical examiner, testified that "at least 65, perhaps 80, percent" of the propoxyphene-associated deaths in his jurisdiction were suicides. Our analysis of data available to us led us to a similar conclusion.

The 1975 Finkle study found that 42 percent of propoxyphene-related deaths also involved alcohol (both DAWN and the Finkle study confirm that concomitant ingestion of other drugs and/or alcohol characterizes about 80 percent of total propoxyphene cases). Those who abuse alcohol constitute one of the most suicide-prone populations. A large number of the decedents in the Finkle study had a prior history of "emotional problems" (nearly 82 percent), and many were under psychiatric treatment at the time of death. There were even fifty propoxyphene-associated deaths officially

classified as nonsuicidal in which there was a documented history of one or more previous suicide attempts.

The aggregate of social, religious, and financial forces operating on medical examiners result in underreporting of suicide. HEW's vital statistics experts generally concede this, and the same point is made in the sociological and psychological literature.

DAWN medical examiner data indicate suicide as the manner of death in 42 percent of propoxyphene cases. For DAWN emergency room mentions, suicide attempts/gestures are recorded as the motive in 56 percent of the citations (DAWN-VI). We isolated the specific DAWN emergency room cases where the outcome was indicated as fatal and looked for the same case subsequently mentioned by a DAWN medical examiner; we found thirty-eight such case sequences. Sixty-one percent were reported to be suicides by the emergency room and 58 percent determined to be suicides by the medical examiner. Although thirty-four out of thirty-eight cases (89 percent) were classified in manner of death as suicide by either the medical examiner or the emergency room, there was agreement between medical examiner and emergency room with respect to suicide in only eleven of the thirty-eight cases (29 percent). Clearly, "manner of death" characterizations in DAWN must be evaluated carefully.

That propoxyphene-related suicides are understated in DAWN is suggested by the following additional considerations:

1. On a city-by-city basis, the incidence of all propoxyphene-related deaths (both suicidal and nonsuicidal) correlates equally well with the overall suicide rate and the propoxyphene-associated suicide rate for those cities.

2. An evaluation of DAWN medical examiner laboratory data provided on the IMS DAWN tapes indicates that, in a large proportion of the cases not classified as suicide, concentrations of propoxyphene were detected that required the ingestion of amounts that could not reasonably have been taken accidentally.

3. The demographic profiles of propoxyphene medical examiner cases align well with those of explicit drug suicide. Propoxyphene emergency room case demographics also align well with independent studies of those attempting drug suicide.

Laboratory analyses are of prime importance in reaching a decision as to whether a death is an "accident" or a

suicide. Dr. Lawrence V. Lewman, of the Oregon State Medical Examiner's Office, testified during the recent Senate hearings that 60 percent of the propoxyphene-associated cases in his state were accidents. With Dr. Lewman's cooperation we obtained and reviewed the twenty-two Oregon cases attributed to propoxyphene during the period January 1, 1978, through May 31, 1978. See Exhibit F, attached.

Analysis of the laboratory data in these twenty-two cases fails to disclose a single case that can reasonably be called accidental. Of the twenty-two, only three cases reported blood propoxyphene levels within therapeutic range. All the others had much higher concentrations. With respect to the three cases involving the relatively lower blood propoxyphene levels:

- One involved a lethal level of methadone.

- In another, alcohol was present at nearly twice the legal drunk-driving limit.

- A third had ingested enough diazepam to achieve thirteen times the recommended therapeutic concentration and enough amitriptyline to achieve fifty-four times the therapeutic concentration of that drug.

Dr. Lewman based his view primarily on theories involving the relative concentrations of propoxyphene and its principal metabolite, norpropoxyphene. The possible role of norpropoxyphene in propoxyphene toxicity is discussed later in this presentation.

It is of interest at this juncture to assess the toxicological consequences of a substantial decrease in propoxyphene availability. The state of California's Medicaid program ("Medi-Cal") does not reimburse for propoxyphene products, and, as a result, propoxyphene prescribing in California is less than the national average. How is the need for analgesia satisfied in both the Medicaid and non-Medicaid sectors in California? Consistent with Dr. William Beaver's Senate testimony that, if propoxyphene were to be less available, codeine use will increase, codeine combinations dominate the California prescription analgesic marketplace. Are there toxicological insights in DAWN paralleling these marketplace differences? To evaluate this situation, we examined the latest DAWN Quarterly (April-June, 1978) and compared the three California SMSAs[1/] (Los Angeles, San Francisco, and San Diego) with the national DAWN averages. Examining the percentage of DAWN emergency room and medical examiner mentions accounted for by propoxyphene and by codeine produced the following:

1/ Standard Metropolitan Statistical Areas.

		California (LA, SF, SD)	DAWN Total+	California vs. National
Propoxyphene	ER:	1.34%*	2.2%**	-39%
	ME:	6.54***	7.0****	-6.6%
Codeine	ER:	1.78*	0.6**	+197%
	ME:	7.48***	4.8****	+56%

*Percent of total California SMSA ER mentions (6,556)
**Percent of total national DAWN ER mentions (44,355)
***Percent of total California SMSA ME mentions (642)
****Percent of total national DAWN ME mentions (1,746)
+Including California

As can be seen, codeine accounted for a much larger percent of medical examiner mentions in the California SMSAs than is true for the United States. The very slight difference in propoxyphene medical examiner mentions in California in comparison with the national DAWN average indicates that limiting the availability of propoxyphene has had little impact on the abuse of propoxyphene, usually with suicidal intent.

Norpropoxyphene: A Factor in Propoxyphene Overdose?

Propoxyphene is an opioid possessing a pharmacological and toxicological profile qualitatively similar to that of the chemically related methadone. It is well absorbed orally and rapidly metabolized by N-demethylation in the liver to norpropoxyphene, the major plasma metabolite, both in man and in the dog.

Norpropoxyphene has little analgesic ("opioid") activity (one-half to one-fortieth that of propoxyphene, depending on the assay method utilized), while its local anesthetic activity is two to three times that of the parent compound. The "opioid" activity is antagonized by agents such as naloxone, whereas the local anesthetic effect is not. At certain concentrations propoxyphene and norpropoxyphene have been demonstrated to delay cardiac conduction and diminish myocardial contractility in laboratory animals, in vitro and in vivo.

After the administration of a single oral dose of propoxyphene in man, plasma propoxyphene concentrations reach peak levels in approximately two hours and decrease thereafter, with a half-life of six to twelve hours. Peak plasma concentrations of norpropoxyphene are noted within a half-hour to one hour following peak propoxyphene concentrations. The half-life of norpropoxyphene is thirty to thirty-six hours.

In human subjects given a loading dose of propoxyphene (300 mg napsylate [N] or 195 mg hydrochloride [HCl]) followed by 100 mg N or 65 mg HCl at four-hour intervals for thirty-one doses (five days), peak plasma concentrations of norpropoxyphene between 1.0 and 1.2 micrograms/ml (with the hydrochloride) and between 0.75 and 1.0 micrograms/ml (with

the napsylate) were noted at about 120 hours, i.e., at about four norpropoxyphene "half-lives."

Single daily doses of 125 mg norpropoxyphene administered to humans for seven days resulted in peak plasma concentrations of norpropoxyphene of 0.25 to 0.55 micrograms/ml and elicited no overt adverse effect.

The toxicological effects of propoxyphene relate to its analgesic (CNS) properties, which are shared to a much lesser degree by norpropoxyphene, and are readily reversed by antagonists such as naloxone. The local anesthetic properties, shared by both propoxyphene and norpropoxyphene but to a greater extent by norpropoxyphene, lack specific antagonists. Since (1) both propoxyphene and norpropoxyphene possess local anesthetic effects not reversible by specific antagonists and (2) in view of the higher plasma and tissue concentrations of norporpoxyphene attained during chronic propoxyphene administration, as well as (3) the relatively long half-life of norpropoxyphene, questions have been raised regarding the possible role of the local anesthetic properties of the parent compound and its principal metabolite in propoxyphene-induced toxicity.

Compounds possessing local anesthetic activity also modify cardiac conduction. Since electrocardiographic

changes have been reported in some cases of propoxyphene overdosage in humans, it has been suggested that the local anesthetic effect of norpropoxyphene (and propoxyphene) might contribute to the toxicity or lethality of propoxyphene overdose by a deleterious effect on cardiac conducting tissue.

The effects of propoxyphene and of norpropoxyphene on cardiac conduction have been studied in vivo and in vitro in laboratory animals, and these studies are reviewed in the Blue Book that you received earlier. Therefore, I will not review the animal data at this time. Much of the knowledge concerning propoxyphene and norpropoxyphene pharmacology has come, understandably, from Lilly research. Lilly researchers have published their results regularly in refereed scientific journals, and this work has been confirmed and extended from time to time by other investigators, notably by Amsterdam and by Lund-Jacobson. References to the latter are cited in your Blue Book.

During the recent Senate hearings on propoxyphene, Dr. Lewman, the medical examiner from Oregon, stated that in patients taking propoxyphene every few hours, "The propoxyphene is being rapidly metabolized while the toxic [italics added] nor-propoxyphene metabolite is constantly building up because of its long half life." What Dr. Lewman fails to

recognize is that norpropoxyphene concentrations reach a plateau at which they remain, given a constant dosage situation. This plateau, reached in four or five half-lives, or about 120 hours, results from an equilibrium state wherein rates of excretion and synthesis of norpropoxyphene (by hepatic demethylation of propoxyphene) are equal.

If chronic norpropoxyphene toxicity exists, it would most likely reflect its local anesthetic effects on myocardial conduction.

In a study conducted at the Lilly Clinic, Wishard Memorial Hospital, Indianapolis, electrocardiograms were constantly recorded on Holter monitors during chronic propoxyphene administration to two male volunteers, ages fifty-six and sixty. After a six-day control period a single 300 mg dose of propoxyphene napsylate was given, and blood samples were obtained at various intervals over the next forty-eight hours. Maximum concentrations of propoxyphene and norpropoxyphene observed in these two subjects were 0.25 and 0.37 (propoxyphene) and 1.1 and 1.4 (norpropoxyphene) micrograms/ml, respectively. From day 9 through day 15 the subjects received propoxyphene napsylate 100 mg every four hours (i.e., 600 mg/day). Day 16 through day 25 served as the posttreatment control period. Neither subject manifested

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any change in PR, QRS, or QT_c during the period of propoxyphene administration, in comparison with pretreatment or posttreatment control tracings. Ventricular premature beats were observed slightly more frequently in one subject during treatment, while a slight decrease in ectopy was noted in the other. Neither change is significant.

Propoxyphene napsylate has been evaluated by Tennant (J. Natl. Med. Assn., 66:23-27, 1974; J.A.M.A., 232:1019-1022, 1975) for heroin detoxification and maintenance. Under double-blind conditions, twenty-nine adults were admitted to a 180-day maintenance program. About one-fourth of the patients remained in the study more than ninety days; a few remained for as long as two years. The maximum daily dose of propoxyphene napsylate was 1,200 mg, starting with 400 mg per day. Patients who received a single dose of 600 mg reported short-term dysphoria, but otherwise no serious toxic effects were noted. Electrocardiograms, chest x ray, and electroencephalograms were evaluated before and at the third and sixth month of the study. The ECG tracings were reviewed by a cardiologist and no changes were observed, nor were changes observed in the other examinations.

Bigeminal cardiac rhythm has been described relatively frequently in cases of propoxyphene overdose, and it is of some interest to note that in the case reported by McCarthy

and Keenan (J.A.M.A., 187:164-165, 1964) "a bigeminal rhythm developed but it responded well to intravenously administered procaine amide hydrochloride." Procaine amide is an antiarrhythmic agent with potent local anesthetic effects.

Review of published case reports of propoxyphene overdose that include electrocardiographic commentary indicate that, with rare exception, ECG abnormalities subside or disappear once adequate ventilation is restored and anoxia and acidosis are overcome. It is important to realize that ECG changes may revert to normal as ventilation is restored, over an interval of a few minutes to a few hours--intervals too brief, in view of the long half-life of norpropoxyphene, to have allowed for much, if any, lowering of norpropoxyphene concentrations in blood or tissues.

During the recent Senate hearing on propoxyphene, FDA Commissioner Donald Kennedy called attention to the higher mortality rate from propoxyphene overdose among people twenty to forty years of age in comparison with those over sixty, although the number of propoxyphene prescriptions is approximately the same for both groups. The fatality rate in the younger group was five times that in the older group, a group in which sudden cardiac death is much more frequent and in which one would expect any cardiotoxic effect of propoxyphene most likely to become evident.

It is worthy of note that the initial new drug application for Darvon, submitted in March, 1957, now almost twenty-two years ago, included studies of cardiac function in anesthetized dogs given continuous intravenous infusions of propoxyphene until death. No significant ECG changes were observed except for minor changes just prior to the death of the animals. It was concluded that propoxyphene had no deleterious cardiac effects.

Additional cardiac studies were reported in the NDAs for Darvocet^{R} and Darvon-N^{R} in 1968. In the former, anesthetized cats were given intravenous propoxyphene, 5 mg/kg, and slight prolongation of the PR interval was noted. A dose of 0.5 mg/kg had no effect on the ECG. The NDA for Darvon-N notes that no significant effects on cardiac rhythm were observed when anesthetized cats were given 5 mg/kg propoxyphene intravenously. Also reported is a study of the hydrochloride and napsylate salts administered to conscious dogs in doses of 40 mg/kg orally (by gavage). No effects on cardiac rhythm were noted.

A study in dogs recently submitted for publication by Lilly pharmacologists is worthy of brief review. The metabolism of propoxyphene is quite similar in the dog and man, and results of the investigation are reassuring for man.

Propoxyphene hydrochloride was administered orally to four dogs every eight hours for nineteen days. The initial dose was 20 mg/kg, three times daily, an amount ten to twelve times the recommended human dose. This dose was increased to 60 mg/kg three times daily in increments of 5 to 15 mg/kg every three or four days. The dogs remained ambulatory, but anorexia, tremors, emesis, and sedation were noted periodically.

Plasma concentrations of propoxyphene, 2.3 ± 0.5 micrograms/ml, and norpropoxyphene, 18.4 ± 4.7 micrograms/ml, were greater than those generally regarded as lethal in man. Tissue concentrations were in excess of plasma concentrations.

Electrocardiograms showed a 10- to 30-percent increase in the PR interval (A-V conduction time) with the initial dose. However, there was no further increase in the PR interval until after the 60-mg/kg dose was reached. At this high dose a moderate tachycardia (132/minute) and increased amplitude of P, QRS, and T waves were noted.

Summary

The possibility that the effects of norpropoxyphene on cardiac conduction play a role in propoxyphene toxicity

merits further study. Certainly there are measurable, although relatively minor, effects on myocardial conduction, demonstrable by in vitro and in vivo animal experiments. Reports of human toxicity that provide cardiac and electrocardiographic commentary (many of these are reviewed in the Lilly Blue Book) strongly suggest that cardiocirculatory disturbances--such as arrhythmias, ventricular fibrillation, and cardiac arrest--arise mainly from severe anoxia, due to respiratory depression and apnea, acidosis, which may be severe, and electrolyte imbalance. Central nervous system depression per se may directly interfere with cardiopulmonary and circulatory function.

The possibility that norpropoxyphene may play a role in cardiac manifestations of severe drug overdose cannot be excluded, but there is no clinical evidence to show that it does. The central nervous system depressant effects of propoxyphene itself (notably anoxia and acidosis) can account for the cardiac effects that have been observed in overdose cases.

Additional Studies

Lilly has indicated consideration of additional studies, including a continuation of the update by Dr. Finkle of those medical examiner offices surveyed in his 1975 study.

Information derived from such an update, when compared with the earlier data base, should afford a basis for determining trends.

Lilly also has under consideration the possibility of a prospective study of medical examiner and emergency room cases to develop in-depth and accurate information on the circumstances of drug misuse in accidental and intentional overdose situations.

In testimony during the recent Senate hearings several suggestions for additional studies were made, and the company has these suggestions under consideration.

Conclusion

In summary, Lilly believes that propoxyphene is a safe and effective analgesic when used as directed. The company does not believe that death or serious injury has resulted from the proper use of propoxyphene products. All reliable data indicate that propoxyphene-related deaths are associated with improper use.

Data both from the DAWN system and from independent reports by toxicologists indicate that propoxyphene-associated deaths, which reached a peak in late 1976 and early 1977,

are decreasing in frequency. A high percentage of these deaths have been determined to be suicides by medical examiners and coroners. The laboratory data on many of the deaths classified as accidental indicate blood and tissue concentrations of propoxyphene and other drugs far in excess of those that could be expected from use of such drugs at recommended doses.

Propoxyphene has not been associated with significant "street abuse" and its dependence liability is limited.

Lilly does not believe that propoxyphene products should be placed in Schedule II of the Controlled Substances Act. Nevertheless, the company will continue to cooperate with the Food and Drug Administration, the Drug Enforcement Administration, and this committee in their further evaluation of propoxyphene.

# # #

Darvocet^{R} (propoxyphene hydrochloride and acetaminophen, Lilly)
Darvon^{R} (propoxyphene hydrochloride, Lilly)
Darvon-N^{R} (propoxyphene napsylate, Lilly)

EXHIBIT A

(TABLE I)

ASSOCIATIONS WITH DEATHS: 1977
(DAWN, NPA DATA)

Drug Group	Total RX's	Coroner Mentions	Coroner Mention/ Million RX's	Group Rank
I. Barbiturates*				
Secobarbital				
Pentabarbital	3.8	1071	282	1
Amobarbital				
Secolamobarbital				
II. Other Sedative-Hypnotics*				
Methaqualone	6.5	326	50	2
Ethchlorvynol				
Glutethimide				
Chlor hydrate				
III. Benzodiazepines				
Diazepam	80.2	552	7	5
Flurazepam				
Chlordiazepoxide				
IV. Major Tranquilizers				
Chlorpromazine				
Thioridazine	16.1	147	9	4
Trifluoperazine				
Haloperidol				
V. Other Common Prescription Analgesics				
Fiorinal +/- codeine	63.8	346	5	6
Codeine -/- other analgesics				
Pentazocine +/- other alangesics				
VI. Propoxyphenes				
Alone +/- other analgesics	33.5	607	18.1	3

*Phenobartital and meprobamate were intentionally excluded since their prominant use as anticonvulsant and "muscle relaxant," respectively differs from other drugs in the same pharmacologic category.

Source: Appendix B of Commissioner Donald Kennedy's statement of February 5, 1979, before the Senate's Select Committee on Small Business

EXHIBIT B

(TABLE II)

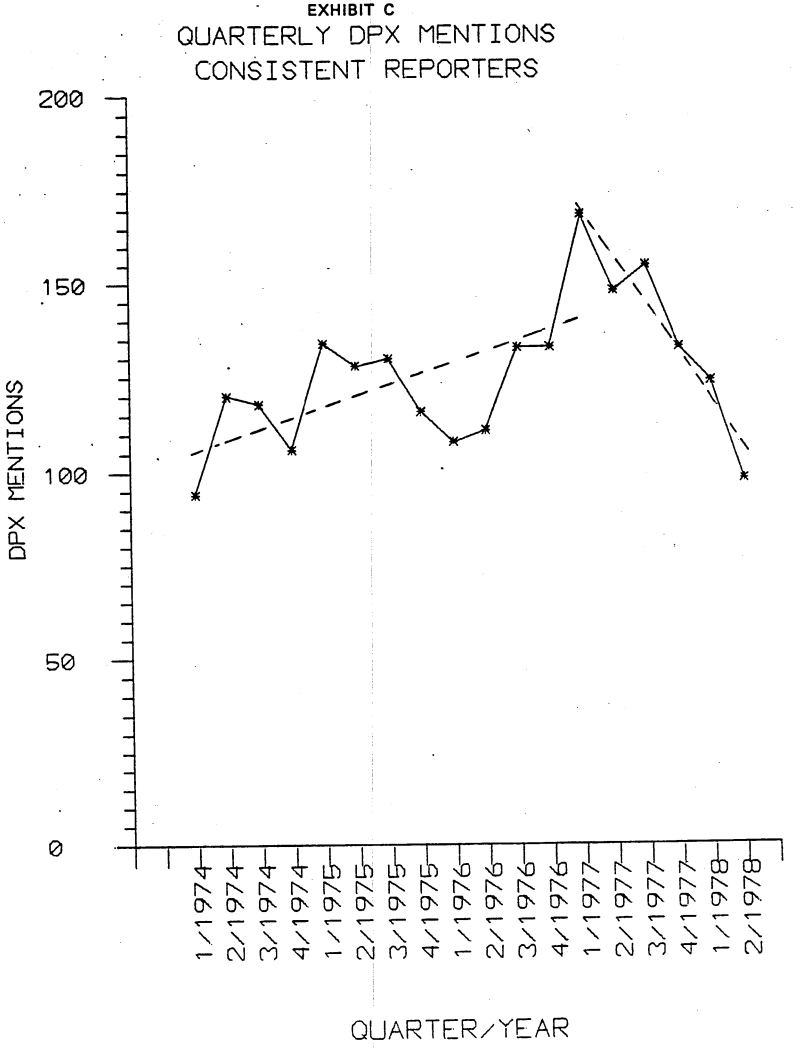
COMPARISON OF PROPOXYPHENE WITH OTHER DRUGS (NPA, DAWN DATA) -1977

ALL REPORTERS

Drug	Total RX's (in millions)	ER Mentions	Coroner Mentions	Coroner Mentions/ER Mentions	Coroner Mentions/Million RX's	Relative Rank
BARBITURATES						
Secobarbital	1.2	2457	350	.14	292	3
Pentobarbital	1.3	946	272	.29	209	4
Secobarb/Amobarb	1.0	3093	326	.11	326	2
Amobarbital	0.3	130	123	.95	410	1
Phenobarbital	7.8	2989	254	.08	32.6	9
BENZODIAZEPINES						
Diazepam	53.6	21678	418	.02	7.8	18
Chlordiazepoxide	13.0	3411	54	.02	4.2	22
Flurazepam	13.6	4643	80	.02	5.9	19
OTHER SED/HYP						
Meprobamate	8.2	1238	96	.08	11.6	16
Methaqualone	1.0	2405	62	.03	62.0	6
Ethchlorvynol	1.7	2202	135	.06	79.4	5
Glutethimide	1.8	639	94	.15	52.2	7
Chloral hydrate	2.0	618	35	.06	17.5	14
TRANQUILIZERS						
Trifluoperazine	3.0	1072	6	.01	2.0	24
Thioridazine	6.8	2175	74	.03	10.9	17
Chlorpromazine	4.7	2404	64	.03	13.6	15
Amitriptyline	9.0	3281	386	.12	42.9	8
Imipramine	4.6	921	74	.08	16.1	14
Doxepin	4.1	1397	104	.07	25.4	10
Haloperidol	1.6	1058	3	.01	1.9	25
ANALGESICS						
Morphine	0.6	134	0	-	-	
Codeine & Codeine compounds	49.8	3597	274	.08	5.5	20
Fiorinal	7.5	1204	0	.01	-	25
Fiorinal w/codeine	2.3	130	1	.01	.43	26
Pentazocine	3.5	1079	71	.07	20.3	11
Pentazocine comp.	.7	4	0	.01	-	28
Aspirin	NA	7184	156	.02	-	-
Acetaminophen	NA	2559	77	.03	-	-
Propoxyphene	33.5	4179	607	.15	18.1	12
OTHER						
Diphenhydramine	10.8	1113	23	.02	2.1	23
Diphenylhydantoin	8.6	2271	41	.02	4.9	21
Methapyrilene/ scopolamine (OTC)	NA	1725	1	.01	-	-

Source: Appendix B of Commissioner Donald Kennedy's statement of February 5, 1979, before the Senate's Select Committee on Small Business

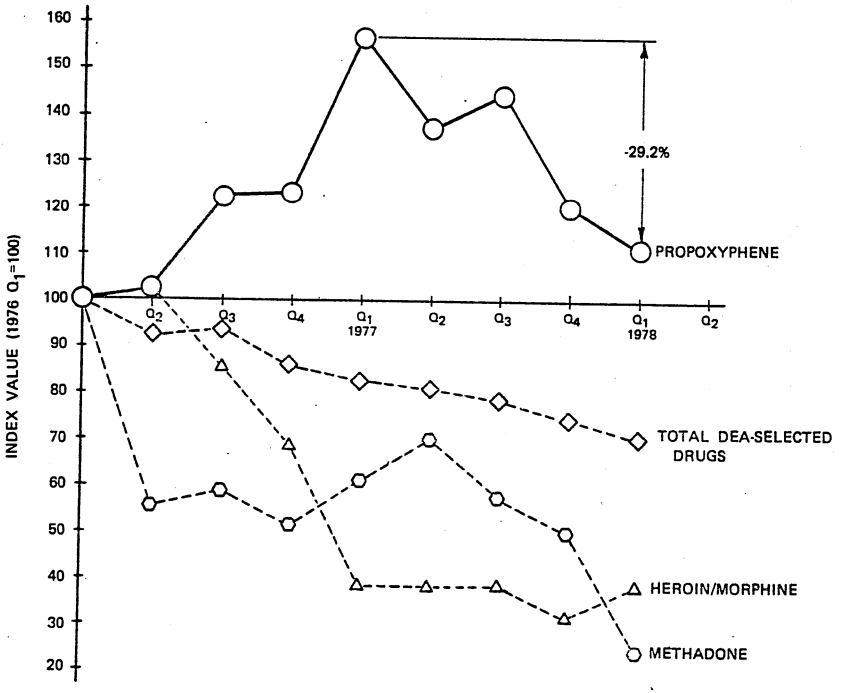
EXHIBIT C



* TOTAL DPX

EXHIBIT D

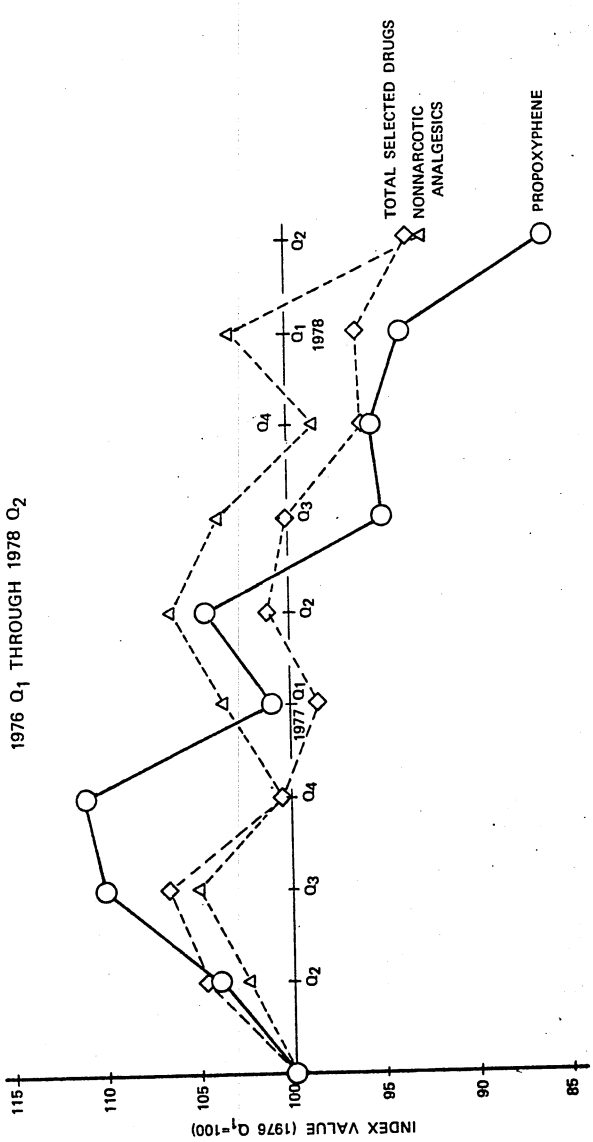
TRENDS IN DAWN MEDICAL EXAMINER MENTIONS;
CONSISTENT REPORTERS, TOTAL SELECTED DRUGS;
1976 Q_1 THROUGH 1978 Q_1



SOURCE: DAWN QUARTERLY (April-June, 1978)

EXHIBIT E

TRENDS IN DAWN EMERGENCY ROOM MENTIONS;
CONSISTENT REPORTERS, TOTAL DEA-SELECTED DRUGS;
1976 Q_1 THROUGH 1978 Q_2



SOURCE: DAWN QUARTERLY (April-June, 1978)

EXHIBIT F

ADDITIONAL CASE DETAIL ON OREGON MEDICAL EXAMINER CASES ATTRIBUTED TO PROPOXYPHENE; JANUARY 1, 1978, THROUGH MAY 31, 1978. SOURCE: OFFICE OF OREGON STATE MEDICAL EXAMINER.

Case and date	Propoxyphene level measured mg%	Multiple of maximum therapeutic concentrations in normal subjects**	Norpropoxyphene level measured mg%	Other agents measured	Concentration (mg%)/estimated total	Multiples of therapeutic concentrations in normal subjects
1, 1/4/78	1.8	36-90	3.6	Alcohol	.06%	
2, 1/13/78	0.63	13-32	~ 3.2			
3, 1/23/78	0.65	13-33	9.1			
4, 1/30/78	0.22	4-11	0.53	Meprobamate	1.7/1.5g*	4X 400mg
5, 2/4/78	3.2	64-160	2.6	Alcohol	.24%	1.6X Driving limit
6, 2/7/78	0.37	7-19	1.4	Alcohol	.15%	1.0X Driving limit
7, 3/1/78	0.4	8-20	1.6			
8, 3/21/78	0.3	6-15	none	Diazepam	0.4/270mg*	27X 10mg
9, 4/8/78	0.1	2-5	0.36	Methaqualone	Trace	
10, 4/9/78	0.25	5-13	~ 1.0	Diazepam Alcohol Acetaminophen	0.3/200mg* 0.14% 18.0/23.3g*	20X 10mg 0.9X Driving limit 40X 650mg
11, 4/9/78	3.3	66-165	12.6	Amo/Secobarbital Diazepam Alcohol	0.3/141mg* /265mg* 0.5/330mg* 0.16%	33X 10mg 1.1X Driving limit
12, 4/11/78	0.9	18-45	1.0	Phenobarbital Alcohol	0.7/48mg* 0.02%	
13, 4/16/78	0.9	18-45	3.9	Dilantin	1.8/1200mg*	12X 100mg
14, 4/16/78	0.25	5-13	0.75	Diazepam	0.6/400mg*	40X 10mg
15, 4/19/78	0.05	1-3	0.4	Methadone (gastric methadone	0.04/75mg* 47mg)	
16, 4/23/78	0.1	2-5	0.6	Diazepam	Trace	

continued

EXHIBIT F (CONTINUED)

ADDITIONAL CASE DETAIL ON OREGON MEDICAL EXAMINER CASES ATTRIBUTED TO PROPOXYPHENE; JANUARY 1, 1978, THROUGH MAY 31, 1978. SOURCE: OFFICE OF OREGON STATE MEDICAL EXAMINER.

Case and date	Propoxyphene level measured mg%	Multiple of maximum therapeutic concentrations in normal subjects**	Norpropoxyphene level measured mg%	Other agents measured	Concentration (mg%)/estimated total	Multiples of therapeutic concentrations in normal subjects
17, 4/28/78	0.1	2-5	0.2	Stelazine	(not measured)	
18, 4/30/78	0.05	1-3	0.1	Alcohol Acetaminophen	0.26% 5.0/6.48g*	1.7X Driving limit 10X 650mg
19, 5/15/78	0.2	4-10	1.0			
20, 5/28/78	0.2	4-10	0.9	Alcohol	0.08%	
21, 5/29/78	0.55	11-28	0.9	Glucose	17 mg%	
22, 5/31/78	0.01	.2-.5	1.5	Diazepam Amitriptyline	0.2/133mg* 0.09/1360mg*	13X 10mg 54X 25mg

*Baselt, R. C., et al.; "Therapeutic and Toxic Concentrations of More Than 100 Toxicologically Significant Drugs in Blood, Plasma, or Serum"; Clin. Chem., 21(1): 44-62, 1975

**Achieved in normal subjects with the ingestion of three capsules of either 65mg propoxyphene hydrochloride or 100mg propoxyphene napsylate. One dose every four hours is the recommended regimen. The first number shown on each line is the estimated multiple for the chronic propoxyphene subject and the second number is the estimated multiple for a one-time ingestion.

Senator NELSON. Senator Weicker?

Senator WEICKER. A great deal of attention has been given to the effectiveness of propoxyphene compared to other analgesics. Commissioner Kennedy noted the most popular propoxyphene containing products are those products containing other analgesics such as aspirin. Does the combination of propoxyphene with aspirin produce a synergistic result that a double dose of aspirin would not?

Dr. FURMAN. When you say "synergistic" that implies that 2 plus 2 equals 7 or 8. I think the feeling is that the combination of the two produces a greater analgesic effect than either one alone, and that is not a synergistic effect.

There is a very sound pharmacologic reason for combining propoxyphene, which is a centrally acting analgesic agent in the sense that codeine is, with something like aspirin or acetaminophen, which has a peripheral site of action.

There is evidence that the reason aspirin is effective is that it blocks the synthesis at the site of pain, injury, or wound, of agents such as prostaglandins. By combining centrally acting agent such as propoxyphene with a peripherally acting agent such as aspirin, you have the best of two worlds, so to speak. You can get effective analgesic in most instances with doses that do not elicit unwanted side effects, and it is quite understandable and quite reasonable that the combination product would be the more popular one because it makes the most sense.

Senator WEICKER. Can all those persons who now use propoxyphene safely use other analgesics, such as aspirin, or codeine, to obtain the pain relief they get from propoxyphene?

Dr. FURMAN. The key word in your question is "safely." There are individuals who, because of disease states or idiosyncracies, can take one analgesic and not another.

I do not think one would be wise to make a blanket statement that those who receive analgesia from propoxyphene can safely switch to codeine or aspirin and expect to get the same analgesia.

Senator WEICKER. Dr. Finkle's study showed that most of the deaths associated with propoxyphene involved use of the drug in combination with alcohol or other drugs such as tranquilizers. This raises what seems to me to be an entirely different problem than the one that has been layed at your doorstep during the course of these hearings.

What is your view insofar as what the pharmaceutical industry, or the FDA itself, can do in regard to educating the public in this area?

Dr. FURMAN. Well, we have educated, and will continue to educate, physicians in respect of the proper use of propoxyphene products.

We are in the process of modifying our package literature to provide the physician with more adequate information on the management of overdose; but I think what you are touching upon, Senator Weicker, is the overall problem of a pill-popping, drug-abusing society. If one takes a look at the suicide rate per 100,000 in the United States over the last few years, one gets really quite depressed at the realization that thousands of people are killing themselves one way or another. Some of these individuals are using drugs; but, I submit, is the situation improved if they sit in a car with the motor running and the garage door shut, or blow their brains out with a gun, rather than use a drug to do this? We still have a societal problem of considerable dimensions.