COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

HEARINGS

BEFORE THE

SUBCOMMITTEE ON MONOPOLY

OF THE

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

NINETY-FOURTH CONGRESS

SECOND SESSION

ON

PRESENT STATUS OF COMPETITION IN THE PHARMACEUTICAL INDUSTRY

PART 31

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HEARING DATES

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

TUESDAY, NOVEMBER 9, 1976

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

The subcommittee met, pursuant to notice, at 10 a.m., in room 318, Russell Senate Office Building, Hon. Gaylord Nelson, chairman, presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; and Karen Young, research assistant.

Senator NELSON. The Monopoly Subcommittee of the Senate Small Business Committee today commences 5 days of hearings on the anti-obesity drugs, which are generally amphetamines and amphetamine-related drugs.

The latter include such drugs as phenmetrazine—Preludin—phentermine — Ionamin — diethylpropion — Tenuate — chlortermine—Voranil—and others. Fenfluramine—Pondimin—appears to be more like the hallucinogens rather than amphetamines.

At one time the amphetamines were the largest selling group of antiobesity drugs, but after being placed in schedule II of the Controlled Substances List with an assigned quota, the demand shifted over to the amphetamine-related drugs, which remained in schedules III and IV.

In 1975, 5.5 million prescriptions were written for the amphetamines and 19.9 million for the amphetamine-related antiobesity drugs.

Manufacturers' sales of antiobesity drugs for 1975 are estimated to be:

Amphetamines	$20,056,000
Nonamphetamines	64,594,000
Total	84,650,000

Estimated retail sales are in the vicinity of $170 million. Illegal street sales would increase this amount considerably because of the higher prices demanded.

The amount of sales does not reflect the impact of these drugs on society. As far back as 1969 the Economic and Social Council of the United Nations concluded that (*a*) "In some countries there is in-

creasing misuse, especially by young people, of central nervous system stimulants notably of the amphetamine type," and urged that (*b*) "Immediate action is necessary to combat this threat to the health of mankind."

In 1970, U.S. legal production of amphetamines exceeded 10 billion pills—tablets and capsules—in 1971, the figure probably exceeded 12 billion.

In 1972, production fell, because the amphetamines were given manufacturing quotas, and former users were then diverted to amphetamine-related drugs.

According to Dr. Lester Grinspoon's "The Speed Culture":

> Amphetamines were unique: never before had a powerful psychoactive drug been introduced in such quantities in so short a period of time, and never before had a drug with such a high addictive potential and capability of causing long-term or irreversible physical and psychological damage been so enthusiastically embraced by the medical profession as a panacea or so extravagantly promoted by the drug industry."

Most studies have shown that these drugs as an adjunct to diet have a "trivial" advantage over diet alone. As a matter of fact, the weight loss occurs principally in the first few weeks and then levels off. The labeling calls for use for no more than "a few weeks." According to FDA's Advisory Committee on Metabolic and Endocrine Drugs, however:

> The increased weight loss appears to be related to variables other than the drug prescribed, such as the physician-investigator, the population treated, and the diet prescribed.
>
> Studies do not permit conclusions as to the relative importance of the drug and non-drug factors on weight loss.

In addition, the FDA Advisory Committee insisted that:

> The natural history of obesity is measured in years, whereas the studies cited are restricted to a few weeks duration; thus, the total impact of drug-induced weight loss over that of diet must be considered clinically trivial. The limited usefulness of these agents must be measured against any possible risk factors inherent in their use.

The amphetamines have been widely abused in numerous populations and evidence will be presented during these hearings that the newer drugs of the amphetamine family as well as the nonamphetamine drugs do not have higher benefits or lower risks than older available drugs.

According to an article which appeared in Pediatrics of February 1973, and signed by the Committee on Drugs, its consultants and others of the American Academy of Pediatrics:

> More than ten years ago Japan banned the use of amphetamines. The United Kingdom restricted distribution of amphetamines to hospital pharmacies in 1968. Sweden categorized amphetamines as a narcotic in 1944 because of abuse; and in 1965, phenmetrazine (Preludin) and in 1968, methylphenidate (Ritalin) were removed from the market.
>
> The Health Protection Branch of the Department of National Health and Welfare of Canada, with the endorsement of the Canadian Medical Association (and others) has moved to prohibit the use of amphetamines and related compounds for weight reduction purposes as of September 1, 1972.

The purpose of these hearings, therefore, is to ascertain whether the possible benefits of the antiobesity drugs outweigh the risks both to the individual and to society, and whether these drugs should continue to be marketed for the purposes claimed.

It has always been our policy that every viewpoint on all subjects before this committee is sought.

These hearings are no exception to that rule. Representatives of the Pennwalt Corp., the largest manufacturer of these products will appear later in the hearings.

Any other companies manufacturing these products are welcome to appear as witnesses upon their own request at anytime.

We are pleased to have with us this morning a group of very distinguished witnesses, Dr. Lester Grinspoon, associate professor of psychiatry, Harvard Medical School, and director of information and evaluation, Massachusetts Mental Health Center, Boston, Mass.

Dr. James J. Nora, professor of pediatrics and director of pediatric cardiology, University of Colorado Medical Center, Denver, Colo.

Dr. Sumner Yaffe, professor of clinical pharmacology and pediatrics, University of Pennsylvania, and director, division of clinical pharmacology, Children's Hospital, Philadelphia, Pa.

And Dr. Thaddeus Prout, associate professor of medicine, Johns Hopkins University and chief of medicine, Greater Baltimore Medical Center, Baltimore, Md.

Dr. Allen Goldman will not be here this morning, but Dr. Yaffe will read Dr. Goldman's statement. Dr. Goldman is associate professor of pediatrics, University of Pennsylvania, and director, teratology unit, Children's Hospital, Philadelphia, Pa.

Our first witness this morning will be Dr. Grinspoon.

Doctor, we are pleased to hear from you this morning.

Your statement will be printed in full in the record.[1]

You may present it as you desire, and if you wish to expand upon it extemporaneously, you may do so.

STATEMENT OF LESTER GRINSPOON, M.D., ASSOCIATE PROFESSOR OF PSYCHIATRY, HARVARD MEDICAL SCHOOL, AND DIRECTOR OF INFORMATION AND EVALUATION, MASSACHUSETTS MENTAL HEALTH CENTER, BOSTON, MASS.

Dr. GRINSPOON. Thank you, Mr. Nelson.

First, as I said, I apologize for the length of my statement.

I have provided up a brief history of amphetamines, and I simply summarize as follows: The drug was first synthesized in 1887 by a German pharmacologist. Not much attention was paid to it, and it was put back on the shelf, and it was not investigated until 1910 by G. Barger and Sir H. H. Dale, but again very little came of it until 1928, when an American by the name of Dr. Gordon Alles, who was looking for a synthetic ephedrine substitute, that is, a synthetic amine substitute for ephedrine, began to experiment with it.

Ephedrine was widely used in the treatment of asthma, and there was concern that the natural sources would soon be exhausted.

Gordon Alles looked at amphetamine and dextro-amphetamine, and found through experimentation on himself that there drugs produced a sense of alertness that they combatted fatigue, and it gave a euphoric sense of confidence, even though they kept him awake late into the night.

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[1] See prepared statement of Dr. Grinspoon beginning at p. 14704.

He was shortly approached by F. B. Nabenhauer of a drug company, which persuaded him to sell his patent rights.

They were interested in this drug for their new "Benzedrine" inhaler, which they were about to market, and indeed, was marketed in 1932. At that time anybody could get the Benzedrine inhaler from grocerystores or drugstores without a prescription, and it was very shortly after that that it was discovered that this indeed could be abused. People would take the inhaler apart, and they could dissolve the contents in alcohol, or even swallow it whole, and discovered they could get quite a high from it.

The drug was packaged in pill form just a few years later, and within a few years of that time 50 million units of the drug were being produced, and as I think I noted in your statement, by 1958 3½ billion units were being produced in this country, and 10 years later, 8 billion, or enough for 35 to 50 pills for every man, woman and child in this country.

Now, World War II gave an enormous boost to the acceptance of these medicines in this country, but by far the most important factor in the enormous and widespread acceptance of these drugs in this country was the way the medical profession perceived this class of drugs as a panacea. As an illustration of this, in 1946 a physician by the name of W. R. Bett wrote an article in which he asserted that there were 39 clinical utilities for this drug.

It was a virtual panacea. It was said to be useful for such diverse syndromes as hiccups, irradiation sickness, hypertension, "caffeine mania." and schizophrenia.

At the present time the medical profession is somewhat divided on what it believes are appropriate utilities of this drug.

Certainly obesity is the condition for which amphetamines are most commonly prescribed, but before I discuss their efficacy in the treatment of this condition, I will briefly consider some of the toxic effects of emphetamines.

Now, of all the myths surrounding the amphetamines, that of their alleged "non-addictiveness" is today the most transparent, even though when these drugs were first introduced they were almost universally hailed as having little or no addictive potential.

I am reading now from the bottom of page 7.

This is not surprising; almost every drug which is now condemned as addictive was vouchsafed by the official medical establishment as extremely useful and nonaddicting when it was first introduced.

For example, when morphine was acetylated in 1898 the new drug was heralded as a nonaddictive cure for opium and morphine addictions.

In fact, enthusiasm was so high that the drug's name was taken from "hero"—it was called "heroin."

Accordingly, the only surprising fact about the controversy over the addictiveness of the amphetamines is that it has persisted for so long, despite early strong evidence that these new drugs were substances which were especially euphorigenic.

Indeed, cases of addiction were reported almost immediately, but the drug industry was so successful in reinforcing and sustaining early medical enthusiasm that even as late as 1958 C. D. Leake categorically

stated that "No clear case of addiction to d-amphetamine has been reported."

However, Leake admitted at the very end of his book that he had not become aware of the Japanese situation until "this book was in galley proof."

During World War II millions of Japanese soldiers, aviators, sailors, and civilians engaged in defense. munitions, and government work took tons of "wake-amines," especially methamphetamine—sold as "philipon."

After the war military stockpiles of amphetamines flooded an exceedingly depressed and disillusioned but determined and growth-oriented civilian population, and the immediate result was the overnight eruption of an unprecedented epidemic of drug abuse and addiction.

By 1954 it was estimated that there were 500,000 to 1.5 million Japanese amphetamine abusers, about half genuinely addicted.

Despite the minimization of the amphetamine abstinence syndrome in the medical and lay press, and the parallel exaggeration of the unpleasantness of the average heroin addict's abstinence syndrome, withdrawal from amphetamines can be most distressing.

Since the individual who is "crashing" from high-dose amphetamine abuse appears to be sleeping well a good deal of the time, he is often considered to be merely exhausted.

But the picture of the amphetamine abstinence syndrome that has recently emerged is as unpleasant and painful as the traditional reputation of heroin withdrawal.

Extreme lethargy, fatigue, anxiety, terrifying nightmares, and suicidally severe depression are common.

The individual is usually completely disoriented, bewildered and confused. He is apt to be extremely irritable and demanding—which drives people away just when he most needs their help.

His psychic disruption and loss of self-control may lead to violent acting out of aggressive impulses. He has headaches, he has trouble breathing, he sweats profusely, and his body is racked with alternating sensations of extreme heat and cold and excruciating muscle cramps.

He characteristically suffers painful gastrointestinal cramps. Especially if he is alone, and despite his sometimes incredible hunger, he often lacks the strength to eat at all, aggravating his condition through malnutrition.

As early as 1935 reports began to appear in medical journals suggesting that "Benzedrine" might cause serious cardiovascular disturbances. The following year the first such concrete evidence was published by E. W. Anderson and W. C. M. Scott, who administered "therapeutic" doses—10 to 30 milligrams—of "Benzedrine" to 20 "physically fit" and "normal" subjects in a controlled laboratory experiment.

Almost without exception their subject exhibited pallor and flushing, palpitations, and changes—usually marked increases—in pulse rate and blood pressure.

Now, 10 to 20 milligrams is not an uncommon dose for someone to take who is being treated for obesity.

In six cases the effects were more severe and included collapse, multiple extrasystoles, heart-block, and pain in the chest radiating into the left arm.

From 1939 to 1962, at least 54 cases of acute physical amphetamine poisoning were published in the American and British literature, and many reports came in from nations like Japan and Sweden, where severe intravenous amphetamine epidemics broke out earlier than in this country.

In addition, in 1962, B.H. Ong noted that in 1958 alone 38 separate cases of acute amphetamine poisoning in children under 5 years of age had been reported to the Boston Poison Information Center.

Similarly, 52 different cases of very young children suffering from acute physical reactions to amphetamine were admitted to one Toronto hospital from 1960 to 1963.

P. H. Connell, searching for instances of amphetamine psychosis up to 1956, noted that all but 10 of 92 cases also suffered moderate to severe physical signs and symptoms, including flushing, pallor, cyanosis, fever, tachycardia, serious cardiac problems, markedly elevated blood pressure, hemmorhage or other "vascular accidents," nausea, vomiting, difficulty in breathing, tremor, ataxia, or loss of sensory abilities, twitchings, tetany, convulsions, loss of consciousness, and coma.

Mr. GORDON. How do the children get the drugs?

Dr. GRINSPOON. The children get the drugs accidentally; taking them out of medicine cabinets is the most common way.

Mr. GORDON. But they are not prescribed for children?

Dr. GRINSPOON. No, except for hyperkinetic children. Mostly they are accidentally ingested.

Since high-dose and/or intravenous abuse of amphetamines has become increasingly more popular since the early 1960's, a whole new spectrum of serious physiological reactions have been reported.

By 1966 cases of severe serum hepatitis resulting from intravenous abuse of amphetamines were being regarded as fairly common occurrences: One physician reported that at least 11 cases had resulted from a 2-day "meth party" in Salt Lake City that year. At about this same time several independent Japanese, British, and American investigators began to speculate that intravenous abuse of speed could cause permanent or long-term brain damage.

In 1970, the first clinical evidence of this was reported by a team of California researchers headed by B. P. Citron, who had observed 14 young drug abusers suffering from "necrotizing angiitis," a disease characterized by widespread small blood vessel deterioration, including rupture of the vessels supplying the brain.

Although the researchers could not conclusively prove that methamphetamine was the only cause they did note that all but two of the 14 admitted to intravenous abuse of methamphetamine, that one of the 14 had used speed exclusively, and that all four of the patients who died had been heavy speed abusers.

Mr. GORDON. If I may interrupt, the FDA has prohibited parenteral methamphetamine to be marketed for obesity.

Now, as I understand it, methamphetamine is soluble in water, is that correct?

Mr. GRINSPOON. That is correct.

Mr. GORDON. How meaningful is this prohibition?

Dr. GRINSPOON. Anybody who wants to abuse it intervenously can dissolve amphetamine in water and inject it.

In fact, there is greater risk in doing that than there is with pharmaceutical materials which are sterile and carefully prepared.

Homemade intravenous injections are not, so there is more danger there.

Not only can they inject only the amphetamines, but it may be coupled with something else, and in fact, a number of young people have done this, and particles in the retina of the eye have appeared, which have been visualized on examination by ophthamologists.

Furthermore, they pointed out that they had found no evidence of necrotizing angiitis in a number of similar young drug abusers who had not taken amphetamines, but had used equivalent amounts of all the other "hard" drugs reported by the 14.

In late 1971, two papers by another group of California researchers led by C. L. Rumbaugh presented observations and experimental findings that have all but conclusively proved Citron's initial theory.

These investigators subjected 19 multiple-drug abusers ranging in age from 16 to 39 to cerebral angiography, an X-ray technique in which a dye is injected into a patient's circulatory system, allowing physicians to examine him for possible blockage of the arteries supplying his brain.

Rumbaugh and others found that 14 of their 19 patients showed moderate to severe occlusion, and the other 5 showed at least minimal brain damage of this sort.

Although all of the patients either admitted to or were suspected of amphetamine abuse, they had abused so many other drugs that it was impossible to blame speed as the sole or primary etiological agent.

Accordingly, Rumbaugh and others administered methamphetamine by needle to five monkeys at dosages roughly equivalent to 50 to 100 milligrams for humans.

Ten minutes after the first injections the researchers noted decreased caliber of many of the smaller arteries supplying the brain, with either slowing or total blockage of blood flow in some arteries in four out of five monkeys. At the end of 2 weeks of every-other-day injections, autopsies revealed irreversible damage to the brain. Rumbaugh has recently pointed out that these investigations and laboratory experiments strongly suggest that intravenous methamphetamine is the likely cause for the abnormally high incidence of "stroke" victims among the 15 to 25 age group in the Los Angeles area. Rumbaugh stresses that a stroke-type reaction may follow even low-dose oral use of amphetamines, because of the wide variations in susceptibility to the toxic effects of amphetamines.

It is perhaps easiest to grasp a sense of the real dimensions of the psychological dangers inherent in amphetamine use if we consider only the most serious and disruptive effects. Although restlessness, dysphoria, logorrhea (excessive talkativeness), insomina, some degree of confusion, dizziness, transient nausea, tension, anxiety, and fear to the point of acute panic have been reported by a large number of authors, these effects are probably best considered as inseparable components of the amphetamines' alerting, stimulating, and "euphoric" properties. But amphetamine psychosis, even though it was once considered

extremely rare, has undergone considerable reevaluation since 1958, when P. H. Connell published his now famous monograph.

The first medical report to call attention to the possibility of amphetamine psychosis was published in 1938 by D. Young and W. B. Scoville. In the early 1940's there were a few similar reports from Switzerland and Germany, but very few evaluations of amphetamine psychosis had been published before Connell's pioneering work. Reviewing all the French and English literature, he was able to find only 36 cases. O. J. Kalant, in a subsequent review of the international medical literature up until the publication of Connell's book, uncovered 35 additional cases.

But even if Connell had come across more reports, he probably would have persisted in his motivating insight regarding the strikingly close clinical symptomatology presented by patients suffering from amphetamine psychosis and paranoid schizophrenia.

Accordingly, he launched a personal 3-year investigation of patients admitted to five London hospitals, and discovered 42 unmistakeable cases of amphetamine psychosis that would have otherwise undoubtedly gone undetected.

In addition, colleagues who learned of his efforts reported another 14 substantiated cases to him.

Connell stressed that, despite his earlier suspicions, he was quite surprised to find such a relatively high incidence of amphetamine psychosis.

Connell's findings stirred interest and more exact diagnosis. In the 5-year period immediately following his book's publication, 118 more cases of amphetamine psychosis were reported, as compared with only 71 in the 20 years after Young and Scoville's initial report.

Mr. GORDON. Is there any way of ascertaining in advance a person's susceptibility to the toxic effects of amphetamine?

Dr. GRINSPOON. There is none.

Mr. GORDON. If not, then how can a physician who prescribes these drugs adhere to the medical doctrine of "Primum non nocēre"; that is, first do no harm?

Dr. GRINSPOON. Well, as I mention at the close of my statement, I think that is the way in which physicians have not been as responsible about these drugs as I believe they should be.

Now, it is true there are some people who are particularly vulnerable to the effects of amphetamines.

For example, someone with a congenital vascular problem in the cerebral circulation; but generally speaking, these people are unknown until an accident occurs.

One just does not know it if the patient happens to be a person who is particularly susceptible; there is no way of knowing in advance.

If he has a history of it, then you do know, but certainly a doctor who is quite knowledgeable about amphetamines certainly would not give them to such a person.

I should mention that amphetamine psychoses are so common now that people do not bother to report them.

Prior to Connell's work, it had usually been assumed that only persons who were in some peculiar way "latent schizophrenics" or "prepsychotics" would ever develop psychoses after even massive and prolonged doses of amphetamines.

But Connell strongly opposed this assumption. At least 6 of the 40 patients for whom adequate personal psychiatric histories were available appeared to have been perfectly normal prior to the development of their amphetamine psychoses, and a clear majority were described as "friendly and good mixers," certainly not schizoid personalities.

That a psychosis may be induced in essentially normal people by amphetamines has been substantiated by at least two clinical experiments using human volunteers conducted by a group of researchers at the Vanderbilt Medical School.

In the first experiment, four healthy males between the ages of 25 and 33, who had no previous history of amphetamine psychoses or schizophrenia, and were described by the investigators as having "warm, boyish personality traits" were administered hourly doses of 10 mg dextroamphetamine, unless some significant or potentially dangerous physiological changes were noted.

Two of the patients were able to tolerate "relatively large" amounts of amphetamine for 24 hours, at which point they both developed severe psychoses.

The other two patients were given amphetamine at a much slower rate, because they showed either slight hypertension or fever very early in the experiment.

Since their dosages were low and infrequent, they were both able to withstand the psychosis production effects of amphetamine for 5 days.

However, after 170 hours these two subjects also began to exhibit "unequivocal" and "florid" psychotic symptoms, whose onset was "abrupt" and which included "paranoid ideation which was fairly well organized."

Soon afterward the same group of investigators repeated almost exactly the same clinical experiment, observing the reactions of six male volunteers, aged 25 to 27, who had been judged by an independent psychiatrist to be of normal intelligence and normal—nonschizoid and nonparanoid—personality.

Furthermore, none showed any signs of brain damage or mental abnormalities as judged by clinical examinations, clinical tests, and psychological examinations.

The same procedure was followed as in the earlier experiment, except that doses ranged from 5 to 10 mg per hour.

Because two subjects had experienced a previous amphetamine psychosis, extra precautions were taken, and they were each limited to a total of 110 mg per day.

One of these two subjects was the only one of the six who did not develop a severe amphetamine psychosis. The total cumulative doses of the other five ranged from 120 mg—1 day—to 700 mg—5 days.

The psychoses were almost identical with those experienced by the initial group of subjects.

In commenting on the implications of both studies, the researchers emphasized that even short-term administration of dextroamphetamine to persons who were nonpsychotic could precipitate a paranoid pschosis, and that their experiments definitely ruled out the up till then widely accepted hypothesis that only "previously borderline psychotics" would sustain an amphetamine psychosis.

Senator NELSON. If I may interrupt, when the drug is withdrawn, what happens to the psychosis, what modification?

Dr. GRINSPOON. Yes, the amphetamine psychosis is so close from a clinical point of view to a paranoid schizophrenic psychosis that they very often are confused by clinicians.

Indeed, there are only two ways of making the diagnostic distinction.

One is to get a history of use of amphetamines, and it does not have to be at very high dosage.

More constantly, it is a high dosage, and then for some reason there is usually an increment of dosage just before the psychosis; so if you get such a history, you get a urinalysis, and this has to be done within 48 hours. And I should say the third diagnostic criterion is that in the case of amphetamine psychoses, the psychosis usually disappears within 4 to 5 days. It is certainly gone within a week.

However, there are some patients whose psychoses last much longer, and it appears to me that these are patients whose egos are already pretty fragile, and the straw that breaks the camel's back, so to speak, is the use of amphetamines. This is the exception. Generally speaking the person who has an acute amphetamine psychosis is one who is psychologically pretty well put together and the psychosis will disappear within a matter of days of withdrawal of amphetamines.

Senator NELSON. I noticed in some of the literature before me, there is some indication that the paranoid psychotic may be dangerous to himself and to others under these circumstances.

Dr. GRINSPOON. Yes, that is certainly true.

One of the things I was going to get to, which I will touch on very briefly, is that people have talked about a number of drugs, and their capacity for violent criminal behavior.

The drug which is probably most dangerous from that point of view is actually amphetamines; alcohol is a close second, but amphetamines seem to have as an inherent psychopharmacological property of the drug, a capacity to induce impulsiveness, paranoia, and the need to express some kind of motor behavior, so that people who are paranoid, even before they become overtly psychotic, constitute a danger.

I will skip over the next paragraph and address myself to the problems of obesity.

Obesity continues to be the condition for which the largest amounts of legitimately obtained amphetamines are most casually and frequently prescribed, but despite enthusiastic early reports as to these drugs' efficacy in dietary regimens, expert medical opinion is gradually recognizing that obesity, far from being a semihumorous or cosmetic difficulty, is in fact a complex, long-term problem involving critical psychological and social determinants.

No one really knows its causes. It is defined as a state in which fat accumulates because food intake, in terms of caloric content, is greater than energy output.

Genetic, glandular, and other physical and physiological causes play a statistically small role in obesity—probably in less than 10 percent—usually the obese person simply overeats.

According to one study, only 12 percent of 96 very obese patients attributed their condition to glandular disease; the rest admitted that overeating was the cause and referred to psychological factors like nervousness, family difficulties, and ingrained habits.

Many investigators suggest that obese patients need psychotherapy; otherwise, no dietary regimen or chemotherapy will rectify or control their excessive eating.

Apart from uncommon metabolic aberrations, the principal factors governing appetite are social and psychological.

Some people are trained in childhood to overeat; others move in social and business circles where food and alcohol are present in abundance and one is expected to partake.

With effort, habits can be broken and living circumstances altered. Emotional problems are far more difficult to deal with. Chronic tension and depression unusually strong oral drives, low capacity to delay gratification, and the substitution of food for other forms of pleasure—all common in cases of obesity—increase the likelihood of becoming dependent on drugs, including amphetamines.

Most troubled obese patients will not persist in their efforts to diet. The few who do and lose some weight regain it. A drug that reduces appetite without requiring solving the patient's emotional problem seems a reasonable alternative to what would otherwise be the almost certain failure of these individuals to lose weight if they were to depend solely on willpower.

But the wisdom of such a solution must be examined. Do clinical and experimental studies reliably establish that amphetamine and its congeners have a measureable anorectic effect?

If so, are the benefits great enough to justify their use despite the long-term adverse effects?

For example, this is such a common thing that people eat with certain kinds of mild depression and anxiety.

President Taft, as you may know, only weighed about 320 before he entered the White House, and then he shot up to 400 pounds. After his term in the White House, he was able to go down to his subprevious 320 pounds.

There is still no real understanding of how amphetamine reduces appetite. Experiments with animals have demonstrated that it is not a function of local effects on the gastrointestinal tract. There is some evidence that lesions in the hypothalamus may result in a substantial increase in appetite.

If some obese people actually have a dysfunction of the hypothalamus, it is possible that amphetamines reduce appetite by their effect on this area of the brain.

However, if this mechanism exists at all, it is probably secondary to the central stimulating effect. It has been suggested that diuresis may cause some of the weight loss associated with the use of amphetamine. Both diuretic and antidiuretic effects have been reported, however, and the role of diuresis in true weight loss is far from clear.

Mr. GORDON. You are saying that even if these drugs were effective, they do not really reach out to the basic problem of obesity?

Dr. GRINSPOON. That is absolutely correct. They do not solve the basic underlying problem.

Mr. GORDON. Well, the studies that were done on these antiobesity drugs were short-term studies, 8 to 12 weeks.

How do we know whether the people who were using the antiobesity drugs, did not go back to their former eating habits and regain weight?

Dr. GRINSPOON. As a matter of fact, I am about to get to that.

In 1938 a research group led by Poul Bahnsen compared 100 normal subjects receiving amphetamine with an equal number receiving placebo; 19 of the active drug group and 1 control reported a reduction in appetite.

The first attempts to apply these observations to the clinical management of obesity were made that same year by M. F. Lesses and A. Myerson, and by P. Rosenberg in 1939; both papers reported favorable results.

Since then a long series of reports and clinical studies has agreed with them. For example, S. C. Harris, A. C. Ivy, and L. M. Searle found that seven obese patients lost more weight when taking amphetamine than when taking placebo.

Those who lost most were the ones who ate least, so the main cause of weight loss was apparently suppression of appetite rather than something like higher activity level.

Harris also conducted another experiment in 1947 to investigate the possibility that weight can be lost with amphetamines even when caloric intake is maintained.

Ten volunteer medical students agreed to eat 3,000 calories per day. During weeks 1 and 2, the students received no medication, and during weeks 3 and 4, they received placebo.

During this control period totaling 26 days, there was an average weight loss of 0.7 pounds. This the authors attribute to the fact that for some of the subjects a 3,000-calorie diet was inadequate to maintain body weight.

For study weeks 5 to 13, half of the students received 10 milligrams of dl-amphetamine before each meal, and the other half received 5 milligrams. During week 5, the subjects in both groups lost an average of 1 pound. However, the amounts leveled off quickly, and the total average loss for the active medication phase was only 1.85 pounds. The authors concluded that reduction of caloric intake, not increase in motor activity or metabolic rate, is the essential variable in weight loss from amphetamines.

Another useful study was conducted by D. Adlersberg and M. F. Maver on 299 obese patients who were being treated in a clinic of a large general hospital.

Treatment groups were arranged as follows: Group A patients were treated with dietary restrictions alone; group B began with this, but after 2 to 5 months oral thyroid medication—2 to 3 grains desiccated thyroid daily—was added; and group C, after 3 months of dietary restriction, received amphetamine sulphate—5 to 10 milligrams twice daily, 1 to 2 hours before lunch and dinner.

Although all three groups lost weight, group C—diet plus amphetamine—was the most successful. However, dosages had to be increased over time to maintain weight loss and overcome tolerance.

A useful contribution of this study is the authors' attempt to differentiate between long- and short-term results.

The most impressive weight losses for all three groups occurred in the first 1 or 2 months. Overall, amphetamines emerged as superior to the thyroid regime: but interestingly, in the long run diet alone compared favorably with diet and amphetamine.

Further data on tolerance are supplied by Gelvin and McGavack, who studied 27 obese patients attending the Welfare Island dispensary. They took an initial dose of 15 milligrams of Dexedrine per day, rapidly increased to a maximum of 30 milligrams, and were permitted to eat as they pleased.

After 8 weeks, 47 percent were maintaining a weight loss of 1 pound per week; after 12 weeks, only 23 percent continued to lose even that much.

Twenty weeks after the beginning of treatment only one patient was still losing weight.

The use of amphetamine to correct faulty eating habits has been suggested, but studies with animals have shown how difficult this is. Harris gave intramuscular injections—2.5 to 20 milligrams d-amphetamine sulphate—to dogs 1 hour before feeding, with the result that food intake was substantially decreased.

In the case of one dog—16 kilograms in weight—who was given injections of 10 milligrams per day, food consumption was reduced by 87 percent and body weight by 27.4 percent within 32 days.

After 30 days, an injection of saline solution was substituted for the amphetamine. The animals' appetite immediately increased greatly; obviously conditioning by the amphetamine regime could not be sustained without the anorectic effect of the drug itself.

Similarly, the experience of most physicians treating patients for obesity suggests that little long-term learning effect can be attributed to the amphetamine regime; most patients, once they stop using amphetamines or become tolerant to them, resume their former eating habits.

A second series of papers on obesity and amphetamines emerged in the 1950's, heralding the use of combination drugs in which amphetamine was supplemented with a barbiturate, in most instances amobarbital.

The advantage was reported to be an easing of the emotional extremes found in obese patients.

These studies, most of them uncontrolled and methodologically unsound, stated that patients lost weight, as with amphetamine alone, but also improved in mood.

No data indicated that the combination drugs were any more effective than amphetamines alone.

In the late 1950's a third series of studies began to appear, dealing with the effectiveness of new amphetamine congeners or new forms—for example, "timed release" packaging—of already existing amphetamines.

These drugs all share the same basic chemical skeleton and have effects, including adverse ones, very similar to amphetamine sulphate, although it was claimed for one drug after another that it had fewer "side effects."

W. Modell writes that:

> It seems unlikely that any minor structural change in this group which continues the same theme will separate the action that may be clinically undesirable. Yet it is precisely this which is inferred from many claims made for these drugs, namely the recurrent claims for reduced incidence of insomnia, anxiety, and nervousness, with potent anorectic effect.

Still, they were sometimes compared with dextroamphetamine or a combination drug and found superior.

I. H. Kupersmith conducted what he termed a "comparative clinical investigation" in which he employed ephedrine-ethylenediamine complex, d-amphetamine sulphate, d-amphetamine sulphate with a barbiturate, and placebo.

The weight changes per month in descending order were −11.3, −7.7, −3.0, and +1.2 pounds. In their eagerness to establish the superiority of the new amphetamines many authors failed to build even minimal controls into their research designs.

The Kupersmith data come from three different groups of subjects at different times and places. The only demographic data he includes are that they were "overweight subjects" or "overweight patients."

From such data it seems likely that the most important independent variable was the researcher's desire for the results to come out as they did.

A 1959 article by S. C. Freed and E. E. Hays on the drug Ionamin is representative of the kind of anorectic drug evaluation reports that have appeared in reputable medical journals during the last 35 years.

The authors do not indicate how their subjects were selected, but it is apparent that they did not use any nondrug, placebo-administered, or even dextroamphetamine-treated control group or attempt to follow-up their patients after cessation of Ionamin treatment.

Furthermore, the data they present are sparse and incomplete; they do not even provide information on how obese any of their subjects were before beginning their drug and diet regimens.

From the limited data they supply, we can calculate that one group of 60 patients treated with fairly high—30 milligrams daily—doses of Ionamin lost an average of less than 7 pounds over the 1-month period.

This is not very convincing when one considers that the weight of many people who are not taking any drugs or making any effort to lose weight may fluctuate almost as much as this in a month and still be well within normal limits.

The authors also minimized the "side reactions" to Ionamin, asserting, for example, that the insomnia often experienced was "somewhat different from that occurring during amphetamine therapy," in that and the psychological impact of a new therapy. But even if we compared to the nervous overexhilaration which (has) * * * prevented sleep following amphetamine treatment."

If this statement deserves any credence—not that it necessarily does—it suggests that Ionamin is more likely to lead to drug abuse than racemic amphetamine; people generally do not persist in taking drugs they consider unpleasant.

Freed and Hays claim that Ionamin is "chemically and pharmacologically different from amphetamine." However, the following year W. Modell emphasized that:

> Phenyltertiarybutylamine resin * * * advertised as not being an amphetamine drug, is a carboxylic acid-type of exchange resin which contains substituted phenylbutylamine moieties that are released in the gastrointestinal tract.
>
> As shown in the formulas, the amine itself clearly belongs to the amphetamine series.

Ten years later, he devoted only two brief sentences to the alleged unique mode of action and value of Ionamin in his comprehensive and

objective edition of *Drugs of Choice:* "All systemic effects, therefore, stem from an amphetamine-like action. There is no good evidence that this is in any way a superior member of the group." Not surprisingly, the drugs used by Freed and Hayes were supplied by the manufacturer.

The vast majority of the clinical investigations on the anorectic effects of amphetamines yield, to one degree or another, favorable results.

This judgment must be qualified, however, because excellent results are obtained in the early stages of almost all types of treatment because of the initial willingness of subjects to cooperate with a new physician and the psychological impact of a new therapy. But even if we consider amphetamines generally useful in this respect, and I certainly do not, we must still come to grips with the question of adverse effects.

Much of the obesity literature minimizes the number and severity of these effects or actually states that there are none.

Finch, for example, claims that:

> Dexedrine sulphate is a nontoxic safe drug which may safely be used in obstetric patients to aid them in preventing excessive gain of weight.

Studies like this have led to large-scale prescription of amphetamine to pregnant women when there is evidence that it may be a teratogenic agent.

An amphetamine derivative called fenfluramine, sold in the United Kingdom, Europe, and Australia as "ponderax," seems to be a highly specific appetite suppressant with low CNS—stimulating and euphoric properties and low-addictive potential.

Even so, Oswald and his coworkers cautiously conclude only that it *may* be preferred to other amphetamines.

They emphasize that:

> Most slimming pills are also "pep pills" and invite abuse. Past experience leads to scepticism when claims are made that a new appetite-reducing drug does not affect alertness or mood.

Other clinicians, mindful of amphetamines' potential for harm, assert that in weight reduction the exposure is limited to a relatively short period.

But, though this may be the intention, it often does not turn out that way.

People who have problems controlling their need for constant gratification, as indicated by compulsive eating, find it hard to put aside a medication that makes them "feel good."

What is more, many patients consider their attempt to lose weight doomed to failure once they have lost this "magic" potion that protects them from themselves.

When the drug is discontinued, a psychological vacuum is created which has to be filled with food. On occasion, patients have gained back even more weight than they lost, a condition commonly known as the "rebound phenomenon."

So, although short-term use of the drug causes a short-term weight loss, it also helps the patient avoid the issue of changing his eating habits.

I doubt the wisdom of using amphetamines for weight reduction under any circumstances. Although they can cause a 3- to 4-week euphoric "high" that may have as one of its "side effects" a diminished

food intake and consequent weight loss, after this period they are no longer effective as anorectics unless the user increases the dose, thus initiating a pattern of abuse.

And after use is discontinued, the average person quickly gains back the weight he lost—or more.

In short, there seems to be few conditions which justify the prescribing of amphetamines; the exceptions are a very select group suffering from certain varieties of narcolepsy and a number of truly hyperkinetic children, and in these cases amphetamines should be prescribed only after a careful weighing of their potential dangers against their possible value.

Mr. GORDON. Doctor, as far as the needs of the people with narcolepsy, there are alternatives to amphetamines, are there not?

Dr. GRINSPOON. That is correct.

But it is not an antiobesity drug. It is not used as an antiobesity drug. I would suspect that if it might, one could then conceive of a drug company taking and promoting its anorectic factor, and using it in treatment of obesity.

That is what has happened with so many of these drugs with what were originally considered to have so-called side effects; let us say a patient in the 1930's was treated for depression with amphetamines, and then it was noted that the drug had an anorectic effect. It was considered a side effect, a bad effect, because indeed you did not want to have a patient with this kind of depression, especially where he was not eating, to have any of this side effect.

Mr. GORDON. When you referred to the amphetamines in your presentation, you also included amphetamine-related drugs?

Dr. GRINSPOON. Yes.

Mr. GORDON. Fenfluramine is a little different?

Dr. GRINSPOON. Yes.

Mr. GORDON. As a matter of fact, in an article that appeared in Clinical Pharmacology & Therapeutics in 1975——

Dr. GRINSPOON. Is that the John Griffith article?

Mr. GORDON. It is by Griffith and Jasinski.

Dr. GRINSPOON. All right.

Mr. GORDON. Dr. Jasinski is going to testify tomorrow. He likens fenfluramine to LSD rather than amphetamines.

Dr. GRINSPOON. Yes. You see, one of the things I did not get into is that this simple molecule has an extraordinary way of being modified in the laboratory.

It is estimated there are potentially 2,000 amphetamine derivatives.

We have only begun to open the door to these drugs.

Now, one whole area of modifying this molecule is in the direction of the so-called hallucinogenic amphetamines.

There are a number of drugs on the street now which are in fact, used by many people who are interested in psychedelic experiences, and some of these drugs are in fact amphetamine derivatives.

Fenfluramine seems to be a drug which is sort of midway, pharmacologically midway between the more established amphetamine drugs and hallucinogens.

It seems to bridge those two general classes.

Mr. GORDON. Now, if it is so easy to concoct a lot of different types of drugs that are related to amphetamines, would it not be your opin-

ion that we better do something about these drugs right now, before they proliferate on the market?

Dr. GRINSPOON. There is no question that something ought to be done about them, and there is no question that they will proliferate, not only in terms of numbers of any individual drug being available, but in terms of the actual kinds of drugs; new synthesized versions of these drugs are going to be around in the future, there is no question about it.

The problem is what to do about it, because, you see, the other thing about the simplicity of this molecule is that anybody who has taken an organic chemistry course in college can buy some very simple equipment, for about $25 and set up what is called a garage speed laboratory, where illicit amphetamines are produced.

It is very simple to produce it that way, and one cannot talk about banning the basic ingredients that are so commonly needed and used in industry; there is no way of preventing the development of illicit amphetamine laboratories.

Let me finish the last couple of sentences of my statement.

Individual physicians—not only psychiatrists, but specialists in all areas, as well as general practitioners—who have overprescribed amphetamines in the past should be willing to recognize how they may have denied a patient help for his real problem in the very act of complying with his overt request for a pill.

The near-epidemic extent of amphetamine abuse which exists in this country today is at least in part a result of the medical community's basic unwillingness to recognize that fulfillment of its first responsibility is not always identical with the most immediate alleviation of pain and suffering.

That concludes my prepared statement.

Senator NELSON. Thank you, Dr. Grinspoon.

I have some questions which I think I will withhold for the whole panel until all of the testimony is in, so that each of you may wish to comment.

Our next witness is Dr. James J. Nora, professor of pediatrics and director of pediatric cardiology, University of Colorado Medical Center, Denver, Colo.[1]

You may proceed, Dr. Nora.

STATEMENT OF JAMES J. NORA, M.D., PROFESSOR OF PEDIATRICS AND DIRECTOR OF PEDIATRIC CARDIOLOGY, UNIVERSITY OF COLORADO MEDICAL CENTER, DENVER, COLO.

Dr. NORA. Senator Nelson, Mr. Gordon, ladies and gentlemen, my charge, as I understand it, is to speak to the possible role that amphetamines and related drugs may play in the production of birth defects, if there is exposure at a vulnerable period of embryonic or fetal development, and if there are both a genetic predisposition to react adversely to these drugs and a genetic predisposition to some form of maldevelopment.

All of the qualifications of the previous sentence must be applied to amphetamines and to most potential teratogens.

[1] See prepared statement and attachments of Dr. Nora beginning at p. 14913.

Mr. GORDON. Is it possible to ascertain in advance whether a person is predisposed to react adversely to amphetamines?

Dr. NORA. This is an area for the next couple of decades of work, determining who is at risk for development of the various birth defects, who is at risk to respond adversely to certain agents.

I think that one area where it has been pursued a great deal, and must be pursued a great deal more, is to find those things in the environment that will produce coronary heart disease.

It is not quite as far advanced in the areas of birth defects, and in identifying the individuals at risk.

Unfortunately, there is no simple skin test or blood test that would help us identify who would be at risk in taking amphetamines.

Fortunately, there are few agents in our environment that possess the disastrous teratogenic potential of thalidomide or rubella virus. And, conversely, under the right combination of genetic predisposition and exposure at a vulnerable period of development, one could project that almost any agent that has pharmacologic activity could be teratogenic.

Between these extremes, I believe there exists a number of agents causing birth defects in enough susceptible individuals to constitute a significant health hazard. It is in this latter category that I believe dextroamphetamine may belong.

Some of my coworkers and I have devoted a not inconsequential portion of our research activity to investigating such teratogens, which are difficult to identify in the epidemiologic sense.

To give an example: Thalidomide causes malformations, including a rare sentinel anomaly, phocomelia, in 50 to 80 percent of infants who have had a maternal exposure during the vulnerable period of embryogenesis.

With these factors in favor of prompt detection of the teratogen, thalidomide was on the market for over 2 years before the first suspicions about its safety were voiced.

How much more difficult is it to implicate a "low risk agent" that causes maldevelopment in only 1 percent of exposures?

Yet, if the exposures are frequent, say, in 10 percent of pregnancies, then 3,000 malformed infants would be delivered in the United States each year as a result of taking such a "low risk agent."

The pitfalls in conducting epidemiologic studies that will yield a confident answer as to whether or not an agent is teratogenic are many.

In brief, precise verification is essential in both retrospective and prospective studies. But, even with careful verification, the possibilities for systematic bias and the limitation in the type of data obtained—no population frequency rates—make retrospective studies less conclusive than prospective ones.

The published studies of the potential teratogenicity of amphetamines are retrospective.

Prospective studies, in which one could be more confident, have not been done. The reason is simply this: Prospective studies require many more patients and no one to date has accumulated a large enough series to address this question prospectively.

Senator NELSON. Have there not been animal studies?

Dr. NORA. Yes; and I will discuss this in detail a little later, but the proper study of mankind is man and what one finds in an animal may not really relate too well.

Senator NELSON. It is difficult to conduct such studies on humans, but in the case of animals, is it not possible to get relevant data?

Dr. NORA. The traditional animal models do not always yield the data one desires. Thalidomide did not yield the patterns that were found, and in some species it was not teratogenic at all in these traditional models, and yet it turned out to be disastrous in humans, so you can get some peripheral evidence, and I will discuss this in a little bit.

Senator NELSON. It may not be relevant, and it may be a long time ago, but I recall in one of the cases where it was indicated there was very serious side effects of thalidomide, and they dropped these investigators and got some others, and I do not recall what the investigators found that aroused their suspicions to warn the company, but I do recall it was those investigators.

Dr. NORA. The investigators getting positive results probably were using an animal model appropriate to the study, and the best animal model is a primate of some sort which is more closely related to a human.

Mr. GORDON. Is it not also correct that the results of animal studies resulted in the FDA's withholding marketing approval for thalidomide?

Dr. NORA. That could be one of the influences. I am not privy to what went on at that time.

We have considered that amphetamine provides a good model to illustrate the obstacles in the way of reaching confident conclusions about the presence or absence of teratogenic effect of a given agent.

Our own experience with this drug may be summarized briefly. In 1962, the mother of an infant born with transposition of the great vessels—a complex and frequently fatal congenital malformation of the heart—expressed more than the usual concern about the cause of the heart defect in her infant son.

She volunteered that she had taken amphetamine diet pills during her pregnancy and asked directly if the amphetamine could have caused the problem.

We were unable to find any evidence in the literature of such an association and so reassured the mother.

But within 2 weeks we encountered two more such cases of transposition and first trimester exposure to amphetamines.

These three cases represented a very provocative epidemiologic cluster.

At this point we began three studies:

1. A retrospective study to compare histories of maternal exposures to amphetamines in congenital heart patients and in normal children;

2. An animal homology study to see if we could produce transposition of the great vessels giving amphetamines to mice and chicks: and

3. A prospective study, starting with mothers prior to delivery who had documented amphetamine exposure in the first trimester and were awaiting the outcome of their pregnancies.

We reported the results of the animal studies in mouse first, and in mouse, chick, and drosophila later.

Amphetamine produced malformations in all three models. But this doesn't mean it produces malformations in humans.

The fact that three phyla were affected, and that two strains of one species were also affected was suggestive of the teratogenic potential of the drug.

An unexpected finding that greatly influenced our thinking about the etiology of congenital heart diseases in general was that in one species of mouse we caused ventricular septal defect and in another species we caused atrial septal defect.

We were unable to produce transposition.

It appeared that amphetamines brought out the malformation to which the strain was predisposed. And it was this observation that led us to the belief that there must be a predisposition—a malfunction and a predisposition—to react adversely to an agent which must be given at the vulnerable period of development as the three essentials of teratogenesis.

The first retrospective study of congenital heart patients was inconclusive. We did not find a statistical difference at the 0.05 level. After publishing these findings we redesigned our protocol, admitted younger patients into the study—to reduce material memory bias—and tightened our verification procedures.

We tightened our verification procedures and made absolutely sure that there was adequate evidence from more than one source that the person did indeed have the drug at the time she was supposed to have taken it.

After 2 more years we analyzed our new data, found a statistically significant difference between the congenital heart and control groups, and were forced to retract our previous report that there was no significant amphetamine influence in congenital heart disease.

Thus two studies by the same investigators led to opposite conclusions. We believe the second study to be the more reliable one.

It has already been pointed out that retrospective studies are less conclusive than prospective ones, so we put our eggs in the basket of a large obstetrical practice that used amphetamines liberally.

I carefully avoided telling the obstetricians which of the many drugs on our questionnaire we were most interested in, but a medical student working with me spilled the beans and the obstetricians immediately stopped using amphetamines and lost interest in our project.

By the way, that was at a time when malpractice insurance was $60 per year. You can imagine what a threat such studies are now. We did publish a small prospective study of 240 patients, eight of whom delivered infants with malformations, three of which were associated with maternal exposure to amphetamines.

The loss of a prospective study of sufficient size was probably of positive benefit to the patients, but it has obviated our reaching the confident conclusions we desired.

Since I have brought up the subject of malpractice suits, I would like to call attention to a trend which I consider to be indefensible.

From the number of communications I receive from legal firms all over the country regarding the role of maternal drug exposure in birth defects, it appears that some of our legal colleagues believe that the

way to demonstrate that a drug is a teratogen is through passionate litigation rather than through dispassionate investigation.

The idea has been fostered that one need only to demonstrate the possibility that a given agent could have caused a malformation in an individual. But as I have said, and I believe that most teratologists would agree, under the right conditions almost any drug can be teratogenic.

However, the question we are addressing here is whether or not amphetamines cause birth defects to the extent that they represent a significant health hazard.

From our retrospective data and the peripheral evidence from experimental studies of mechanisms of action in animal models, I would give a qualified yes to the question.

There have been a number of other retrospective studies published by other investigators of teratogenic effects attributed to amphetamines and related sympathomimetic drugs, such as phenmetrazine.

Levin found a significant increase in biliary atresia following maternal exposure to amphetamines, and we have some confirmation of this in our study.

Matera and coworkers reported an infant with exencephaly, which is one of the prominent malformations we found in our mouse studies, so here again animal studies offered supportive but not conclusive evidence.

Nelson and Forfar in a retrospective study of 1,369 patients found an excess of infants with maternal exposure to appetite suppressants among those with abnormalities.

Lenz found a case of diaphragmatic hernia and Powell and Johnston, two cases, following maternal phenmetrazine administration.

Moss found limb anomalies in the infant of a mother who had taken phenmetrazine.

It should be noted that all of these studies are retrospective and some are merely case reports, but they contribute to a sizable volume of evidence which supports the possibility that these drugs are teratogenic, despite the fact that the definitive prospective study has not been performed.

If appetite suppressants, which is just a polite term for "uppers", had a useful function in the medical armamentarium, one could not accept the present retrospective data as sufficient evidence to abrogate the use of these drugs.

We are currently trying to resolve the problem of conflicting retrospective data regarding birth defects and the "Pill" and various progestogens and estrogens through a prospective study.

The point is: The world needs the "Pill" or some agent that can perform its function equally well.

I am frankly unable to identify a similar need for amphetamines and related drugs.

Mr. Chairman, the references to my prepared statement follow.

Senator NELSON. Are you saying you find no need for amphetamines at all?

Dr. NORA. I am not finding it the way the world needs the "Pill."

I think there is no great need for appetite suppressants, but the type of need we have is for some medications that are for very specific indications, such as narcolepsy and hyperkinesis.

I think you have to look at the risk/benefit ratio.

I think the risk/benefit ratio to the use of amphetamines as appetite suppressants is very, very unfavorable.

Senator NELSON. I will ask the panel to address that question when we conclude the testimony.

Dr. NORA. Thank you, Mr. Chairman.

That concludes my prepared testimony.

Senator NELSON. Our next witness will be Dr. Thaddeus Prout, associate professor of medicine, Johns Hopkins University and chief of medicine, Greater Baltimore Medical Center, Baltimore, Md.

Dr. Prout, you may proceed.

STATEMENT OF THADDEUS E. PROUT, M.D., ASSOCIATE PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, AND CHIEF OF MEDICINE, GREATER BALTIMORE MEDICAL CENTER, BALTIMORE, MD.

Dr. PROUT. Thank you, Mr. Chairman.

I appreciate the opportunity of being here.

In order to save time since I know you have a tight schedule, I will place my prepared statement on file, restrict my comments to one or two areas of importance.

Senator NELSON. Your statement, Dr. Prout, will be printed in full in the record, and you may comment extemporaneously, or however you desire.[1]

Dr. PROUT. Thank you, sir.

First, I place in the record the conclusions and the recommendations of the Committee for the Evaluation of Anorectic Drugs of the FDA, of which I was chairman.

The committee had recommended that all of the anorectic drugs with abuse potential be placed in schedule II of the Comprehensive Drug Abuse Act.

Senator NELSON. You are talking about amphetamines that are already there. Are you also talking about the related drugs?

Dr. PROUT. All of these drugs were not there at that time, and we were addressing ourselves to those that were not. We found no reason to conclude that they should not be placed in schedule II also.

Senator NELSON. That was the recommendation?

Dr. PROUT. Yes. The study had been undertaken to study the possible benefits of these drugs in obesity.

Senator NELSON. Which committee is that?

Dr. PROUT. This was an ad hoc committee appointed by the FDA under my chairmanship.

Senator NELSON. When was that recommendation made?

Dr. PROUT. In the fall of 1972.

Senator NELSON. They are all related?

Dr. PROUT. All had abuse-potential with one exception. But some of the comments this morning were pointing that our knowledge may change and fenfluramine which was believed to be an exception may now come under the same suspicion. At that time it was a new medication, and we did not have sufficient evidence to see that it might have an abuse potential as well.

[1] See prepared statement of Dr. Prout beginning at p. 14921.

Fenfluramine is less of a central nervous system stimulant than the other drugs in this class. If anything, it appeared to have a depressing effect, but that in itself raised the question of whether it might have abuse potential in some other way. I think the comments this morning have pointed out that the continued surveillance of this drug class might have some merit——

Senator NELSON. You said this is an ad hoc panel?

Dr. PROUT. Yes, an ad hoc committee of the FDA.

Senator NELSON. Selected by whom?

Dr. PROUT. Selected by the Commissioner, I presume.

It was selected in part from the Committee on Endocine and Metabolic Drugs, of which I am also chairman.

Senator NELSON. And the recommendation was that all of the amphetamines and related drugs be put in schedule II? That was a unanimous recommendation?

Dr. PROUT. Yes, it was a unanimous recommendation.

These recommendations, Senator Nelson, are listed verbatim on page 3 of my prepared statement.

Senator NELSON. Page 3?

Dr. PROUT. Yes, of my prepared statement.

Senator NELSON. And those recommendations were made in 1972?

Dr. PROUT. Yes, in the fall of 1972.

Senator NELSON. So that is 4 years ago?

Dr. PROUT. Yes.

Senator NELSON. Has the FDA taken any action that you are aware of in respect to those recommendations?

Dr. PROUT. Some, but not all of these medications have been placed in schedule II, and they appear to have drawn the line between those that had an abuse potential, and those already known to be under abuse in the street.

The FDA apparently saw themselves as a surveillance agency that could in fact watch street traffic, and, if necessary act on the basis of new information by rescheduling the agents in III and IV to schedule II if necessary.

Senator NELSON. You are identifying in your statement those that were placed on schedule II following the recommendations of the ad hoc committee, and those that were not? Do we have a list of them?

Dr. PROUT. Yes, we do.

Senator NELSON. Are they in your statement?

Dr. PROUT. No; the actual schedules are not in the statement, but they are readily available from the FDA. I could make a reasonably accurate compilation of them, but I think you would prefer to go to the official record.

Mr. GORDON. As I understand it, Mr. Chairman, the amphetamines, phenmetrazine—Preludin—and methylphenidate—Ritalin—which Ritalin incidentally is for weight control, were put in schedule II, and the so-called nonamphetamines such as Ionamin, Pondimin, Tenuate, and others were put in schedules III or IV.

Dr. PROUT. Yes, all of the rest are either III or IV, including the newer ones that were under study at that time.

Senator NELSON. Go ahead.

Dr. PROUT. I think that placing some of these drugs in schedule II had two effects. First, there was a fall in the sales of those which were

actually placed in schedule II. However, this did not completely prevent the abuse of all schedule II drugs. Preludin, for example, still seems to be high on the abuse list, and this is particularly true here in the District of Columbia.

The second effect was predictable. Sales of amphetamine-like compounds which were not placed in schedule II had a marked increase in use with the expected rise in sales.

One of these was cited on national television because of the particularly aggressive promotional techniques of one company and for its rather high increase in sales.

These drugs are now know to be subject to street abuse. If you look back to the list of the recommendations of the committee for the FDA, my first recommendation would again be that all of these drugs with abuse potential be placed in schedule II.

Second, it has been demonstrated that the amphetamines and their related compounds have such trivial effectiveness in the treatment of obesity, that we should look again at questions of whether or not obesity should continue as an indication for their use.

Obesity is the major medical excuse for the manufacture of amphetamines. It now seems reasonable to state that the risk of overproduction of the drugs and their excessive abuse far exceeds the benefits that might be cited in the treatment of obesity. Only a few patients in association with rigid dieting, believe that the so-called anorectic drugs were the causative agent in their weight reduction. Most patients get no benefit from their use and risk the development of addiction.

I would, therefore, recommend that obesity be *withdrawn* as an indication for the therapeutic use of these drugs.

This action has in fact been taken by Canada and some other countries, and in my own State of Maryland. Maryland has a model law that might be duplicated in the Federal statutes.

Senator NELSON. Did you say the State of Maryland?

Dr. PROUT. The State of Maryland has withdrawn obesity as an indication for prescribing amphetamines.

The effect of eliminating obesity as an indication for use and of putting these drugs on schedule II, would in effect take them off the market. Up to 90 percent of the medication appears to be prescribed for obesity and production could probably be reduced to 10 percent or less of present production rates. As a result there would be much less drug to spill over into the street. I believe this would reduce the legitimate manufacture of these drugs by 85 to 90 percent.

Senator NELSON. You are saying 85 to 90 percent of its current use is for obesity, that is, prescribed in the case of obesity?

Dr. PROUT. That is correct.

Of course, we do not know exactly where the product is going and that is another reason for our prime concern. As has been brought out here this morning the production of these medications is far in excess of any use that we might be expected for treatment of obesity, and the other medical indication. Placing them in schedule II, and withdrawing obesity as an indication for their use, would in fact, make a very impressive impact on the amounts of medication available, and it could only be used for the other indicated medical uses from that time on.

Senator NELSON. If I recollect correctly, there are some 70,000

pounds produced amounting to 12 billion pills, was that somebody's testimony?

Dr. PROUT. The testimony this morning was 8 billion units, enough to give 35 doses to every man, woman and child in the United States.

Dr. GRINSPOON. The figure is that it was estimated that it would go to 12 billion.

Senator NELSON. Twelve billion tablets?

Dr. GRINSPOON. Yes; by units, I mean tablets, capsules, what have you.

Senator NELSON. And so you give a ballpark figure, you would be recommending a reduction from 12 billion to 1 billion?

Dr. PROUT. Yes; something in that order. The important thing is that it can be reduced within the year, or certainly by next year.

Senator NELSON. What you are saying is leave it on the market for hyperkinesis and narcolepsy indications?

Dr. PROUT. In the State of Maryland there is a third category of unusual and rare conditions, which is a legitimate use.

This includes a few patients such as those with Parkinson's disease, or other individuals with neurological problems, seen in large clinics, for individuals who have certain forms of pathological obesity, such as the Pickwickian syndrome and for which amphetamines might be used. This syndrome may include narcolepsy as a part of it. There are a number of other rare uses.

Senator NELSON. I was wondering how accurate are the figures that we have on the incidence of hyperkinesis and narcolepsy.

Dr. PROUT. I do not think we have any hard data on the figures, estimates vary from various regions of the country, but the highest I have seen is that 3 percent of schoolchildren may have a "hyperkinetic syndrome."

Dr. GRINSPOON. There was one estimate by HEW, I believe they projected there might be as many as 4 million children who suffered from hyperkinetic syndrome.

I think that is a vast overstatement, but even if one took it as an outside figure, it is very difficult to assess.

The closest we could come to for narcolepsy is a figure of something in the order of 20,000, and I think that is probably a liberal estimate.

Senator NELSON. What are the estimates of the number of patients who are receiving amphetamines for weight control purposes?

Dr. GRINSPOON. I do not know what that number is.

Senator NELSON. Go ahead.

Dr. GRINSPOON. When I said 4 million, that is the number of children who are not being treated. That is the estimate of the number who might be suffering from hyperkinetic syndrome.

Mr. GORDON. My impression is that these drugs are not indicated for hyperkinesis, but rather for minimum brain disfunction as evidenced by hyperkinesis.

There are a lot of kids that are hyperactive. Does that mean we have to give these kids drugs?

Dr. PROUT. Are you asking me?

I personally do not think so, and I think that the 400,000 estimate is probably about the same as the 3 percent. These schoolchildren are elementary schoolchildren and children in junior high school.

The "hyperkinetic," or the "hyperactive," syndrome may disappear spontaneously.

Dr. YAFFE. Not very many of these children in my opinion need drugs for their management.

Senator NELSON. Go ahead, Dr. Prout.

Dr. PROUT. I think when obesity is eliminated as an indication most of the amphetamines will be withdrawn from the market. Certainly all of the combinations of drugs including these amphetamines will be withdrawn, but this prohibition should be extended to the amphetamine-like compound as well.

Finally, I think if we are going to have any new preparation of these drugs, or any other substituted amines for the treatment of obesity that they must pass the test of efficacy and safety that the FDA requires, perhaps more rigidly based on FDA protocol in order to eliminate any trivial products.

I think there is one further extension of this that might actually be voiced here as well. The Federal Government spends an enormous amount of money and effort trying to take over-the-counter products for obesity off the market as well.

There have been two suits, one by the FTC, and one by the U.S. Postal Service, related to propanolamine. This is a very wasteful way to spend the taxpayer's money, when we could in fact eliminate them all at once rather than drug by drug.

As we chase each one of these manufacturers through their trade name, they have only to come back under a new name and a new trade name, to be back in business. That makes it very difficult to fight on a one-on-one basis, and I think the sweeping review of that whole area is well worth this committee's surveillance.

This is where the original FDA Committee, in its earlier recommendations, fulfilled it charge in its single-purposed review of whether or not these drugs were or were not useful in the treatment of obesity. But I now think we should probably also go to other considerations and this is the practice of the pharmaceutical companies of bulk shipping of these drugs directly to clinics.

Senator NELSON. I did not understand that. This is what?

Dr. PROUT. As noted in my prepared statement there is a practice in the pharmaceutical companies of making bulk shipments of these drugs directly to certain clinics.

Now, if these facilities will in the future be unable to stay in business if obesity is withdrawn as an indication for use it will be very hard to justify the sending, a bulk shipment of 100,000 doses to any single clinic or individual. The risk here is in losing track of the drugs. Surveillance, even of the drugs in schedule II, would be very, very difficult to follow under these circumstances.

A second important point to be reviewed is the whole basis of the relationship of pharmaceutical houses to the medical profession which needs to be looked into. Indeed, Senator Nelson, you touched on it this morning when you noted that certain investigators who come up with "bad answers" may no longer be supported by drug companies for their "research." Or to state it positively, one finds that the pharmaceutical companies are very likely to support "research," "consultation," "teaching," "goodwill," or whatever other term might be used to describe the favor that they curry from these excess funds that

go into medical facilities. I think it is important that we have some way of looking into the total extent of this cash flow. In brief, I would say that we should have a better surveillance of the way pharmaceutical companies support this kind of "research."

Indeed, there are already ways in which pharmaceutical companies can contribute to a general research, and use acceptable protocols under tight surveillance, by utilizing review procedures by organizations independent of pharmaceutical companies. Contributions to medical research are very much needed and I am sure there are ways in which this can be done, but I believe we should look into the ways in which their present tactics are tied in with the so-called "research."

A third area of concern it seems to me actually brings up an area in which I touched upon before this committee in 1972. I had suggested at that time that Congress establish a committee of "blue-ribbon untouchables" very similar to the Council on Pharmacy and Chemistry previously active in the American Medical Association.

This possibility deserves further thought and discussion, especially since it drew the fire of no less a spokesman of the AMA than the late Dr. Morris Fishbein.

Such a committee I think would have a number of important functions, one of the things that seems to be missing in the Federal Government is that of having a responsible agency which authorizes, or looks into the way money is spent for drugs. Millions of dollars are spent on worthless drug products by the many medical facilities of the U.S. Government at this time, and I think we must look into this and eliminate the waste.

This committee could implement another thing that has been touched on this morning, and that is the necessity of having phase IV studies. We do not wish to impede the bringing of important new drugs into medical use. What we do wish to emphasize is the fact that many drugs come to medical use in which the long-term effects are in fact not known.

Dr. Nora and others have touched on the fact that long-term studies of a retrospective nature are not usually very productive. Phase IV study implies that continuing information will be gathered after the drugs are put on the open market in order to retrieve long-term answers to the questions of efficacy and safety. It seems to me this needs to be looked into.

This "blue-ribbon" committee should have one other function. As I had previously proposed, there is need for consumer information on drug usage, and a need for the production of a consumer package insert. This is also a recommendation I made before this committee in December 1972. I think the people expect to have this kind of consumer education, and I do not believe it can wait until other anticipated far-reaching legislation in the health insurance field comes down.

Finally, there is a very difficult new area of concern which I can only look upon without definite knowledge of how it might be solved.

The pharmaceutical houses have stepped into a void of continuing medical education. I am not sure how we can again gain control of postgraduate education of the medical profession, but as we go into a period in which the Federal Government becomes more and more interested in medical practice we must all look into this more carefully.

There should be teaching programs which involve medical schools, community hospitals, and people that are knowledgeable in the medical fields to bring new information into practice. I have gone into some detail in the submitted paper.

Mr. Chairman, I have completed comment on my report to you. Briefly, I would hope:

One, that the former recommendations of the committee be implemented.

Two, that obesity be eliminated as a medical indication for the use of the agents under description in which the so-called anorectic property goes hand in hand with abuse potential.

Three, that over-the-counter nostrums advertised for the purpose of reducing obesity be eliminated that are continuing to be used by the citizens in a worthless manner for large sums of money.

Four, that the activities of the pharmaceutical industries be reviewed as to the ways in which they influence the practice of medicine.

Five, that consumer education be addressed.

And, finally, six, that although there is no easy solution, the manner by which the medical profession and the Federal Government can replace the pharmaceutical manufacturers as the principal purveyors of postgraduate medical training be sought.

I have suggested that this might be done through a traineeship-type of program for clinical pharmacologists. I believe that is the only way it can be done.

Senator NELSON. What is that?

Dr. PROUT. That this is the only way it might be done.

Senator NELSON. What might be done?

Dr. PROUT. That we might establish a method by which continuing medical education could be supported by something other than the pharmaceutical houses in order to prevent this continuing delusion of postgraduate medical education.

Thank you.

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

Our next witness is Dr. Sumner Yaffe, professor of clinical pharmacology and pediatrics, University of Pennsylvania, and director, Division of Clinical Pharmacology, Children's Hospital, Philadelphia, Pa.

Dr. Yaffe is also to represent Dr. Allen Goldman, associate professor of Pediatrics, University of Pennsylvania, and director, teratology unit, Children's Hospital, Philadelphia, Pa.[1]

Please proceed, Dr. Yaffe.

STATEMENT OF SUMNER J. YAFFE, M.D., PROFESSOR OF CLINICAL PHARMACOLOGY AND PEDIATRICS, UNIVERSITY OF PENNSYLVANIA, AND DIRECTOR, DIVISION OF CLINICAL PHARMACOLOGY, CHILDREN'S HOSPITAL, PHILADELPHIA, PA.

Dr. YAFFE. Senator Nelson, Mr. Gordon, I am delighted to be here.

I have two roles as I understand it this morning.

One is to introduce the testimony of Dr. Allen Goldman, who is associate professor of pediatrics in my institution at the University of

[1] See prepared statement of Dr. Goldman beginning at p. 14696. See also prepared statement of Dr. Yaffe beginning at p. 14967.

Pennsylvania, and also director of the teratology unit at Children's Hospital in Philadelphia.

Dr. Goldman's statement, I believe, is available. I would just like, if I may, rather than to read it, to highlight it, and to leave out certain portions.

Senator NELSON. That would be fine, Dr. Yaffe.

The statement by Dr. Goldman will be printed in full in the record, and you may comment on it, also.

Dr. YAFFE. Thank you.

Dr. Goldman, at the very beginning of his statement, mentions the continuing problem of birth defects, which I think is certainly worthwhile in reiterating, and that birth defects cause about 560,000 deaths annually.

He points out that the survivors are afflicted with blindness, hearing impairments, heart or circulatory defects, mental retardation, and other malformations. He then goes on to cite the continuing usage of drugs by pregnant women.

This is on page 2. Paraphrasing some of this, he mentions the fact that despite the tragedy, women continue to take drugs, whether at the advice of their physicians, or over the counter, on their own advice, they take large numbers of drugs during pregnancy. There are some data mentioned from several recent studies, one in the United Kingdom and Scotland, 1973, and another from Texas.

An enormous number of drugs are taken by women while they are pregnant. I would guess that they continue to take the same drugs when they are not pregnant. I should also like to emphasize that these drugs were not taken to save the mother's life or to treat the fetus, but rather to relieve symptoms, and this is a very important point, that many of these symptoms are mild and innocuous.

Therefore, in my opinion, the drugs need not be taken by the women, and, were this so, we would be in an era of very decreased drug administration, consumption during pregnancy, with probably a decrease in the rate of congenital malformations. Then Dr. Goldman goes on to discuss the problem of teratogenicity in general terms, mentioning the fact that in the usual production of anatomic malformations, it is only the first 2 or 3 months of pregnancy where we are concerned. Drugs that are known to cause human malformations fall into four categories, the first would be the anticancer drugs, the second being the steroidal sex hormones, androgens, estrogens, and progestins. These hormones have been associated with very delayed and long-term effects of drugs. Fifteen or twenty years after the fetus received the drug, the effect was noted in the vagina in females exposed to these drugs, and more recently, we have seen effects in the male fetus now also in young adults. They have anatomic problems with their urinary system, and problems with infertility, decreased sperm production, and capability. I think the concept is that defects may appear many decades after the administration of a drug, and I think people now are not using these specific drugs as they did in the forties and fifties to treat women who are pregnant.

Now, the third area that Dr. Goldman mentioned is alcohol, something that for surprising reasons, has only been recently brought to our attention. A specific type of malformation has been reported. The final group which he mentioned is that characterized by thalidomide,

a drug which I do not have to mention here. He then goes on to discuss what he calls hard teratogens, those exemplified by these four classes, and soft teratogens. He classifies the antiobesity drugs, the amphetamines, as soft, and points out the difficulties in ascertainment, when you have a low-level of frequency. Dr. Nora has expounded in much greater details, I will not repeat this, his opinions about the teratogens and the antiobesity drugs, but it is worthwhile to point out that one needs a minimum number of 18 cases of congenital heart disease per 1,000 exposed fetuses to be able to distinguish that from background——

Mr. GORDON. That is anatomical?

Dr. YAFFE. Yes; and that leads me to the last point, which I would like to emphasize, of Dr. Goldman's, and that is possibility of a functional effect, that is, effect upon the central nervous system. Although we do not have any human evidence, we do know that dexamphetamines administration can produce an effect on brain function, even though there is no congenital malformation.

I bring to your attention the fact that these drugs are used to minimize weight gain, and during pregnancy this is not a proper use of the drugs, the indications are not proper.

Dr. Prout mentioned that the limited evidence about the efficacy in the first place, but I do not even have to get into that, because I think weight gain during pregnancy is a physiological effect, something that really does not need treatment, unless it is perhaps extremely excessive.

I think obstetricians have changed their thinking from 10, 20, 30 years ago, when women were ordered not to gain very much weight, and now there is a more generous weight allowance during pregnancy, so that the state of nutrition of the fetus will not be compromised.

Mr. GORDON. There are a number of days when a woman can be pregnant without even knowing it, are there not?

Dr. YAFFE. Absolutely.

Now, that is my interpretation of Dr. Goldman's remarks.

Now, if I may, I would like to move into the other area, the other role, which I have been asked to testify by the d-amphetamine and related central nervous system stimulants in children. The substance of my testimony is contained in the article which Senator Nelson mentioned in the introductory remarks. This article appeared in Pediatrics in February 1973, which was written while I was chairman of the Committee on Drugs of the American Academy of Pediatrics.

Here again, I would like to give you some paraphrasing of this article, and underscore certain points which are contained in it.

I might say at the outset that we were prompted to prepare this commentary as an educational resource for pediatricians, who are members of the Academy of Pediatricians.

We were prompted to develop this commentary for two reasons, one, the rescheduling of several of these compounds into schedule II in 1972, which has been mentioned by Dr. Prout, and, second, that in our neighboring country, Canada, the use of amphetamines for the treatment of obesity was prohibited.

We did have representation on the Committee on Drugs from the Health Protection Branch in Canada and in some way, the Canadians

were ahead of us, and had prohibited this indication for the prescription of this drug, and this class of drugs.

Senator NELSON. What year was that?

Dr. YAFFE. Year 1972, fall of 1972.

Senator NELSON. And it is in the market for what specific purpose?

Dr. YAFFE. As far as I know, Senator, it is in the market for the two reasons in which we endorsed its prescription, that is for the hyperkinetic syndrome, minimal brain disfunction, which was mentioned before, and, second, for the treatment of narcolepsy, which was also mentioned.

There is no other indication I would agree on, with the rare indications, which Dr. Prout mentioned, in adults, but for children, these two indications. I might say, narcolepsy in children is a very, very rare disease. If you can use the record of the Mayo Clinic, they saw 400 children over a 7-year period, in which they had seen many of the children throughout certainly the Midwestern portion of this country. So it is a very rare disease, and hardly enough to warrant the large-scale production of amphetamines which has already been mentioned.

Senator NELSON. Let me ask one more question.

Does Canada have the same system, the schedule II-type thing, and what is happening to the use of the drug in Canada? Do you have any statistics?

Dr. YAFFE. I am sorry, I do not know but I would think they would have some way to control production.

Senator NELSON. We will have some testimony on that, also.

Dr. YAFFE. To continue, therefore as far as the hyperkinetic syndrome is concerned, I think Mr. Gordon mentioned this, I would support what he said, that methylphenidate, although still classed as an amphetamine, is probably the drug of choice among pediatricians in this country.

That is a drug which has not been promoted as an antiobesity agent, so we then come in conclusion in this paper to a recommendation that—as others have made this morning—in 1973, amphetamines be removed as antiobesity drugs, and that the usage be limited to the two indications, one being narcolepsy, and the other being the hyperkinetic syndrome associated with minimal brain disfunction.

Senator NELSON. That would be your recommendation?

Dr. YAFFE. Yes.

Senator NELSON. Would that be the judgment of your colleagues who are knowledgeable in this field?

Dr. YAFFE. Yes, I would believe so, Senator.

May I just add one other statement about obesity itself, which has been discussed in terms of the causation of obesity. This in my opinion is in many instances a disease. The antecedent for obesity begins probably in early infancy, and it is due to excessive feeding by many parents in our society. As a consequence the number of fat cells in the body become increased. The very eloquent work of Dr. Hirsch and Dr. Knittle in New York, have clearly demonstrated that if you are overfed while an infant by your mother or father, you will have an increased number of fat cells. There is very little that can be done when you are an adult about your obesity. You have a drive to eat, and it seems to me that perhaps we should place the emphasis on

proper feeding habits of infants, rather than trying to treat adults with drugs, because they overeat.

Now, I would agree that there are many other emotional and psychological reasons for overeating, that may occur later on, but it is true there are a large number of obese adults that have their origin in infancy. In fact, I have just seen an article in the New England Journal of Medicine which was published this summer, from Rochester, N.Y., which has examined this point. This article which is entitled "Childhood Antecedents of Adult Obesity," with a subtitle, do chubby infants become obese adults. The authors state and prove in their summary of children whose records were available in the Rochester area, 15 to 20 years after they were seen by their pediatrician, that the antecedents do begin in their infancy.

If you are overweight as a young infant, chances are very great that you will be overweight as an adult.

Thank you.

Senator NELSON. Thank you very much.

I would like to ask the panel a question, the 1962 law, known as the Kefauver amendments requires substantial evidence of effectiveness, based upon well-controlled scientific studies by qualified investigators. I think that is a fair paraphrase of the provision in the statute. I would like to hear your opinion on the following question: Based upon the knowledge we now have, and the understanding in the statute as to substantial evidence of effectiveness based upon well-controlled scientific studies by qualified investigators, would these amphetamines and amphetamine-related drugs meet the efficacy standard of the statute, to be admitted into the marketplace as a prescription drug for antiobesity treatment?

Well, Mr. Gordon reminds me that the other aspect of the law is safety, but given the law as to safety and as to efficacy, I would like an opinion from each of you as to whether you believe that they are now qualified to be admitted under the law to be used for the purpose of treatment of obesity?

Dr. YAFFE. I would like to give a qualified answer if I may.

I think there is some evidence of children, in that in the short term, I am now talking of several weeks, amphetamines are effective as antiobesity agents, but after 1 month the effect decreases markedly, and unless the dose is increased significantly, which is not a good idea, because of the risk for side effects and abuse, then there will be little efficacy.

Certainly there is not any substantial evidence of efficacy, certainly not in the way in which these drugs are used, on a chronic basis, there is no substantial evidence of efficacy, and the safety of course as Mr. Gordon mentioned, and as we have heard would hardly recommend these drugs for use in prescriptions.

Senator NELSON. You would say it is hardly recommended for what?

Dr. YAFFE. I would hardly be induced to use these drugs for obesity because of their overriding toxicity.

Senator NELSON. Dr. Grinspoon?

Dr. GRINSPOON. Senator Nelson, I believe that this whole class of drugs would not pass the test of efficacy for the treatment of obesity, and that they would not be considered drugs which do not impose

significant risk, therefore, I would definitely say that they would not pass such a test.

In fact, while I think the drugs are usable for narcolepsy and hyperkinetic syndrome, I would add then that where narcolepsy is concerned, it may very well be that it would be a struggle to get them by an efficacy criterion, because indeed, as was pointed out, if people who suffer the numerically largest form of narcolepsy, take a nap for 5 or 10 minutes, that is the best treatment of all. So the biggest risk to people with narcolepsy may be the taking of these drugs, so if they just take a nap, and they recognize the problem, as employers must, this usually works quite well, so that there is no reason to take drugs.

As to the question of hyperkinetic children, I think at this moment, there are some children for whom it is efficacious, and the benefits exceed the risks; however, new treatments are coming along, there are other ways to approach it, and I look to the day when regarding the treatment of hyperkinetic children, we would question whether amphetamines is the best way.

My concern about the treatment of hyperkinetic children right now is that many children do not suffer from this very poorly defined syndrome known as minimal brain damage, and I think it is very important for a physician to be quite responsible in diagnosing this illness.

Senator NELSON. Dr. Nora?

Dr. NORA. If I were in this hypothetical position of being able at this moment to accept or reject the use of this drug in the marketplace for antiobesity, I would certainly reject it.

I do not think on the basis of its efficacy or safety, that it is a drug that should be admitted for that purpose.

I would have some more reservations about rejection for some other purposes, but I think that the problem of abuse enters the picture, and I am not sure that I see a great need for the drug in the physician's armatarium.

The only exceptions perhaps are hyperkinesis and narcolepsy.

Senator NELSON. Dr. Prout, do you want to answer that?

Dr. PROUT. I think I have in a sense already answered it. Certainly in my own view, the trivial loss of weight seen with these drugs does not come up to evidence of efficacy. In the future, we will have to deal with the question of what is a reasonable amount of weight loss, for which the drug might be prescribed.

Even if this were a small amount, a half a pound a week, but there was *no risk*, and did not require discontinuation of the drug, or you were able to continue the medication for a lifetime, then we would have a very efficacious drug. So the definition of efficacy and safety is easier perhaps in the drugs we have today. The measure of what would be efficacious and safe in the future, will lead us back to the necessity of making that judgment on the basis of phase IV studies, in addition to phase III-type studies.

Mr. GORDON. The phase IV long term studies?

Dr. PROUT. The long term studies in which evidence of the lack of safety can be amassed over a period of time. Since obesity is a lifetime problem, it is not sufficient to look at their effectiveness in periods of only 8 to 12 weeks.

Senator NELSON. In the earlier testimony as part of the panel, you have recommended that at the least the obesity indication be removed and put on schedule II.

Do you or do you not believe that it would meet the standards of efficacy in terms of the current statutory meaning that proof of efficacy must be based on well-controlled clinical trials by qualified investigators and considering the safety question? Do you think that if the application were now pending, and on the basis of what we know, would you approve these drugs for the treatment of obesity?

Dr. PROUT. I think it would not now qualify, and I would recommend that obesity be withdrawn as an indication for its use.

Mr. GORDON. I have a couple of questions.

This is a quotation, an excerpt from an FDA document which we have, and I will read it.

"Larger questions of long-standing remain unanswered such as the long-term effect on morbidity and mortality of the use of anorectics. These questions are of basic importance, since the usefulness of the drugs depends in large part upon the assumption that they somehow help prevent the adverse effects of obesity."

This document also states:

"In addition to evidence of abuse of amphetamines, evidence also exists in fair quantity for abuse of phenmetrazine—Preludin—and diethylpropion—Tenuate. For other anorectics evidence of abuse is scanty or lacking. Experience with other abusable drugs has shown, however, that documentation of abuse lags markedly behind abuse, and, when it appears, is only the tip of the iceberg."

Do you agree that it is desirable to use pharmacologic and chemical data to predict abuse before it occurs?

Dr. PROUT. I think this is the basis of our declaring that a drug has abuse potential. We were able to look at a large number of animal experiments in which the central nervous system stimulatory effect of a drug was easily documented. From that point of view, one could predict, since this is the effect that it was sought in the street, that as one group of drugs becomes more difficult to procure, the others will be tried and selected on the basis of their abuse usefulness. I think it is important not to wait until abuse is shown in the street, but to predict that *possibility* on the basis of *abuse potential*, and it is the reason why the FDA Committee drew the line right there.

Dr. GRINSPOON. I would agree; it seems to me ridiculous to wait until a drug is abused on the street.

There is no question we can predict which drugs will be abused, and certainly the people who argue that a drug has certain characteristics such that it will not be abused. The burden of proof should be on them.

In India about 10 years ago methaqualone was sold, and there was a lot of experience in Britain, and it was brought to the United States and sold here about 4 years ago. It was very clear at that time that it could be abused, and it is being abused on the street now, it was something absolutely predictable.

Dr. NORA. I would be in agreement with the others.

Dr. YAFFE. Yes.

Mr. GORDON. One more question.

In view of the "trivial," this is the word used by the Food and Drug Administration, benefits to a few individuals, and the danger to both

individuals and to the public, would you consider these drugs, if they remain on the market, as a hazard to the public health?

Dr. GRINSPOON. I would certainly consider them a hazard to the public health.

There is no question in my mind that there is far more harmfulness in the general use of amphetamines for the treatment of obesity in this country than benefit from them, and, therefore, they are clearly a hazard to the general health.

Dr. PROUT. I think the question has to be answered, Mr. Gordon, based on whether or not we can in fact control their use in any reasonable way.

I think that we should work within the system as much as possible, because there are legitimate medical uses for these medications and we might use this group as a reasonable class to discuss the process, and there might be ways by which their use could be brought to public benefit. I think that the sharp limitation quotas and withdrawal of obesity as an indication for use would allow us to use them in other ways.

There is some experience, for example the Canadian experience, which we have not examined in detail before this committee, and which I trust will be used to help to answer that question. Their experience will show that they have been able to control these drugs to some degree.

I think we ought to focus on the fact that some of the problems, that Japan, and particularly Sweden, has had in protecting their citizens against the abuse of drugs, has been in large part related to the fact that they have had very little help in the worldwide community. It seems to me we ought to look at this problem in the United Nations and elsewhere, as an important member for the world community. We must look at this problem on a worldwide basis.

I think our posture here in the United States will be very important but we do have to learn how to control this problem in some way.

Mr. GORDON. Then what is the answer? Is there an answer to it?

Dr. PROUT. The answer is there *may be* a hazard to the public, and there *are* abuses, and I think we have to learn how to control them. Taking them off the market entirely, and eliminating their use, I think is probably possible but there is a whole score of agents which are used from this family, nose drops and sinus tablets, which are not under discussion, all of these things will have to be looked at. The drug abuse question has got to be seen in a broader sense.

In my earlier testimony I was not able to go into this, but I think we will have to look at the whole family and the whole problem in a very realistic way.

I believe scheduling has got to be pushed to the ultimate, as well as the establishment of quotas, the curtailment of influence of pharmaceutical houses, and their whole use of the medical profession but, the education of the public, and the education of the medical profession, are all part of that question.

Mr. GORDON. You said before that the antiobesity drugs should be taken off the market?

Dr. PROUT. Obesity taken off as that indication for their use. This sharply curtails their use in that field.

Mr. GORDON. There are many drugs that have no other indication.

Dr. PROUT. Then by definition, that should come off the market. If obesity is withdrawn, then those agents which have no other proposed use would in fact be withdrawn from the market.

Senator NELSON. Thank you very much, gentlemen, for your very valuable testimony.

We certainly appreciate your taking the time to visit with us, and to come here to testify before the committee.

The hearings will resume tomorrow in this room at 10 a.m.

Thank you, gentlemen.

The subcommittee stands in recess.

[Whereupon, the subcommittee was recessed at 12:25 p.m.]

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

WEDNESDAY, NOVEMBER 10, 1976

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

The subcommittee met, pursuant to recess, at 10 a.m., in room 318, Russell Senate Office Building, Hon. Gaylord Nelson, chairman, presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; and Karen Young, research assistant.

Senator NELSON. The subcommittee will please come to order.

Our first witness today is Dr. Donald R. Jasinski, chief of the clinical pharmacology section of the National Institute on Drug Abuse, Addiction Research Center, Lexington, Ky.

Dr. Jasinski, we are pleased to have you here today, and appreciate your taking time to present your testimony.

Your statement will be printed in full in the record, and you may present it however you desire.

STATEMENT OF DONALD R. JASINSKI, M.D., CHIEF, CLINICAL PHARMACOLOGY SECTION, NATIONAL INSTITUTE ON DRUG ABUSE, ADDICTION RESEARCH CENTER, LEXINGTON, KY.

Dr. JASINSKI. I choose to read the statement.

Senator NELSON. Fine.

Then please proceed.

Dr. JASINSKI. Mr. Chairman and members of the subcommittee, my name is Donald R. Jasinski. I am a physician who is a commissioned officer in the U.S. Public Health Service.

I hold the position of Chief, Clinical Pharmacology Section, of the National Institute on Drug Abuse Addiction Research Center, Lexington, Ky.

For over 40 years, the Addiction Research Center has conducted studies in volunteer prisoner addicts to assess the abuse potential of psychoactive drugs proposed for introduction into therapeutics.

Such studies with narcotic analgesics have proven to be a valid means of protecting the public health.

In the last 6 years, the comparative pharmacology of stimulant drugs has been studied in order to assess the abuse potential of these drugs relative to dextroamphetamine and to provide a basis for scheduling decisions under the Comprehensive Drug Abuse Prevention and Control Act of 1970.

The principal underlying assessment for abuse potential is the identification of a prototype drug which has been abused and is judged to be a danger to the public health.

All drugs having a similar mode of action and sharing the same profile of pharmacologic effects are viewed as having a potential for abuse.

Amphetamine, the prototypic drug for antiobesity agents, produces characteristic and reproducible alterations in mood, feeling states, and perception in our addict population.

Volunteers can distinguish these amphetamine-induced subjective states from those produced by agents such as morphine or pentobarbital.

One type of change is "euphoria" or feelings of well-being and elation which are felt to be related to the ability of amphetamine to initiate and maintain drugtaking.

In addition, amphetamine produces other characteristic effects including increases in blood pressure, decreases in pulse rate, increases in body temperature, decreases in the amount of food eaten, and a slight increase in pupil size.

From our studies, d-methamphetamine, methylphenidate, phenmetrazine, l-ephedrine, diethylpropin, phentermine, and benzephetamine all produce typical amphetamine-like effects.

These drugs differ from one another in milligram-for-milligram potencies. In sufficient doses, however, all can produce the same degree of effects.

Please note the following table.

[The table follows:]

Equivalent euphorogenic doses

	Milligrams
Subcutaneous studies:	
d-amphetamine	10
d-methamphetamine	10
Methylphenidate	20
Phenmetrazine	40
Ephedrine	50
Diethylpropion	140
d-amphetamine (oral)	10
Oral studies:	
d-amphetamine	10
Phentermine	20
Benzphetamine	50
l-ephedrine	50
Diethylpropion	70

Dr. JASINSKI. In contrast, our studies also indicate that the appetite suppressants fenfluramine and chlorphentermine are not typical amphetamine-like agents.

Fenfluramine in low doses can produce feelings of well-being or elation.

Large doses more characteristically produce unpleasant subjective states.

Subjects clearly distinguish the effects of amphetamine from fenfluramine and more frequently identified fenfluramine as LSD or barbiturate-like substances.

A further difference is that fenfluramine has little effect on blood pressure and body temperature, but produces a marked increase in pupil size.

Three subjects had visual and olfactory hallucinations, distorted time sense, fleeting paranoia and sexual hallucinations.

Mr. GORDON. Dr. Jasinski, what do you mean precisely when you say the amphetamines and their relatives all produce typical amphetamine-like effects?

Do they also have the same potential for abuse? Is that what you mean?

Dr. JASINSKI. We administer these drugs to subjects in single doses under double-blind circumstances. This means both the subject and the person making observations are unaware in that particular circumstance, of the dose, and the exact nature of the drug. The subjects are asked to relate the feelings which the drug produces and to identify the drug.

Under these circumstances the subjects cannot distinguish these drugs from amphetamines.

In addition, when one looks at other effects which are produced—such as decrease in the amount of food eaten, the changes in pupil size, the change in body temperature, the change in blood pressure—all these drugs produce effects which are very similar to those of amphetamines.

In addition, one characteristic effect is the well-being or euphoria which is seen in a population which has history of drug abuse. All these drugs, like amphetamines, produce these feelings.

Mr. GORDON. Fenfluramine is different; it is more like LSD, is that correct?

Dr. JASINSKI. Some of our subjects said it was LSD.

We do not have experimental data in this regard. This would require specific experiments to answer this question which would involve a direct comparison to LSD. We do not have this data.

Mr. GORDON. I read your article on comparison of fenfluramine and amphetamines in man, and I will read this to you:

> In support of Levin's studies, fenfluramine was observed to have hallucinogenic activity in three of five subjects who experienced syndromes characterized by visual hallucinations, sensory distortion, fleeting paranoia, derealization, depersonalized awareness, somatic symptomatology, labile mood, a modest increase in pulse rate and blood pressure, mydriasis, and hyperactive tendon reflexes—the last not measured systematically.
>
> This configuration resembles that produced by a number of hallucinogens, including LSD and certain ring-substituted amphetamines. This similarity, plus the cases cited by Levin, suggests that LSD-like, rather than an amphetamine-like abuse potential should be considered. This issue aside, hallucinogenic and dysphoric symptoms may well limit the therapeutic utility of fenfluramine as an anorexiant.

Dr. JASINSKI. Yes, sir.

Mr. GORDON. Then it seems you would agree that this drug should not be used for that purpose, is that correct?

Dr. JASINSKI. No; I think the meaning of that statement was somewhat different.

This drug, when used therapeutically by the physician may make the patient feel bad. Then patients will not take the drug, or will complain to the physician. As a result the physician will not find this particular drug useful. The meaning of that statement was that though this was not an amphetamine-like drug, these effects might limit fenfluramine's usefulness in therapeutics, and that——

Mr. GORDON. I do not understand this.

Does fenfluramine make you feel good, or does it make you feel bad?

Dr. JASINSKI. It will do both. In low doses, in some of our subjects, they felt good.

With the long-term administration, or with very large doses, patients might feel bad.

The literature on the use of fenfluramine has reported feeling states of sedation, and lethargy. The drug does not make people feel particularly good when they take it therapeutically.

I think that this may be a limitation on its usefulness as an appetite suppressant mainly because of consumer acceptance.

Mr. GORDON. Please proceed.

Dr. JASINSKI. Chlorphentermine markedly increases pupil size, produces sedation which is regarded as unpleasant rather than euphoric, decreases appetite without producing increases in blood pressure or body temperature.

Some subjects were grossly sedated by chlorphentermine, but no hallucinatory syndromes were observed.

Abuse potential judgments from pharmacological studies can only be validated by comparison with actual incidences of abuse of available drugs.

In this regard, methamphetamine, phenmatrizine and methylphenidate are three of the drugs pharmacologically equivalent to amphetamine.

At times all have had a high incidence of abuse equaling that of amphetamine. On the other hand, three antiobesity drugs, diethylpropion, benzphetamine, and phentermine are also amphetamine-like drugs which are abused.

The incidence of abuse of these drugs is much less than that of amphetamine. One source of information on abuse incidence is the Drug Abuse Warning Network—Project DAWN—which is a program cosponsored by the National Institute on Drug Abuse and the Drug Enforcement Administration.

This program tabulates drug mentions associated with drug-related deaths from medical examiners and drug-related medical or psychological emergencies from hospital emergency rooms and crisis centers.

In calendar year 1975, the number of mentions in Project DAWN for diethylpropion and phentermine were only 5 to 8 percent of those for amphetamine.

According to the National Prescription Audit for this same period, the number of new prescriptions written for these drugs were 40 to 50 percent of those for amphetamine, suggesting that the lower incidence of abuse cannot be accounted for simply by differences in the relative amounts prescribed by physicians.

Similarly, the number of mentions for benzphetamine is only 1 percent of those for amphetamine, while the number of new prescriptions are 6 percent of those for amphetamine.

Senator NELSON. May I ask you a question, Doctor?

Dr. JASINSKI. Yes.

Senator NELSON. In the middle of page 3 you mention three antiobesity-like drugs, and you name them. Are they also amphetamine-like drugs?

Do these three drugs that you mentioned have any indicated use for obesity?

Dr. JASINSKI. As far as I know, Senator, yes, they are only used as antiobesity drugs now.

Senator NELSON. And you indicated they are subject to abuse, but much less than amphetamines?

Dr. JASINSKI. Yes.

Senator NELSON. Are you familiar with any studies indicating the efficacy of these three drugs as antiobesity drugs?

Dr. JASINSKI. The specific examples, I do not think I can quote offhand.

I know the literature in general, but I have not personally conducted any studies of the antiobesity effects of these agents, so my knowledge would only be from the literature. This is not my area of expertise, the area of obesity.

Senator NELSON. Doctor, you mentioned methylphenidate. I want to remind you it is not an antiobesity drug. It is not one of the indications.

Dr. JASINSKI. Yes.

Senator NELSON. You state that the DAWN program tabulates drug mentions associated with drug-related deaths from medical examiners and drug-related medical or psychological emergencies from hospital emergency rooms and crisis centers.

Why is this a good measure of drug abuse?

Are you not assuming that abuse of a drug necessarily culminates in death or a hospital emergency room?

Dr. JASINSKI. I think there are a number of reservations about this data. The difficulty is that we have very few other systems which gather data in abuse incidence. Its advantage is the large data base which is a very extensive survey from many sources.

I think Project DAWN was instituted in 1973; however, the use of this data and its validity is just beginning to develop.

It is about the only source of data we have, but I think it is certainly characteristic of the situation. We do not have a particular survey of the situation at the present time.

You must have an ongoing survey. The second issue is among what sources of populations does one look. Here I think the judgment is made, and I had nothing to do with Project DAWN, to examine public health problems and medical problems from people who would come into contact with the physicians. To collect epidemiological evidence on drug abuse becomes very difficult since it is usually a clandestine activity. These people generally only surface in contact with law enforcement agencies, or when they come in contact with medical agencies, so it becomes a difficult problem in how to approach this. DAWN is the only ongoing data that we have.

Senator NELSON. It does not measure drug abuse?

Dr. JASINSKI. No, it measures medical incidents which occur for the particular drug.

It has been used as a crude index of drug abuse.

Senator NELSON. Is there any way to extrapolate such figures from the statistics of those who end up requiring medical care, hospitalization—some of the consequences of drug abuse?

Dr. JASINSKI. There is, for example, the Project DAWN reports prepared by the National Institute of Drug Abuse and the Drug Enforcement Agency which contain a profile on individual drugs. In this a number of questions are asked of the people who have been in trouble. Why they took the drug, the reason for taking the drug, the source of the drug—and I do not remember this exactly, for amphetamines, but I think—whether they took this for pleasurable effects, or they felt they were dependent upon the drug. I know they had the age range of the patients broken down, and this data is published from the period of 1973.

Senator NELSON. But do they intend to extrapolate from these statistics the total number of people who in fact use the drugs?

Dr. JASINSKI. No, I do not think they do this.

If they do this, I am unaware of this. Whether they have attempted to do this, I just don't know.

An additional NIDA-sponsored survey conducted from October 1974 to May 1975 supports these conclusions from DAWN.

In this study, 2,510 men representative of all men in the general population who were 20 to 30 years old in 1974, were surveyed for their nonmedical use of stimulant drugs.

The specific stimulant drugs reported were amphetamine, methamphetamine, methylphenidate, phenmetrazine, and biphetamine.

There were no mentions of diethylpropion, benzphetamine, or phentermine.

Similar considerations also indicate a relatively low incidence of abuse of both fenfluramine and clorphentermine, two agents which are not pharmacologically equivalent to amphetamine.

The assessment studies in prisoner addicts are valid measures of abuse potential; however, it must also be concluded that factors other than pharmacological equivalence determine the incidence of abuse of a drug.

In the case of drugs marketed as appetite suppressants, these factors are not known but experience suggests that at any point in time the incidence of abuse of a drug is determined by customs, fads, attitudes, type of pharmaceutical preparation and knowledge of the drug's actions.

In addition, certain properties of the drugs themselves may limit attractiveness to the drug abuser. For example, drugs which cannot easily be dissolved in water are less attractive to the addict who injects drugs.

In retrospect, the comparative pharmacology and the incidence of abuse support the scheduling decisions made under the Comprehensive Drug Abuse Prevention and Control Act of 1970 concerning the anti-obesity drugs.

On the one hand, amphetamine, methamphetamine, phenmetrazine, and methylphenidate are recognized as having similar abuse potential, and as such have been placed in schedule II.

On the other hand, a number of other appetite suppressants have not been extensively abused to date. These drugs have been placed in schedules III or IV.

Mr. GORDON. Doctor, you mentioned attitudes, they can change, can they not?

Dr. JASINSKI. Yes, sir.

Mr. GORDON. I understand that Preludin has become one of the most widely used drugs in the District of Columbia area.

The price in the street is about $10 per pill.

We received a call from the Police Department of Louisville, Ky., that Preludin is the most popular street drug there, also.

The price is about $8 per pill.

In an undated FDA document, we have statements that documentation of abuse lags markedly behind abuse, and when it appears, is only the tip of the iceberg.

My question is, why wait until there is an epidemic, why not use pharmacologic and chemical data to predict abuse before it occurs?

Dr. JASINSKI. I think this may be justified in certain instance from a historical perspective. It depends on how one directs one's thinking, and one's bias in the particular area.

My particular bias is toward the practice of medicine, and making a rational scheduling policy such that scheduling does not affect the patient who may be using the drugs in legitimate circumstances and for legitimate needs. We know many drugs which have required uses in medicine, and which benefit the patients, also have other properties leading to self-ingestion. At times the people will use these drugs to such a point that they will experience toxic effects, or will engage in behaviors which our society condemns.

In these instances we must, in my opinion, be as much concerned about not removing drugs from patients inappropriately. We must make decisions on a relatively rational basis.

I think from a historical perspective, we have had a number of drugs which have been pharmacologically equivalent, but which have been used by physicians, and in a sense by people without creating major public health problems.

Mr. GORDON. But it is not an antiobesity drug, so you are really creating a straw man.

We are talking about antiobesity drugs. We are not talking about that type of a drug.

Now, given the very limited use, the FDA says that the benefits are clinically trivial, those were the exact words used by the FDA, by the advisory committee. Given these trivial benefits, and given the abuse potential, and other side effects, how do you figure the benefit-to-risk ratio?

Dr. JASINSKI. What I am talking about is the relative risk.

The data which I have bears on relative risk from a particular toxic effect, which is the ability to induce and maintain self-ingestion behavior.

Now, this is a risk which occurs with all the compounds.

On the other hand, I have no data on the benefits. All of these decisions come from benefit-to-risk ratios.

I think that within the Comprehensive Control Act, as I would see it, there is only one distinction. If one says these drugs are not therapeutically useful, then all of the drugs would go to schedule I.

The difference of schedules between II and III, and IV and V, are not based on relative therapeutic ability of drugs.

I think they only call for having an accepted medical use.

If the drugs do not have approved medical utility, then I think all drugs would go into schedule I.

Senator NELSON. If they have no efficacy at all, they should not be on the market at all.

Dr. JASINSKI. That is right.

Senator NELSON. So you would not permit them, in effect, on the market?

Dr. JASINSKI. That is correct. I think in terms of the data, the decision to market these or not market these was not my mandate, nor within my ability.

Mine was only to assess the relative abuse potential and the risk to public health from the ability to self-ingest, and I think the benefit part of the ratio factor is another question which I have an opinion, but I do not have expert testimony.

Senator NELSON. Just so the record will be clear, then you, in evaluating these various drugs, in making judgments about abuse potential, you are not concerning yourself necessarily with the question of whether or not they meet the standards of the law of safety and efficacy?

Dr. JASINSKI. That is true.

Senator NELSON. So you may have a drug on the marketplace that you conclude does not have much risk of being widely abused, but you are not reaching the conclusion whether or not it has any value for the treatment of any condition?

Dr. JASINSKI. That is true.

Senator NELSON. You are dealing with abuse problems?

Dr. JASINSKI. That is true.

Senator NELSON. Unrelated to the question of efficacy of the drug in treating a particular condition?

Dr. JASINSKI. That is true.

Senator NELSON. All right.

Dr. JASINSKI. For clarity, the scheduling of drugs, and the data which we generate, many times will affect questions of efficacy in an indirect way. It is obvious that if the drug is controlled on the basis of pharmacological data in a very high schedule, the manufacturer may choose not to market the drug.

If it is marketed, the physician may choose not to use this drug, and select an agent which is on a lower schedule, so our data does affect the pattern in which drugs are used.

Some would argue that all drugs which have pharmacological equivalence to amphetamine should be placed in schedule II in order to protect the public health.

My own opinion is that this action would in certain instances be detrimental to the public health. The group most directly affected would be those patients using the drugs in a therapeutic situation since restrictive controls make them less available to the consumer.

This situation is most clearly illustrated with ephedrine. In contrast to amphetamine, ephedrine is not used as an antiobesity drug, but is used mainly in the treatment of asthma to relieve spasms of the bronchioles in the lungs.

An amphetamine-like spectrum of pharmacologic effects, including euphoria, indicates that ephedrine has an abuse potential.

Ephedrine is available in small amounts in a number of over-the-counter preparations and can be purchased without a prescription.

The incidence of abuse of ephedrine is quite low and there is no evidence of danger to the public health.

Under the present circumstances, the control of ephedrine is unwarranted, especially since the major consequences would be to decrease the availability and increase the cost to patients with chronic asthma.

In conclusion, the utility and need for assessment studies to protect the public health is self-evident, especially in those instances where new agents are being introduced into therapeutics.

It is in the interest of public health that we make rational scheduling decisions to forewarn the therapist of the dangers of the drugs he may prescribe and to assist him in their rational use.

At the same time, inappropriate controls must be avoided since this would place unnecessary burdens on the patient.

Our studies with stimulants have demonstrated that drugs which are structurally dissimilar to amphetamine can produce amphetamine-like effects and have abuse potential.

A similar situation exists with substitutes for narcotics where a large number of synthetic and structurally unrelated drugs produce effects similar to morphine and heroin.

Further, drugs which are structurally similar to amphetamine do not necessarily produce amphetamine-like effects.

In this regard, we have only preliminary data on two recently introduced antiobesity agents, cloretermine and mazindol.

We have not studied phendimetrazine. Unfortunately, further data on these agents will not be obtained.

Mr. Chairman, this concludes my formal testimony. I will be pleased to answer any questions you and other members of the subcommittee may have.

Senator NELSON. We have asked all of the questions we have. Thank you very much, Doctor.

Dr. JASINSKI. Thank you very much.

Senator NELSON. Dr. Thomas M. Gellert of Huntington, N.Y. was to appear also this morning, and he has wired the committee that he would be unable to get here, so we hope to have him testify next week.

Our next witness is Dr. Barrett Scoville of Washington, D.C.

I believe he was formerly associated with the Food and Drug Administration.

Would you please identify your work with the Food and Drug Administration?

STATEMENT OF BARRETT SCOVILLE, M.D., OF WASHINGTON, D.C.

Dr. SCOVILLE. I formerly directed the Division of Neuropharmacological Drug Products, which is one of the six FDA drug review divisions.

Senator NELSON. Your statement will be printed in full. You may present it in whatever way you desire.

Dr. SCOVILLE. Thank you, sir.

I will read the statement.

Mr. Chairman, members of the subcommittee, I am here to provide you and the public with information on the decisions made about anorectic drugs—drugs used in treating obesity—during the time I worked in the Food and Drug Administration, and about my current personal opinions on what modifications of those decisions may be desirable, as well as on any other matters you wish to ask me about.

I have testified before this committee in the past about the FDA review of drugs used in treating obesity.

To recapitulate, in 1971 and 1972, the Food and Drug Administration was confronted with decisions on the efficacy and safety of old and new anorectic drugs, some 11 chemical entities in all, over 130 drug products.

The questions about efficacy included questions on the amount of weight loss, if any, associated with the use of anorectic drugs by obese patients, the duration of administration of the drugs, and possible differences in efficacy among the different chemical entities evaluated.

The safety questions involved chiefly the public health hazards of a special toxicity, that of the potential of these drugs for producing dependence and for being abused.

Data bearing on the efficacy questions included over 200 controlled trial involving almost 10,000 patients, trials carried out by drug manufacturers and submitted to FDA as part of various applications.

The data on safety were a more heterogeneous assemblage of different sorts of evidence—chemical, animal, and human—which might have some bearing on abuse potential and other safety questions.

The efficacy review involved an unprecedented reexamination of all individual patient data sheets, representing 70,000 patient visits, computerization of the data, and FDA reanalysis of the data, using its own computers and statisticians—who deserve much credit for the massive job.

In making the final decisions on the drugs, the FDA was advised by a consultant panel headed by Dr. Thaddeus Prout. The former Council on Drugs of the American Medical Association, headed by Dr. Harry Shirkey, also gave us its opinion on the proposed actions.

The institutional FDA decisions were embodied in a comprehensive memorandum proposing various alternatives with the pros and cons of each, the final decisions being initialed by the Commissioner of Food and Drugs.

In carrying out the decisions, the FDA itself implemented decisions with respect to marketing approval and relabeling.

Decisions on controls to be imposed because of abuse potential were and are the primary responsibility of the Bureau of Narcotics and Dangerous Drugs, now the Drug Enforcement Administration, al-

though the FDA does have major statutory responsibilities in this area, too.

Recommendations were forwarded to the BNDD and controls were imposed by that agency.

The results of our review, which ended in the latter half of 1972 with implementation of the decisions in early 1973, were as follows:

First, a consistent policy and set of regulatory actions for all anorectics, based on a better characterization of their limited but unequivocal superiority to nondrug therapy and including recommendations that they be used only for short-term use as adjuncts to diet.

Second, the elimination of a large number of combination drug products. Only two major combination products remain on the market, with litigation ongoing.

The position of the manufacturer of these drugs, Smith, Kline & French, appears ethically and legally weakened by their failure to report important adverse information on the abuse potential of one of their products.

Mr. GORDON. Could you elaborate on that, please?

Dr. SCOVILLE. This was pointed out in a Federal Register notice of 1973.

The decision may have to be decided in court or in a hearing of this nature. Representatives of SKF came to FDA, bearing marketing studies which they felt supported their claim that their drug has little or no abuse.

Independently, it also turned out they had in their possession a separate study carried on by contract, showing that their drug was known and shown to be sold in the street.

This was a study that they did not submit. This selective submission of evidence to the FDA seems to strike at the very basis of our current regulatory process.

Mr. GORDON. I have some more questions along those lines.

What finally happened? Is not this a violation of the law?

Dr. SCOVILLE. In my perception of the events, if they turn out to be true, it will be against the law.

Mr. GORDON. You said if it turns out to be true, you think there was a violation of the law?

Dr. SCOVILLE. Yes. If the facts are correct, yes.

Mr. GORDON. If the facts are correct—you think there was a violation of the law?

Dr. SCOVILLE. Yes.

Mr. GORDON. Has there been anything done about that as far as you know?

Dr. SCOVILLE. Well, the FDA put this statement in what is called an opportunity for hearing, a proposal to withdraw approval of new drug applications.

Mr. GORDON. That was in 1973?

Dr. SCOVILLE. Yes, sir.

I am somewhat sympathetic with what appears to be the untimely response of the FDA, in that they are involved in large numbers of responses to notices of opportunity for hearings, for a very large number of drugs which are under the DESI review.

I am sure they have a document in preparation dealing with this issue, but it has not to my knowledge been yet published.

Mr. GORDON. Eskatrol, I think, is a $5½ million a year item, so obviously the company would be very anxious to keep it on the market.

Is Dexamyl the other one?

Dr. SCOVILLE. Dexamyl is the other; yes, sir.

Third, controls bearing on abuse potential were imposed on eight of these drugs for the first time, in a precedent-setting class action.

Fourth, all injectable anorectics were eliminated from the market.

You may wish to know what I think of these decisions with the benefit of hindsight, over 3 years after the fact.

I believe that the basic efficacy decision remains a good one. Obesity remains a chronic disease, extremely difficult to treat, and even the limited efficacy of anorectic drugs is better than nothing.

The safety decisions appear in need of revision. It is my understanding that you will hear the Government data suggesting or showing that amphetamines remain the leading stimulant drug of abuse—with the possible exception of cocaine—in spite of the most restricted measures.

If so, it would seem reasonable to withdraw approval of amphetamines for use in obesity, for which safer drugs are available.

In a parallel fashion, the use of any other schedule II drugs in obesity should be examined to see if there may be a similar abuse problem.

Senator NELSON. On the question of efficacy, Dr. Prout testified yesterday, and he was the chairman of the special committee which was advisory to the FDA, and their conclusion after their studies was unanimous, which was that amphetamines should be removed from the market for purposes of treating obesity, because their effect, to use their words, was trivial, and the abuse widespread.

You seem to be saying two things, if there is abuse, somehow or other the abuse ought to stop, and that you think that it meets standards of efficacy.

Do you agree with the FDA's special committee headed by Dr. Prout that they should not be used at all, or should be put in schedule II?

Dr. SCOVILLE. I think, sir, that the language of the group was that all of the anorectics produced about the same amount of weight loss, and so if that is so, and I believe it is, as far as data distinguished between the drugs, then the question becomes one of relative safety. You might ask, why not get rid of the most dangerous and leave the safe ones available for us to treat obesity. I suggest it would seem to be reasonable for the Government to do that.

Senator NELSON. Yesterday, I believe, all of the witnesses—possibly one had slight reservations—at least three of them agreed with Dr. Prout—Drs. Grinspoon, Nora Prout and Yaffe—indicated that there ought not be indication for use of obesity, that that indication ought to be removed if the results were trivial, and three of them indicated that under today's standards of efficacy, they do not think the drug ought to be on the market in the first place.

Dr. SCOVILLE. That is where I am personally disagreeing.

Senator NELSON. For purposes of treating obesity?

Dr. SCOVILLE. I believe that the most dangerous, the most abusable of these drugs should be removed because of their abuse potential. There is a spectrum of abuse potentials, ranging from amphetamines on the one hand, down to some of the other drugs, perhaps those which have a substituted benzene ring, chlorphentermine perhaps, having

less abuse potential. It is my value judgment that obese people need treatment, that drugs are a reasonable form of short-term treatment of obesity, that the obese should not be deprived totally of drugs because of the abuse potential.

Senator NELSON. I guess I am still puzzled by this.

You stated, it is my understanding, that amphetamines—Let me read this.

> It is my understanding that you will hear government data suggesting or showing that amphetamines remain the leading stimulant drug of abuse—with the possible exception of cocaine—in spite of the most restricted measures. If so, it would seem reasonable to withdraw approval of amphetamines for use in obesity * * *

You are saying that if that abuse is statistically proven, which the testimony thus far asserts, that you would prohibit their use in the treatment of obesity, is that correct? I am referring to amphetamines.

Dr. SCOVILLE. Yes, sir.

Perhaps there is a confusion of terminology.

By some people amphetamines is used loosely to include all anorectic drugs.

I am trying to use it in a more specific way as referring to one of approximately 11 chemicals, one which has the most abuse potential of any of the 11.

My statement does not apply to all anorectic drugs, but only to a specific group among them.

Amphetamines and anorectics are not synonomous in my terminology.

Mr. GORDON. Amphetamines and anorectics are not synonomous?

Dr. SCOVILLE. Not synonomous, yes.

Senator NELSON. But I take it you are saying those amphetamines, or any other—correct me if I am wrong—are subject to widespread abuse. If they are, they should not be in the marketplace for the indicated purpose of treating obesity?

Dr. SCOVILLE. That is my feeling.

Senator NELSON. All right.

Dr. SCOVILLE. Along those lines, I go on to point out that the other anorectics were quite difficult to evaluate for abuse or abuse potential in 1972. Data were scanty, and none had been subject to epidemic abuse.

We nonetheless recommended control on grounds of abuse potential. It is my understanding that in the interval, some of these drugs have been better tested, with confirmation of their abuse potential, and that observers of patterns of abuse have seen abuse potential turn into actual abuse in the street for some of these drugs.

You have or will have obtained testimony on this problem from more expert witnesses than me.

If the data are as I suggest, they will support greater controls for some of the drugs currently in schedules III and IV.

Thank you.

Senator NELSON. Thank you, Doctor Scoville.

Mr. GORDON. The Food and Drug Administration has made an overall study. They pooled several hundred studies, and then made one big study out of it. They ran it through a computer, is that correct?

Dr. SCOVILLE. It was analyzed, study by study.

We did so-to-speak place all drug-treated patients and placebo-treated patients into two separate pools to see what happened, but that was not the basis for the decision.

Mr. GORDON. I have a document here that I ask be put in the record in the appropriate place.

Senator NELSON. So ordered without objection.

Mr. GORDON. This is a document that was submitted by the Federal officer from the Food and Drug Administration to the HEW panel.

In it, he states as follows:

Of the 206 studies reviewed, 122 were contained in just three NDA's. As can be seen from the following tabulation derived from data accumulated by FDA statisticians, the reviewing physicians deemed less than half of the 122 to be adequate to permit valid conclusions:

NDA number and name of drug	Reviewing physician	Does study permit valid conclusions?			Total
		Yes	No	Uncertain	
16-618—Pondimin	Dr. Freeman	0	21	0	21
	Dr. Wright	0	16	0	16
16-880—Voranil	Dr. Trilling	33	18	3	54
17-247—Mazindol	Dr. Woo	16	6	9	31
Total		49	61	12	121

In spite of the above, the statisticians were instructed to include all 122 of their computer analysis.

The above judgments of inadequacy were based primarily on the inadequacies of, and deviations from, the clinical protocols; the objections raised in my Medical Officer Reviews—copies of which were submitted to Commissioner Schmidt on March 7, 1975—included serious doubts as to the validity of some of the lab data and hence are additive, rather than merely corroborative of the above tabulation.

Will you comment on that, please?

Dr. SCOVILLE. I do not suppose he comments on what conclusions would be permitted by excluding the studies that were found inadequate.

Mr. GORDON. The writer says the above judgments were based primarily on inadequancies of the data and deviation from the clinical protocol.

And he goes on as I had read.

Dr. SCOVILLE. Well, that is his opinion. Subsequent to the medical officers' individual overall reviews, each individual patient was reviewed, coded, key punched, and went through the computer.

I know the medical officers did not and could not have looked at each data sheet on the scale subsequently done.

Mr. GORDON. Actually he cites four physicians, four medical officers. They are Dr. Freeman, Dr. Wright, Dr. Trilling, and Dr. Woo.

As I see it, they put it together, they took the reviews of these four physicians, so you have really five people making this claim, people who reviewed each of these drug applications.

Dr. SCOVILLE. Well, I think Dr. Knox would agree that he has fairly strong feelings about the use of anorectics, which are known inside the FDA and not on the outside.

In order to avoid bias on the part of medical officers, we took pains to analyze every single patient, and have somebody inspect every patient data sheet before it was used in the analysis, and we tried to overcome personal bias by reviews.

Mr. GORDON. It is not just Dr. Knox, but it is four other physicians, so you would have to say five of them were biased.

Dr. SCOVILLE. Well, it is hard to argue with those, without going back and reviewing the ways the opinions were expressed, and the basis.

I gratuitously suggest that even in the worst case, it is unlikely that all 22 studies on a single drug were invalid, which is what one of the medical officers proposed.

Senator NELSON. I think this raises some important questions, but the Food and Drug Administration will appear.

We do not expect you to recall off the top of your head all of these statistics without having them before you, so we will put these questions to the Food and Drug Administration.

Dr. SCOVILLE. Thank you, sir.

Mr. GORDON. Now, in the FDA document dated February 17, the reviewing medical officers claimed the total weight loss for those groups on diet plus drugs was small compared to those on diet alone.

I will read this:

"It is generally agreed that there is a definite danger of abuse connected with the use of these drugs.

"While there is no unanimity of opinion as to the efficacy of these drugs, the following opinions merit careful consideration:

"The British Medical Association has concluded that 'These drugs should be avoided so far as possible in the treatment of obesity * * *'

"Arthur Grollman has stated that '. . . There is no evidence to indicate that these agents suppress appetite as has been claimed, which is the basis usually for advocating their use. The only rationale for their use is the hope that by counteracting the depression induced by hunger the patient is better able to abstain from overeating. However, the anorexigenic agents have proven of little efficacy in actual practice * * *'

"* * * The results obtained with anorexiant agents therefore (1) are in many instances inferior to those obtained with unsupplemented diets, (2) show the same marked variations present in the tabulated results of diet alone, and (3) indicate that the newer agents often compared poorly with the older ones whose deficiencies they presumably were intended to correct. * * *

"* * * I stand with a minority of physicians in feeling that these drugs no longer have any place in the practice of medicine, with one or two rare exceptions. * * *

"I understand that one or two other countries have actually banned the use of those highly dangerous drugs. There is no justification for our continuing their 'legal' use. To continue it would be simply to perpetuate one more massive inconsistency in our standards of morality.* * *

"The present labeling fails to give the physician any idea of the degree of efficacy which has been demonstrated in the MDAs for these compounds. It is unlikely that anyone reading the present labeling would suspect that the supporting data in the MDAs revealed such a limited degree of efficacy. Although we customarily do not include such information in package inserts, the amphetamines constitute a special case and must be dealt with accordingly. * * *

"I urge that the labeling of these compounds be revised to include, in each case, a factual tabulation of the actual amounts of weight lose which have been reported by the various investigators, to include the duration of therapy, so that the physician will be in a better position to decide as to whether or not use of a sympathomimatic amine is warranted. The common practice of expressing results in terms of rate of weight loss per week is particularly objectionable and should be discontinued. * * *"

What can you tell us about the quality of testing to establish efficacy of antiobesity drugs, and would you say in retrospect, that they met the standards envisaged by the law?

Dr. SCOVILLE. The ones that were used in the review, in the opinion of those that had the studies computerized, did meet the standards of the law.

I cannot give you details about individual investigators. I think we would have to go through case by case, if there were some suspicious things that anybody wished to bring up.

I would have to say that in the general approach, the FDA reviews the documents, and anything suspicious is looked at more carefully.

Occasionally field investigations are carried out.

Mr. GORDON. Here is a letter signed by Dr. Jennings dated February 19, 1970, that the drug Voranil was not approvable. He stated that "Bias has been introduced into the statistical analyses by deleting data from certain investigations in such a manner as to exclude unfavorable findings."

Can you recall how often you found this kind of tactic?

Dr. SCOVILLE. I do not recall.

May I ask the date of that?

Mr. GORDON. February 19, 1970.

Dr. SCOVILLE. The general approach when bias is detected is to inform the manufacturer of it, and a common response to such a statement is for the data to be resubmitted in a format determined by the FDA in a way in which the FDA tries to lay it all out so as to eliminate a potential for bias.

It is to eliminate potential for bias that we went over every patient report form.

Mr. GORDON. Did you find this is a common thing, this type of withholding of essential information, or using statistics in such a way that you get a favorable finding?

Dr. SCOVILLE. It is hard to be sure of motives.

In the case of inadequacy of statistical analysis, it is usually due to inferior motives or inferior abilities, and it is difficult to tell which.

Mr. GORDON. That is all.

Senator NELSON. Thank you very much, Dr. Scoville. We appreciate your taking the time to come and present your testimony this morning.

Dr. SCOVILLE. Thank you very much.

Senator NELSON. Our next witness is Dr. Eugene Jolly, president, Biometric Testing, Inc., Englewood, N.J.

Dr. Jolly, we appreciate your taking the time to appear here this morning.

Your testimony will be printed in full in the record.

You may present it however you desire.

STATEMENT OF EUGENE R. JOLLY, M.D., PH. D., PRESIDENT, BIOMETRIC TESTING, INC., ENGLEWOOD CLIFFS, N.J.

Dr. JOLLY. Thank you, Senator.

Senator Nelson, Mr. Gordon, it is a privilege to be here with you today to provide a summary of my findings resulting from clinical investigations of amphetamines and related drugs used as adjuncts in

the treatment of obesity and my thoughts in regard to the applicability of these drugs in clinical medicine.

It is a particular honor to discuss these matters with you, Senator Nelson, one of the truly distinguished citizens of my home State.

By way of introduction, Biometric Testing, Inc., is an independent testing laboratory, engaged in clinical research performed for the food, drug, cosmetic, and chemical industries on a contract basis.

As a recognized clinical pharmacologist with over 20 years of experience in drug research and development, my technical function is to design appropriate studies on test products, closely monitor their progress, evaluate responses to the test products and provide a comprehensive interpretation of the data obtained.

I should emphasize that I am a researcher and do not practice medicine.

Our list of sponsors includes a wide sprectrum of large, intermediate, and small firms. Of particular interest is our work for the small drug manufacturers. It is probable that we have conducted more bioavailability comparisons with generic drugs than any other research group in the world.

We are well known by both the industry and the Food and Drug Administration for our work in this field.

Senator NELSON. How many personnel do you have, and what are their credentials?

Dr. JOLLY. We have about 30 right now.

Senator NELSON. Thirty?

Dr. JOLLY. About 30.[1]

Well, actually my associate, he is an internist and gastroenterologist.

Senator NELSON. You have an internist and a gastroenterologist?

Dr. JOLLY. Yes.

We also have many physicians who assist us. There are specific tests, let us say we have a phase I test of a new drug, which requires constant physician monitoring, we will have outside physicians come in routinely.

We have dermatologists who will do skin work.

Senator NELSON. These would be specialists who are practicing, but are not employees of Biometric Testing?

Dr. JOLLY. That is right.

Senator NELSON. And who work on a contract basis?

Dr. JOLLY. Yes.

Senator NELSON. Within your own organization, how many full-time employees do you have?

Dr. JOLLY. About 30.

Senator NELSON. What scientific, medical, and pharmacological specialties are represented?

Dr. JOLLY. At one time we had two nurses. We have a full-registered nurse, and at one time we had two, but our business decreased, and we have one now.

Senator NELSON. Full-time internist?

Dr. JOLLY. The internist, Dr. Tessler, is on call at all times, but he is not on the premise at all times.

Senator NELSON. Does he have a practice?

[1] Dr. Jolly subsequently submitted the following: "Actual count 25."

Dr. JOLLY. Yes, he is on the staff with several hospitals in the city.

We have several medical technicians, and then we have a few people who have been involved in research, who are not actually trained with medical-technical degrees and medical technologies, but they have been associated with research over the years.

Until recently, we had a biophysicist, but he left us recently.

Senator NELSON. Do you have any statisticians?

Dr. JOLLY. We have a trainee statistician, and we employ Dr. Hyman Menduke (Jefferson Medical College) on a retainer basis.

We are attempting to improve our capabilities in this area.

We do have computer time, and complete statistical assessments for drug houses, usually major drug firms will do their own analytical work, their own statistical analyses.

They are better equipped for it.

Senator NELSON. What exactly does your organization do? Do you do animal testing?

Dr. JOLLY. No.

Senator NELSON. You do testing at the human being level?

Dr. JOLLY. Yes, volunteers.

Senator NELSON. Pardon?

Dr. JOLLY. They are completely volunteers.

Senator NELSON. But you are testing; do you do the chemical testing and the animal testing, anything like that?

Dr. JOLLY. No.

Senator NELSON. So you are doing the so-called clinical testing on human beings?

Dr. JOLLY. Right.

Senator NELSON. Where do you get your patients?

Do you have doctors?

Dr. JOLLY. No.

Senator NELSON. How do you find your patients?

Dr. JOLLY. It is kind of grows like topsy. People enjoy doing research work, and when they find they are treated properly, and what they are doing is explained to them, they will tend to come in time and time again, and participate in tests, and it is good if you have a stable population; but it keeps growing so long as you are in a given area.

Some of them have been coming for the entire 7 years we have been in operation.

They also are given monetary considerations. It is perfectly reasonable, rational and proper that they should be paid for their services, and they can make a little extra money.

I like to think they enjoy it, and get a feeling of participation in the research.

Senator NELSON. You do testing on ill patients?

Dr. JOLLY. No.

Senator NELSON. They are all healthy patients?

Dr. JOLLY. Yes, with few exceptions.

Obesity is a disease, but they are not sick people, so we will accept the obesity state. We will test cold preparations, for example, these subjects are sick, but maybe not sick enough to go to a doctor.

If we find somebody, and we have on many occasions found somebody that requires medical attention, they will be referred or told to go to their own individual physician, and many times we will find people who are ill.

Senator NELSON. So you are testing healthy patients.

What are you testing for?

Dr. JOLLY. Mainly for safety. Sometimes for effectiveness, in the case of amphetamines, this is strictly for effectiveness.

Senator NELSON. So in that testing, what was your protocol?

Dr. JOLLY. The protocol was devised by the company. Very often I will design protocols for people, because I have had a wide experience in this area. But the protocol I received was very, very well designed, and I think Dr. Scoville actually participated in some of the designs, or at least had a chance to review some of them, just to make sure that everything was covered.

Senator NELSON. Did you do any bioavailability studies?

Dr. JOLLY. That is another part of my presentation.

We are probably the largest, we have done more studies than anybody in the world in this area.

There are bioavailability comparisons on antibiotics, let's say, that are marketed, and we have done a tremendous number of those.

Now, these studies, because we want to prove, or we want to determine that the generic drug is equivalent to the referenced standard, and sometimes we find they are not, but most often they are.

Senator NELSON. So if we have a generic producer, he wants to go into the marketplace on an unpatented drug or the patent runs out, and they come to you with their formulation, their compound, you test it to determine whether it achieves a particular blood level or what the bioavailability is on a certain time schedule compared with the standard one in the marketplace, the brand name, is that what you do?

Dr. JOLLY. Yes.

Senator NELSON. All right.

Dr. JOLLY. Those are controlled studies as well.

Senator NELSON. But you do not do any testing on sick patients to determine the effectiveness of a particular drug against a particular target organism?

Dr. JOLLY. No; we practice research only, but I will state this, we do outside clinical work at hospitals, at places overseas, in Haiti we do some work.

Senator NELSON. What do you mean outside hospital work?

Dr. JOLLY. We do not do any clinical work for people and patients in our facility; however, we might conduct a study at New York Hospital, or someplace else.

We do some work in Puerto Rico, and at a hospital under the direction of doctors at the hospital.

Now, what is our function?

Our function is to monitor these studies, the thing is to make sure that they are completing the case reports, the way they were designed, that they are conducting the studies that were designed according to the protocol.

Senator NELSON. That they are what?

Dr. JOLLY. That they are conducting the study designed according to protocol, that they maintain their records, their proper records, and that they maintain all of the data required by that protocol, and perhaps some I might feel would be of interest along with it.

We have also done work in Haiti. These would be large-scale testing, vaccines, for example.

Senator NELSON. Vaccines?

Dr. JOLLY. Yes.

Senator NELSON. Now is that on all healthy patients?

Dr. JOLLY. Those are not specifically under our direction.

They are under our direction, but they are conducted by physicians in these areas.

We monitor them. Usually we will select physicians who are certified.

Senator NELSON. I take it you conduct studies and investigations to determine, then, whether the particular product meets the statutory standard of efficacy.

I assume that is what you must have done with the antiobesity drugs?

Dr. JOLLY. Yes.

Senator NELSON. And so your studies complied with the statute which requires well controlled scientific studies by qualified investigators producing substantial evidence of efficacy?

Dr. JOLLY. I am pleased to assure you of that.

Senator NELSON. So some of the studies involved questions of efficacy, some involved other bioavailability, that sort of thing?

Dr. JOLLY. Basic safety; right.

Can it be applied to the skin without producing sensitivity or irritation.

Senator NELSON. You do, I take it, studies on both prescription and nonprescription drugs?

Dr. JOLLY. Cosmetics as well. Sometimes food. Sometimes we determine the effects of food on situations, stomach acids, this sort of thing.

Senator NELSON. Where is most of your work, insofar as drugs are concerned, in the field of prescriptions or nonprescriptions?

Dr. JOLLY. About half and half.

About half of our work I would say at the present time and during the last year or two has been the bioavailability work, which has been a very important aspect of the Food and Drug Administration. All of us have been interested in generic drugs in the last 2 years.

That has been a very large section of our business. During the last few years we have been involved in phase I testing. This is the test on drugs when they first come out of the laboratory, and these are again extremely complex, and very, very tightly designed tests.

We keep subjects in the unit, during several days. They actually live in the unit, and are fed there. They will have around the clock nursing care and technical people with them. This is phase I work.

Senator NELSON. In your own facility?

Dr. JOLLY. Yes, sir.

I have been told it is one of the finest clinical pharmacology units; best equipped in the country.

Senator NELSON. Did I understand you to say you have done more bio work than any other lab?

Dr. JOLLY. I would say of all of the studies, that would be our greatest number.

Senator NELSON. Were you involved in the studies on bioavailability of chloramphenicol?

Dr. JOLLY. No; I missed that one. Other antibiotics have been tested by us.

Senator NELSON. Antibiotics for bioavailability?

Dr. JOLLY. Yes; we still do a number of them.

Senator NELSON. Does this mean for the purpose of determining for a producer whether or not it is an antibiotic he wants to market, or that it achieves appropriate availability within certain time schedules?

Dr. JOLLY. Sometimes.

We do some for some of the larger companies, where they already are accepted, but they want to recheck their product.

Senator NELSON. You are a clinical pharmacologist; do you have a degree in that field?

Dr. JOLLY. I have a degree in medicine from the University of Michigan. I have a degree in pharmacology from the University of Wisconsin.

Senator NELSON. You say you are not a practicing physician?

Dr. JOLLY. That is correct.

Senator NELSON. Do you have a license to practice?

Dr. JOLLY. No; I never have.

Senator NELSON. You have been in the research field at all times?

Dr. JOLLY. I had been with the Food and Drug Administration for a while, way back.

Senator NELSON. Go ahead. That was just so I could understand fairly well what it is you do.

Go ahead.

Dr. JOLLY. The amphetamine-like drugs fall into the general category of sympathomimetic agents. That is, they mimic a part or all of the responses seen from activation of the sympathetic nervous system, the so-called fight or flight mechanism of the body.

These responses include: An increase in bloodflow to the heart, lungs, skeletal muscle and brain; stimulation of the heart with an increase in cardiac output; dilatation of the bronchi and bronchioles of the lungs to allow more efficient oxygenation of the blood; and, central nervous system stimulation counteracting fatigue and increasing mental alertness.

Metabolic effects include elevation in blood glucose and fatty acids and an increase in metabolism mainly through breakdown of fatty acids.

It is important to recognize that there are numerous drugs in this category which produce sympathomimetic actions in various degrees. Therefore were amphetamine products, for example, to be removed from the market, other commercially available drugs could be substituted for them.

This question will be considered in our discussion as will the possibility of imposing further restrictions on the distribution of some or all of these products.

Of the series, methamphetamine and amphetamine are the most powerful central nervous system stimulants. The stimulant actions of one of these, amphetamine, were first described by Alles in 1933. In 1935, Prinzmetal and Bloomberg initiated clinical use of amphetamine for the treatment of narcolepsy, a disease characterized by inability to stay awake. Since that time, amphetamine products have been employed for a variety of conditions including chronic fatigue, parkinsonism, epilepsy, childhood hyperkinesis, and poisoning by CNS depressants. Of course, the most popular use of amphetamine products today is in the treatment of obesity.

Of the various clinical applications, experts still consider amphetamine as valuable in the treatment of patients with narcolepsy and for children with hyperkinesis in *selected* cases. This condition is very prevalent, experts estimating that some 5 percent of our children are affected to some degree. One of my children, for example, exhibited sufficient hyperactivity, lack of attention span, and associated behavioral problems to require therapy. Similar symptoms were exhibited by some of my other children and drug therapy might have been useful. In retrospect, I probably also presented similar symptoms during childhood. Hyperkinesis in children requires more intensive study and greater recognition. It is frequently associated with learning, speech, and other perceptual deficits. My own son suffered severe emotional problems related to the disease which one psychologist felt represented a borderline psychosis. The mental and emotional scars that are unavoidable sequellae represent the most damaging hazards associated with this disorder. Fortunately, the symptoms usually moderate with age and are seldom apparent in young adults.

Obesity of course is the most prevalent disease in our society. Just from the cosmetic standpoint, the disease can represent a serious threat to well being, and we all appreciate the importance of the quality of life as opposed to its duration. The contribution of obesity to the incidence and severity of other diseases; particularly those involving the lungs, heart, and blood vessels are considered by most experts to be significant. However, epidemiological surveys suggest that remarkable influences on longevity are only seen with early onset obesity; dating back to the teenages, twenties, and early thirties. Conversely, moderate obesity does not appear to significantly change morbidity and mortality associated with pulmonary and cardiovascular disease when weight gains start in later years—after 40. Of course, severe obesity at any age represents a serious disease state which can adversely effect the function of all organ systems.

There should be no question that amphetamine and related drugs are effective adjuncts in a therapeutic program for obesity. Their actions are clearcut and reproduceable.

Senator NELSON. Have you read the literature and the testimony yesterday of the four witnesses who recognize the recommendations of the FDA panel headed by Dr. Prout, that amphetamines' use indicated for obesity should be removed, that the results of treatment of obesity are "trivial," are you aware of it?

Dr. JOLLY. I have become aware of that.

Senator NELSON. Do you disagree?

Dr. JOLLY. No, not really.

My data came from very tightly controlled very definitive clinical investigation.

I was trying to prove that these drugs produced significantly more weight loss than placebos.

Senator NELSON. And was this short term?

Dr. JOLLY. It is short-term, so I do not think the two can be compared, and I do not practice medicine, so I do not think I could argue with the results with Dr. Scoville, for example, who evaluated these drugs to a much greater degree than I.

Senator NELSON. You are looking at it solely from the aspect of the short-term impact of amphetamine related to weight loss, and it was a double blind study?

Dr. JOLLY. Very tightly controlled, very rigid, in everything.

Senator NELSON. So your conclusion is only related to short-term use of the amphetamines in cases of obesity in connection with the diet, versus the placebo with diet?

Dr. JOLLY. Right.

Senator NELSON. And it has nothing to do with the long-term result?

Dr. JOLLY. That is correct.

My evaluation of the research work accomplished with amphetamine-like drugs has been requested. With the disclaimer that specific projects cannot be evaluated with precision unless they are monitored and the data thoroughly reviewed, my general opinion is that the background of animal and clinical work on these drugs is both extensive and adequate to make a judgement of effectiveness under conditions of use. The actions of these drugs are clear-cut and even under relatively lax experimental conditions, should be reproduceable. Controlled studies to demonstrate effectiveness in comparison to placebos require hard work but no unusual skills. Study administrators may frequently be tempted to guess which patients are being treated with active drugs because of the side effects exhibited. This is a research problem common with the study of most pharmacologically active drugs. Experienced researchers discourage such speculation by the technical personnel.

Those who do engage in guessing games will often find out that they were wrong. The actions of a placebo will often match and sometimes exceed those of an active material. Conversely, a very potent drug may not elicit any remarkable signs or symptoms in some individuals. Regardless, when objective endpoints are available, such as actual weight loss, assessments are simplified and data are more concrete. Moreover, when results obtained from a number of research sites prove essentially equivalent, it can be concluded that the findings are valid. On this basis, the effectiveness of amphetamine-like products as adjuncts in the treatment of obesity has been generally accepted by experts qualified by training and experience to make these judgements. Our data, confirmed by other investigators and resulting from separate investigations of amphetamine formulations and two related drugs can be summarized as follows:

1. Patients treated with amphetamines who complete the study requirements, weekly clinical visits, maintenance of the prescribed dosage intake, continued diligence during study periods ranging from 8 to 16 weeks, on the average will lose more weight than patients who

are maintained on placebo medication during equivalent periods of time.

2. Weight loss in both placebo and treated groups are more notable when dietary plans are detailed and maximum caloric intakes are calculated for each patient on the basis of height and body build, in contrast to weight losses associated with less rigid programs involving nonspecific dietary restrictions.

3. Fewer patients treated with placebo can maintain the personal motivation required to complete a weight reduction program, in comparison to patients treated with an amphetamine formulation or related product. There will be significantly more dropouts in the placebo group prior to completion of the study requirements.

4. The most important aspect in a weight reduction program is personal motivation. Unless highly motivated an individual cannot stay on a diet and no program will be successful.

5. Patients do not appear to become resistant to the effects of amphetamine, rather they gradually lose motivation.

6. Very obese patients have great difficulty in reducing caloric intake and losing significant amounts of weight with or without an amphetamine crutch. Such individuals are often called compulsive eaters or food addicts.

7. The amount of attention paid to the trials and tribulations of obese subjects is directly proportional to the success attained. Reviewing progress, counseling, gentle persuasion and strong encouragement are important facets of a weight-reduction program.

A rather dramatic illustration of the profound influence of the human psyche on eating habits is afforded by reviewing results of administration of sympathomimetic drugs to experimental animals. In the so-called lower forms these drugs are truly anorexigenic—appetite reducing—drugs. Most of us regard our canine friends as the most hedonistic of all creatures when it comes to food. Yet dogs given amphetamine will frequently stop eating entirely and literally starve themselves to death. The effects in rats and monkeys are a little less extreme but still remarkable. None require diet programs, motivation, tender loving care or any of the other forms of psychological bolstering so important for humans.

Clearly, if we resembled our animal predecessors just a little more closely, amphetamines might be fine, reasonably safe drugs for treatment of obesity. True, they may produce numerous side effects such as anxiety, tenseness, restlessness, throbbing headaches, tremors, weakness, dizziness, and palpitations and, most important, difficulty in sleeping. But the side effects are usually controllable by dose reductions and tend to abate with continued use.

Surprisingly, the stress which amphetamines induce on the system does not appear to produce any appreciable harm with moderate doses during short periods, except possibly to individuals with advanced cardiovascular disease.

Rather the problem with the amphetamines as with many other drugs which affect the central nervous system relates to that intricate, mysterious, perverse tissue mass, the human brain; responsible for the indefinable human psyche. During a relatively short span of availability, amphetamines have emerged as major drugs of abuse.

In consideration of the number of very unpleasant side effects a reasonable question is why? Like most drugs subject to abuse, amphetamines produce desirable responses that for some individuals outweigh any associated discomfort or, in gross overdosage, physical distress.

Compulsive users of amphetamines fall into roughly two categories. Individuals who consume therapeutic doses or doses only slightly in excess of therapeutic doses routinely, but not necessarily daily, fall into the first category. Such individuals have learned to rely on the drug to help them cope with the demands of their social environment. Amphetamines produce an elevation in mood and increased alertness. They counteract fatigue and improve the ability to concentrate. Physical performance may be enhanced considerably at times. Perhaps the most insidious perceived benefit is an increase of initiative and self-confidence.

Even though, on occasions, paradoxical responses occur, it is easy to understand how the student, the athlete, truckdrivers and other individuals who receive rewards for either intense or prolonged efforts can be hooked. Consider also the overworked or harassed executive who finds that amphetamines improve the quality and quantity of his work output, while increasing self-confidence and the housewife who may use the drug simply to counteract boredom.

Some of these mildly addicted individuals use the drug for years and don't present any remarkable social problem except occasional distressing loquaciousness. With moderation, amphetamine effects sound good and have a definite appeal. Unfortunately all is not as rosy as it sounds. Users have difficulty sleeping and tend to either become exhausted or to use sedatives starting the classical "upper-downer" cycle. Some find alcohol an effective antidote for the stimulant side effects. Alcohol and sedatives as a whole are really more pleasant drugs and can become a far greater problem than the amphetamines. Actually people don't become physically dependent on amphetamines. They can stop use without any terribly unpleasant responses. But they can and do become physically dependent on alcohol and some even to the sedative hypnotic drugs.

Other problems associated with chronic use are less well defined; however, mental depression and gastrointestinal diseases appear to be relatively frequent concomitants of routine amphetamine intake. Nevertheless, the most important side effect of weight reduction programs in which amphetamine is employed as an adjunct, is chronic compulsive use of moderate doses.

Experts regard even this form of abuse as more often a result of experimentation and subsequent reinforcement of a sensation of need for the drug in order to function, rather than as an iatrogenic medically induced problem. This pathway appears to be characteristic of all drugs of abuse. However, susceptibility to moderate abuse seems widespread and the risks involved are undoubtedly real, even during periods of short-term use adequately supervised by competent physicians.

Self-administration of gross overdoes of amphetamine-like products either orally, by inhalation or by intravenous injection represent a second and extremely hazardous form of abuse. Such activities are restricted preponderantly to members of our "drug culture." Individuals

who employ large doses of amphetamine, methamphetamine or similar drugs usually abuse other central nervous system drugs including alcohol, opiates, barbiturates and marihuana. It seems that any mechanism that can provide them with a means of escape from the expectations and impingement of society, their conscience and even consciousness, is subject to adaptation by these individuals.

Amphetamines are valued because of a "rush" sensation produced particularly when injected. The exhilaration experienced reportedly resembles a sexual release. Cardiovascular and CNS side effects are of course magnified and it is difficult to understand how any degree of pleasure can compensate for the associated unpleasantness. I've only seen the results of acute amphetamine abuse on one occasion during a day-long visit at the home of a university professor, a psychologist by training. On arrival in the morning, his wife appeared to be floating on air. She remained that way until shortly before our departure in the evening, when she collapsed into a deep sleep. During the day she would not or could not maintain a given conversation or sit for any length of time. She was inordinately garrulous and obviously edgy. This response was purportedly the result of sniffing a quantity of dextroamphetamine.

Most of us have seen the results of chronic, gross amphetamine abuse on TV, or at least read descriptions in the lay press. The anorexic actions of the drugs are illustrated by the fact that chronic users generally appear emaciated. But signs of mental disturbances are also obvious during periods of prolonged and repeated use. Diminished intelligence level can be appreciated particularly in previously highly intelligent individuals. Delusions and frank hallucinations are common. Feelings of persecution, suicidal urges, and even homicidal responses are characteristic of this category of amphetamine addiction. Deaths resulting from amphetamine overdosage can occur, but most often are a result of administration of companion drugs. Actually, it is amazing how resistant the cardiovascular system of the human being is to this form of grievous assault; particularly when one considers that the death rate from cardiovascular disease remains our leading killer.

Fortunately, when an amphetamine addict is "dried out" mental and physical pathology usually prove reversible. Nor do chronic, high dose, amphetamine abusers suffer withdrawal symptoms seen with addiction to depressant drugs; unless they happen to be addicted to any of these materials at the same time. Also, gross amphetamine abuse is usually episodic rather than continual as with classical opiate, sedative addiction. However, the property of tolerance to high doses is shared by this group. A dose of amphetamine which might prove fatal to a normal person may be employed routinely by some. Finally, it should be emphasized that this form of addiction to amphetamine is regarded by many experts to present the greatest potential for social aberrancies of a hazardous nature among the whole group of drug abuse problems. These individuals can be mutilators of children as well as adults, rapists and cold-blooded killers. One wonders for example, if the Manson cult were amphetamine freaks.

The issue remains whether the risk to benefit ration associated with the therapeutic use of amphetamine for obesity, or any other disease, is

sufficiently low to justify their continued commercial availability. At present straight amphetamine and methamphetamines are included in schedule II of the Controlled Substances Act along with morphine, cocaine, and other drugs of abuse. Should these two drugs in particular be relegated to category I, thereby prohibiting any form of commercial distribution? Should their use be restricted to cases of narcolepsy or childhood hyperkinesis in which they may well represent drugs of choice?

Those who hold that an elevation to the category I status would be overkill point out that initial results obtained through imposing the category II restrictions have been moderately effective in diminishing the low-dose amphetamine abuse problem and that with improved surveillance this form of moderate abuse will be effectively retarded. Many have doubts that a category I status would have any appreciable effect on severe abuse incidence in spite of increased effectiveness of our enforcement officials.

The street price of amphetamines, which rumor tells us is presently about $3 per dose would certainly increase which may afford some deterrent action; but, more likely, such an increase would prove of greater efficacy in supporting the ventures of organized crime.

Speaking to the pro-category I question, the therapeutic merit of amphetamine products are probably not sufficiently remarkable to dictate that they remain available even with further labeling restrictions.

Senator NELSON. What are you saying? That they not be marketed at all?

Dr. JOLLY. I think I am hedging a little.

Senator NELSON. All right.

Dr. JOLLY. The next sentence I think really says what I mean.

It seems unlikely that clinicians on the whole would strenuously object if the amphetamine products were completely banned; particularly if they could be assured that deletion of these occasionally very useful drugs would not be an exercise in futility.

Senator NELSON. You say it is unlikely?

Dr. JOLLY. I think so. You have seen that, obviously yesterday.

Particularly I think many of them have some doubts about the value of taking drugs off the market realistically, because it seems to me it is frequently an exercise of futility.

It really does not stop the horrible problems, and many of them feel that there ought to be better ways.

An investigative reporter, with whom I have become friendly recently disclosed to me that reliable information exists suggesting that other sympathomimetic drugs are presently achieving the widespread abuse category.

He specifically designated the drug, phenteramine as a popular amphetamine substitute.

This drug is presently listed among the drugs with low abuse potential in category IV. Our work at Biometric Testing, Inc., indicates that at effective therapeutic doses some of the sympathomimetic side effects may occur—dry mouth, palpitations, nervousness—but that the mood-elevating, antifatigue actions associated with amphetamine and methamphetamine are minimal.

Most investigators would discount a significant abuse potential for phenteramine and similar drugs on the basis of the data available in the literature.

The drugs have just not proven to elicit sufficiently rewarding responses in comparison to associated discomfort.

Yet, we cannot sell the human animal short. A lesser crutch will frequently be acceptable if the parent is not available, even though it is reasonable to assume that unwanted side effects will be proportionately amplified with higher doses.

Although not as extensively studied as amphetamine, phenteramine, and other drugs with similar activity have been well characterized pharmacologically.

Jerome Jaffe in the standard test, Goodman & Gilman cites the work of Martin and his associates—Clin. Pharmacol. Ther. 12:245, 1971—which suggest that some representatives of the series can produce central nervous system stimulation in experimental animals comparable to that of amphetamine depending upon the dose administered.

Since human investigations have been restricted to recommended doses, the relevancy of these data in humans cannot be defined. However, as a response to the invitation to discuss this problem with you I have explored this possibility further.

A former classmate and expert in the pharmacology of drug addiction, Dr. Gerald Deneau, and we have heard from Dr. Jasinski on the same thing earlier, provided me with data showing that primates under given conditions will self-administer some of these presumably less stimulant sympathomimetics. These data support the work of Martin, and others, and suggest that the appreciated amphetamine responses might be obtainable with elevated doses.

It is difficult for me to judge what the relevancy of these data are.

Any evidence suggesting a significant abuse potential requires critical evaluation before conclusions are warranted.

To achieve a conclusion that a given amphetamine-related product possesses abuse potential of an order to dictate added sanctions, it should be possible to document an increasing incidence of abuse.

In contradiction to my reporter friend, another close observer has failed to note any remarkable or alarming upsurge in recreational, nonmedical use of the amphetamine-related drugs.

He states that fenfluramine, a newer introduction more likely to produce drowsiness than stimulation, appears to present as many problems as some of the older products.

Yet, on the basis of limited data, it seems that baboons, at least, do not enjoy fenfluramine and will not self-administer the drug abnormally. Perhaps baboons are more discriminating than humans.

Undoubtedly our DEA, regulatory officials will be able to provide us with more definitive information in regard to the current incidence of cases of confirmed abuse of amphetamine-related drugs; particularly the incidence associated with the inhalation and intravenous routes of administration.

We do not know what the abuse potential is for these related drugs at this date. I think we have to find out.

If indeed the related drugs prove to possess an abuse potential approaching that of amphetamine, then clearly they should be placed in category II.

If new findings illustrate that a drug is favored by the "drug culture" as an agent of gross abuse, it may well merit category I status. Under any circumstances, we should remain diligent in defining degrees and hazards of abuse associated with these drugs retained on the market, and any potential substitutes should they be withdrawn. Thank you very much.

Senator NELSON. Thank you, Dr. Jolly.

We appreciate your taking your time to come and to present your testimony here today.

The hearings will recess until tomorrow morning at 10 a.m. in the same hearing room.

So we stand in recess, and we do thank all of the witnesses for appearing today.

[Whereupon, the subcommittee was recessed at 11:55 a.m.]

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

THURSDAY, NOVEMBER 11, 1976

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

The subcommittee met, pursuant to recess, at 10 a.m., in room 318, Russell Senate Office Building, Hon. Gaylord Nelson, chairman, presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; and Karen Young, research assistant.

Senator NELSON. The Monopoly Subcommittee of the Senate Small Business Committee will please come to order.

Our first witness this morning is Dr. Everett Ellinwood, associate professor of psychiatry, Duke University Medical Center, Durham, N.C.

We are pleased to have you here this morning.

Your statement will be printed in full in the record.[1]

You may present your statement however you desire.

If you would pull the microphone up close, it would help, because the acoustics are very poor in this room.

STATEMENT OF EVERETT H. ELLINWOOD, JR., M.D., PROFESSOR OF PSYCHIATRY, DUKE UNIVERSITY MEDICAL CENTER, DURHAM, N.C.

Dr. ELLINWOOD. Thank you, Mr. Chairman.

I have worked for many years now with most of the central nervous system stimulants, both in a clinical setting as well as in a basic research laboratory.

In considering the anorectic drugs currently in use, it is important to distinguish between the central stimulant effects and anorectic properties.

The amphetamines are perhaps the best prototype of anorectic drugs, having strong central nervous system stimulant activity as well as anorectic properties.

[1] See prepared statement and attachments of Dr. Ellinwood beginning at p. 14666.

I have a table, Mr. Chairman with a listing of the anorectic and stimulant drugs

[The table follows:]

TABLE I.—DEA SCHEDULE, GENERIC EQUIVALENTS, AND TRADE NAMES OF PRESENTLY MARKETED STIMULANT DRUGS IN THE UNITED STATES

DEA schedule	Generic name	Trade name
II	Amphetamines:	
	d amphetamine	Dexedrine, Obotan.
	d, l amphetamine isomers	Benzedrine, Biphetamine, Delcobese, Obetrol
	Methamphetaimine	Desoxyn, Fetamin.
	d amphetamine+amobarbital	Dexamyl.
	d, l amphetamine+prochlorperazine	Eskatrol.
	Other stimulant drugs:	
II	Methylphenidate	Ritalin.
II	Phenmetrazine	Preludin.
III	Benzphetamine	Didrex.
III	Chlorphentermine	Pre-Sate.
III	Clortermine	Voranil.
III	Mazindol	Sanorex.
III	Phendimetrazine	Bontril, Melfiat, Obe-Nil, Stratobex, Bacarate.
IV	Diethylpropion	Tenuate, Tepanil.
IV	Fenfluramine	Pondimin.
IV	Phentermine	Ionamin, Fastin.

Dr. ELLINWOOD. Methylphenidate and phenmetrazine also have strong stimulating properties similar to the amphetamines.

In considering the usefulness of these stimulant properties, there are two specific medical uses on which a consensus among physicians is held:

(1) Their use in hyperkinetic children; and

(2) Their use in narcolepsy.

In both these conditions, one is faced with deficiencies in arousal and attention mechanisms.

Hyperkinetic children demonstrate a remarkable inability to focus their attention on specific tasks or interests before them. They are especially distractable and susceptible to extraneous stimuli from the environment.

In a school situation, they are incapable of handling the repetitious tasks requiring focused attention, such as reading and writing.

Stimulants have also been generally accepted as a specific treatment for narcolepsy, an uncommon condition which is characterized by sudden attacks of sleep and weakness during normal waking hours, and unusual periodic sleep patterns at night.

Stimulants, and especially amphetamine, have been found to change what is at times an incapacitating condition to an ability to return to work, to drive a car, and to carry out in a relatively normal fashion, tasks requiring vigilance and attention.

Without the stimulants, the individual would periodically fall asleep as many as 6 to 20 times a day, and at times and conditions that would be compromising and dangerous.

There is a disagreement over the use of anorectics having pronounced stimulant properties in weight reduction regimes.

This disagreement arises primarily because many individuals who have originally taken the stimulants for weight reduction appreciate the energizing and euphoric effects and continue to take the drugs for reasons other than weight reduction.

In my opinion, general long-term use of amphetamines or other stimulants for weight control should be discouraged strongly.

The current practice of using the more potent stimulants for weight reduction during a 2- to 3-week startup period to allow the individual to gradually cut down his food intake patterns then discontinue the medication, needs also to be questioned.

Several clinicians, Penick, 1969; Feinblatt, 1961; Fineberg, 1967, have specifically recommended this regime as being effective in a weight-control protocol.

The Federal Drug Administration has previously reviewed the drug trial data on the effectiveness of the whole gamut of anorectic drugs in weight reduction regimes and it would appear that they are, indeed, effective.

In this unpublished study, Scoville, 1972, using 206 anorectic drug trials which had been submitted to the FDA, the FDA researchers placed the raw data in a common format and subjected it to a total analysis; they indeed demonstrated that there was a significant effect—at least out to 16 weeks—of these anorectic drugs on weight loss.

Usually, the weight loss amounted to 1 pound per week more than a simple diet alone with placebo.

For the most part, the researchers at the FDA felt that the majority of the studies were well done, especially those accomplished on the basis of 3- and 6-week studies.

The 1-year studies were not well-controlled and did not have good followup.

Mr. GORDON. May I interrupt at this point, Dr. Ellinwood.

Dr. Scoville, whom you referred to, was here yesterday, and he was unaware that many of these studies on which you based your statement were found to be inadequate by at least four or five of FDA's medical officers. There has always been disagreement among the medical officers in the Food and Drug Administration concerning the efficacy or the adequacy of evidence showing that these drugs are effective. I would like to point out to you that this particular study is a pooled study which included many individual studies. In fact, more than half of them were inadequate, and apparently did not satisfy the law involving substantial evidence.

Dr. ELLINWOOD. I will have to leave that to the researchers at the FDA.

Obviously one could question many clinical studies, but on the basis of the information I have, they have considered most of the studies to be adequate.

I do think a word of caution is needed in that these studies are based on short-term effects of weight reduction, and if one follows any type of treatment program for obesity for any length of time, the task of keeping weight down in these individuals is extremely discouraging.

Most researchers—Stunkard and McLarenhume, 1959; Penick, 1969—report that only a small percentage of patients maintain their weight loss at the end of a year.

Others—Penick, 1969—have cautioned against the total pessimistic view, in that treatments may have been effective in helping overweight patients from gaining even more weight.

There is no hard data to support the issue one way or the other, and one could certainly conceive of anorectic drugs being used on a short-

term basis in order to help the patient establish habit patterns, or become involved in behavioral programs which would foster long-term weight reduction.

The main question in evaluating anorectic drugs is not just their therapeutic effectiveness, but also the trade-off against the abuse potential of these compounds.

In a later section of this statement, we will discuss the point that the toxic impact of amphetamine-like stimulants on the individual, and indeed on society, is significant.

We should strongly encourage attempts to reduce the use of compounds with potent stimulant properties.

Another major question is whether there are anorectic drugs which have less of the stimulant abuse potential but which are still effective anorectics.

At this point it should be stated that none of the anorectics have been proven to be absolutely free of some form of abuse potential, yet there may be a new group of relatively nonabused anorectics emerging; that is, the ring-substituted amphetamine analogues.

Now, I am not going to go into the chemical makeup of these substitute compounds, except I think the evidence is accumulating that they may be different than the chain substituted compound.

To date, the side-chain substituted amphetamine analogues, when tested in self-administration animal models, and in other tests for stimulant properties, all appear to have some stimulant potency.

Although weaker than dextroamphetamine and methamphetamine, as well as phenmetrazine, these compounds would appear to have sufficient stimulant properties to be abused by some individuals.

Conversely, the major dependent abuse cycles have not been established with most of these compounds as has been noted with the above primary stimulants.

The ring-substituted amphetamine analogues, fenfluramine and chlorphentermine, are amphetamine congeners which have anorectic effects apparently without major psychostimulant or sympathomimetic effects, that is, cardiovascular stimulant effects.

When tested in man, these drugs instead of producing a stimulant effect, appear to have more sedative properties.

Studies using drug abusers to test for euphoric and arousal effects indicate that they do not perceive fenfluramine or chlorphentermine as having the euphoric and arousal effects in the same way as most CNS stimulants.

A word of caution is needed for fenfluramine, in that high doses induced psychotomimetic effects—Griffith, 1976; Gotestam and Gunne, 1972—that is, visual and olfactory hallucinations—Griffith, Nutt and Jasinski, 1975—rapid mood swings, distorted time sense and fleeting paranoia.

The psychotomimetic effects of fenfluramine should be evaluated carefully since there is one report in the literature—Levin, 1973—indicating that a South African group of drug abusers had used this compound for its hallucinogenic properties.

Remember, we are talking about a very high dose usage of this compound.

There have not been similar reports, to my knowledge, in the United States.

With chlorphentermine, one needs to consider that there have been isolated reports of pulmonary hypertension, again which have not been reported, to my knowledge, in the United States.

Thus, these two ring-substituted compounds should be carefully examined, both in the basic research laboratories as well as clinically.

Basic research with these two compounds has demonstrated a marked attenuation of stimulant properties as well as the indicators of abuse potential.

In the case of fenfluramine, it is one-twentieth as potent as amphetamine in elevating blood pressure in rats, and has no effect on body temperature—Bizzi and others, 1970.

Fenfluramine, as well as chlorphentermine, suppress feeding in rats without the induction of locomotor stimulation—van Rossum and Simons, 1969.

In the self-administration technique for assessment of abuse potential, fenfluramine has been demonstrated to be a compound for which neither rats—Baxter and others, 1973—nor monkeys—Griffith, 1976; Woods and Tessel, 1974—will self-administer.

Self-administration data for chlorphentermine is more equivocal, in that rats have been demonstrated to self-inject this compound as they do amphetamine, phenmatrazine, and diethylpropion—Baxter and others, 1973—however, monkeys show little evidence of self-administration—Yanagita, unpublished results.

To continue the example with fenfluramine further, in actual practice as an anorectic, fenfluramine has been demonstrated to decrease food intake in many species, including man—see Stunkard and others, 1973.

Those studies have demonstrated more of a sedative effect chronically with fenfluramine than for either placebo or amphetamine when administered for weight reduction.

Finally, although there is a report of the use of fenfluramine for its hallucinogenic properties, there have been no published reports of dependence patterns following several million prescriptions in the United States.

I would like to present my recommendations on the basis of this statement, and then go into what I think is the major abuse potential of these compounds, the strong stimulant compounds, in man.

In the light of these differences among anorectic compounds, a more rational approach to the abuse potential problem of anorectics would be to encourage discriminating basic research and preclinical evaluation of these compounds for the tradeoff for their anorectic properties and potential stimulant abuse properties.

Furthermore, rescheduling the anorectics with stimulant properties could encourage physicians to be more careful in their prescribing criteria.

This observer would consider moving phentermine—Ionamine and Fastin and diethylpropion Tenuate and Tepanil at least into schedule III.

Mr. GORDON. May I interrupt.

Why schedule III? It has no effect on medical practice.

As a matter of fact, Dr. Crout in a document states as follows:

"Schedule II of the CSA, the most restrictive for marketed drugs, requires nonrefillable prescriptions, special records, and manufactur-

ing quotas, among other things; schedule III and IV have little but psychological impact on the practice of medicine, requiring only a special symbol on the labels and labeling and a practitioner's BNDD number on the prescription. The schedules of the act include three anorectics—methamphetamine, the amphetamines themselves, and phenmetrazine."

Dr. ELLINWOOD. That exactly will be my point.

As I said, I will consider at least moving it into the III category.

Let me go ahead and finish that.

I think that will clarify your question.

In addition, based on basic research in self-administration models or evidence of euphoriant effects in man, compounds such as benzphetamine, clortermine, mazindol, and phendimetrazine as well as diethylpropion and phentermine, might be considered for schedule II.

Placing these compounds in schedule II would require that the physician explicitly write these prescriptions without refills.

This would place considerably more emphasis on reevaluation for subsequent prescription writing.

The more potent stimulants such as dextroamphetamine, methamphetamine and phenmetrazine currently under schedule II should be considered for possible discontinuance of their use as anorectics.

Certainly these compounds have been demonstrated to have considerable abuse potential.

Use of potent stimulants for hyperactivity in children and narcolepsy should be maintained.

Senator NELSON. You would remove the indication for anorectic purposes from the drug labeling, I take it?

Dr. ELLINWOOD. For those compounds, for dextroamphetamine, for phenmetrazine and methamphetamine.

I think there are sufficient other compounds with less of the stimulating properties that one could use for this.

Finally, physicians might be encouraged to consider prescribing one of the ring-substituted compounds dependent on their evaluation of the patient for an initial weight reduction regime, at least before the more euphoriant and stimulating compounds are considered.

Obviously, education of both physicians and the public is a major means of facilitating this process.

I would like to go now into the impact of stimulant abuse on the individual and perhaps on society.

In determining the impact of stimulant drugs on the individual and society, one can consider a host of potential changes including the morbidity and mortality rate among amphetamine abusers; the potential for an emotionally apathetic state following chronic abuse and withdrawal which has been described both in this country as well as Japan—Tatetsu, 1963; Utena, 1966; Ellinwood, 1973.

In addition, there is evidence from chronic intoxication animal studies that nerve cell death takes place in brain areas which in part mediate alerting and emotional arousal—Escalante and Ellinwood, 1970.

Studies in monkeys have demonstrated a long-term, perhaps permanent, depletion of an important neurotransmitter—dopamine—which lasts for at least 3 to 6 months following high dose amphetamine maintenance—Seiden, and others, 1976.

Thus, there are clinical descriptions as well as basic research indicating that there may be long-term changes following chronic amphetamine intoxication.

Senator NELSON. What is the effect of that, of whatever long-term changes that may occur?

Dr. ELLINWOOD. You mean in humans?

Senator NELSON. Yes.

Dr. ELLINWOOD. Well, it is very difficult to document this, but there are many, many cases, reports, and histories of individuals, which report emotionally apathetic, fatigue states involving long-term use of amphetamines, at times some difficulty remembering.

Now, I need to add, however, that critical studies of individuals with neurological tests have not demonstrated intellectual deficits, so I think one needs to consider that also.

Perhaps the major issue relating to impact on society is that of criminal activity.

Obviously, the drug marketplace is an unstable arena in which crimes against property can become a part of the stimulant abuse pattern—Smith, 1972.

One crucial question is whether stimulants specifically induce violence in abusers.

In order to obtain a perspective of the effects of amphetamine on aggressive and violent behavior, one should compare them with the effects of other drugs.

The concensus among those who work closely with problems of abuse is that opiates do not induce unwarranted violence and, in fact, are likely to inhibit tendencies toward violence, even though addicts are frequently involved in potentially explosive criminal situations—Kolb, 1925.

On the other hand, for years alcohol and sedatives have been associated with an increase in violence which is thought to be secondary to a lowering of impulse control—Guize, and others, 1962.

Reports from law enforcement personnel and psychiatrists, as well as from drug users themselves, have indicated that high dose amphetamine use may also be related to aggressive behavior—perhaps more specifically than some of the other groups of drugs.

That is, such high dose use may actually facilitate aggressive behavior rather than just lowering impulse control—Ellinwood, 1969, 1971a; Kramer, 1969; Smith, 1972.

Chronic high-dose use of amphetamines, which leads to behavioral aberrations including psychosis, is considered by clinical observers to be a volatile state and is the one not infrequently implicated in violent or assaultive behavior.

In contrast, several survey studies, where arrestees are interviewed concerning their drug use—that is, the spectrum of low-dose and high-dose use—indicate that amphetamine use per se is not specifically related to violent crimes—Blum, 1969; Eckerman, and others, 1971; Greene, and others, 1973; Tinklenberg, and others, 1974.

Thus, it appears that the violent activity most frequently appears not with low or moderate doses of amphetamine, but with the chronic high dose stage of unstable and/or psychotic behavior.

Often the amphetamine-induced paranoid ideation or emotional liability leads to the violent act or even overt homicide—Ellinwood, 1971b.

Not infrequently, the amphetamine abuser committing homicide is attacking an imaginary assailant or persecutor created in his paranoid delusional thinking.

The violent act may take place in a state of terror or panic, often secondary to misinterpretation of events or delusions.

Perhaps equally important is the influence of amphetamines in creating:

1. Impulsive or reactiveness, and

2. a liability of mood in which the user abruptly vacillates from a warm congeniality to fiercely hostile moods for the most trivial of reasons—Kramer, 1969; Ellinwood, 1971a.

The drug subculture of amphetamine abuser, of course, is involved frequently in criminal activity in order to support drug use.

The amphetamine abuser may suddenly panic and react violently while involved in an armed robbery.

At times, this reaction is touched off by a bizarre feeling such as being suddenly and furiously angry because the storekeeper "smiled at me."

In the study of amphetamine abusers committing homicide—which I carried out—Ellinwood, 1971a—7 of the 13 subjects were acutely psychotic and delusional at the time, and this disturbance of thought appeared to be directly related to the homicide.

Four persons were primarily in an amphetamine-induced emotionally labile state.

Paranoid ideation may have been involved in these cases, but it was not the most salient feature.

Two persons with low impulse control had also been drinking at the time the homicide occurred.

In two cases, homicide was associated with armed robbery and this appeared to be the primary contributing condition.

Although the killers were high on amphetamines at the time, it is difficult to assess the relative importance of this and other factors since by far the most important factor was the flow of events associated with the armed robbery.

Both of these men stated that they were obtaining money to buy drugs. Twelve of 13 persons committing homicide were carrying concealed weapons at the time.

Many speed users carry weapons, ostensibly for a variety of reasons including:

1. For use in armed robbery.

2. Because of their suspiciousness and fears—often he has "heard someone breaking in at night" or he becomes increasingly fearful of his persecution and begins carrying a gun, and

3. There is a certain amount of "cowboy and Indian" braggadocio involved in carrying guns by speed users.

Anyone working with amphetamine addicts will hear stories of individuals sitting all night with a loaded gun waiting for fantacized intruders to enter.

Under these conditions, speed freaks have been known to shoot at hallucinated noises or images.

Amphetamine facilitated violence is not peculiar to the United States; similar reports of bizarre aggression as well as homicide come from Sweden, Japan, and England.

Noda, 1950, reported that during the Japanese epidemic of amphetamine abuse, in a 2-month period 31 of 60 convicted murderers had some connection with the misuse of amphetamines—Rylander, 1969—reports that there had been 3 murders, 1 manslaughter, and 21 assault and battery crimes committed by the 146 stimulant addicts admitted to his Swedish Forensic Psychiatry Clinic.

There had been 109 crimes committed against property some of these crimes were associated with aggression.

In his original monograph on amphetamine psychosis—Connell, 1958—states that hostile aggressive behavior was observed in 22 percent of the subjects included in his series from England.

In a recent study by the—Kalant, 1976—examining deaths reported by the coroner in the Province of Ontario in 1972 and 1973 which were related to amphetamine use, they found that 17 of 26 were deaths of a violent nature.

Seven were due to accidental violence, usually, due to poor judgment; seven to suicide; and three to homicide.

Among the suicides, there was a high incidence of self-inflicted fatal gunshot wounds.

Two suicides followed the killing of a police officer with subsequent impending capture by the police.

One male was shot by a policeman after attacking him with a knife.

From perusal of both the reported homicide cases and those of assault, it is apparent that many drug users move through three fairly distinct phases leading to the violent act.

The three phases consist of: First, chronic amphetamine abuse; second, an acute change in the individual's state of emotional arousal; and third, a situation that triggers the specific events leading to the act of violence—Ellinwood, 1971a.

The phase of chronic abuse often sets the stage; it includes changes in the individual's frame of mind involving suspiciousness, paranoid thinking, and fearful regard of his environment.

It is during this period that he obtains and begins to carry a concealed weapon.

Armed robbery as a means of supporting the drug habit and conflicts over drug dealing also are segments of the setting that derives from chronic drug use.

The second phase, involving a sudden change in emotional arousal and/or a loss of intellectual control, is often secondary to a variety of factors, including a sudden increase in the dosage level—or acute use in a person with low tolerance—chronic loss of sleep, and the use of other drugs, especially sedatives and alcohol.

In this emotional and cognitive framework, the person often misinterprets his environment and becomes increasingly fearful.

The emotional misinterpretation may be quite subtle; for instance, a sudden and overwhelming interpretation of a minor "clue" that fits into the person's delusional system.

On the other hand, it may be a very gross misinterpretation of the entire environment; strangers suddenly becomes sources of persecution.

Often the person mistakes a stranger for a persecutor, or, alternately, for a friend—Ellinwood, 1967; 1969.

This phase of sudden misinterpretation of the environment is associated with an intense sense of reality.

Within this framework, a minor incident can trigger the violent act. Often the threatening incident is half real and half misinterpreted.

In nine of the cases in this study, the murder was committed on the basis of an instant decision or impulse secondary to a perceived danger. There were, however, four other cases in which some forethought was involved in the intent.

One man "tracked down" his victim.

Even within this context of pursuit of the victim, there is often a singular event that triggers the violence.

In fact, in Smith's 1972 descriptions, nonfatal pursuits are not uncommon—Kramer and others, 1967—have stated that these games are often only half serious. Thus, although chronic amphetamine abuse may set the stage for violence, it is the phase of acute changes in sensibilities that is actually associated with misinterpretation and the violent act.

At this point, a note of caution is indicated. Homicides related to amphetamine abuse certainly pale in significance when one considers the incidence relative to alcohol related violence.

This does not mean that the fewer episodes of stimulant facilitated homicides are not critically important, but we should maintain a perspective with respect to alcohol.

Finally, the question can be asked whether there are residual psychological changes that remain after one has developed the amphetamine psychosis.

The amphetamine paranoid psychosis is a well-known phenomena associated with chronic amphetamine use—Connell, 1958; Kalant, 1966.

Although single large doses of amphetamine can produce a toxic hallucinatory paranoid panic state, amphetamine psychosis most often results from chronic abuse and develops gradually; when seen by the examining physician, the process often has extended to the point where a picture of paranoid schizophrenic-like psychosis is present—Ellinwood, 1969.

In fact, many patients have not infrequently been wrongly diagnosed as such.

The paranoid syndrome usually does not begin until after the initial few weeks, or even months of amphetamine abuse.

Mr. GORDON. Doctor, may I interrupt you just 1 second?

You mentioned alcohol. In one of your journal articles you referred to poly-drug abuse, and you state:

> Reports on several persons who have committed quite serious assaults indicate that when combining amphetamines with other drugs, staggering amounts of alcohol or sedatives can often be consumed. Without the amphetamine use, the individual would have passed out.

Would you say this is an additional danger of amphetamines?

Dr. ELLINWOOD. Yes; I would say so.

Mr. GORDON. That you would consume much more alcohol?

Dr. ELLINWOOD. Yes; and the combination often ends up with a fairly activated individual, who has lost a considerable amount of his judgment.

Otherwise, a similar amount of alcohol, he would frequently pass out.

When the individual who had been taking amphetamines chronically combines it with alcohol, he loses a considerable amount of judgment.

It tends to wax and wane depending on the drug cycle and dosage level.

Hallucinations tend to dissipate 2 or 3 days after cessation of amphetamine use, yet delusions continue up to 2 weeks and have been noted in some patients for as long as 1 year or more.

The amphetamine psychosis usually is a distinct syndrome characterized by delusions of persecution, ideas of reference, visual and auditory hallucinations, changes in body image, hyperactivity, and excitation—Connell, 1958; Kalant, 1966; Ellinwood, 1967; 1969.

Whereas the amphetamine psychotic process usually takes a reasonable period of time to develop into its more organized form, once established, moderately high doses can retrigger the psychosis rather rapidly in individuals who may have been abstinent from amphetamines for over a period of 1 year—Kramer, 1969; Bell, 1973; Ellinwood, 1973.

The Japanese—Utena, 1966—also describe a tendency for the psychotic symptoms to recur not only with subsequent amphetamine administration, but also under stress.

Since the more aberrant behavior induced in animal models of chronic intoxication can also be triggered by single moderately high dosage—Ellinwood, 1971b—the clinical data needs to be taken seriously and examined further. This evidence, plus the observation of chronic delusions in some amphetamine addicts seriously raises the issue of chronic persistent behavioral effects.

In summary, my recommendations are based on the fact that obesity is known to contribute to a decreased longevity; thus, it is important for clinicians to have means of establishing weight reduction regimes.

Many consider the development of an anorectic without stimulant abuse potential as a goal not only worthy, but obtainable.

There is a considerable body of knowledge on the neuro-pharmacology and neurophysiology of eating behaviors.

In addition, there are assessment techniques currently available for determining in the laboratory relative stimulant abuse potential for potential anorectic drugs.

The total abolition of anorectic drugs would reduce the pharmaceutical industry's search for the nonabused anorectic. There are examples of compounds currently on the market that appear to point in the right direction.

Proper use of our current knowledge base and further research will contribute to the goal of developing better nonabused anorectics.

I would suggest establishing an independent FDA review committee that would provide guidelines for the basic and preclinical research needed to establish the therapeutic efficacy and abuse potential of new anorectic compounds.

Use of our current knowledge could very accurately discriminate the compounds that will demonstrate abuse potential and those that will not.

In the interim, I would recommend additional rescheduling of the anorectics with stimulant properties to encourage physicians to be more careful in their prescribing criteria.

This rescheduling would exclude at this time the ring-substituted anorectics until there is sufficient data to indicate that these compounds have an abuse potential.

The more potent stimulants, such as dextroamphetamine, methamphetamine, and phenmetrazine, currently under schedule II should be considered for possible discontinuance of their use as anorectics.

Finally, it would be helpful to have some means of monitoring and restricting physicians and/or obesity clinics that overprescribe the stimulant anorectics.

Mr. Chairman, that concludes my statement.

I have the references at the end of my prepared statement that I would like to have made a part of the record.

Senator NELSON. Without objection, so ordered.

Mr. GORDON. Doctor, in Psychiatry in March 1971, you discussed the histories of persons that had marginal schizophrenia, and after taking amphetamines, they deteriorated rapidly.

Now, this kind of condition would be contraindicated for the prescribing of amphetamines; is that correct?

Dr. ELLINWOOD. Certainly.

Mr. GORDON. Now, when a person goes to a so-called fat doctor, do you think he is going to be given a psychiatric examination?

Dr. ELLINWOOD. Probably not.

Mr. GORDON. So since violence and crime ensue, or can ensue, the consequence of amphetamine use can be very serious both to the individual and to society, as you stated before. You would agree with that, I presume?

Dr. ELLINWOOD. I would.

Mr. GORDON. Now, three of the cases had low tolerance, had taken large amounts of amphetamine, and developed paranoia status.

You also state it is not the amphetamine intake that is important, but it is the relationship to the level of tolerance.

Now, is it possible or practicable for the prescribing physician to determine the level of tolerance for the patient?

Dr. ELLINWOOD. No; I do not see that as being probable.

He could certainly determine the tolerance, but it is really not very feasible in standard medical practice.

I want to emphasize one thing, that in describing the toxic effects of stimulants, we have been talking about the more potent complex that includes the dextroamphetamine, the methamphetamine and preludin, and I do not think we have any direct evidence that the compounds that fit in between those, or fit below those compounds in their stimulant potency have induced the chronic states that I have been describing.

This is one of the reasons I have recommended that we take the compounds, the more potent stimulant compounds, out of the anorectic use category for these drugs.

I am not, however, recommending taking out all of those compounds, because we do not have direct evidence that they caused these chronic problems that we have been describing.

Mr. GORDON. But can they cause them? We do not know. Before you put a drug on the market, shouldn't you have to show whether it causes this or does not cause that symptom?

Dr. ELLINWOOD. I think we could get evidence of that. I think the most important thing is whether they have sufficient euphoria properties which indicate they will be abused. I think we do have tests now in both the clinical laboratories as well as basic research laboratories, that can provide us with fairly good evidence of the potency of these compounds in at least a few patterns of behavior.

There are fairly good tests now, that can give you a reasonable picture before they come on the market, but we do not have a complete picture for all of the compounds that are on the market.

Mr. GORDON. Well, don't you think we should have a picture before we put a compound on the market, is that not required by law?

Dr. ELLINWOOD. I think that is a reasonable assumption.

Mr. GORDON. Thank you.

Senator NELSON. The amphetamines, of course, have been on the marketplace long before the 1938 requirement of proof of safety, and much longer before the 1962 provision for efficacy. As to the amphetamines, we are dealing with a drug that did not have to meet at that time a safety and efficacy standard.

Are there any statistics available that would indicate, that would show what percentage of the drugs used for anorectic purposes were in fact highly stimulating amphetamines?

Dr. ELLINWOOD. What percentage?

Senator NELSON. Yes. People go to a physician for treatment of obesity, and get prescriptions for drugs. What percentage of those prescriptions for that purpose are in fact amphetamines, the highly active stimulants?

Dr. ELLINWOOD. I think those prescribing habits have changed dramatically, at least since 1968.

There has been a shift in the prescribing habits.

Senator NELSON. That was because they were put on schedule II?

Dr. ELLINWOOD. Yes, because they were put on schedule II, and the absolute production of these compounds was of course reduced.

I think there has been a gradual shift to the less potent compounds, but I do not have statistics on that.

Senator NELSON. We will ask the FDA when they appear next week.

Mr. GORDON. Mr. Chairman, I ask that the two articles by Dr. Ellinwood be placed in the record at the appropriate place.

Senator NELSON. The two articles will be made a part of the record.

We thank you very much, Dr. Ellinwood, for appearing and presenting your testimony.

Dr. ELLINWOOD. Thank you, Mr. Chairman.

Senator NELSON. Our next witness will be Reverend Reginald Yake, executive director, Teen Challenge Training Center, Rehrersburg, Pa.

Reverend Yake, your statement will be printed in full in the record.

You may present it however you desire, and if you wish to make additions to the statement, extemporaneously, you may do so.

STATEMENT OF REVEREND REGINALD YAKE, EXECUTIVE DIRECTOR, TEEN CHALLENGE TRAINING CENTER, REHRERSBURG, PA.

Reverend YAKE. Thank you, Mr. Chairman.

I just wanted to state I am appearing for others.

I am reading their statements. It is not mine.

It was advised that they should not be present. They are presently in attendance at the Teen Challenge Training Center, and the Justice Department recommended along with yourself that possibly I appear in their stead because of damaging of their future, possibility of future incriminations from future work, or desires of their future plans, so as a result, the individuals that I am going to be referring to are anonymous, and this is to protect them.

Senator NELSON. But they are individuals who are now in your training center?

Reverend YAKE. Yes.

Senator NELSON. They are currently there?

Reverend YAKE. Yes.

Senator NELSON. So you are simply presenting on behalf of each of them their own statement about their involvement with amphetamines?

Reverend YAKE. Right.

Senator NELSON. And do you have a statement of your own, observations concerning your experience with them with your center?

Reverend YAKE. Right.

Senator NELSON. Go ahead.

Just be sure you identify what is your statement, your own statement and conclusions, so that the reporter has it correct in the record, distinguishing between yourself and that of the individuals.

Reverend YAKE. OK.

This is a statement that we will call Mr. B.

He states as follows:

In regards to the series of hearings on the antiobesity drugs which include amphetamines, I am sending you my story of involvement.

My name is Mr. B, and I am 22 years of age. I am from the south shore of Massachusetts. I am presently in the Teen Challenge Training Center in Rehrersburg, Pa. I was placed in the program on December 1, 1975, by the courts of Massachusetts for a drug-related crime, facing 2½ years with another trial pending.

My involvement with amphetamines was not as a user, but as a seller.

At the time, my habit was with heroin, for 3 years at $25 a day, and some barbiturates.

Selling the speed only helped support my drug habit. The girl that I lived with at the time was also involved quite heavily with the flow of amphetamines. She was sentenced to a year imprisonment in DeLand County in Florida in the year 1973.

My involvement with speed began when I obtained the name of a doctor who was known to give out prescriptions for amphetamines quite freely.

I bought this information for the price of 50 percent of my pills for the next three visits with the doctor.

Senator NELSON. What information was that? The information where to get it?

Reverend YAKE. Where to get it from the doctor, yes, the information was to know the doctor's name.

Senator NELSON. And so he paid somebody 50 percent of the sale value of the pills to get the doctor's name where he could go to get the amphetamine?

Reverend YAKE. Yes.

Later on in the statement, he refers to the fact that this is a saleable item on the street.

[Mr. B continues:]

The doctor that I was seeing was giving prescriptions for Biphetamine #20—Black Beauties—and he, the doctor, would also direct me to a certain drugstore where I could have my prescription filled.

The visit with the doctor would cost me $6 or $8 and the prescription itself about $7. With this small investment, I could turn the script over on the street for anywhere from $60 to $100. Demand was always greater than the supply with this particular drug—speed—and this always enabled me to get my price.

Senator NELSON. He sold the prescription?

Reverend YAKE. No, he filled the prescriptions, and then he sold the drugs to make the money for his heroin habit.

[Mr. B continues:]

At the time I was getting this drug, I weighted 170 pounds and my height was 5 feet 8 inches. The doctor kept a record of this each time for Government records.

My further involvement was when I obtained the name of another doctor in the area who also gave out prescriptions for speed. His procedure was the same as the first doctor, but he gave out scripts for phenmetrizine tablets.

Senator NELSON. When he says scripts, does he mean prescriptions?

Reverend YAKE. Yes.

Senator NELSON. I see.

Mr. GORDON. I think he is referring to phenmetrizine.

Reverend YAKE. OK.

[Mr. B continues:]

The law states that these drugs are to be given out to the patient only once a month, 30 capsules or pills when overweight.

As far as the second doctor is concerned, he was within the law, but I was seeing him three times a month under three different names without a disguise.

At the same time, I was still seeing the first doctor. As time went on, I started selling the name of the doctor to other people the same way I got it, only I got paid in cash.

I also got the idea from a guy that I often met in the doctor's office to bring along with me some girls to see the doctor for the same reasons as mine and have them get scripts or prescriptions for me to sell and in return for them, I would supply them with a very small amount for their present need.

The guy—another dealer—who gave me the idea of getting girls to work for me was presently doing this himself with various doctors.

While in this business with speed, I came across the names of other doctors who also gave out freely prescriptions for speed, but I didn't have the time to bother with them.

I was busy enough with the doctors I was already involved with. I might add though that there were several other doctors that I tried to obtain speed from and I was turned away with a flat no because they knew what I was up to.

The doctors that I dealt with were real quacks and I feel strongly that they knew what I was up to, because I had gone as far as refusing to leave a doctor's office until he gave me what I wanted.

I hope and pray that this statement has some effect on the present situation in dealing with the leniency of giving out pharmaceutical prescriptions.

I believe strongly that although restrictions may be tightened because of the outcome of this investigation, this alone will not solve or even help solve the drug problem in this country, until individuals—drug users—are dealt with individually as part of this society and not as a problem that everyone wishes they could sweep under a rug and be rid of.

The drug addicts, when dealt with, need to see and understand what the truth really is about this life here and to feel that they are a part of something. I feel the only cure for the individual to be able to see the real truth in life would be for someone to lead him or her to the truth of Jesus Christ.

[End of Mr. B's statement.]

Now, I talked to Mr. Gordon on the telephone, and I asked him if he could be a little more specific on some of the situations, in that he would not be appearing here for cross examination, and so there is another page, a subsequent page he has written up.

[Mr. B continues:]

The doctor's office, at all times, would be packed with young people ranging in age from 18 to 35 or 40. From their conversations I could tell what their motive was for seeing the doctor.

All of them were after prescriptions for speed, of which this was phenmetrizine.

The people there were from different cities, Boston, Fall River, Brockton, and so forth. They traveled from all over to this doctor. How did they find out about this particular doctor?

News in the street travels fast.

The other doctor who gave out biphetamines also had an office packed with patients, but he also had some older folk that were there for reasons other than to obtain speed.

The people there for prescriptions for speed greatly outnumbered the older patients. I learned from being in this con game with doctors that there were various other ways to get other prescription drugs from doctors.

For example, in order to get a certain drug, you would have to have a certain story for the doctor to believe, but not everybody knew these stories.

I am talking about barbituates and Delada now. These stories would cost money along with certain doctors' names. I am just trying to show how easy it is for someone that is a good con to be able to get what he wants from certain lenient doctors.

Also all of these doctors kept records of these visits for the Government or the medical association to inspect if ever necessary, so I see that it is not only the doctors that are lenient but the people that are over them also.

Most people using speed in the street do not see themselves as drug users because they are usually house mothers, college students studying for exams or just the good people in society that are very social.

This speed, which they do not call it, is just something to pick them up; it does not make them silly or incapable of doing work, but in fact helps them. They do not realize its potency and effect on their lives until it is too late.

Then they find they cannot function without it, and when they are deathly sick because of the lack of nutrition that they deprive their bodies of when they take these so-called diet pills, and then they find out they are a nervous wreck because of the abnormal effect of the drug, such as being able to stay awake for maybe 24 hours, 48 hours or even 72 hours at a time. Diet pills are being used for everything but dieting. Oh yeah, it is popular around heavy drinkers; speed allows the drinkers to drink in excess without falling all over the place.

I have nothing against the medical profession or the laws of this country, but there is always one bad apple in every bunch, and the odor of this rotten apple is smelled by everyone and takes away the sweet fresh fragrance of the other good apples.

[End of Mr. B's statement.]

So yesterday I asked the individuals in the program, and the Teen Challenge Training Center—we presently have 130 fellows in residence—if there were any others that had experiences, and I gave to Mr. Gordon this morning a briefer statement from an individual from the Washington, D.C.-Baltimore area, and it is brief, and I will read it.

[Statement read of other witness:]

On or about the early part of 1970 myself and several friends were involved in the purchase of methadone in the southwestern part of Washington, D.C. We were able to purchase as much methadone, which on some days ranged up to the hundreds of dollars worth, as we were able to pay for.

The doctor was completely aware of what was going on and made no effort to hide it. Not too far from this same location was another doctor who was doing the same exact thing. The drugs which were purchased were taken to Baltimore where they were sold on the streets for higher prices.

From about the middle of 1973, up till the latter part of 1975, I was involved in the buying of pills through doctors in the Baltimore area.

This was set up so that I had medical assistance and could go to various doctors during the day. I was able to purchase various types of drugs, including valium, parest, nembutal, seconal, turinals, placidyalls, and many others, including class A narcotics.

These doctors were aware that I was on a drug program, and still would prescribe drugs. The doctors, some, not all, were careful of how they dispensed the drugs. They would prescribe only enough for 1 month's supply, but would prescribe several different types of medication.

Other doctors would insist that several different people would come so they could prescribe to them, but I would receive the drug after we left the office.

Some, though, would prescribe a large amount and tell you not to come back. On one occasion I can recall, I told a doctor I was strung out on valium, and needed to be detoxed off of them, I was told I could handle it myself if he could prescribe a large amount.

He did so willingly. This I did on several different occasions, to the same doctor.

On another occasion in the Baltimore area, my girl friend was approached while in a doctor's office and asked if she would exchange sex for an assorted amount of drugs.

There are many, many instances I could give you of how doctors have sold drugs to myself and many of my friends, knowing they were being used illegally.

[End of statement.]

I have a third statement, but it is very brief, from the fellow from the New York City area.

Senator NELSON. Is he in your center?

Reverend YAKE. Yes, all three of these individuals are in our training center.

[Statement read of additional witness:]

I am here to inform you that I had the distasteful confrontation in meeting and dealing with the so-called doctors of this day and time.

I am not referring to all doctors, but specifically some who should have their license terminated for a period of time.

These particular doctors offer you any kind of drugs for a price, knowing that they are very dangerous to withdraw from. They offer you barbiturates in quantities, for cash money, I believe they should be under strict control in terms of dispensing these drugs. I was getting it from five different doctors while under the influence of alcohol and Methadone, this mixture will kill any creature on earth.

Today there are many young people that are turning to drugs because they are very simple to get their hands on.

I pray to God that there would be something done about this. We are dealing with precious lives. God bless you.

[End of statement.]

Senator NELSON. Concerning your center, is it for the care of only people who have drug addiction problems?

Reverend YAKE. Primarily drugs, second alcohol, and third, troubled youth.

Senator NELSON. And what is the incidence of amphetamine abuse among the individuals in your center?

Reverend YAKE. Teen Challenge Training Center has been in operation since 1962, and for many years our primary intake has been among the heroin users.

In fact, in our research that was conducted in 1968, we had 89 percent heroin users.

I do not have statistics today to tell you of the breakdown of the various types of drugs, but I would say the majority of the fellows at the training center presently, and we have 130, is on the barbiturate-amphetamine area.

Senator NELSON. One or both?

Reverend YAKE. One or both.

Very seldom do you see a drug addict that is an abuser coming to our center that is strung out on one particular type drug anymore.

It is what they call the polydrug use, so it ends up one time he will take one type, and another time he will take another type.

Senator NELSON. And that over half of your current census involves amphetamine and barbiturates?

Reverend YAKE. I would be safe in saying that; yes, well over half.

Senator NELSON. This is not particularly relevant to these hearings, but were these prescriptions prescribed in this fashion reported to the authorities by anyone?

Reverend YAKE. No, we do not get involved with that as a rule.

We have had a lot of unfortunate situations with guys coming in. We had a fellow that came in the Teen Challenge program in the Chicago area, he happened to be from Wisconsin, and this fellow had 2 years of college, but when he walked into the Teen Challenge Center in Chicago, he could not write his own name, and if you were to ask him what his birthday was, he told me afterward, he had said it was seven garbage cans in January, and he would have thought he was carrying on an intelligent conversation, he was so messed up with speed, and we had another fellow from Long Island, who likewise was in college, and he could not carry on a coherent conversation when he came to Teen Challenge, because of the effects and abuses of the drugs.

Senator NELSON. How successful is your program in permanently getting them off of the drugs?

Reverend YAKE. Well, we made a research, as I said, in 1968, we stuck our neck out and put it on the line.

For years, we had felt that Teen Challenge had a viable program, and the research was concluded last year.

We are talking of 1968, which was primarily heroin, and we have not updated this as of now, but we were told that anyone who is off of drugs 5 years by society is considered cured, so in 1973 we applied for a grant for 1968, and was turned down.

We kept the same year of 1968, and we reapplied in 1974, and we were granted a grant by HEW, and it started in September of 1974.

Now, we are getting feedback from this particular grant now, and if we take Government standards of drug free after 7 years, taking 1968 graduates in 1975, we were 86 percent, but we do not consider that successful, because we feel that a guy cannot be an alcoholic and drinking a six pack, especially drinking on weekends, or to be a drug addict, he cannot be popping a few pills and smoking marijuana and likewise drinking a six pack.

Our philosophy is complete abstinence, and we saw 70 percent after 7 years documented by NORC out of Chicago, were cured, and had stayed cured from drugs.

Senator NELSON. Do you have any statistics on how the patients in your center were first introduced to the drugs?

Reverend YAKE. No, we do not.

Senator NELSON. Do you take a history when they come in?

Reverend YAKE. Yes, we do, but we have never compiled them as such.

I have a report that comes on my desk every month of the intake of fellows, like we have a group of fellows that come in every month, and a group that graduate every month, and it is an 8- to 9-month training program at the training center, and I have a list of all of the various types of drugs, how many years they have been in jail, how many years they have been on drugs, and this type of information, but we have never compiled it in statistics.

Mr. GORDON. You mention doctors as the original source.

Now, is it your impression that the principal source of the drugs which are used for drug abuse comes from doctors?

Reverend YAKE. As statements have been given to you and to us, I would say they are one of the very strong contributing factors.

Now, the one fellow, I read his statement for you, from South Shore, Mass., his primary function was a drug pusher; however, the

other fellow from Baltimore, or Washington that I read to you his statement, after a period of time, he started to buy drugs by bypassing doctors, and started to rip off drugstores himself, and so I would say many times individuals get started on this, or they get it on such easy accessibility of it in schools, or on the street, because of someone's abuse with the doctor, that, you know, this is hard to prove, but these guys are out pushing drugs on the street, are getting it from doctors and other people are buying them from them.

Senator NELSON. Thank you very much for taking time to come this morning and to testify.

Reverend YAKE. Thank you.

Senator NELSON. Our next witness is Mr. Larry Hicks, Teen Challenge Youth Center, Rehobeth, Md.

STATEMENT OF LARRY HICKS, TEEN CHALLENGE YOUTH CENTER, REHOBETH, MD.

Mr. HICKS. I do not have a prepared statement as such.

I believe I was called here primarily to speak from a position of ex-drug user and drug seller.

I am currently living in the Bowie area of Maryland, and was working as the director of Teen Challenge Center in Rehobeth, Md.

Senator NELSON. As a director?

Mr. HICKS. Yes, and became related to Teen Challenge, because I was paroled there from a conviction, a drug conviction, and from the Maryland Correctional Institution, and I guess, for all of my life, I used drugs for about 10 years, and when I say used, I also mean selling, and because I did not have to work that way, I could stay high longer.

I became associated with amphetamines, or speed in 1967, and used it, as often as I could until 1971, and sold it whenever possible, because there was money in it.

It was a good drug to sell, and there was a large demand for it, it was quite popular, and from working in the Teen Challenge Center, it still is very popular today. It has not changed.

My own personal experience with the drug, most of the amphetamines that are found coming from physicians, dextroamphetamine sulfates, dexedrine tablets, benzedrine tablets, biphetamines, biphetamine T-20's, dexoxyn, a pill made by Abbott, and in the realm of personal use, most of these were secured in smaller quantities, most of the Smith-line products, dexedrine and benzedrine, things of that nature, we got from a friend's wife who worked in a doctor's office.

Apparently the doctor must have received a lot of samples of these drugs, and she was able to take them home, and they had kind of a little drugstore at their house.

You could get anything you wanted. The only drugs that were really available in quantities to sell for me personally were the dexoxyn tablet made by Abbott, I believe, which was, it was a one-time thing, I would say there were several thousands of them available, and this was in Buffalo, N.Y., and a white pill with a mark on it, what I do not know who makes it, but we called them crossroads, that was available in tremendous quantities.

Senator NELSON. Is that an amphetamine?

Mr. HICKS. It was a stimulant. I do not know the chemical nature of it. There was literally thousands of them available.

Senator NELSON. Available how, where?

Mr. HICKS. That came through a contact in North Carolina.

I do not know how he secured them.

The only other pill that was available in any large quantity over any period of time is the black beauty, a biphetamine pill, I think it has always been around, as long as I was in the drug-selling business.

Personally, when I lived in New York, I had a friend in Batavia, N.Y. which is about 30 miles outside of Buffalo, who was selling me the black beauties, and on one specific instance, he told me that I could secure as much as 25,000 of them, and unfortunately, for me at the time, I did not have the money to do it.

I did purchase several thousand of them from the fellow at different times, 500 being the largest quantity at one time.

He related to me that his contact got them from the factory, but I do not know personally about that.

Mr. GORDON. That is the Pennwalt Corp.

Mr. HICKS. At the time they had RJS on it, and then later on, when I moved down to the Washington area, and began buying the black beauties, at this time I was securing them from a doctor, I noted they had a different symbol, I believe that was the Pennwalt Corp.

Mr. GORDON. They changed the name.

Senator NELSON. At what price were they?

Mr. HICKS. I cannot recall. I believe it was like 30 some cents a pill.

Senator NELSON. And what would they then sell for on the street?

Mr. HICK. At that time, you could sell them for, depending on who you sold them to, anywhere from 75 cents to a dollar.

Now they are much higher. I do not know about them today, but in 1970, they had gone up from a dollar to $3.

Senator NELSON. Sold on the street?

Mr. HICKS. Yes, street value.

Senator NELSON. Do you recall what the price was if you bought them in a pharmacy?

Mr. HICKS. I think when I got the script filled, it would cost me about $6 for 30 of them.

Senator NELSON. How many a day would a drug user be likely to use?

Mr. HICKS. It would depend on how long he had been using them.

The majority of the people I knew would probably use maybe two or three of them per day.

Other people I know at times I was using them, I would be using 8 or 10 a day, because you needed more later to stay up, otherwise you would go to sleep, and one of the things you did not want to do was go to sleep.

Senator NELSON. What was the main source of these drugs that people such as yourself would use and sell them? What was the main source?

Mr. HICKS. It would depend on which drug it was.

The black beauties initially came from when I was living in Buffalo, came from an individual in Batavia, who said he secured them from a fellow at the factory.

I cannot verify that. In Washington, I secured them from a physician, and the other drugs, as I said, I got them from a fellow who was, his wife worked for a doctor, and brought home the samples, the white cross. That came from a drug dealer down in North Carolina.

I do not know where he secured them.

Senator NELSON. In the course of the period you were using and selling the drugs, was your source frequently or infrequently a physician?

Mr. HICKS. Only a physician on one instance.

Senator NELSON. Only in one instance?

Mr. HICKS. Yes; I never had to rely on them before, and I was not that aware of the accessibility.

I was usually looking for a larger quantity.

From the physician you could always secure a script for usually 30 pills, and we would have to go back the next month, and get another script, and go back the next month, and it seemed like too much hassle to go around and find 10 doctors to get enough pills, when you could find one person and buy them from him.

Senator NELSON. What was the price you would pay per prescription, do you recall?

Mr. HICKS. From the doctor, it cost $5 a visit.

Now, you went in, and he took your blood pressure, and weighed you, and asked you what you would want, and you told him, and he wrote the script, and you gave the $5, and you had to go out and fill it.

Senator NELSON. He just asked you what you wanted, and he gave you what you asked for?

Mr. HICKS. Yes.

Senator NELSON. No quarrel about whether you needed it or not?

Mr. HICKS. No.

Senator NELSON. From your experience and that of others, how easy did it appear to be to go to this physician and get a prescription?

Mr. HICKS. His office was always full, and I found out I was able to take several of my friends with me, and they secured them for themselves.

At the time, it was a difficult period. I was not really dealing that heavily, and I had just been arrested, and I did not want to get arrested again, so I was laying a little low.

Senator NELSON. You are no longer associated with the Rehobeth Teen Challenge?

Mr. HICKS. I just resigned and moved back to the Washington area, and I will be taking up a position of teaching a course in drug administry at a school being formed in Washington.

Senator NELSON. Thank you very much, Mr. Hicks, for taking the time to come.

Mr. HICKS. Thank you.

Senator NELSON. Our next witness is Mr. Edward King, deputy director, Town of Huntington Youth Bureau, Huntington, N.Y.

Your statement will be printed in full in the record.

STATEMENT OF EDWARD A. KING, JR., A.C.S.W., DEPUTY DIRECTOR, TOWN OF HUNTINGTON YOUTH BUREAU, HUNTINGTON, N.Y.

Mr. KING. Thank you.

Mr. Chairman, I am deputy director of the Town of Huntington Youth Bureau, and program director of the town's community-based drug program.

My testimony today is based on over 7 years of experience in my present position with Huntington township, which is a large Long Island suburb of New York City, with a population of 220,000 people.

In 1968, the town of Huntington established the first town-level youth bureau in New York State, funded by the New York State Division for Youth, and our youth bureau was among the very first agencies to receive State funds to operate a community-based program for the prevention and control of youthful drug abuse in 1970.

In 1971, the town of Huntington instituted the first voluntary amphetamine ban in the United States.

Senator NELSON. You say the town of Huntington instituted the first voluntary amphetamine ban in the United States.

What does that mean?

Mr. KING. That means that physicians in the town of Huntington got together and agreed not to prescribe amphetamines.

Senator NELSON. All right.

Mr. KING. Except in the very rare cases of narcolepsy and hyperkinesis.

At that time there were only two cases of narcolepsy identified in Suffolk County over a 2-year period.

Senator NELSON. How many cases of hyperkinesis?

Mr. KING. A small number of hyperkinesis cases.

The national incidence that year was about 3 percent of all children between the ages of 5 and 12 that suffered from hyperkinesis.

The town's comprehensive youth plan includes eight private, nonprofit corporations known as youth development associations serving local neighborhoods within the township, and several support programs in the areas of job development, summer camps, runaway placements, family advocacy, and court diversion, as well as the drug program which consists of a hotline, counseling center, and outreach workers assigned to the local youth development associations.

We feel that our eight youth development associations on contract with the youth bureau provide the key to the development of program strategies specific to reducing drug abuse.

They are operated by local boards of community citizens—adults and youths—and are in the best position to recognize local problems and their solutions in cooperation and coordination with our youth bureau professional staff.

This elaborate system of citizen involvement in local government includes—in addition to local neighborhood boards—center councils, task forces, special committees and program volunteers, working with

the understanding and support of the appointed members of the youth board and the elected officials of the town council.

We describe this grass-roots volunteer effort with obvious pride, Mr. Chairman, to illustrate the importance of the work of this committee.

With all of this local community concern and effort translated into quality programs and professional services, we will ultimately fail to free ourselves of drug abuse unless institutionalized forms of drug abuse are addressed at the Federal level.

Senator NELSON. What do you mean by institutionalized forms of drug abuse?

Mr. KING. I mean, particularly relevant to our discussion here today, the abuses of amphetamines by so-called weight clinics and weight doctors. I would go beyond that myself, in my own personal opinion, to include, for example, additives and preservatives in the foods we eat to make them more conveniently and more efficiently produced and marketed by big industries, to maintain their profit levels.

Senator NELSON. When you say institutionalized forms, you are referring, I take it, to the legal prescribing?

Mr. KING. Legitimized sources, yes.

Senator NELSON. Legitimized sources of amphetamines?

Mr. KING. Yes; and I would like to offer a very specific illustration at this time. In February of 1972, the town of Huntington provided expert testimony in the person of Edward M. Gurowitz, Ph. D., then director of clinical services of the town's narcotic guidance council, before a Senate subcommittee chaired by Hon. Paul G. Rogers, dealing with the very same concerns over amphetamine abuse which we are addressing here today.

In that testimony, Dr. Gurowitz referred to a doctor with a "diet practice" with offices in the same building as our town's counseling center, and also housing the Suffolk County Methadone Maintenance Clinic. He spoke of his difficulty in explaining this to young clients who saw long lines of people, many of them young, few of them obese, waiting to obtain drugs for weight control.

The situation was aggravated by the fact that many of these clients were court remanded for treatment after arrest and conviction for their illicit drug abuse, and had real feelings about the daily parade of "legitimized" drug traffic which they were witness to.

The following steps were taken on the local level: The Suffolk County District Attorney's Office was alerted to the situation; the Suffolk County Medical Society was informed—but the doctor was not a member, and they could impose no effective sanction—the town's counseling center was moved to a new location; and, soon after, the county's methadone clinic moved away also. As of this writing, this same doctor remains under investigation of the Drug Enforcement Administration, and in active practice in the same location with an estimated weekly caseload of over 800 patients.

In January of this year, one of those patients, a 20-year-old female, came to our counseling center with the hope of breaking a 1-year addiction to amphetamines.

The pills were given to this client on a regular and unregulated basis. She stated that she was given the pills directly by the doctor, and that she was able to get more than the usual weekly allotment of 21 pills with ease.

She further stated that, after the first visit, no significant examination was made of her physical or emotional condition.

During that year, before she came to us, she was often deeply depressed, had visual hallucinations, was delusional in her thinking, and attempted suicide on three separate occasions. She was hospitalized each time.

On February 2 of this year, we referred her to a local detox unit, and they referred her to a local residential treatment program. She withdrew after 2 days, but our followup determined that she remained detoxified for 2 months before she returned to the doctor's office for more pills which she received.

On May 4, in the presence of one our workers, she wrote a letter to the doctor, and told him of her addictive history with the pills he had been giving her, and pleaded with him to never give her pills even if she begged him.

I wish that I could say that this is an atypical and overly dramatic case, Mr. Chairman, but this sad story is unusual only in the sense that this young woman came for help.

When amphetamines are involved in an established pattern of drug abuse, deep depressions, aggressive acting out, paranoia, suicidal tendencies, and resistiveness to change are the common traits.

Mr. GORDON. Mr. King, may I ask you a question concerning the doctor you mentioned. Does this practice include only obesity cases?

Mr. KING. To the best of my knowledge, yes, sir.

They are not really obesity cases in the sense that many of the clients seeing him are thin.

He sees more people who you would characterize as underweight than you would characterize as overweight, in my opinion, from the people I have seen coming and going from his office, and from the people he has seen who have come to us.

This is only one doctor who illustrates the problem. He is not the only doctor who practices medicine in this fashion within our township.

Mr. GORDON. And is he and the others also found to be the principal sources of speed?

Mr. KING. Yes, sir, of the young people we have seen in the program, a very large majority of them who have problems with amphetamines, obtain their amphetamines from one of these three doctors.

Some of them obtained their amphetamines from two or three of these doctors.

Mr. GORDON. How many cases have you had during the past year or so of amphetamine abuse?

Mr. KING. Coincidentally, our capacity for our program in the course of the year, the number of clients we can effectively work with, is 800, which happens to be the weekly caseload of one of these doctors.

Out of those 800 people, roughly 30 in the course of a year are characterized as having a problem with amphetamines in conjunction with other drugs.

Out of those 30, only about 3 obtained their drugs illicitly.

Senator NELSON. Of the 30 that came to your clinic, only 3?

Mr. KING. Yes. Of those we were able to contact through outreach and bring into our program.

Senator NELSON. Only three of them obtained illicitly the drugs, were these all amphetamines, or was it a mix of various kinds?

Mr. KING. They were all taking amphetamines, or amphetamine-like stimulant drugs, that they had obtained through these doctors.

The doctors used a variety of drugs, they do not use the same drug at all times.

The drug delcobese, known on the street as 697's, that is the drug enforcement number, seems to be the most common right now.

Senator NELSON. Twenty-seven out of 30 received them through their physician?

Mr. KING. Yes.

Senator NELSON. Go ahead.

Mr. KING. Just as these hearings on antiobesity drugs are part of a larger study of the development, marketing, and distribution of prescription drugs in general, the abuse of amphetamines is usually combined with the abuse of tranquilizers, sedatives, and barbiturates obtained, far too often, from other doctors.

Many adults in town, as well as young people, find themselves on a chemical roller coaster of "ups" and "downs."

The suburban housewife seems to be a particularly high-risk population for this kind of drug abuse. Some start with depressant drugs, develop tolerances, and then go to a "weight doctor" for amphetamines to help them get up in the morning.

Others get "strung out" on their increased tolerance for amphetamines and go to another doctor where they present the symptoms of extreme fatigue, anxiety, and tension, and tranquilizers or sedatives are prescribed.

We have found very few amphetamine abusers in our township who have obtained their drugs from the street in recent years. This is not the case with tranquilizers, sedatives, and barbiturates, which are more common in general and more available in the illicit drug traffic.

If we could somehow control the production of tranquilizers, sedatives, and barbiturates so that tomorrow they would be available for only the appropriate medical uses, I would think twice before doing it. I certainly would not want to drive in heavy traffic the next day.

The kind of human services necessary to enable less fortunate members of our society to cope in a healthy and responsible way with the stresses and anxieties of modern-day life are simply not in place.

This is not to say that depressant drugs are not grossly overproduced and overprescribed. They most certainly are, and Federal controls are urgently needed. However, these controls should be developed carefully and instituted with caution. A phase-in period of several years in which production limits would tighten in set steps would allow for the necessary ongoing evaluation which this effort would require.

Amphetamines are a different story. The testimony of Dr. Gurowitz 5 years ago carefully established 1,200 kilos as a reasonable national production limit for amphetamines. This would provide an adequate supply to supplement the nonamphetamine drug of choice—Ritalin—for the treatment of the rare conditions of narcolepsy and hyperkinesis. The latter condition is presently thought by many to be caused,

at least in part, by allergic reactions to dyes and preservatives in foods; yet another form of institutionalized substance abuse.

It seems to me, Mr. Chairman, that amphetamines are the place to start with strict controls on production. While the abusers of depressant drugs are often self-medicating to control the symptoms of underlying emotional turmoil, amphetamines only aggravate and intensify those very same symptoms.

The person with underlying hostility becomes more hostile. The person with underlying depression becomes more depressed. The person with underlying psychosis breaks more completely with the realities around him.

The overall impact of this aggravated and intensified conflict on family life is beyond calculation, but most certainly widespread and tragic in its effect.

We, in the town of Huntington, are pleased and grateful that this committee is once again focusing attention on the critical need to curtail the overproduction of commonly abused prescription drugs by big industries throughout our Nation.

By broadening the focus of our public concern over drug abuse in this way, we can take real steps to demonstrate integrity in our national effort.

Young people abusing drugs obtained on the street have been scapegoated for too long in our so-called "war on drug abuse."

Young people in general are extremely sensitive to hypocrisy, and would be quick to recognize any real steps to deal fairly and squarely with institutionalized drug abuse as also being steps to reduce significantly the alienation young people feel from this national effort at the present time.

Your leadership will go a long way toward uniting young and old alike in a national effort to find healthy and responsible ways to limit and control drug abuse and the closely related human abuses of all kinds.

We thank you for the opportunity to be a part of that process and stand ready to assist in any way possible.

Thank you.

Senator NELSON. Do you have a residential center, or is this all outpatient?

Mr. KING. This is all in the community, an outpatient, counseling program. Although one portion of our program is a clinical counseling center, where we do more intensified counseling, the backbone of the program is involving young people, both drug users and nondrug users alike, in the governing of their local communities, in terms of developing programs and services for themselves and other people in the neighborhood.

Senator NELSON. Did you say you have at any single time about 800 clients?

Mr. KING. That is an annual capacity. We work with, in the neighborhood of 300, 315 or so at any one given time, at the present, with our present staff.

Senator NELSON. You have about 300 enrolled at any one time?

Mr. KING. At any one time, yes, sir.

Senator NELSON. How long generally is the program?

Mr. KING. The program has been in operation for 6 years now.

Senator NELSON. For the treatment of the individual?

Mr. KING. It varies from person to person, Senator.

The average is roughly in the neighborhood of 16 weeks, in terms of us counseling with them intensively, and working with other aspects of our comprehensive youth plan, in developing possibilities for involvement in constructive activities for that person to address himself to. Beyond that, we do not really measure as part of our drug program.

Senator NELSON. Are all or most of the clients residents of the community?

Mr. KING. Yes; they are all residents of the community, with rare exceptions. When someone comes to us from outside the township, we see them, we do not turn them away, but I would say about 98 percent of the people we work with come from within the geographical township of Huntington.

Senator NELSON. What is the population within the geographical area?

Mr. KING. Two hundred and twenty thousand people.

Senator NELSON. And within that township, do you know how many physicians prescribe?

Mr. KING. Three who are outstanding, two doctors prescribe almost exclusively amphetamines.

They do not actually prescribe them, they give them away, and charge for the office visit.

Senator NELSON. There is no particular indication for their use, for control of obesity, as you said earlier?

Mr. KING. First of all, I do not feel they have value in the control of obesity, and, second, people obtaining the drugs are not obese, and some of them are almost thin enough so you can see through them.

Senator NELSON. What is the age group you deal with mostly?

Mr. KING. Mostly between the ages of 12 and 22, with the largest majority being around the ages of 15, 16, 17.

Senator NELSON. And in taking this history, how were those 12, 13, 14, 15 year olds introduced to the drug use?

Mr. KING. With the amphetamine abusers, they are an older population.

Senator NELSON. It is an older population than the general population of drug abuse?

Mr. KING. Yes, and I would say they are more toward the upper scale of the young people we deal with.

They are in their late teens and early twenties, for the most part, and they were introduced to those drugs by doctors.

That is particularly sad in a number of ways, especially in the sense of a young boy or girl, who is going through a lot of emotional and physical changes in adolescence. He becomes overweight because of overeating, out of emotional need at one time or another, or just because of physiological change, they are awkward and clumsy at the time, and they are very highly motivated to do something about their overweight condition, and they really become sitting ducks for doctors who practice in this way.

They go to the doctor, respecting his authority, respecting his position in society, and they go to him for medical help. They are doing the responsible thing, and through that treatment, they become

drug abusers, and, very often, they can become arrested for that drug abuse, if they happened to obtain the drug from a friend, who also goes to the same doctor, instead of from the doctor directly.

Senator NELSON. Thank you very much, Mr. King, for taking the time to come here today to present your testimony.

We do want to thank all of the witnesses for appearing at these hearings. The next hearing will be in this same room on Thursday, November 18, at 10 a.m.

The subcommittee stands in recess.

[Whereupon, the subcommittee was recessed at 11:40 a.m.]

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

THURSDAY, NOVEMBER 18, 1976

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

The subcommittee met, pursuant to recess, at 10 a.m., in room 318, Russell Senate Office Building, Hon. Gaylord Nelson, chairman, presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; and Karen Young, research assistant.

Senator NELSON. The subcommittee will please come to order.

Our first witness today is Dr. John Henderson, of Ottawa, Canada.

Dr. Henderson, the subcommittee is very pleased to have you here today to testify at these hearings.

Your statement will be printed in full in the record. You may present it however you desire.[1]

STATEMENT OF JOHN W. D. HENDERSON, M.D., OTTAWA, CANADA

Dr. HENDERSON. Thank you very much, Mr. Chairman. Indeed, it is a pleasure for me to come to Washington, and I would like to make one or two points prior to getting into the statement I have written.

The first thing I would like to say is that I am a physician. I am not a public servant in Canada. I still practice medicine.

My postgraduate work was done in Chicago and in Boston, and I now practice in Ottawa.

I do not represent the Government of Canada, although I am a consultant to our Department of Health and Welfare. Many of the decisions we made some 4 years ago regarding the type of drugs we are interested in this morning, I was involved in, and, therefore, I must take some responsibility for them.

I am also here representing the Canadian Medical Association, for I am the chairman of the special committee of that organization concerning drug therapy; this is known as the Subcommittee on Pharmacotherapy. Thus I would like to speak this morning more as a physician than as a representative of the Government of Canada, although what I want to talk about was very much a joint decision made by the medical profession in my country, and the Government of Canada.

[1] See prepared statement and attachments of Dr. Henderson beginning at 14729.

Senator NELSON. In the making of that decision, did you have an official role?

Dr. HENDERSON. Yes, sir. I state in my statement that I was chairman of the Special Amphetamine Ad Hoc Committee, which was a committee to look into the whole question of amphetamines and their place in medicine.

I would like to say that I will try not to be presumptuous that we have the answers to the problem.

We made some decisions about amphetamine availability in 1972, and these became enacted in our laws in 1973.

Some of the decisions we made in good faith at that time, we would not make now. Four years makes a big difference when one is looking at the potential for abuse of drugs, potential for misuse of drugs, and the incidence of side effects some of which we did not know about 4 years ago. I think that today we might make some different decisions.

Senator NELSON. I did not hear that.

Dr. HENDERSON. We were not aware 4 years ago of some of the side effects, some of the long-term effects, what people like to call today drug adverse effects, or drug adverse reactions.

I have provided a table which was given me by our Department of Health and Welfare. It is labeled "Table I, Designated Drugs in Canada." On that sheet, we have demonstrated a series of numbers representing drugs either manufactured in Canada, or imported into Canada between the years 1967 and 1976. On the bottom half of the table are figures for the same drugs which have been exported from Canada.

We have made a decision in Canada that although there is a large number of drugs which one can call amphetamines, there are true amphetamines and amphetamine derivatives. In 1972, we put those members of the family that seemed to us to have the greatest potential for misuse and abuse and harm to our society into a special restricted class. We chose amphetamines, meaning the L-form, dextroamphetamine, benzphetamine, methamphetamine, phendimetrazine, and phenmetrazine.

We decided to designate only these as "special amphetamines," Senator Nelson. Other members of the amphetamine class we chose to regard as potentially less harmful amphetamine congeners. The undesignated members include methylphenidate or Ritalin, and a number of drugs which are primarily prescribed for obesity. Since that there have been some new anorexiants introduced to the market. One is known as Mazindol, which although not chemically derived from amphetamine, shares several properties with amphetamines.

You can see, therefore, that it is a large family. It is pharmacologically correct to say they are all amphetamines, and, therefore, there should be no difference in regulations between the top group—very dangerous—and the bottom group—less dangerous—but for reasons I will come to a little later, we decided to draw a line somewhere, and "designate" only those which I have shown on table I.

After consultation with several expert members of the medical profession in our country, and a survey of the world literature, we were still uncertain whether or not there are diagnoses for which these drugs are really indicated. If there are conditions for which these designated amphetamine drugs are prime choices, then obviously they

should be made available to the medical profession. Our first job in the special committee, therefore, was to have a look at the therapeutic indications for the use of these particular drugs.

The way in which this control system was introduced in Canada, was through the political forum.

Our then Minister of Health and Welfare, Mr. John Munro, stated in our House of Commons that he had been advised that only two diagnoses, narcolepsy and hyperkinetic disorders of childhood were true indications for these drugs.

This was not the impression of many physicians in Canada. The committee, however, started from that viewpoint, and then began to look at other possibilities.

We agreed unanimously that these drugs were not antidepressants but rather that they are stimulants; they do have anorectic properties, possibly as a side effect. Primarily, however, they are central nervous system stimulants, and have no real place in modern medicine as antidepressants.

New antidepressant drugs have become available to medicine in the last few years which we feel are much more effective and safer than the amphetamines.

It was the opinion of some that amphetamines can increase the physical activity and brighten the outlook of depressed people, but it was our impression from the literature of the time that increased activity in acutely depressed people sometimes in fact raises the possibility of suicide, rather than decreases it.

We felt that there was no place for these drugs, for maintenance of amphetamine-dependent persons.

We did not feel that these designated drugs should be used for the treatment of obesity, especially as other drugs were available for this purpose.

We also felt that these drugs should not be used for the treatment of disorders of the muscles and nerves—musculo-skeletal diseases.

There were differences of opinion about the use of these drugs in the condition known as idiopathic edema, swelling of the lower extremities mainly in women. An increase in physical activity seems to benefit some of these patients, but we thought the vast majority of these people do not require amphetamines, and so we did not regard it an appropriate diagnosis for them.

On page 4 of my statement, Senator Nelson, I mention nonnarcoleptic hypersomnia. This means people who have an overwhelming problem because they fall asleep at inopportune times. An alternative diagnosis often cannot be made.

We are not entirely sure what this particular problem is, although it is seen in various disguises. In the Pickwick Papers of Charles Dickens, you may remember the fat boy who used to travel on the stagecoach, and who kept falling asleep. These people are obese, they have a great problem in breathing. They in fact underbreathe, and very often during sleep they stop breathing for short periods. They are blue in color, have muscle twitching, and they are forever asleep. It is a very distressing situation.

It does appear that some of these people might be benefited by the use of amphetamines. In recent years, however, it has been established that other drugs can also be used.

For example, female sex hormones may benefit some of these unfortunate persons.

I believe we should await the results of considerable research being conducted now in the field of sleep.

We chose not to include this diagnosis as a justification for treatment with amphetamines.

Amphetamines have been combined with pain relieving medications for many years, especially in the treatment of painful menstrual cramps. I believe that has been an area of misuse, and many young women have become somewhat dependent on stimulants and amphetamines as a result of there being given these drugs for too long. Because nervous system stimulation is pleasant, the drugs that produce this effect begin to be used at times when there is no actual problem. It then can become a habit.

This does not mean they have absolutely no place in pain relief. The amphetamines as a stimulant of the central nervous system distract people from some of their discomforts. However, we were concerned about the widespread use of amphetamines in our society by gynecologists and family physicians, and we felt the risks outweighed the benefits, and that therefore we should not approve this as a diagnosis. We, therefore, reached a consensus on a small number of diagnoses for which these amphetamine drugs could be legally prescribed by Canadian physicians.

Mr. GORDON. You are including the congeners?

Dr. HENDERSON. I am talking purely at the moment of the amphetamines, benzphetamine, methamphetamine, phendimetrazine, and phenmetrazine.

I am still talking about those drugs above the line which I drew. Narcolepsy is one diagnosis that we felt justified amphetamine drugs.

There are conflicting reports about the number of people who have narcolepsy. In the United States the number varies from a few hundred to 20,000.

Part of the problem is that we have no definite diagnostic criteria for this particular diagnosis. Many of these people do not need any drugs. They perhaps need special advice; they may require to have special consideration at work; and be allowed to take a nap in the middle of the day. However, some find this particular problem overwhelming, and falling asleep if you are working in a dangerous environment could be extremely hazardous. So this diagnosis may well justify use of amphetamines.

Our second approved condition is hyperkinetic disorders in children. I think, however, that there is almost more confusion here than there is about narcolepsy.

I personally worry more about this diagnosis. I believe we have been too sloppy in our thinking about what is hyperactivity, or hyperkinesis and what should be called the hyperkinetic syndrome, where the child's behavior is self-destructive, who cannot learn, and who is almost impossible to handle in the classroom.

It is my opinion that the number of children with this particular syndrome is really quite small, whereas the number of hyperactive children is quite large.

Some of them are hyperactive in school because they are bored. Children who are bright, with a high IQ, but who are bored, and cause classroom trouble, do not need drugs at all.

There are also drugs other than amphetamines which can be given to children with hyperkinetic disorders. Antidepressants can be used, but these too may create problems, for some of them may provoke an epileptic fit. Therefore, because there is no one universally effective drug for these children, we do need to have available to us a small number of amphetamines.

We may, however, not need any of our designated ones. Below our line, there is methylphenidate and this can be used equally well for this diagnosis.

Allied to this diagnosis is the phrase minimal brain dysfunction, or minimal brain disorder. This is mixed to some extent with the hyperkinetic syndrome.

We are not quite sure what is meant by it. Most of those children show some degree of mental retardation, usually minimal, and usually there is a slight abnormality in the electroencephalogram.

If they are badly retarded, or if there is quite a bit of brain dysfunction, amphetamines may make the condition worse. There is no real way at the moment of telling in advance. Therefore, the only way to try to help these children is to use an amphetamine and see what happens.

Epilepsy. Some of our pediatricians, especially those interested in child neurology, felt there were some forms of epilepsy which benefit from amphetamines. Some stated that children taking other anti-epileptic drugs sometimes became quite retarded, and need a stimulant to counteract some of the slowing down side effects of the other necessary drugs.

I am not certain in 1976 whether this is still a fact worth considering. Similarly, my fifth diagnosis is Parkinson's disease. Sometimes the stimulation provided by amphetamines does seem to improve their ability to move around, to walk, and to live a reasonable life.

There are other uses which are related to anaesthesia where the amphetamines can be used to raise blood pressure.

Mr. GORDON. Dr. Henderson, may I interrupt you for a second? You stated that there are doctors who feel the drugs may increase mobility, and so forth.

I was just wondering if this "feeling" is sufficient to approve a drug for a particular use by Canadian law; do you need adequate and well-controlled studies?

Dr. HENDERSON. Yes; we try to evaluate studies, of course. We recognize, however, that therapeutics is not an exact science, and that we have to proceed on a preponderance of evidence handed to us. Most of the time we have some physicians saying one thing, and others saying another.

We try to be as fair as possible, and we try to stay on the safe side by not taking away medication that might help some unfortunate people.

In fact, for Parkinson's disease amphetamines are hardly ever used in our country. I feel that well-controlled studies are lacking in this particular area, and I am very doubtful about the efficacy of amphetamines for this disease. If I were to go back now as chairman of the committee, I think I would have general agreement on that point.

Senator Nelson, my table I demonstrates that when it became public knowledge in 1972 that steps were going to be taken to control

the medical use of amphetamines, a sudden change occurred. You may see the 756 kilograms imported in 1971, suddenly dropped in 1972 to 32½ kilograms. On January 1, 1973, our law designated the five conditions as the only medical diagnoses for which these drugs could be prescribed.

Senator NELSON. What conditions?

Dr. HENDERSON. The five narcolepsy, hyperkinetic disorders in children, minimal brain dysfunction, epilepsy, and Parkinsonism.

You may see in table I, that 32.457 kilograms has dropped to 1.395 kilograms in 1973, and down to 0.475 in 1975—less than a half of 1 kilogram imported into Canada in 1 year.

This, however, is quite adequate for the medical needs.

I think the drop is quite dramatic.

Senator NELSON. It is not manufactured in Canada?

Dr. HENDERSON. No, sir.

The only substance which is manufactured in Canada, phendimetrazine, which although manufactured, is not marketed in Canada.

It is all exported.

Senator NELSON. Why is this not marketed in Canada?

Dr. HENDERSON. It is not prohibited. It has never been put on the Canadian market. Thus, it is not being prescribed in Canada. Phendimetrazine is the only amphetamine derivative that has been manufactured in our country.

Mr. GORDON. What is the 1976 production for amphetamines?

Dr. HENDERSON. That is a purely chemical use; it has nothing to do with drugs.

I cannot tell you which particular industry it was, but amphetamines are used as a basis for other chemicals. It was certainly nonmedical.

Senator NELSON. All of these are amphetamines or related?

Dr. HENDERSON. No, sir, those shown on table I are the five we felt to be the most dangerous of the entire family.

I will refer now to the question of obesity. You may see on the second long page, entitled "Antiobesity Market, 1971–75." The statistics here were derived from IMS Canada.

What we did here was to take the 1971 market as 100 percent. That was well before we changed our regulations. Thus the lefthand side represents percentage change.

Senator NELSON. This is all for the treatment of obesity?

Dr. HENDERSON. Yes.

In 1972 we had a drop in both the true amphetamines and amphetamine congeners, and in 1973, 1974, 1975, the amount of amphetamines of the type we have controlled in a rather drastic manner, has stayed very, very small.

It is, however, obvious there has been an increase in prescribing of the amphetamine congeners, and this would be about a 10-percent rise from 1973 to 1974 and about the same for 1974 to 1975.

I have looked at what is happening in 1976. It would seem there has been a rise, perhaps half the amount of the previous year.

Mr. GORDON. The ban on prescribing amphetamines for obesity has brought about a shift in demand to the nonamphetamines, the congeners; is that correct?

Dr. HENDERSON. That is correct, Mr. Gordon.

What has happened is that physicians knowing that the drugs as Mazindol are not restricted, and not subject to the strict regulations of the top five of the amphetamines, are prescribing those.

I do not know whether or not this increase, Senator Nelson, which is measured by the IMS in terms of dollars spent, might be due to inflation, and not an actual increase in use of the drugs. I also wonder whether or not the increased demand for these drugs might be related to increase in population. The population of Canada increased, during the years 1972–73, by 1.3 percent, between 1973–74, and this year it will be about 1.4 percent. Therefore, an increase in population may have to be considered, but it does not really explain why more money is being expended for these amphetamine-derived anorexiants.

Senator NELSON. What is the difference between the congeners and the amphetamines in terms of their effect on the user?

Dr. HENDERSON. The amount of stimulation, Mr. Nelson, is less, but chemically they are amphetamines. They all demonstrate in a pharmacological sense some central nervous system stimulation.

Senator NELSON. Are they dramatically less stimulative?

Dr. HENDERSON. I would say measurably less, rather than dramatically less.

I think there have been improvements. An example is the drug fenfluramine. It may be true that this particular drug does not cause measurable euphoria in most persons who take it.

It is the only one that I use in my own practice. Fenfluramine, is a special kind of modified amphetamine which has hardly any noticeable stimulation. Possibly because of this the drug is unpopular in our country. People do not like it, people do not want repeat prescriptions of it, because they say it makes them drowsy. It does not "pick them up," and it causes in some people a degree of nausea, and some diarrhea. Therefore, the drug is rather unpleasant for the user. People say that they would rather do without it. This is entirely different for dextroamphetamine, which causes a very measurable degree of euphoria.

Senator NELSON. Is fenfluramine indicated in Canadian medical practice for any other specific purpose other than as an antiobesity drug?

Dr. HENDERSON. No, sir.

Senator NELSON. What kind of studies have been done to show an effect on obesity?

Dr. HENDERSON. Most studies have been uncontrolled; this is a great problem with most of the anorectics.

Most of them have consisted in measuring weight change over a period of weeks or months.

Weight of course varies on its own. With almost any drug that you start with, people become enthusiastic, and during this period stick with their diet.

People who are obese and having trouble are eating not because they are hungry. The stimulus for a person to raid the refrigerator at 12 o'clock at night is not really because of hunger. It is somehow or other they feel better after they have had something to eat.

The eating in itself is a way of making them feel good. To take away physiological appetite by making a person feel nausea, as one could do with, for example, table salt, is not the way to treat a person

with a compulsive eating problem. Simply removing physiological hunger is not really a rational way of dealing with what is fundamentally a psychogenic problem in over 80 percent of the people who are having serious trouble with their weight.

Senator NELSON. But in the graph you lump together all of the amphetamines?

Dr. HENDERSON. Yes, except fenfluramine. Also not included is mazindol, because it has only very recently been released as a drug on our market. I have no real data for it.

I looked at some other possibilities, and I would like to try to explain why more money is being spent on these amphetamine congeners specifically marketed as appetite depressants or anorectants. In our country, we have a National Health Service. Everybody, therefore, has access to a physician, without paying an extra fee. Under such a comprehensive prepaid medical insurance plan, more people go to their doctors, and the doctors are busier than ever. More people are asking for all sorts of medication, and possibly this particular area of requests for drugs for weight problems is simply one of many such requests for drugs.

The other point is that with the older drugs that we designated, the effects were good only for 4 to 8 weeks. The patients became tolerant, and this meant they had to take a higher dose of the drug, or they simply lost the anorexiant effect. Doctors did not like to see people increasing their dose because of the chance of side effects, such as some degree of irritability, tremor, possibly some change in blood pressure, and a raised heart rate.

Newer drugs such as mazindol seem to have a much lower potential for tolerance. At least it takes a lot longer to become tolerant.

The drug seems to be effective for up to 15 or even 30 weeks instead of the 6 to 8 weeks of the older ones.

This means if a patient goes back to a physician, and says "Yes, I am doing well; I managed to stick to my diet reasonably easily and I am losing 2 pounds every week," the physician is more likely to represcribe. So the very fact that we have developed drugs which seem to be effective for long periods of time, means that any one patient probably receives more of them. Therefore, more money is being spent on these particular drugs.

Senator NELSON. Do any of these drugs shown on the dark part of the graph, the congeners, show an indication of the kind of addictiveness that occurs as a consequence of the use of amphetamines?

Dr. HENDERSON. Yes, they do to some extent.

We chose to exclude a few drugs from our strict restrictions on use because of the need for some degree of flexibility in the management of depression, not because of obesity.

In about 1971 and 1972, as a result of a number of good scientific papers, we felt that amphetamines as such had no place in the treatment of depression. We felt that possibly there was some medical indication for methylphenidate in the hands of skilled psychiatrists for some cases of depression where fast action was desirable.

At that time it was our opinion that the congeners were not causing any medical or social problems, so to speak.

That has changed since 1972. Last week I saw a large amount of diethylpropion which had been manufactured illicitly. It was not of

high quality, but nevertheless it was diethylpropion. The synthesis is apparently easy for anybody with some knowledge of chemistry.

So we are indeed seeing abuse of at least one of these congeners which was legally marketed for obesity. I think it is quite obvious that no one will market an illicit drug if there is no "street" market for it.

The stimulant properties of some of these congeners seem to be leading to nonmedical use of them. Therefore, there is now justification in Canada to reexamine whether or not the extent of our restrictions has been adequate, or now needs further tightening.

We cannot really ignore the fact that drug abuse is beginning to appear with some of these amphetamine congeners.

Senator NELSON. Are all of the congeners imported into Canada, or are some of these manufactured?

Dr. HENDERSON. None being manufactured that I know of.

Senator NELSON. Does the Canadian Government limit the amount imported?

Dr. HENDERSON. No, to my knowledge, it does not impose any quota on amounts.

They are controlled by the schedule which limits them to prescription, and other than over-the-counter sales that is about the loosest kind of control that exists!

Senator NELSON. And all of these in the colored section of the graph are specifically indicated only for obesity?

Dr. HENDERSON. Yes, they are approved for that purpose only; that is correct.

Senator NELSON. If some of them are being used, as you put it, for nonmedical purposes, and if in fact it is found that they are widely used for that purpose, does their use for controlling obesity have a benefit-to-risk ratio sufficient to leave it in the market for that purpose? Or are the costs, so to speak, in the ratio too great to allow it to be in the market?

Dr. HENDERSON. In my own opinion, Senator Nelson, the risks are higher than the benefits. I would state however, that it is difficult to assess accurately the risk benefit, for in most cases medical opinion is divided.

We have not been teaching a methodology of risk-benefit for drugs to our students or to our practicing physicians. It seems obvious that we should in the future.

The only drug I prescribe for obesity is fenfluramine. I think its potential for abuse is very small. After trying it patients prefer not to continue with it for long, but it does act as an anorectant for several weeks or a month or two.

I use it for people who have said they have tried all sorts of diets. Some have been in Weight Watcher-type organizations, but for one reason or other they have not succeeded in losing weight. Nothing has worked for them and they are depressed people.

They do not like themselves as obese people. They really do want to lose weight, but they "cannot." Therefore they are, in their own eyes, failures, and they come virtually with tears in their eyes.

It becomes important to try to persuade these patients, that it is a question of food intake that creates obesity. If one can demonstrate that he/she can lose weight, even a few pounds a week, if he sticks to

a specific diet, perhaps just a low carbohydrate diet, without an increase in fat or protein, the first success has been achieved. After the second or third week, they may have lost 6 or 7 pounds. Suddenly the personality begins to pick up. Something at last is working for them.

I make it clear to my patients they will not get it for longer than 3 or 4 weeks. It is purely to demonstrate they can and will lose weight if they maintain a specific diet regimen.

I have not used the newer drug, mazindol. It may or may not have advantages over fenfluramine. I simply do not know.

Mazindol is not an amphetamine derivative but has a separate molecular configuration. However, it has all of the effects of amphetamines.

Senator NELSON. All of the effects?

Dr. HENDERSON. Yes.

At the clinical level, it would be hard to say it is not an amphetamine, although chemically it is not. The advertising of the drug by the company tells doctors that it is the first nonamphetamine anorectant. It also declares that the side effects will be the same as the other amphetamine congeners. It is my suspicion that it will turn out to have the same potential for central nervous system stimulation as the rest.

Mr. GORDON. Dr. Henderson, if I may interrupt a second, we had testimony last week from Dr. Jasinski of the Addiction Research Center that he had done some work on fenfluramine, and he found that it has the same effects as LSD.

Will you comment on that?

Dr. HENDERSON. It is a very peculiar drug.

One could not have predicted much difference from other similar drugs from the original pharmacology.

It affects various parts of the brain, but in terms of an electroencephalogram, it is obviously stimulating the subcortical area.

It is a depressant on other parts of the brain.

The overall effect is drowsiness rather than stimulation, but that does not mean that it is not a stimulant.

It has some effects on sleep which are quite unusual. As you know, the amphetamines of all types can produce hallucinations, and fenfluramine can do the same thing.

This is why I am very cautious in my use of it. I never give it on a chronic basis. I do not give it to people who for one reason or another should not receive amphetamines of any kind. There are minimal effects however on blood pressure and the heart.

I could practice without it. I believe that no patient would really suffer from its absence if it were not available.

I am not sure that all physicians would agree with me. Some of them might think of fenfluramine as a useful crutch, which at the moment has less potential for dependence or abuse than older amphetamine anorexiants. It is because physicians still find anorexiants to have some clinical use that both older and very new drugs like mazindol are widely prescribed.

However, even the manufacturers of anorexiant drugs make it quite clear it will only work if the person maintains a strict diet at the same time.

People who take these drugs unfortunately do not lose their interest in food.

Senator NELSON. Of course, if they take an interest in their diet, and they stick to it, they would lose as much as if they did not take the drug at all.

Dr. HENDERSON. That is correct.

These drugs act as distractors. They distract a person's attention away from the fact they want more food. That is all they are doing in my opinion.

It may even be questionable to say that they are anorectics, or that they are appetite depressants. A true anorexiant effect is seen in patients who are taking one of the cardiac drugs, such as digitalis. Sometimes these patients, after they have built up their blood concentration, simply do not want to eat, and cannot eat. They are not interested in food.

Now, of course, there is no way digitalis could or should be marketed as an anorectic, but indeed it has this effect—but it is a side effect.

Amphetamines are not anorectic in that sense, but because of the distraction, and the feeling that life is fun, surroundings are enjoyable and the person feels good maybe for that period of time, he or she does not have to eat to feel content. Eating behavior however, has not been changed by these drugs. Unless eating behavior, that is, one's attitude toward the cooking of food, and the eating of food does change then there is no long-term benefit from them. It is because of this, that I believe that these drugs have a very limited role to play in the management of obesity.

Mr. GORDON. I would like to read a statement from Dr. Jean Mayer, that he made before our committee 4 years ago, in 1972.

This is on pages 1264 and 1265, and he says:

> However, as far as the general public is concerned, I think we would be deluding ourselves if we thought that even with this association of obesity and disease the health considerations were, in fact, the primary motivation of our federal citizens who seek to reduce. The primary motivation is a cosmetic one rather than a health one, and we have to address ourselves to the problem of obesity knowing that in the mind of a great many of its sufferers we are dealing with a cosmetic problem at least as much as we are dealing with a health problem, and that the almost desperate motivation of many of the sufferers in seeking relief has much more to do with benefits which they think will accrue to them here and now in terms of attractiveness to the other sex than because of the benefits to health in the long run. * * *
>
> I am stating all this by way of a background because I think we have to realize that the motivation in the mind of the patient is often very different from that which is discussed when one speaks of obesity as a purely medical problem. * * *

Would you like to comment on that?

Dr. HENDERSON. Yes. Just 2 weeks ago, Mr. Gordon, I saw a university student who was grossly obese, who had said he had tried to diet, but had not succeeded in losing anything more than 1 or 2 pounds. I asked him about his motivation for wanting to be thinner. In the jargon of the campus, he said that the real reason was that he was not "drawing the birds" as well as he had before.

I did not quite understand, so he explained that drawing the birds means drawing the attention of young ladies. The reason he wanted to lose weight was that he felt he was no longer physically attractive to the coeds on the campus. I agree that a great deal of this need to be thin is cosmetic. Sometimes, however, cosmetic motivation is not

altogether a bad thing; for it can be turned around to good purposes. I think that most of us would agree that small amounts of obesity, 5 to 10 pounds overweight, does not matter much, and a lot of our obsession with slimness is a question of fashion more than with health. There is no doubt, however, that people who are 20 percent or more overweight, have a higher incidence of all kinds of problems. There is a health aspect to this kind of obesity. To remedy this kind of obesity, some kind of lasting motivation is necessary.

If I may, I would like to move into the question of a methodology of thinking about drugs. In medicine and in pharmacology, we tend to think of them as a medical scientist would, but I fully realize that is perhaps no longer enough.

We have recently been faced with all sorts of drug problems, involving drugs of licit and illicit origin and we are still concerned with alcohol, cannabis, many drugs which have their origin with illicit manufacturers—amphetamines—although many are not of illicit origin but rather diversions from originally legal sources. I thought I would try to devise a method of looking at the social impact of drugs. In some cases, drugs as a family, and sometimes as individual drugs such as cannabis. I first took a look at benefits of the drug's availability. Of course, for many people, drugs do not have just medical benefits, but possess what they regard as recreational benefits.

For example, alcohol does more harm to our society than any other drug, but prohibiting its use was a social failure. Obviously our culture claims that in alcohol use there are recreational benefits.

I have set down a number of questions about the availability of drugs made available to the public directly; or available through the practice of a physician's prescription. Does it cure anything? Or does it provide only temporary relief of a discomfort? Does this drug interfere with other drugs that may have to be taken, or even with dietary substances?

Does it lack idiosyncratic or unpredictable reactions?

How beneficial are the effects when compared with the toxicity? This is an important feature when one considers antiobesity amphetamine-type drugs.

Is it reasonably priced on the market? Are there any social benefits, or just various degrees of intoxication, when this drug is used?

With regard to risks, I decided to look at it from several points of view. The first concerns various aspects of health. Does it impair learning abilities, life skills, and formal education? Does it impair brain function in any way?

Does it lead to undesirable conseqeunces of a chronic sensory deprivation? What does it do to us as a society if a high proportion of us shield ourselves from the "harsh" realities of life?

Does it cause any other kinds of organic problems, for example, liver, kidneys, and so forth?

Does it affect nutrition as alcohol does?

Is it likely to be lethal if taken in overdose? What are the long-term effects if this drug is used in recreation?

From the viewpoints of personal and public safety, does it lead to any kind of deviant behavior? Does it lead to aggressive behavior—including sexual aggression? Does it lead to any form of violent behavior?

I think that some of the amphetamines and drugs like cocaine have demonstrated increased aggressiveness.

Is the drug associated with loss of psychomotor and judgment control?

Is the criminal element in society involved in obtaining the substance? The safety effect here is tied to guns, thefts, assaults, blackmail, and such other hazards.

Does it lead to increased risk-taking behavior?

Does it lead to flattening of effect, lack of emotional responses, including healthy anxiety, healthy concerns, justifiable fears?

How great are the safety risks to individuals, communities, and larger society, when used recreationally?

Many drugs do, including the amphetamines, make a person feel good—euphoria—and in this altered state may drive a car faster, and so on.

Risk-taking behavior leads to many problems.

We all need some degree of anxiety, and the taking of psychoactive drugs can lead to a situation that precludes benefits derived from emotional responses to life.

More difficult to look at is the question of drugs as they affect the social order and culture.

Two countries have been brought to their present states by a great deal of hard work, perseverance, and guts. A "chemical" society that becomes reliant on uppers or downers—stimulants or tranquilizers—may change in terms of the character of its people. So with that in mind, I ask more questions. Does chronic use of this drug lead to noncoping behavior or to low self reliance if the drug is withdrawn?

Would widespread use lead to loss of productivity and creativeness? Is use of a drug associated with recruitment of nonusers? Can its use lead to a lowering of ethical and moral values within society? Is it associated with amotivational states? Is it associated with economic losses to the community?

Does a given drug lead to "anarchic" inclinations when used nonmedically? What I mean by that is an attitude of hostility to authority—"no one is going to tell me what I can and can't do."

Last but certainly not least, I have looked at the risks of psychoactive drugs in terms of potential for creation of states of dependence of addiction.

I know of course that the Food and Drug Administration, and the Drug Enforcement Agency here in the United States, are extremely interested in this aspect.

I have worked with several members of the U.S. Government within a committee of the World Health Organization, to try to develop methodologies, whereby we can predict and assess the likelihood of states of psychological or physical dependence developing as a result of use of any psychoactive drug. I believe that the amphetamines, and the antiobesity congeners should be looked at closely from this viewpoint.

Again I have asked a number of questions. Does dependence occur after regular low-dose use? Does dependence occur only after heavy use? Is psychological dependence problematic? Does use result in physical addiction?

How great are the reinforcing properties? I am using reinforcement here in its psychological sense. If a drug creates a pleasureable effect, so that after its use one feels great, we probably will want to use it again. Thus begins habituation.

I am presently carrying out a psychoactive drug survey in which I have tried to answer these questions. One such profile that has been engendered is for the drug methylphenidate as shown on the sheet which I have made available to you. There are obviously some benefits, and because of this the drug is readily available. What about risks?

There are probably some with respect to safety, especially in terms of risk-taking behavior. In terms of the social order, yes, there may be some, but certainly not of a high order.

Methylphenidate is slightly different in a chemical sense from pure amphetamine, but it is a member of and as you probably know, that family. In the World Health Organization convention on psychotropic drugs, methylphenidate is regarded in the same way as other amphetamines are. The recommendation of that particular convention is that methylphenidate should be regulated and subjected to the stringent controls used for amphetamines.

With that, I agree.

In summary, Senator Nelson, I would like to say that I am glad that Canada took some action in 1972 and 1973 to remedy overuse of amphetamines. The drugs which we controlled have remained controlled. We set therapeutic guidelines for their use. We left the door slightly open to physicians in Canada by saying, "If you personally feel you need to use this drug for conditions outside of this list of approved conditions, get in touch with us and we will discuss the situation."

We have had about 250 requests of this type from physicians per year since 1973. The number stays about constant. We have never actually refused to allow a physician to employ amphetamines if in his best judgment he feels he has tried everything else, and this particular patient needs them.

Despite various arguments from individual physicians, I do not think we want to increase our approved list in any way. The concept of restricting the number of diagnoses as indications for drugs is a new one for our country, and it was necessary to do a fair amount of selling of this to the Canadian Medical Association.

Senator NELSON. When you say restrict, did you mean restricting indications for use?

Dr. HENDERSON. Yes. For example, if a Canadian physician prescribes benzphetamine or methamphetamine as a stimulant for kids playing ice hockey, he is in fact doing something which is illegal.

Amphetamines are not approved as a stimulant for say, truck drivers who drive all night and want something to stay awake. Neither are they to be used for obesity. A doctor is in fact breaking Canadian law by prescribing a designated amphetamine—for example, phenmetrazine—for obesity.

A physician is allowed to prescribe amphetamines only for the designated conditions that I earlier outlined.

Physicians in general do not like to be limited. They want to have total freedom to prescribe as we think is indicated.

I just wish that medical knowledge in clinical pharmacology was a lot better. I think a lot of irrational prescribing was and is going on,

and I say this repeatedly in my own country. Not only have I in mind this particular area of psychoactive drugs, but other drug groups such as antibiotics. We are obviously not doing as good a job as we should in our medical education, to teach rational therapeutics.

I am more than a little embarrassed to see that Canadian physicians seem to be prescribing more and more of these amphetamine congeners for the treatment of obesity.

They obviously are obeying the law. There is no problem there, but they seem to have fallen for the concept that there is a large place in practice for the congeners.

What we shall do next, I do not yet know. I would be happy to have another look at the whole situation, and I hope that in the next 2 or 3 months we will be reconvening our committee to formulate further recommendations.

I personally feel we should make some changes in our older recommendations to the Government regarding amphetamine controls. These must be such however that they will not hurt any patients. We can indeed hurt people who have become dependent on drugs, when these are taken away from them in a sudden drastic manner. For this reason any curtailment of use of amphetamine congeners must be planned and introduced congeners.

I would like to proceed thinking about drugs in terms of risks and benefits, and to introduce some of these concepts more thoroughly into our medical schools. Doctors in general have not taken sufficient regard to the social consequences of use of many classes of drugs, which are now widespread in our society.

Senator NELSON. For the National Health Program, Canada produces a formulary of approved drugs?

Dr. HENDERSON. No, sir.

There has however been talk of that very thing. We presently use a book which is comparable to the Physicians' Desk Reference. In Canada it is known as the Compendium of Pharmaceuticals and Specialties.

Senator NELSON. Who publishes it?

Dr. HENDERSON. The Canadian Pharmaceutical Association publishes it.

The book is derived from the approved product monographs of the companies.

The publishers have an editorial board of physicians and clinical pharmacists. In some provinces there are special plans for people on welfare, old-age pensioners, and for these patients there are special lists of drugs that are available free. But there is no Canadian drug formulary.

We have essentially the same number of prescribed drugs on our market as you have. They can all be prescribed for our patients with the one exception of the amphetamines, which can be prescribed only for five designated conditions.

Senator NELSON. But the drugs in Canada are approved generally for the same uses as they are in this country; are they not?

Dr. HENDERSON. Yes; that is true.

Senator NELSON. And when the Canadian panel decided to recommend that amphetamines would no longer be indicated for obesity, you still had the congeners that could be used for weight control.

If a number of the congeners are strongly stimulative also, in a similar way as amphetamines, why did the panel permit the congeners to go on the market? Was it lack of knowledge?

Dr. HENDERSON. In 1972, we were of the opinion that phentermine and a few other congeners did not have the potential for abuse that existed for say, phenmetrazine. We thus chose at that time to recommend that some congeners should remain uncontrolled at least for the time being. We said that we would attempt to review our decisions every 2 years. We knew we were making decisions which might not be long-lasting.

It is only in the last year and a half that some of us have become convinced that a number of these congeners do have a risk of abuse. By asking the questions that I have outlined I have come to the conclusion that the risks are greater than the benefit.

As an example, the drug Benzphetamine—by trade name—was marketed in our country by Upjohn. The company however has simply withdrawn the drug from the market. They seemed to realize that amphetamine prescribing was not really a logical way to treat obesity, and now that Canadian law has so restricted its prescribing, the actual market is too small to be profitable. I wonder if at the level of the drug manufacturing companies, a number of them are not beginning to wonder whether or not these stimulant drugs really are a benefit.

That is not to say that new drugs for obesity might not be beneficial in the future. There is genuine interest and a genuine concern to find drugs with less toxicity, and with less potential for both abuse and for dependence. The new drug mazindol seems to be a step in this direction.

Research is still going on in this area of appetite suppression. I am not very optimistic about any of these drugs, but on the other hand, I cannot say that a good appetite suppressant is either impossible or unwarranted.

Drugs can be a temporary crutch for some patients. But in addition to drugs that we need to achieve with our overweight patients is a better way of thinking, perhaps through group therapy such as that provided by Weight Watchers. This is where in fact I send all of my overweight patients. I persuade most of them to join one of these kinds of lay organizations, and two-thirds at least of them benefit from referral.

Senator NELSON. Well, thank you very much, Dr. Henderson, for your very thoughtful contributions.

We appreciate your taking so much of your valuable time to come to testify.

Dr. HENDERSON. Thank you.

Senator NELSON. Our next witness is Dr. Carl Chambers of Miami, Fla.

Your statement will be printed in full in the record.

You may present it however you desire.

STATEMENT OF CARL D. CHAMBERS, PH. D., PRESIDENT OF PERSONAL DEVELOPMENT INSTITUTE, AND PROFESSOR AND DIRECTOR OF THE INSTITUTE FOR PUBLIC HEALTH RESEARCH, ANTIOCH COLLEGE AT COLUMBIA

Dr. CHAMBERS. Thank you, Mr. Chairman, members of the subcommittee.

I am extremely grateful for your invitation to appear before your subcommittee to share with you my research on the patterns of use of amphetamines and related drugs.

With your permission, I would like to share two types of research experiences with the subcommittee.

First, I would like to share the experiences derived from conducting some 35,000 face-to-face interviews with persons in 17 States and the District of Columbia.

Senator NELSON. Were these 35,000 interviews conducted by you personally?

Dr. CHAMBERS. I was the senior investigator, but I did not do all of them.

Second, I would like to share the experiences derived from conducting 935 interviews with known drug abusers in nine cities from throughout the country.

After a brief prepared statement of these experiences, I will be happy to answer any questions the subcommittee may have regarding these studies.

Between 1970 and 1976, I was the senior investigator responsible for conducting substance use surveys within the statewide general populations of Arizona, Delaware, Florida, Indiana, Iowa, Minnesota, Mississippi, New Jersey, New York, North Dakota, North Carolina, South Carolina, South Dakota, Utah, and Wyoming. I have also been responsible for conducting the same surveys among the citizens residing throughout the District of Columbia and the citizens residing in selected multiple county areas of Arkansas and Pennsylvania. These surveys have resulted in some 35,000 interviews with persons carefully selected to represent the total populations age 14 and above who resided in these areas. Each person was interviewed in private by trained interviewers concerning their use of prescription psychoactive drugs, nonprescription psychoactive drugs sold over the counter, alcoholic beverages and illicit drugs. Viewing these data in the aggregate has brought us to the following conclusions:

The use of amphetamines to diminish fatigue or for their energizing effects is significantly related to both sex and age. For example, our projections indicate some 63 percent of everyone who uses amphetamines as "pep pills" are males even though males represent only 46 percent of our population above the age of 13. Correspondingly, persons age 14 through 24 represent only about 26 percent of our total

population but contribute some 55 percent of all prescription "pep pill" users.

Although there has been considerable discussion about the use of prescription "pep pills" among certain occupational groups such as truck drivers and students, our data suggests the highest rate of use of the prescription "pep pills" is probably among sales workers.

Senator NELSON. May I ask you a question.

You stated the persons in the age groups of 14 to 24 represent only about 26 percent of population, and some 55 percent of all prescriptions.

Why would the physicians be prescribing pep pills to all groups of 14 to 25?

Dr. CHAMBERS. I have no idea, sir.

Senator NELSON. Why did those in that age group who were interviewed say that they sought prescriptions?

Dr. CHAMBERS. Our task was not to determine "why". They were asked specifically about their use of "energizing pills", and where they got them. They did get them by prescription, and indeed, the vast majority paid for that prescription indicating the prescription was legally theirs.

Senator NELSON. Which pills?

Dr. CHAMBERS. Dexadrene and Benzedrine primarily.

Senator NELSON. That is not the indicated use for them anyway, is it?

Dr. CHAMBERS. No, sir.

Senator NELSON. So you have a situation in which in this group, 55 percent of those who got prescriptions were made——

Dr. CHAMBERS. We asked specifically, when we talked about amphetamines with the respondents, if they sought the prescription for the energizing effects, or for diet pills, and these are all people who sought the pills for their energizing effects.

Senator NELSON. And these were people who in fact did not get them off the street, but got them through a prescription by a physician?

Dr. CHAMBERS. Yes. However, in the majority of the cases they did not take the drug as it had been prescribed, but they did get it by prescription.

Senator NELSON. What was the drug prescribed for?

Dr. CHAMBERS. We have not had access to such a prescription audit.

The only thing we know is that the prescription was made out, and he received the drug.

Senator NELSON. This is 55 percent of all those who used pep pills among the 35,000 who were interviewed?

Dr. CHAMBERS. Yes, sir.

Unfortunately, neither other investigators nor I have been able to look closely at the relationship between one's work and the use of these prescription energizers.

For example, I have some information that the use of these drugs among service and protective workers, migrant workers and those in competitive sports is considerably greater than current empirical data would suggest.

The use of the amphetamines and amphetamine-containing diet pills ostensibly for their hunger suppressant effect is also significantly related to both sex and age.

If I was called upon to characterize the primary consumers of prescription "diet pills," unquestionably I would project them to be women between the ages of 18 and 34.

Senator NELSON. Is this again from your list of 35,000?

Dr. CHAMBERS. Yes, sir. I would further characterize them as housewives who are not employed outside the home or women who are working in sales or clerical jobs.

Our data indicate that the vast majority of these women obtain these drugs through legal prescriptions but that they do not take them as they were prescribed. Substudies of these women show that regardless of why they begin to use these drugs, most ultimately begin to increase the prescribed dose or extend their use and take them because of the drugs production of a "sense of well being."

The use of amphetamines as "pep pills" and as "diet pills" appears to be proportionately distributed throughout the race/ethnic groups.

I believe some brief mention of the use of the nonprescription stimulants sold over the counter should be made as there is some evidence that the use and abuse of these drugs is increasing and any controls placed on the prescription stimulants will probably compound these increases. The consumption of over the counter stimulants occur more among men than women and more among younger persons. The use of nonprescription stimulants appears to be proportionately distributed throughout all of the socioeconomic and ethnic groups. Of significant concern to my colleagues and me, is our projection that the majority of the regular consumers of these over-the-counter drugs are workers who operate or are around machinery and motor vehicles. Unfortunately, the extended use of these stimulants only masks the fatigued state of the body and cannot fully restore the sensory perception and reflex action which has been lost through fatigue.

I am sure the subcommittee is most interested in the precise number of people in this country who habitually use these drugs. Unfortunately, neither I nor any investigator I know can give you precise numbers. All any of us can give you will be projected numbers based upon various surveyed populations. With such a qualifier clearly understood, let me give you the numbers our research would suggest. Assuming our some 35,000 people are representative of everyone in the country, we would project the following:

Some 6 million people above the age of 13 have used amphetamine "pep pills" with some 1,500,000 having done so recently and some 750,000 being current regular users of these drugs.

Some 12 million people above the age of 13 have used amphetamine "diet pills" with some 3 million having done so recently and some 1,500,000 being current regular users of these drugs.

Senator NELSON. Is this an extrapolation?

Dr. CHAMBERS. Yes.

Senator NELSON. How was your sample of 35,000 selected?

Dr. CHAMBERS. We picked them primarily by age group. We broke the population into five age cells, and once the interviewing is done, we weigh the total back into the total population.

Senator NELSON. It was a random sample?

Dr. CHAMBERS. Random down to the household, and then we interviewed specific age and sex groups within the households.

Senator NELSON. So what was that figure again, based on that, how many million have used them?

Dr. CHAMBERS. Six million have used them—above the age of 13—and 1½ million have used the amphetamines recently.

Senator NELSON. Have used the prescription drugs?

Dr. CHAMBERS. Prescriptions, yes, sir.

A million and a half have done so recently, we believe within the last 30 days, and probably 750,000 now are currently regular users of these drugs.

Some 16 million people above the age of 13 have used nonprescription stimulants of whom as many as 3 million having done so recently. Probably as many as 500,000 people use one of the nonprescription stimulants every week.

As I indicated in my introductory remarks, I would also like to share with the subcommittee my recent experiences in interviewing known drug users concerning their use of amphetamines and related drugs. I believe the subcommittee should be aware of these users and the implications of this use as these users are normally excluded during even carefully designed general population surveys.

If they are identified they are less likely to respond honestly to interviewers who are not known to them. Of equal importance, these types of users make no pretense to claims of use to diminish fatigue or to lose weight. They choose drugs to use solely for their potential for producing euphoria.

During last year, Leon Hunt, a mathematical epidemiologist, and I were asked by the Drug Enforcement Administration's office of Science and Technology to conduct a study among known drug abusers relative to the potential for abuse or nonmedical use of various legally manufactured psychoactive drugs including the amphetamines and related drugs. As the final report of this total research effort is available to the subcommittee from the Drug Enforcement Administration, I won't take up your valuable time in a full elaboration of the study. I will abstract from the study those findings which I believe are most relevant to your current inquiry.

In brief, the study called for us to review the drug history records and to interview random samples of narcotic abusers and abusers of nonnarcotic drugs who were undergoing treatment for this abuse in nine cities. Records were reviewed and drug abusers were interviewed in the following cities: Miami, Fla., Greensboro, N.C., Washington, D.C., Atlantic City, N.J., New York City, N.Y., Des Moines, Iowa; Kansas City, Kans.; Phoenix, Ariz.; and San Francisco, Calif.

A total of 3,598 records were reviewed and 935 drug abusers were interviewed.

Our analytic technique was first developed to describe the epidemic nature and spread of heroin in a community. The technique collects the year of first use of a drug and groups these experiences to determine if the event is occurring randomly or is the result of contagious transmission from one user to another. The following results and generalizations should be of special relevance to your current inquiry.

Sixty-two percent of all the drug abusers we interviewed had histories of abusing amphetamines. However, among drug abusers whose primary drug of abuse was not heroin, the prevalence of amphetamine abuse was as high as 85 percent. Of interest, 63 percent of all abusers of amphetamines had been introduced to the drugs by their friends or

peers and only 23 percent had been introduced to amphetamines by a drug dealer.

Fifteen percent of all the drug abusers we interviewed had histories of abusing phenmetrazine—Preludin. Not unexpectedly those who abuse phenmetrazine were most frequently introduced to the drug by friends or peers.

Amphetamine abuse in Miami has shown the epidemic characteristics since 1968. There is some evidence that the abuse of phenmetrazine—Preludin—and phentermine—Ionamin and Fastin—may be becoming popular substitutes for the amphetamines.

Amphetamine abuse in Greensboro is an endemic or stable problem with drug dealers more frequently introducing new users than in any other city we studied. Phenmetrazine (Preludin) abuse has become a popular drug of abuse and appears to be primarily imported from the Washington area.

The amphetamine epidemics Washington has experienced in the past may have been replaced by the abuse of phenmetrazine—Preludin.

Amphetamine abuse in New York City is an endemic or stable problem when viewed in its totality with microepidemics occurring within neighborhoods. Our data are too sparse, however, to identify these neighborhoods in time and place.

Amphetamine abuse in Atlantic City is an endemic or stable problem. Phenmetrazine—Preludin—abuse may also have become endemic

Amphetamine abuse in Des Moines was probably epidemic during the 1966–71 period when it probably became endemic. Phenmetrazine—Preludin—abuse has become epidemic. Des Moines was one of the few cities we studied which reflected considerable experimentation with a wide range of amphetamine related drugs.

Amphetamine abuse in Kansas City is an endemic or stable problem. Phenmetrazine—Preludin—abuse has, however, shown the characteristics of contagious transmission.

Amphetamine abuse in Phoenix can be viewed as epidemic and probably has been since 1968. Phenmetrazine—Preludin—abuse is probably endemic or stable.

Amphetamine abuse in San Francisco can be viewed as epidemic and has been since 1966. Phenmetrazine—Preludin—abuse is probably endemic or stable.

In summary, our study among known drug abusers indicates the continued popularity of the amphetamines as drugs of abuse.

In addition, the abuse of phenmetrazine—Preludin—has become epidemic in some cities and appears to be spreading into others.

Senator NELSON. You are saying 2 million used the amphetamines?

Dr. CHAMBERS. Ostensibly for weight control.

Senator NELSON. But in fact as a stimulant?

Dr. CHAMBERS. Yes, sir. They made them feel good.

Mr. GORDON. Do you have any figures showing the use of these drugs by income groups?

Dr. CHAMBERS. I have by socioeconomic group.

The groups break the population by parental education, income and occupational. This is in a sense "economic," and it appears that amphetamines prescribed for their energizer effect, do show major social-

economic differences. The bulk of their use occurring in the middle range of the socioeconomic groups. With the diet pills, there is a virtual exclusion of the very low classes, but widely distributed otherwise.

Senator NELSON. Over what period of time did that survey of 35,000 occur?

Dr. CHAMBERS. I did the first one in New York State, and that occurred in 1970.

I did the last one in 1975.

Senator NELSON. Is that going to all or just several of the States?

Dr. CHAMBERS. In all, we have done 17 different States, plus the District of Columbia.

Senator NELSON. Did you extrapolate from this survey of 35,000 a figure that would indicate from that a percentage of people in the whole population who are involved in some form of drug abuse?

Dr. CHAMBERS. Well, it depends on how you define drug abuse.

What we are suggesting, if you control only for the amphetamines——

Senator NELSON. If what?

Dr. CHAMBERS. If we control only for amphetamine use, and we define abuse as that use which occurs as a result of not getting the drug by your prescription, or that involves extension of that use, or the expansion of that use, and define all of these things as abuse, roughly 65 to 70 percent of all users abuse the drug.

Senator NELSON. Sixty-five to 70 percent of all users are abusing the drug?

Dr. CHAMBERS. If you use that kind of definition, yes.

I am not sure how many of these are actually disfunctional as a result of that use.

Senator NELSON. And that figure was 65 percent?

Dr. CHAMBERS. Sixty-five to 70 percent.

Senator NELSON. Of all users?

Dr. CHAMBERS. People do not appear to be able to use the stimulant drugs as they are prescribed.

Senator NELSON. Do not appear to what?

Dr. CHAMBERS. To be able or willing to use the stimulant drugs as they are prescribed.

The vast majority of our cases indicate they extend the time of use or increase the dose.

Senator NELSON. And that 65 percent who are abusers, represents what percent of the population?

Dr. CHAMBERS. I have no idea.

My guess is that you are talking in the neighborhood of 65 percent of roughly 4 or 5 million people.

Senator NELSON. Thank you very much for your very valuable testimony.

We appreciate your taking the time to come.

Dr. CHAMBERS. Thank you.

Senator NELSON. Our next witness is Dr. Thomas M. Gellert from Huntington, N.Y.

I appreciate your taking your time to come here, Dr. Gellert.

You may present your testimony however you desire.

STATEMENT OF THOMAS M. GELLERT, M.D., HUNTINGTON, N.Y.

Dr. GELLERT. Thank you, Mr. Chairman.

I am here today as a private practitioner, and, therefore, for myself, and as an unofficial representative of 250 physicians who decided to attack this problem of drug abuse, particularly amphetamines, and without waiting for guidelines, prohibition, and coercion, and I also speak as one who has been active in the county medical association of the county and the city of Huntington, and which is made up of 200,000 people on the eastern end of Long Island, and also as one who understands somewhat the governmental problems, and as one who has also served on the county board of health.

We in Huntington are very proud of our efforts, and are gratified by the results, but now, 5 years after deciding to stick to our principles, we are convinced that some form of Federal regulation is necessary if we are really to succeed.

Our community is Huntington, N.Y., and just a couple of weeks ago, when "60 Minutes" came on, we were sort of designated the amphetamine capital of the universe.

This is certainly not the case, but I would like to tell you how this came about.

We in Huntington are a township of about 200,000 people, we consider ourselves quite enlightened. We were among the first in the country to set up the youth board, an organization responsible for handling problems with our youth.

I believe you have already heard from some of our representatives who spoke before this subcommittee last week.

When heroin became a problem in our community, our hospital donated facilities, our hospital-pharmacy donated time and the nurses donated their time, and we set up a free methadone clinic to help control the heroin difficulty, and then when amphetamines appeared on the scene, Huntington physicians decided to stop writing amphetamine prescriptions.

We hoped that by this voluntary act that we would remove a sizable number of these drugs from circulation and reduce the number of drugs which could be abused.

To accomplish this task we conducted seminars, distributed the latest scientific data, held hospital staff meetings, and met with community agencies.

After examining the evidence it was clear to anyone familiar with evaluating scientific data that, except for the rare problems of narcolepsy and the treatment of certain types of hyperactive children, amphetamines had no bona fide use in the practice of medicine.

Specifically, there was more than enough evidence to support the conclusion that amphetamines had no place in the treatment of obesity.

Overnight the prescribing habits of Huntington physicians changed. From several hundred amphetamine prescriptions a year, the average pharmacy found it was dispensing only one or two amphetamine prescriptions a month.

Some pharmacies filled none over periods of several months.

Some time after our voluntary amphetamine ban, I recall speaking to a pharmaceutical house representative who observed that contrary

to his expectations the amphetamine ban extended to all antiobesity drugs and an expected increase in the writing for nonamphetamine anorectics never materialized.

Huntington physicians had apparently decided that drugs in general had no place in the treatment of overweight patients. This philosophy of therapeutics has not changed in the past 5 years. The new physicians in town have been quick to learn of our amphetamine ban and their cooperation has been exemplary.

Senator NELSON. Is that number, 250 physicians, the total number in the Huntington township?

Dr. GELLERT. That is right.

If we have become so successful in this effort, why am I here today asking for Federal help to control the production and distribution of amphetamines and related drugs?

Despite the honest effort of 99 percent of the practicing physicians in our community, some duly licensed doctors have decided to confine their practices to the drug treatment of obesity in our community. It has been an outrageous situation.

They meticulously observe the existing laws, and they hand out a staggering amount of legal amphetamines each day.

They are not members of our medical community. They do not practice in our hospitals, nor are they members of our medical society. Thus they escape the censure of their peers and the constraints which might be placed upon them.

In the town of Huntington there are two such physicians. The youth board of Huntington township recently conducted an unofficial tally of the number of patients seen by one of these doctors in a typical week. Approximately 800 patients were seen. Over a several week period, they ranged from 800 to 1,100 patients.

Senator NELSON. Does anyone know what the standard fee for the consultation and prescription is?

Dr. GELLERT. I do not know what the fee is, but I know that figure is available.

Senator NELSON. That meant somebody could find out what is being charged?

Dr. GELLERT. I would imagine $10 or $15.

Senator NELSON. That is the only purpose for which these people go to these two doctors?

Dr. GELLERT. Yes, sir.

Senator NELSON. All right.

Dr. GELLERT. As a part of his treatment program, this particular doctor distributes amphetamines to all comers. Patients are literally lined up outside of his office. And by no means are all of those in line obese.

By a calculation, if he sees a patient, he asks the patient to come back every 2 weeks, he probably prescribes 42 tablets, amphetamine tablets, over those 14 days, that is 3 tablets a day.

When you multiply that by 42 times 800, and then multiply the number of tablets he is dispensing in a week, and then multiply that by let's say 50, this figure comes out to over 1½ million amphetamine tablets a year.

Forgetting for a moment those who seek out this man to obtain a supply of "uppers" to get through the day, such doctors have a ready-made parade of victims in any community.

They are the tired, overweight housewives; the self-conscious overweight teenagers; or, for that matter, any overweight citizens.

These people see in the "diet doctor" an easy solution to their problem and they end up captive to his drugs, needing them just to "keep going."

One such physician can easily prescribe more than a million amphetamine tablets in the course of a year. Undoubtedy, in our community this man's practice is assisted by the unavailability of amphetamines elsewhere.

This is the outrageous part. This man comes and opens his practice, and he gets everyone he wants on amphetamines, because they cannot get it anywhere else.

Senator NELSON. Among the physicians in the county, you end up with some patients then coming to the physicians who do prescribe for treatment for some side effect, as a consequence of their taking the drug?

Dr. GELLERT. Yes; I think everyone who practices primary medicine, internal medicine, or family practice, sees patients who of course are certain they have a thyroid problem, because they are overactive, and they have the shakes, and they cannot sleep, or they have lost too much weight, and one of the first questions we ask is, what medicines are you taking, and more times than we would like, we find that they are on amphetamines.

Some of our old patients withhold this information from us, because they are embarrassed, that they have gone elsewhere to seek a drug we would normally not prescribe.

Senator NELSON. I see.

Dr. GELLERT. And, Senator Nelson, a great deal has been said about why did not the physicians police their ranks.

We are asked, why don't we do something about these people.

We would like to, we would like to very much.

As I mentioned before, frequently, presently they lie outside the normal channels of control, they are not members of our society, they do not practice with any staff of the local hospitals.

Until recently in the State of New York, to discipline the physicians, to take away his license, was almost an unheard of affair.

It required getting involved with the department of education, they were the ones who held our licensing permits, and they were the only ones who were able to handle this, and it would appear that indeed, that instead of cooperating with the State medical society, that we were often at odds with our State medical society, but recently our Governor, Governor Carey, signed into law a change in the procedure, and we now have a disciplinary board, which is set up in the department of health, and do have input, the physicians do have input, they do have input to the board, but the financing is so poor that investigative studies cannot be done, and we are way behind in cases that should be looked into, including people like those men who are pushing pills in our community.

Now, we have heard a lot of expert testimony this morning. I was more than impressed with Dr. Henderson and Dr. Chambers' testimony, and I certainly believe that amphetamine should be barred for the use of obesity.

While we certainly have fewer amphetamines in our town than our neighboring communities, how much better it would be for the collective health of our citizens if effective restraints could be placed on the distribution of all amphetamines.

If it could be shown that amphetamines and related antiobesity preparations were of value in treating obesity perhaps one could argue that the obvious disadvantages to their use were outweighed by the advantages.

The fact is that these drugs are, at best, only briefly effective in the treatment of the overweight patient.

Indeed, the preponderance of evidence is that amphetamines have no long-term value other than the placebo effect present when taking any sort of medicine for any sort of condition.

If amphetamines were effective and necessary in treating obesity it should follow that during the 5 years since the Huntington amphetamine ban our community would now have a larger number of overweight citizens. This is not the case.

Those who advocate the use of currently available "drugs" in the treatment of obesity argue that the supposed appetite suppressant effects of these drugs provide the patient with an initial success in therapy which may spur him on to continue his weight reduction program drug-free.

The extrapolated conclusion, I imagine, would be that to deny the public these drugs would make obesity more difficult to treat.

I certainly do not believe the facts support this conclusion. It is like telling an alcoholic that if sometimes we fill you full of tranquilizers and get you off alcohol for a week or two weeks, or a month or two, it will solve your problem.

We know that that is not the case, when we stop the tranquilizers, he goes right back to the alcohol.

Rather the key to treatment of obesity is motivation, and without it, the drug or diet cannot succeed.

As a physician whose practice of internal medicine includes large numbers of desperately ill cardiac patients, I have had considerable experience in the successful treatment of large numbers of overweight patients.

The key to success is motivation. Without it no drug, no diet, no acupuncture, nothing can succeed.

It is the physician's job to present to the overweight patient the reasons why he must lose weight.

He must get to know the patient, the patient's family, and the patient's problems.

He must convince him of the necessity for losing weight and the logic of his arguments must be inescapable.

Where emotional factors prevent success in a weight reduction program psychological counseling is in order.

When such an emotional impediment to weight reduction exists, the last thing a physician should do is to prescribe a habit-forming drug.

It would seem ridiculous to take a patient who has an emotional

problem, to take this patient and put him on a drug that would make the patient an addict, that would be ridiculous.

I am convinced that drugs have no place in the treatment of obesity. I am convinced that the medical world can practice better medicine without the antiobesity drugs.

I am convinced that the overwhelming majority of physicians believe as I do. I am disheartened by the presence of that small number of physicians who capitalize on the habit-forming character of the "diet pill."

They threaten the success of the amphetamine-free environment which my colleagues and I are attempting to build. Frankly, they are a public health menace.

I believe there is a method of controlling the injudicious distribution of amphetamines. The solution is straightforward, and it has precedent. Last month a patient of mine with a painful cancer required methadone for relief of his agony. Other narcotics had proved ineffective or unusable because of his multiple allergies. The drug was provided through normal channels of distribution with the understanding that it was to be used as an analgesic, not for the treatment of drug addiction.

I received a telephone call from the pharmacist who filled the prescription, and the pharmacist pointed out that I can use this drug only for analgesia, and to use it for any other purpose would be contrary to law.

This is a unique situation. The FDA has been reluctant to involve itself in the doctor-patient relationship. Except for regulations pertaining to the use of new drugs or drugs being investigated for efficacy and safety, the FDA has not involved itself in regulating the prescribing habits of physicians. I believe this to be laudable. In the instance of methadone, however, it was determined that the absence of tight control of the distribution of this drug constituted a serious public health hazard. The FDA, therefore, used its authority to prohibit the unrestricted distribution of methadone. The FDA requires that any individual or organization using methadone for the treatment of drug addiction must secure a special license and submit to constant supervision. To do otherwise is unlawful.

I propose that the same regulation with restraints be placed on the use of amphetamines. I propose that a special license be required for the use of amphetamines to control obesity and in the control or treatment of drug addiction. I further propose that the existing restrictions on the use of amphetamines be continued for all other uses. In this way the prescribing of this drug will be limited to a 1-month supply which is not refillable and which is dispensed in a specially marked container. I also recommend that the continued use of the nonamphetamine diet drugs be similarly controlled pending further research into their abuse potential. These changes would effectively eliminate the amphetamines from the "diet doctors'" dispensary.

If the deliberations of this committee provide the impetus for the FDA to exercise authority and eliminate the abuse of amphetamines, you will have helped Huntington physicians in their original crusade to ban amphetamines in our community. You will simultaneously aid physicians in communities throughout our country in the control of amphetamine abuse.

Senator NELSON. Let me ask you a question. If they no longer had the indicated use of obesity at all, then I would assume it would not be difficult to stop the abuse.

For example with respect to the two physicians in Huntington, obviously if these drugs are indicated only for narcolepsy, or hyperkenesis, they would not have 800 patients going through their offices. Is that correct?

Dr. GELLERT. Exactly.

Senator NELSON. Are you saying that you think there may be some occasion where it is indicated for use of obesity?

Dr. GELLERT. No; not for obesity at all.

I do not see how one could justify the use of the drugs for obesity.

Several years ago the FDA investigation showed that there was short-term advantage to the use of the drug.

It may be indeed that someone some day will find that there is long-term advantage, but as yet that is not so.

Senator NELSON. You would take the position if a physician desired that it should not be used for obesity, but that if he wanted to, that physician if he had a justifiable reason, that he would get a special license?

Dr. GELLERT. Yes; and if the controls for such distribution of amphetamines is similar to the controls and of the distribution of methadone, I doubt seriously we would be seeing any of these diet clinics in operation.

This could not be justified.

I also believe there is not enough information today that would indicate that the amphetamines and amphetamine-related drugs, I feel they should be moved up, the amphetamine-related drugs, to where the amphetamines are right now, and that is a class II drug which would require special labeling, a nonrefillable prescription, and no more than 1 month prescribing at any one time.

Senator NELSON. Did the lines outside these two obesity doctors' offices get shorter or longer after the "60 Minutes" program?

Dr. GELLERT. Well, certainly the advertising was there, I would not be surprised if they got longer.

Senator NELSON. The real story in Huntington is that all except two physicians in the whole county have agreed that you should not use amphetamines for the purpose of obesity, but the abuse by the two physicians of this agreement has made it impossible for the other 250 to control it?

Dr. GELLERT. In reality we were only able to support one diet doctor before we had the ban. After the ban, the other one joined us.

Senator NELSON. Thank you very much for your very valuable testimony, Dr. Gellert.

We appreciate you taking the time from your busy practice to come before the subcommittee and to present your testimony.

It is very valuable, and we appreciate it.

Dr. GELLERT. Thank you.

Senator NELSON. Our next witness is Reverend Frank Reynolds, national director of Teen Challenge Youth Centers, of Springfield, Mo.

STATEMENT OF REVEREND FRANK REYNOLDS, NATIONAL DIRECTOR OF TEEN CHALLENGE YOUTH CENTERS, SPRINGFIELD, MO.

Reverend REYNOLDS. Thank you, Mr. Chairman.[1]

Teen Challenge is a ministry to street people. It began in 1958 as a ministry to street gangs by David Wilkerson. As the work progressed we began to encounter drug addicts. Many heard the message of hope in Jesus Christ and began to respond in a positive manner.

From this beginning has grown a ministry that now is in 24 States, the District of Columbia, and Puerto Rico, with ministries in 62 cities. Through coffee houses and street workers, Teen Challenge made contact with over 380,000 people in 1975. In our various residential facilities we have 1,000 people any day. I say this to let you know that we have a broad contact with a lot of young people at the street level where the action is.

Our experience has been primarily at the street level, although the past few years we have received more and more people referred by other agencies, both public and private.

Our primary thrust has been to what we have called "troubled youth." This has resulted in our also working in a preventive-type ministry with drug education programs in schools and community youth groups.

Through these presentations we had many opportunities to deal with young people in a confidential manner about their own drug involvement. We were able to get a good reading of what was happening in the drug scene.

In the early 1960's we primarily reached the inner city heroin addicts. With the "drug explosion" of the mid- and late-sixties we began to reach people with various dependencies on many different drugs: Tranquilizers, barbiturates, amphetamines, hallucinogens, as well as alcohol, and the opiates.

Today, most of the drug dependent persons we work with are so-called polydrug users. By that we mean they use many different types of drugs and mix them with alcohol.

My personal feeling is to include alcohol with drugs, but we will not get into that.

I know this hearing is primarily concerned with the use and abuse of amphetamines. But, I think, we are going to be remiss if we do not realize that this is part of an overall problem and, perhaps, a philosophy of the medical and pharmaceutical business.

That philosophy is; that there is a solution to every problem in a pill and its wrong to suffer any discomfort, physical, or emotional. Perhaps, it is a problem of our "cradle to the grave security society."

This is promoted in the advertising, on television, and other media. Since I am concerned primarily with our youth 14 to 25, what are we teaching them? "I have an important meeting, I must be up for it, so I eat or drink something to pick me up so I can put my best foot forward." Then we get pushed out of shape when our teenagers do the

[1] Reverend Reynolds subsequently submitted the following: "It might be added that Teen Challenge is a voluntary program. It is also a nonprofit corporation and is privately funded by contributions. We have not received Government grants. One 1-year grant was received from NIDA for a research study."

same thing for their Earth-shattering date, party, or whatever. "That is different, this is a $500,000 deal," we argue. "But," the young person says, "This is the chance of a lifetime to really impress someone that will change my whole future."

What have we done? Instead of preparing ourselves spiritually, physically, and emotionally we try to substitute an artificial booster or tranquilizer. We do not deal with the real problem.

Let me illustrate. Four weeks ago a young man was released from a certain penal institution. While he was there he got under a lot of tension. So the doctor gave him some Valium. As the tension built so did his intake of Valium, legally. He was released, having completed his sentence, with a legal prescription and is using 40 to 50 milligrams of Valium per day. He is "free" from jail, but he cannot function in the "straight" 8-to-5 society.

Let me add he was 8 years in the penitentiary.

The 40 to 50 milligrams of Valium does not handle the additional tension, so he has added a little alcohol to help out. Now he is in danger of violating the conditions of his release.

What is the problem? Is it tension? Or do we need to dig a little deeper? Then give the individual the coping mechanism to deal with the problem. I have had only 20 minutes with this individual and discovered his tension started when his wife divorced him while in prison. Maybe there was no way to save the marriage, but there is a better way of handling the succeeding emotional problems than a chemical copout.

I am not sure this legislative body can solve the problem, but I believe unless we are willing to see why we get pushed into using chemical substitutes we will continue to seek chemical solutions to emotional and spiritual problems.

Dr. Blum stated in an article in Look magazine, several years ago, in a discussion of various solutions to the drug abuse problem, "If we are looking for a drug to solve the drug problem we will fail. We will never solve the drug problem until we make up our minds what our minds are for."

Now to speak specifically to our experience with the amphetamine group.

By the way, since writing this, I had a man come in, his grandfather called me to visit him in jail, and when I got to talking as to what his problem was, I asked him, what can I do to help you.

I said. why are you in jail?

He said, armed robbery. I said, well, for what? Are you involved in drugs?

He said, yes, and I said, what kind of drugs? I said, I am not the law, not the court, not the lawyer.

What are you taking?

He said the truth, I don't even know what happened, but I had taken some speed and some cocaine, and we had some liquor, and the next thing I knew, I was in jail.

When I woke up, I was here. I don't know what happened, and he is charged with armed robbery, but amphetamines is the basis of it. I found out since he was getting them through his mother.

We first began to see people coming in with this problem in 1967 and 1968. Not large quantities, but when a person had been involved

with heroin and other depressant drugs he would buy "Bennies" to give him a lift to get out and do his "thing" to get the money for the heroin.

When the fad of taking drugs hit our high school and college groups, they would have what some called "cocktail parties." Each would bring the medications from their private drugstore, that is, the home medicine cabinet. All the pills would be put in the bowl. Different parties were run different ways. Some would portion a quantity to each one with no regard to what they took. Others would divide them by color or shape and compare notes.

What was the main problem? Availability—they discovered that with mom's diet pills they could dance and go and go without stopping. Hey man, that's terrific.

Someone thought we could solve the fat problem without discipline and without pain by taking dexedrine or other amphetamines.

The college crew is no different than when I was in school. We did not get our work done until it was due. We did not study until the night before exam. But in the early forties we had to depend upon the coffee pot and cold water in the face to stay awake.

Now, thanks to "better living through chemistry" we can swallow a couple of pills, obtainable legally for the diet, the tired feeling, the depressed state, or whatever other excuse—fancy word for lie—I can convince the doctor of.

Then suddenly you have people living on this stuff. Then comes controls in the early seventies.

By this time we have coming into the program the speed freaks and the spacies. They have in their own words "fried their brains." Where did they get the stuff? One student in the program from an Ohio college, who came into the program in 1970, floated a loan, flew to Mexico and brought back amphetamines of various kinds, manufactured in the United States, and netted $1,700 for the weekend risk and trouble.

The problem arose for him when he became his own best customer. Messed up his mind; could not study, dropped out of school with 1½ semesters to go for graduation.

I am amazed that some, as late as last year, discovered an overproduction with shipment out of the country to be brought back in illegally. This was common knowledge to us working the streets. We assumed if we knew it, certainly, the professional agencies knew it.

Some have told of stealing them off the loading docks by the barrel full.

I do not need to restate the statistics, you have them, undoubtedly, on file.

The last 3 years I have been in an administrative position and only working as a volunteer with troubled people. It is disturbing and frustrating to me to start dealing with people and discover the amount of mood-altering medications prescribed to cover up the problem. Yet, no one stops to try to solve the problem or provide a way of handling and dealing with the difficulties.

At Teen Challenge our approach to the drug abuser has been that your drug taking is not the problem. It is a symptom. We were saying this when others said we were foolish to talk like that.

The problem is inside of you. Invariably when we begin to relate to the needy they would speak of the emptiness inside. Nobody wants the "blahs." And when someone offers a chemical, easy solution, you have a good candidate.

Our approach is first acceptance of them as a person, regardless of their physical appearance.

The speed freak usually comes in skinny and starry eyed, extremely nervous and suspicious. Not trusting anyone. They have been "ripped off" emotionally.

Then we share the love of God we have found and the inner peace we have. The next logical step is, "You can have it, too. God so loved you that he gave His best for you."

Now, here is where we had to regroup our forces. The heroin addict was quite predictable. After he would withdraw, his head was normal.

Not so with the amphetamine user. His attention span is short. He is depressed very easily and is just liable to space out on you.

Another complication we ran into was that the amphetamine user quite often has used LSD, mescaline, and other hallucinogens.

I am not a technical man. So how much of our problems can be attributed to which chemical, is difficult to assess. As I said before, at the street level you do not get someone that does just one drug.

After speeding he knows he is going to crash. When he crashes he knows he is not going to be able to sleep, so he will seek downers—barbiturates.

Most can walk into a doctor and give a good con story and get some sleeping pills. If all else fails, he can put on a scene and get rushed to the emergency ward and compassionate people will give him what he wants. Remember, these people know what symptoms to describe in order to get the doctor to give the "right" prescription, and they do.

We, just 3 weeks ago, had a policeman call one of the workers, brought a girl in, we do not know what she was taking, tried to get her to three hospitals; they would not admit her.

The men drove her to another State hospital, about 40 miles away, they stated their situation, they signed her in, when they got back home, she was there ahead of them with her purse full of pills, and that just happened.

It takes long patience. About the time you think you are making progress, he flips out.

Where with the heroin addict we could put pressure on him and get pretty hardnosed, we find we would have to back off from the amphetamine user, cut down the pressure until he could settle down. I believe it takes the power of God to help and heal some of the scrambled heads we have worked with.

We have not won on all of them, but we have as good a record as any.

Mr. GORDON. As I understand it, it is much more difficult to treat an amphetamine addict than a barbiturate addict; is that correct?

Reverend REYNOLDS. Well, a heroin addict anyway, and even barbiturates, when they get down, the barbiturate man will get a lot of trouble physically, once he gets down.

Mentally, he is in pretty good shape.

These people who are on amphetamines, when we see them, we say, oh, God, give us old-fashioned heroin addicts so we know what they are going to do.

These are kind of unpredictable. They might flip out on you. We do not know what will happen.

Mr. GORDON. Is it your impression that the original source of amphetamines was generally a doctor?

Reverend REYNOLDS. That is a hard one to answer. Those that we work on, there is so much legal and illegal of it that is done.

I would hate to put a percentage figure on it. These people are con artists. They can walk into any doctor's office, and convince him of their symptoms. They know what prescriptions he is to prescribe, so he knows how to get what he wants.

Mr. GORDON. And the doctors take his word?

Reverend REYNOLDS. And they take his word for it.

That is part of their problem, and that is part of our problem.

Mr. GORDON. My mother used to do that. She used to go to the doctor and tell the doctor what was wrong with her.

Reverend REYNOLDS. That is just what they do.

Gentlemen, let me recap.

What is the problem?

One, we are too prone to look for easy, painless solutions to life's problems.

Two, chemicals that can alter the mood are available legally and illegally from "legitimate" manufacturers.

Three, the knowledge that it is available is well advertised.

Four, the whole health-care field has got to shoulder their responsibility in causing the spread of the drug abuse problem.

Five, we can no longer bypass the fact that men have spiritual needs, as well as physical, and social needs.

Some hopeful signs:

One, many of us are redoubling our efforts.

Two, medical schools are now requiring medical doctors to take courses in interpersonal relations.

Three, many professionals are acknowledging that there are spiritual needs that can be met. More cooperation between these two areas is needed.

Four, this hearing is being held and we have been able to share from the street level, where the action is.

For an idea of the effectiveness of the Teen Challenge program you may refer to a study done under grant No. 1 H81 DA 01505-01.

This is the first time we have been able to share some of the things we see from the street side, and we appreciate it.

Thank you.

Senator NELSON. You state on the first page, that you made contact with over 380,000 people in 1975.

These 380,000 are all individuals who were using drugs?

Reverend REYNOLDS. Probably 85 percent will be drug-related of some kind.

Senator NELSON. You said in some residential facilities you have some thousand people a day?

Reverend REYNOLDS. In our total program, we have 1,000 people in residence.

Senator NELSON. When you say in residence, do you have residential facilities for some of your clients?

Reverend REYNOLDS. Right. Our program is 1 year long.

Senator NELSON. How many?

Reverend REYNOLDS. About 2,500 to 2,700 people will complete the program.

Senator NELSON. Two thousand five hundred to 2,700?

Reverend REYNOLDS. Right.

Senator NELSON. And will they all live in a residential setting or residential situation?

Reverend REYNOLDS. During that year.

Senator NELSON. And how many cities do you have residential treatment centers in?

Reverend REYNOLDS. Sixty-two.

Senator NELSON. Sixty-two?

Reverend REYNOLDS. Yes.

Senator NELSON. And they would average what size?

Reverend REYNOLDS. Well, everything from 6 or 8 in some of our facilities, up to 130.

Senator NELSON. And this program is supervised or managed from where?

Reverend REYNOLDS. Well, the program grew like topsy.

In the last 3 years, I have been asked to try to coordinate them.

I live in Springfield, Mo., or I would say my wife lives there, and I just visit.

Senator NELSON. Well, are all of these facilities under the direction of one national organization?

Reverend REYNOLDS. Right. We are just trying to pull an organization together.

Teen Challenge is an incorporated name now, and we are all interrelated.

Senator NELSON. And when was the national Teen Challenge organization created?

Reverend REYNOLDS. Well, my office was created 3 years ago.

Senator NELSON. Did you originate the program?

Reverend REYNOLDS. Well, Dave Wilkerson originated it, but I was with him from the beginning, and I helped organize it.

Senator NELSON. Are you expanding the program into other cities?

Reverend REYNOLDS. Yes; faster than we would like to.

Senator NELSON. What medical assistance, advice, consultation, psychiatric, or otherwise, have you had?

Reverend REYNOLDS. Just on a voluntary basis, we work primarily from the spiritual area, with the cooperation of medical people at our facilities.

Senator NELSON. So you do have volunteer physicians in some communities?

Reverend REYNOLDS. Right.

Senator NELSON. How many communities?

Reverend REYNOLDS. Wherever we have a facility, we try to line up a doctor that will work voluntarily.

Senator NELSON. Do you usually find somebody that will volunteer?

Reverend REYNOLDS. Usually. We have had some problems in a couple of areas.

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

Tomorrow's hearing will resume at 10 a.m. We stand in recess.

[Whereupon, the subcommittee was recessed at 12:35 p.m.]

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

FRIDAY, NOVEMBER 19, 1976

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

The subcommittee met, pursuant to recess, at 10 a.m., in room 318, Russell Senate Office Building, Hon. Gaylord Nelson, chairman, presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; and Karen Young, research assistant.

Senator NELSON. The subcommittee will please come to order.

Today's hearing by the Monopoly Subcommittee of the Senate Small Business Committee constitutes the fifth and perhaps the last day in this series of hearings on the antiobesity drugs.

Our witnesses today are:

J. Richard Crout, M.D., Director, Bureau of Drugs, Food and Drug Administration, and his associates; Frederick A. Rody, Acting Deputy Administrator, Drug Enforcement Administration, U.S. Department of Justice; and Mr. Isaac McGraw, president of the pharmaceutical division of the Pennwalt Corp.

In 1972, FDA's Advisory Committee on antiobesity drugs after considerable study, submitted the following conclusions and recommendations to the Food and Drug Administration:

One, adult obese subjects on diet plus drug tend to lose more weight than those on diet alone.

Two, the amount of weight loss associated with the use of an "anorectic" drug varies from trial to trial.

The possible origins of the increased weight loss due to the various drug effects are not established.

The increased weight loss appears to be related to variables other than the drug prescribed, such as the physician-investigator, the population treated, and the diet prescribed.

Studies do not permit conclusions as to the relative importance of the drug and nondrug factors on weight loss.

Three, the magnitude of increased weight loss of drug treated patients over placebo treated patients was only a fraction of a pound a week. The rate of weight loss was greatest in the first weeks of therapy

for both drug and placebo subjects and tended to decrease in succeeding weeks.

Four, the natural history of obesity is measured in years, whereas the studies cited are restricted to a few weeks duration; thus the total impact of drug-induced weight loss over that of diet alone must be considered clinically trivial.

The limited usefulness of these agents must be measured against any possible risk factors inherent in their use.

Five, the amphetamines including methamphetamine have been widely abused in numerous populations. It is thus in the best interests of the public health to limit the use of amphetamines as far as is compatible with adequate therapy. This is both to minimize the risk of dependence in susceptible patients being treated and to decrease the amount of drugs being distributed, since widespread prescription of a dependence-producing drug inevitably increases the possibility for diversion to nonmedical use and abuse.

Six. Evidence presented for newer "anorectic" congeners of the amphetamine family and nonamphetamine drugs do not set them apart as having higher benefit or lower risks than older available drugs.

Seven. There was no evidence in the data reviewed which showed that combination of an antiobesity agent with other drugs increase the benefits or reduce the risk of the antiobesity agent.

Eight. Obesity is not an indication for the parenteral use of these agents. The principal recommendations of that committee were:

One. That all antiobesity agents reviewed be placed in schedule II on the basis of abuse potential.

An exception was made for fenfluramine which was a new drug and about which little was known at that time.

Two. That combinations of antiobesity drugs with other drugs be removed from the market.

Three. That parenteral amphetamines may not be approved for use in the treatment of obesity.

Four. That the single-entity oral antiobesity preparations including the amphetamines be permitted to be labeled for restricted use in obesity provided that they are used in association with a specific weight reduction program and that the clinically trivial contribution of these drugs to the overall weight reduction is properly emphasized and that the limited usefulness of these agents must be measured against any possible risk factors such as nervousness, insomia, and drug habituation that might be inherent in their use.

Moreover, these agents can only be recommended for use in the treatment of obesity in a carefully monitored and specified weight reduction program under the care of a physician.

What to do about these drugs has troubled the medical officers of the FDA for quite some time. For example, Drs. Elmer Gardner and Barrett Scoville, Director and Deputy Director, respectively, of FDA's Division of Neuropharmacological Drug Products, stated in 1972 at a symposium:

> Ultimately, we must all weigh the potential benefits of these drugs against the risks of the drugs. Here we hope that in giving your opinion, you will consider risk in its largest sense—not simply the innate clinical toxicity of the anorectics, but the risk to the public health of potential abuse. We do want to hear what these drugs mean in medical practice. But we also must think in

the somewhat less familiar terms of drug abuse. Here is a problem from which we cannot divorce our thinking in favor of medical considerations.

Throughout FDA's records there can be found a depreciation of the usefulness of these drugs for antiobesity purposes:

> The degree of extra weight loss was small—a few tenths of a pound a week in many cases—and variations were great.
>
> Larger questions of long standing remain unanswered, such as the long-term effect on morbidity and mortality of the use of anorectics. These questions are of basic importance, since the usefulness of the drugs depends in large part upon the assumption that they somehow help prevent the adverse effects of obesity.

The objective of these hearings, therefore, is to ascertain the present views of the Food and Drug Administration on the safety, efficacy, patterns of use and abuse, and the future of these drugs.

We are particularly interested in hearing:

One. Why the first recommendation of FDA's advisory committee that all these drugs be placed in schedule II was not accepted. This is especially puzzling in view of FDA's testimony before this subcommittee in 1972 that:

> Evidence presented for newer anorectic congeners of the amphetamine family and nonamphetamine drugs do not set them apart as having higher benefit or lower risks than older available drugs. (Hearings: Advertising of Proprietary Medicines, pt. 3.)

Two. Why some combination antiobesity drugs are still on the market. On February 12, 1973, the FDA took steps to remove Eskatrol from the market, but the drug is still being sold—$5.4 million worth at manufacturer's prices.

The sales of another combination, Dexamyl, for 1975 amounted to $2.6 million. In other words, the sales of these two Smith Kline & French drugs, which should have been removed from the market years ago, amounted to $8 million in 1975.

The February 12, 1973 Federal Register also noted that the FDA is aware of a study conducted for Smith Kline & French relating to abuse potential of Eskatrol and which was not submitted to the FDA as required by law.

What action was taken by FDA against this violation of the law?

In the March 30, 1973 Federal Register it was announced that Smith Kline & French had requested a hearing with respect to Eskatrol. The FDA allowed the drug to continue to be marketed pending a ruling on the request for a hearing.

It is now 3½ years later, and the hearing has not been yet held. Why?

We would like to have an explanation of why it was not.

The principal problem, however, is justifying the continued existence of these drugs on the market.

Given a utility which is "clinically trivial," to use FDA's own term, and given the very extensive list of serious risks to individuals and society including the potential and actual abuse, questions have been raised whether their availability for antiobesity purposes constitute a hazard to the public.

Dr. Thaddeus Prout, Chairman of FDA's advisory panel on these drugs, told our committee last Tuesday that he now favors that in addition to placing all these drugs in schedule II, obesity be withdrawn as an indication for the therapeutic use of these drugs.

We look forward to hearing the views of today's witnesses on this subject.

Our first witness is Dr. J. Richard Crout, Director, Bureau of Drugs, of the Food and Drug Administration.

We welcome you here this morning, Dr. Crout. If you would identify your associates for the reporter, and for the record, so we will have all statements appropriately and properly printed, I would appreciate it.[1]

STATEMENT OF J. RICHARD CROUT, M.D., DIRECTOR, BUREAU OF DRUGS, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY RICHARD A. MERRILL, CHIEF COUNSEL, FDA, AND WILLIAM W. VODRA, ASSOCIATE CHIEF COUNSEL, FDA

Dr. CROUT. Thank you very much, Mr. Chairman.

On my left is Mr. Richard A. Merrill, Chief Counsel of the Food and Drug Administration, and on my right is Mr. William W. Vodra, Associate Chief Counsel for Drugs of the Food and Drug Administration.

We welcome this opportunity to appear here today to discuss the activities of the Food and Drug Administration with respect to anti-obesity drugs.

Previous actions by both the FDA and DEA have had an important impact on the availability, labeling, and use of these drugs.

In spite of this, abuse of amphetamines in particular, appears to be a continuing problem in our society. It is appropriate that additional action in regard to amphetamines be considered at this time.

The story I will emphasize in this testimony is that the available data, while preliminary and incomplete, indicate that the amphetamines remain, among the anorectic drugs, the major offenders as drugs of abuse.

This problem cannot be solved by invoking additional controls under the Controlled Substances Act since these drugs are already in schedule II, the most tightly controlled category for marketed drugs. The only meaningful next step which can be taken is to remove the indication for obesity from the labeling for amphetamines or to remove them from the market.

FDA is working with the Drug Enforcement Agency and NIDA, the Federal agencies with detailed information regarding drug abuse, to develop the necessary documentation for such a position.

Abuse of amphetamines continues to occur, with deleterious and often devastating effects on the individual who abuses or becomes dependent upon them.

We must move ahead vigorously in addressing this important problem in drug safety.

Senator NELSON. May I ask a question. I read your statement this morning rather quickly.

Do you know what additional documentation is required?

I recall from your statement, if I am wrong, please say so, I believe there is not any further necessity for large controlled, double-blind studies beyond what has already been done, am I correct?

[1] See prepared statement and appendixes of Dr. Crout beginning at p. 14640.

Dr. CROUT. That is correct.

Senator NELSON. Then what additional documentation do you refer to?

Dr. CROUT. We would have a legal burden of making a safety case using the drug abuse data that are anticipated from our sister agencies to make the case that under the Federal Food, Drug, and Cosmetic Act, those drugs are no longer safe for their labeled use. That is a decision which is contestable, a position which is contestable in a hearing and later in court, so one has to have his legal ducks in a row, so to speak.

Furthermore, an accompanying regulatory action would be a movement of those drugs from schedule II to schedule I.

Senator NELSON. Would be what?

Dr. CROUT. An accompanying action in any removal from the market would be a change from schedule II to schedule I of the Controlled Substances Act, and that too requires appropriate documentation and can be challenged in court.

Senator NELSON. When you say removal from the market, are you saying removal from the market for any indicated uses?

Dr. CROUT. Were that to occur, yes, those drugs would be changed from schedule II to I.

Senator NELSON. How does the legal situation change if the FDA decided to remove treatment of obesity from its indicated use?

Dr. CROUT. The legal situation does not change.

We would have to go through the legal process of issuing a notice of opportunity of hearing, and perhaps having a hearing, for that indication.

Senator NELSON. Are you saying that you have the same legal question and the same problem of removing the drug from the market as you do of changing the indicated use of the drug?

Mr. MERRILL. If I can, Mr. Chairman, let me respond to that.

Because there are some proven indications of these drugs for medical treatment, if we were to take the more drastic action of taking the drugs off the market altogether, it is possible our burden would have to be higher because we might have to show that the risks of abuse in connection with the treatment of obesity outweighed any use including legitimate use of the drug.

If we simply removed obesity as an indication, we would make a case based on balance of the risks and benefits for this purpose. We would also have to decide whether that action would be sufficient, because it would mean that the dosage form was still available in the pharmacy, and still legally available for a physician to prescribe.

Dr. Crout reminds me that there is no misunderstanding, that the legal process through which we must go is precisely the same.

The amount of evidence required to sustain our case might be greater.

Senator NELSON. Let me see now.

With respect to those drugs that are under the 1962 Kefauver amendment, the Food and Drug Administration set up a procedure, and that procedure using the National Academy of Sciences, established panels of experts on each class of drug; right?

Dr. CROUT. Yes.

Senator NELSON. And then the drugs were classed as effective, probably effective, possibly effective, not effective; is that correct?

Dr. CROUT. That is correct.

Senator NELSON. And for those that were classified less than effective, you were required to produce evidence of effectiveness; is that correct?

Dr. CROUT. The manufacturer was required to provide evidence of effectiveness; yes.

Senator NELSON. Yes.

And then if they could not prove evidence of effectiveness, they removed it from the market, which was the consequences of all fixed combinations of anti-infectives?

Dr. CROUT. Yes.

Mr. MERRILL. As you know, it took some time, because the manufacturers disputed whether or not the evidence they submitted satisfied the statutory standard.

Senator NELSON. How does this situation differ? Certainly you could not make a finding of effectiveness based upon the studies. It is seriously questionable by the experts we have heard testify that you could say probably effective.

The best you could say is possibly effective, it would seem to me anyway.

Dr. CROUT. That is not correct.

The anorectic review of 1972 reevaluated these drugs, and they are all effective and on the market at the present time, fully evaluated by that process.

Senator NELSON. Well, the language in that report was that the effect was "clinically trivial," so when you proceed under the 1938 act for proof of safety, and under the 1962 act for efficacy, are you saying you really think the evidence supports the conclusion that they would rank higher than "possibly effective"?

Dr. CROUT. That they are "possibly effective" was the judgment of the panels.

Senator NELSON. Possibly?

Dr. CROUT. Possibly. We have been through the process of evaluating the National Academy's reports, however.

That is what was done in 1972, and the committee report you read from in your opening testimony, your opening statement, referred to the process that occurred at that time.

We followed the advisory group's recommendations and our own anorectic review in upgrading all of those drugs to a classification of effectiveness.

They do beat a placebo in causing increased weight loss in patients who are on a diet, and this has been demonstrated for each drug for a period of approximately 3 months in controlled trails. That was the standard of effectiveness adopted at that time and the standard of effectiveness that is currently described in the labeling for those drugs.

Senator NELSON. But you do conclude now in your own statement today that you have got a whole lot more knowledge about the question of abuse and safety than you had in 1972?

Dr. CROUT. Yes; there is now new information to lead us to reappraise the issue of safety.

The question raised today relates to continuing abuse, even in spite of control of the amphetamines as scheduled.

Senator NELSON. How would you compare your judgment on amphetamines used for treatment of obesity, against your judgment in removing a drug from the market, as the drug which was a combination of tetracycline and novobiocin, which would be called effective in the sense that tetracycline was effective against the target organism properly prescribed. Your conclusion was that in combination the two drugs were antagonistic, not additive, so you removed that combination from the market.

There was no question, I believe, about the fact that that combination would affect the appropriate target organism.

The problem was the side effects as a consequence of using novobiocin and tetracycline in combination, which exposed the patient to the side effects of the two drugs, but only tetracycline was needed.

You, as a doctor, would concede that if you were in some remote part of the world, and if Panalba would affect the target organism, even though the patient might get some side effects, you would use the drug? What argument is there for leaving the amphetamines in the market for the treatment of obesity, when there are other ways to do it, and when the results are clinically trivial?

That is what puzzles me.

Dr. CROUT. The issues in the two cases are slightly different.

In the Panalba situation, the lack of safety applied to the patient for whom it was prescribed.

That particular patient would get a safer drug and just as effective if he took the tetracycline component of Panalba, rather than if he took the combined agents, so that decision involved was a straight benefit-risk judgment about Panalba under the Federal Food, Drug, and Cosmetic Act, where one is thinking of effectiveness versus the safety to the patient.

Now, when we originally determined in 1972 that amphetamines were effective under the Federal Food, Drug, and Cosmetic Act, that same benefit-risk approach taking into account what was said by the experts, led to the conclusion that amphetamines, when used as labeled and as directed over the short term and in the proper dose, met appropriate standards of safety to the particular patient taking the drug.

A new issue arises, however, when patients begin to take amphetamines in excess, or they divert it to drug abusers. Now there is no longer a safety-effectiveness tradeoff in the individual patient. Rather, it is a tradeoff in relation to societal abuse of a drug which would not be considered unsafe if it were, in fact, used only as labeled under the Federal Food, Drug, and Cosmetic Act.

It is this latter question that we have to address at this time.

Mr. MERRILL. There is one other matter relating to the question, and that is what is our legal posture.

That difference is that with Panalba, we had a recommendation from an expert panel that there were not the kind of studies to show the effectiveness that the law required, and we initiated action to remove that drug at that time.

With amphetamines, we had a recommendation in 1970; the agency asked for additional data; some 200 studies were submitted; and,

whether rightly or wrongly, the Agency's experts concluded on the basis of the data then in hand that it was indeed effective. Not greatly so perhaps, but nonetheless effective, so the agency is now on record as stating the firm effectiveness of these drugs, as Dr. Crout suggested, is there, but the issue we are now concerned about is whether or not that small effectiveness is substantially outweighed by the kind of abuse and safety problems we are seeing.

Senator NELSON. Well, there are two questions about safety: One is the widespread abuse of the drug by the users who have no weight problem, and did not get it prescribed for a weight problem; the other is the risks to the individual for whom it is prescribed, who then becomes dependent upon it. There is no supporting evidence that it has any long-term effect at all.

Consider this question: If a new drug application were filed with the FDA, under the safety requirements of the 1938 act and the efficacy requirements of the 1962 act, would you approve these drugs for marketing? Would you not be asking for the effect of their use on obesity over a long term, a year or two at least? Would not you demand of the proposed marketer that he give you controlled studies to show the long-term effect as to obesity, to say nothing now of the possible side effects from the ingestion of the drug?

Dr. CROUT. Let us set aside the drug abuse issue. The answer to your question regarding long-term effectiveness is that that issue was debated in the 1971–72 era, and we reached the conclusion that the effectiveness of this class of drugs should not be evaluated in terms of long-term effectiveness.

The reason for that is that obesity can be considered, if I can make an analogy, as one of several illnesses where dietary therapy is paramount, and the use of a drug is adjunctive.

That is true for the management of ulcer disease, that is true for obesity, that is true for the dietary management of diabetes in patients who are not insulin-dependent. We have not required that drugs for these various conditions have a perfectly demonstrated effect, a completely unequivocal demonstrated effect, on the natural history of those diseases.

They should be considered as an adjunctive therapy to diet for the management of those diseases.

Now, one can argue with that standard. All I can say is that the prevailing practice of medicine has been to support that standard and the prevailing opinion of experts has been to support that standard. In some respects we have to face up to the fact that, while these adjunctive drugs may be clinically trivial over the long term, on the average they may also be useful, even dramatically useful, in some patients. In a sense they are also the only game in town. I think if you have a long-term problem, and dietary management is the key to it, drugs that are of consistent help in any way are welcome to patients and the medical profession, providing there is not an overriding safety issue involved.

Now, our view is today, as you well know, that the above issue may well have become an overriding safety problem for the amphetamines.

We will look at whether it is an overriding problem for the nonamphetamine anorectics also, but I suspect that a strong safety case

against the nonamphetamine anorectics cannot be made at the present time.

Senator NELSON. When you say non-amphetamine anorectics, are you referring to the so-called congeners?

Dr. CROUT. Yes. The ones that are in schedules III and IV today.

Senator NELSON. I think the testimony of some of our expert witnesses is that a number of those are also addictive, highly stimulative, and subject to abuse too.

Dr. CROUT. But I think, as we will see from the graphs here, the evidence is that their degree of abuse is much less than with the drugs in schedule II.

Senator NELSON. Well, all right.

On that point, let me say there is nothing in the statute that I know of that is specific about the long-term, short-term, trivial, clinically trivial, and so forth, so one could come to the conclusion as a result of what we know, it is clinically trivial.

As a matter of fact, it seems to me more logical that it is clinically trivial. It is obviously subject to abuse, and it would be logical for the FDA to tell the producer of that drug to come in and show the long-term effect, not only from the standpoint of the safety to the individual, but the proof of its efficacy in reducing obesity.

Dr. CROUT. Again, I simply have to go back to the analogy with many other drugs. I think your comment applies to many agents that are intermediate between truly symptomatic remedies and those that are truly known to be effective in the cure of diseases.

We have got a lot of remedies in the drug area that are useful on occasion, in individual patients for purposes of helping them alter their own dietary habits, for purposes of treating transient problems. I think that the lack of evidence of long-term effectiveness does not mean we should draw the conclusion they are known to be ineffective over the long term.

It simply means a lack of knowledge.

Senator NELSON. That is not what the law says.

The law says you have to have substantial evidence based upon well-controlled studies, and to say that there is no proof——

Dr. CROUT. Such proof is there for the short term.

There is no requirement in the law that a drug must alter the natural history of disease over the long term.

Now, that can be put in the law and drastically alter the number of drugs we have, but I think one should discuss at length the ramifications—I think first we should consider the consequences of such a change. We must recognize that the bulk of drugs are adjunctive to the natural processes of healing.

Senator NELSON. Well, yes, but we are here dealing with a particular class of drugs—for obesity. What other drugs is there on the marketplace that is addictive, widely abused, in which its effect may be very specialized in individual cases, or short term—what other ones?

Dr. CROUT. Set aside the drug-abuse problem, and——

Senator NELSON. Well, no, you have to include that, because the fact it is addictive and widely abused increases the risk factor, making the benefit-to-risk ratio unfavorable.

Dr. CROUT. I agree with that, and our testimony is that we are prepared to take action assuming a well-documented case for the abuse

problem is shown, which we anticipate to be there. There is no question about that.

Senator NELSON. You anticipate that there will be strong evidence of abuse?

Dr. CROUT. Yes; for amphetamines. I think for the class as a whole, you will find when the facts are all in, that a distinction can be drawn in the abuse area between those drugs on schedule II and those in III and IV.

Senator NELSON. As you probably know, Dr. Henderson, from Ottawa, Canada, who was chairman in Canada of the committee that recommended removal of the indication of amphetamines for the treatment of obesity appeared before this subcommittee. He has now concluded that it should apply to the congeners, also, I believe he said, except for fenfluramine.

I do not know whether he said that.

Dr. CROUT. We will be interested in what Canada does. We are in touch with Canada on this.

Senator NELSON. I think the record shows that Dr. Edwards, when he was Commissioner, said that most studies of these preparations showed efficacy for short periods. The panel suggested that long-term studies should be conducted. This was in 1970.

Have long-term studies been initiated on weight reduction, or have producers of the drugs been requested to produce studies?

Dr. Edwards suggested long-term studies of the effects of these drugs 6 years ago.

Dr. CROUT. I am not familiar with that request.

Mr. MERRILL. There are two parts of the question, I think, Mr. Chairman.

One is whether or not there should be data from well-controlled studies.

Senator NELSON. Pardon?

Mr. MERRILL. I think there are two parts of the question. One is whether or not there should be data from adequate and well-controlled studies, covering long periods, versus very short periods.

Such data covering short periods of use were submitted and evaluated.

Senator NELSON. Such studies were what?

Mr. MERRILL. Such studies were submitted to the agency.

Senator NELSON. Long-term?

Mr. MERRILL. No; I think it is true the manufacturers have not done that so far as we know. I think they may now be doing it, but to span the length of a lifetime——

Senator NELSON. I am not even talking about lifetime.

I am talking of 1 year, 2 years.

Dr. CROUT. Why is that different from 5 years, 10 years, 20 years?

Senator NELSON. Well, if something is good for only 20 seconds, you ought to remove it from the market.

If you are talking about an impact of a half-pound a week, treated for 12 or 13 weeks and then the patient ends up in the same position 12 months later——

Dr. CROUT. How do you know that he ends up in the same position 12 months later?

Senator NELSON. We do not know.

Dr. CROUT. That is an unknown.

Senator NELSON. That is right, but your own panel says that the effectiveness is clinically trivial.

You seem to be taking the position that the burden is on the public to prove that the drug does not work, rather than on the company to prove it is effective.

Dr. CROUT. No; I am taking the position that we adopted a standard of effectiveness urged on us by our advisers, and which represents as far as we can tell the prevailing opinion of experts in the management of obesity, namely that a reasonable standard for effectiveness of drugs in the anorectic class is that they be shown to be effective over the short time, and that is a reasonable standard in our opinion.

That was a ground rule of the 1972 review with Dr. Prout, and it was Dr. Prout's committee's opinion at that time. That was the standard adopted when these drugs were upgraded to effective.

The labeling states clearly this limitation in the labeling.

Senator NELSON. What I read from was the report of the NAS/NRC panel itself, which stated that most studies of these preparations are for short periods, and the panel suggested controlled studies for the long-term facts.

What I am asking is, Has the FDA requested such studies?

Dr. CROUT. That was the NAS/NRC panel's opinion, and it was silent on who should do that.

Senator NELSON. It was what?

Dr. CROUT. That report is silent as to who should do such long-term studies.

Senator NELSON. You mean to say if they are silent, the FDA is disabled from proceeding?

Dr. CROUT. No; I am saying we reviewed it with care, our panel of experts and Dr. Prout reviewed it, and they did not support that recommendation. A reaonable standard for marketing of a different typo was adopted, and that is a standard which is appropriate in our judgment for a variety of drugs that are adjunctive therapy to diets—exactly the same standard that applies to the ulcer field and the diabetes field.

Senator NELSON. Well, as you are aware, Dr. Prout who did head up a panel in 1972, this week in his testimony said—I quote in part, and I ask the other appropriate parts be printed in the record at this point—"Second, it has been demonstrated that the amphetamines and their related compounds have such trivial indications for the treatment of obesity that we should look at questions of whether or not obesity should be withdrawn as indication for their use," and then later on, he said: "I would therefore recommend that obesity be withdrawn as an indication of therapeutic use of these drugs."

[The information follows:]

The second one, of course, is predictable and that sales of amphetamines like compounds which were not placed on Schedule II had a marked increase in use, but not completely unexpected rise in sales.

One of these was cited on television for its particularly aggressive promotional techniques, of one company, that is for its rather high increase in sales.

These drugs are now known to be subject to abuse, and it is on the list of the recommendations if you look back, of the Ad Hoc Committee.

That would be my first recommendation, that the scheduling of all of these drugs with abuse potential be placed on II.

Secondly, it has been demonstrated that the amphetamines and their related compounds have such trivial indications for the treatment of obesity, that we should look at questions of whether or not obesity should be withdrawn as an indication for their use.

This is the major medical excuse for the manufacture of amphetamines, and the risk of overproduction far exceeds the benefits that might be cited through anecdote of a few patients who, in association with rigid dieting, have believed that the so-called anorectics were the causative agent in their particular weight reduction.

I would, therefore, recommend that obesity be withdrawn as an indication for the therapeutic use of these drugs.

This action has in fact been taken by Canada and other countries, and my own State of Maryland, this action was taken there, and I think it is a model law that might be indicated in Federal statute, that it be duplicated in Federal statute.

Dr. CROUT. May I comment on that?

Senator NELSON. Surely.

Dr. CROUT. Dr. Prout is the valued chairman of our indocrinology and metabolism advisory committee. He is also a personal friend. We are in touch. I have not had a chance to talk with him on the phone since that testimony, but let me assure you that his opinions will be taken into account by us.

I suspect, though, if he has changed his mind since 1972, he is changing his mind for the same reason I am testifying. It relates to the safety problems in spite of control under schedule II, and not to any change in the degree of effectiveness of these agents through the years.

Senator NELSON. Of course, effectiveness under the statute, as you are well aware, in vague situations such as this one is a judgmental factor.

There is not a very good test such as one would get with an antibiotic versus a particular target organism which could be demonstrated conclusively in the lab and in the treatment of the diseases of the particular patient.

I agree and think myself personally that the Food and Drug Administration should have asked for some more evidence of its long-term effect, because I doubt that you can justify massively dosing people with a highly stimulating central nervous system drug without some really substantial benefits, and the substantial benefits have never been proven. Are you saying that even if it is highly stimulative to the central nervous system, is addictive, and has trivial clinical results, we think it meets the standards of safety?

Dr. CROUT. I am not saying that.

Senator NELSON. That is where we are at.

Dr. CROUT. I am saying that the standard of effectiveness adopted is one relating to short-term use.

The standard of safety is that the benefits justify the risks to the individual. Were there no issue of abuse, then one would, I think, have little concern about the safety of these drugs for that use.

Today's issue is whether the degree of abuse continuing with drugs that are under schedule II of the Controlled Substances Act is reason to take away that indication, or take them off the market.

Senator NELSON. Would you not agree, though, that this is a semantic question, you cannot separate safety from efficacy?

They are together. It is one ball of wax. There is no way to separate them. The benefit-to-risk ratio is based upon safety and efficacy, and it is all one question.

Dr. CROUT. They are intimately related, but different, and there are different standards that appropriately apply, depending on the kind of evidence you want in the two areas.

The issue of adequate well-controlled trials is paramount to a determination of effectiveness. The issue of adequate well-controlled trials is not paramount to a determination of safety.

We will take information related to safety anywhere we get it. It does not have to come out of well-controlled trials.

In looking at the two together, I agree with you the benefit-risk decision involves safety and effectiveness together.

Senator NELSON. It seems to me that we have got to be looking at it together.

Dr. CROUT. The benefit-risk decision requires they be looked at together.

Senator NELSON. But then you have to look at safety and efficacy. Everybody would agree that chloramphenicol is a very potent drug, very dangerous drug; however, according to the NAS/NRC study, it is indicated only when the patient is seriously ill, his life is threatened with disease, and no other antibiotic will work, so you have a case in which a drug, that everybody will say on its face is unsafe, but it is not unsafe in relationship to this patient, because the disease is a greater threat to his life. The incidence of aplastic anemia that may result from its use, in the one in 20,000, so you do have to look at both together, you agree with that?

Dr. CROUT. Absolutely.

Mr. MERRILL. I think what Dr. Crout is saying is just where we begin to work with DEA to build up our case, and the focus will be on the safety side of the equation, because it is that side of the balance which seems to have shifted since 1972.

Senator NELSON. All right.

It seems to me, with something as trivial as this class of drugs that you ought to be requiring some better evidence of efficacy over the long period. I should imagine that widespread street use would raise questions of safety.

Let me ask you another question. Dr. Henderson from Ottawa, who was on the Canadian panel that I mentioned before, testified that his panel recommended that the indication of obesity for this class of drugs be removed, and this was done. He also said that only in very limited cases, in treatment of obesity—I think that is a fair paraphrasing—would he give fenfluramine, because it was not addictive; that, in fact, lots of patients rejected it because they got upset stomachs or something else unpleasant; that there was no way that it would be abused; and in limited situations, he did use fenfluramine.

Have there been any studies done to compare the effectiveness of fenfluramine vis-a-vis the amphetamine congeners to see how effective fenfluramine is?

Dr. CROUT. There are studies comparing a variety of anorectics, one with the other.

Senator NELSON. They are underway now?

Dr. CROUT. No, they are done.

One of the purposes of the anorectic review in 1972 was to look at all of those studies simultaneously, and when you put them all

together, our judgment is that from an effectiveness standpoint, all drugs in the whole class are roughly comparable.

The effectiveness of fenfluramine in reducing weight is roughly comparable to any other drug in the class.

Senator NELSON. Do these studies show any indication of addictiveness of the fenfluramine?

Dr. CROUT. Fenfluramine went on the market for the first time at that time so the studies we have relating to abuse potential for fenfluramine were animal studies only at that time.

Senator NELSON. Did the animals help to self-ingest themselves?

Dr. CROUT. I believe they did not with fenfluramine. The pharmacology of fenfluramine is more like that of a depressant than a stimulant drug.

Now, an important question right now is whether in street use, after 3 years of experience, fenfluramine is turning out to be abused, for whatever reason.

Senator NELSON. Is there any indication that it is?

Dr. CROUT. I would have to defer to DEA on that.

The prominent safety issue with these drugs relates to their abuse. The intent of the Federal Food, Drug, and Cosmetic Act has predominantly been considered historically to protect the individual receiving drugs. The intent of the Controlled Substance Act is to control the abuse problem. What we are trying to say at this point is that the Controlled Substances Act is not totally successful in controlling the abuse problem, certainly with amphetamines, and perhaps with others in this class. Therefore, we should now go back under the Federal Food, Drug, and Cosmetic Act and consider abuse to society as part of the benefit-risk equation.

Now, that is a proper use of these two laws in our judgment. But if abuse per se is a reason for taking drugs off the market, you do not need a Controlled Substances Act.

The Controlled Substances Act is for the purpose of controlling the abuse of useful drugs, and while you may consider this usefulness to be minimal, they are useful in the treatment of obesity.

Senator NELSON. What is the tool under the act for enforcing the law respecting abuse of legally marketed drugs?

Mr. MERRILL. Under the statute?

Mr. GORDON. Yes.

Mr. MERRILL. The statute permits FDA to change the labeling to omit an indication. The other remedy the statute provides is to remove the drug from the channels of commerce.

We do not now have a useful mechanism for restricting availability of marketed drugs.

Mr. GORDON. Nor any mechanism for proceeding against somebody who is using the drug for nonindicated use?

Mr. MERRILL. We, generally speaking, have said the Federal Food, and Drug Act does not prohibit an individual physician from prescribing a drug for an unapproved use.

We have one case now pending in which we are proceeding against a clinic in the South that has ordered the shipment, for unapproved uses, of a series of drugs for a continuing kind of therapy. We have taken a position in court—it has not yet been adjudicated—that that kind of trafficking in unapproved use of the drug is tantamount to

causing the drug to be misbranded, in other words, that it is illegal under the Federal Food, Drug, and Cosmetic Act.

Mr. GORDON. I assume, then, that most of the problem respecting the misuse of drugs is left up to State medical societies, is that correct?

Mr. VODRA. And the civil law, malpractice law.

Senator NELSON. The reason we raise this is the testimony of Dr. Gellert from Suffolk County, the Town of Huntington, N.Y., population of 200,000, 250 doctors in a remarkable agreement of unanimity respected the wish that they would not prescribe amphetamines for obesity, and none of them do so.

There are two doctors who do not belong to the medical society in the town. There was one fat pill doctor before, and now they have two, and they average 800 to 1,200 patients per week.

I asked him what the fee charge was, he said he did not know.

I think it would be worth finding out, but a certain percent of these patients are of course ending up in the other physicians' offices with problems.

The lineup outside the clinic consists of all kinds of very thin people. Obviously you cannot have 800 a week who, if they are not obese, neither are they narcoleptic adults or hyperkinetic kids.

Now, what is the mechanism, or is there not any for dealing with a case in which these two doctors in that place are abusing the drugs? Their patients just come in, get a prescription, and go out.

Is there any mechanism for stopping that?

Mr. MERRILL. I read Dr. Gellert's testimony, and he suggested that the FDA consider doing what it attempted to do with methadone.

We tried to restrict its availability, and we were sued by the American Pharmaceutical Association, the association of pharmacists who viewed that as a threat to their access in drugs generally.

The district court and the court of appeals here in Washington struck down those regulations, so I guess my answer is the same answer I gave you before, the mechanism available to the FDA under the Federal Food, Drug, and Cosmetic Act is to eliminate the indication or the use of drugs altogether.

Mr. VODRA. I might add that I used to be at DEA, and while I was there and I am sure to this day, they do work on cases of physicians selling prescriptions or drugs to nonbona fide patients, where there is no doctor-patient relationship whatsoever. That is an exceedingly costly approach to use. DEA does not have the resources to police all of the physicians in this country, with all of the various drugs, not only the amphetamines, but narcotics, and so forth.

Senator NELSON. But in these two cases, I would gather from the testimony, that it is pretty clear they are in the business of making a lot of money prescribing addictive drugs to people who do not need them at all for obesity.

Mr. VODRA. If they can establish there is not a bona fide relationship, it is a criminal offense, a felony offense of the Controlled Substance Act, and they can obtain a conviction in the Federal courts.

The Supreme Court has upheld the conviction of a physician trafficking methadone, who in 1 day wrote 240 prescriptions for methadone. The Supreme Court said the physician was subject to the act. It is basically a resource question, not a legal one.

Dr. CROUT. I am told there are several States that have innovative new laws in which the State medical society is asked on occasion to make judgments about professional practice of individual doctors, whether or not they belong to the State medical society, and based upon the recommendations of that committee, the State will take action in revoking a license. So there are some innovative State laws taking place.

You might want to look into that.

What we are saying is that under the Controlled Substances Act, when the Government has the facts, it can move against a physician, but this is relatively difficult.

Senator NELSON. All right.

You may proceed.

Dr. CROUT. Fine.

OBESITY AS A HEALTH PROBLEM

Before turning to the anorectic drugs, it is important that we recognize the public health significance of obesity. Although some may believe that excess weight is merely of cosmetic significance, the fact is that obesity is America's No. 1 nutritional problem. Obesity significantly increases the risk of a number of diseases and complicates many other conditions.

It is usually chronic and is difficult to treat. Successful therapy depends upon vigilance and effort throughout the patient's lifetime. In testimony before the Senate Committee on Nutrition and Human Needs, on July 27, 1976, the Assistant Secretary for Health, Department of Health, Education, and Welfare (DHEW), Dr. Theodore Cooper stated: In recent years obesity has become a public health problem of considerable importance in the United States. Approximately 20 percent of all adults are overweight to a degree that may interfere with optimal health and longevity. Obesity aggravates cardiovascular disease and osteoarthritis and increases the liability to hypertension, atherosclerosis, hernia, and gallbladder disease. Overweight also may facilitate the emergence of latent diabetes in predisposed individuals as they approach an advanced age and adds to the hazards of surgery; it makes for postural derangement, and in extreme cases, it is the cause of obesity dyspnea with pulmonary insufficiency. It is also of interest that the mortality from cirrhosis of the liver in obese males is 249 percent of the expected.

Medicoactuarial statistics make it quite clear that the obese do not live as long as the lean. The chief causes of death among overweight individuals are cardiovascular-renal diseases, diabetes, and disorders of the liver and biliary tract. The burden of obesity is not borne equally among all segments of society. In the United States, it is more likely to be found in the lower socio-economic strata; this association is particularly marked in poor women and to a lesser extent in middle class males.

Again, I would emphasize the statistical importance of obesity in our population and the strong need for and potential benefits of systematic preventive action beginning in early childhood.

ANORECTIC DRUGS

The successful treatment of obesity requires only one essential therapeutic measure—that the patient take in fewer calories than he or she needs for a given level of exercise so that the stored fat in the body is gradually lost as it is burned as body fuel. All supportive measures for the management of obesity—including group therapy—e.g., weight-watchers—special diets, jogging, and drugs—have as their sole purpose assisting the patient to eat less or to increase his or her level of exercise or both. The pharmacological action of drugs in the anorectic class is to produce anorexia, that is, loss of appetite, and thereby to assist the patient in restructuring his or her dietary habits.

There are currently 12 drug entities approved for prescription use in the United States for the treatment of obesity. Three of these, d,l-amphetamine, dextroamphetamine, and methamphetamine have been in clinical use since the 1930's. Six additional anorectic drugs were introduced in the period between 1935 and 1962 before the Kefauver-Harris Amendments: Benzphetamine, phenmetrazine, phendimetrazine, phentermine, chlorphentermine, and diethylpropion. The remaining three—fenfluramine, chortermine and mazindol—were approved for marketing by FDA in 1973. All of these, except mazindol, are related in chemical structure, all have central nervous system effects, and, today, all are scheduled under the Controlled Substances Act.

REGULATION OF ANORECTIC DRUGS

Before highlighting the major past actions of the FDA, it is worth emphasizing that the powers and responsibilities of the Federal Government to regulate anorectic drugs are shared by the Drug Enforcement Administration—DEA—and FDA. In addition, individual States have passed laws and regulations governing abusable drugs. The FDA controls the approval of new drugs for marketing, regulates initial and revised labeling, and recommends to the DEA the selection of an appropriate schedule for a drug under the Controlled Substances Act—CSA. In addition, the FDA provides to DEA information on legitimate medical usage of schedule II drugs which DEA uses in setting production quotas. While the placing of a drug into a particular category under the CSA is the ultimate responsibility of DEA, it is done only on recommendation from FDA after careful review by the FDA scientific staff, consultants and the Controlled Substances Advisory Committee.

The DEA has the ultimate authority to schedule drugs under the CSA, to establish quotas on those drugs in schedules I and II, to monitor the domestic production and distribution of controlled drugs, to regulate their importation and exportation, and to enforce the provisions of the CSA. In selected cases, DEA can act against the prescribing and dispensing of controlled drugs by physicians by invoking penalties against those who are acting outside the legitimate practice of medicine.

The National Institute on Drug Abuse—NIDA—and, in some areas, DEA fund programs to study the potential and actual abuse of drugs, including anorectics. NIDA also funds programs to treat and prevent

drug dependence. At the State level, licensing boards for physicians, pharmacists and pharmacies, hospitals, and other health care units also can influence the prescribing and dispensing practices of health professionals. Furthermore State and local law enforcement agencies, many of which are actively supported by DEA and the Law Enforcement Assistance Administration, police the diversion and illicit traffic of controlled drugs.

Communication among these Federal and State agencies is maintained by regular meetings of the involved officials at both the staff and policy levels. The Interagency Committee on Drug Control, as an example, is a working group which includes membership from FDA, NIDA, and DEA. An FDA/DEA liaison staff group also meets regularly. In addition, the Commissioner of Food and Drugs, the Administrator of DEA, and the Director of NIDA meet personally to discuss policy issues. There is also extensive communication between the field forces of FDA and DEA and their counterparts in State law enforcement and health agencies.

FDA ACTIONS FROM 1960 THROUGH 1971

The Food and Drug Administration has for many years supported stringent controls on the amphetamines. In the early 1960's, prior to any clear Congressional mandate, the FDA undertook investigation and prosecution of traffickers in amphetamines. The 1965 Drug Abuse Control amendments to the Federal Food, Drug, and Cosmetic Act provided stronger regulation over the manufacture and distribution of dangerous drugs, including certain stimulant drugs, and in February 1966 FDA established a separate Bureau of Drug Abuse Control to carry out these amendments. In the first 2 years of the program, FDA carried out over 2,000 criminal investigations, made more than 1,300 arrests, and handled about 300 criminal cases. The FDA made, in addition, approximately 1,100 accountability investigations resulting in 108 civil seizures of depressant and stimulant drugs. Nearly 600 million dosage units of these drugs were removed from the marketplace because no accurate records, as required by the law, were kept by manufacturers.

In April 1968, the Bureau of Drug Abuse Control was merged with the Bureau of Narcotics of the Treasury Department to create the Bureau of Narcotics and Dangerous Drugs—BNDD—of the Department of Justice. In 1973, BNDD became the Drug Enforcement Agency. In October 1970 the Controlled Substances Act—CSA—was enacted and added an important new dimension to the control of abusable drugs.

The CSA originally scheduled only four anorectic drugs (amphetamine, dextroamphetamine, methamphetamine, and phenmetrazine), and these were listed in schedule III. Injectable methamphetamine was controlled in schedule II. In 1971, in response to proposals by BNDD, FDA recommended that these anorectic drugs all be transferred to schedule II. Prompt action by BNDD in making these controls effective resulted in (a) eliminating refills on prescriptions, (b) requiring all prescriptions to be in writing, (c) subjecting manufacturers, distributors, and dispensers to more stringent security requirements for storing these drugs, (d) limiting production to

Government-established quotas, (e) having all shipments among manufacturers, wholesalers, and retailers be done on special BNDD order forms, copies of which were to be immediately provided to BNDD, (f) prohibiting import and export of the drugs without prior BNDD permission, and (g) requiring that reports of inventories and all transactions be sent to BNDD.

Concurrent with these actions, FDA has carried out an active program of surveillance over the advertising of these drugs. Since May 1966, 38 legal, regulatory, and advisory actions related to their promotion have occurred. Of these actions, 27 have been initiated in the last 4 years. These have included two product seizures, three remedial "Dear Doctor" letters; and one remedial advertisement. Common causes of actions by FDA in regard to the advertising of these drugs have been inadequate prescribing information; unwarranted extension of the indications to special groups of patients such as hypertensives, diabetics, and teenagers; implied claims of usefulness beyond the indicated short-term use of a few weeks; and misleading promotion which attempts to understate the potential for abuse.

The FDA advertising rules require that all promotional labeling and advertisements for these drugs meet the usual requirements for prescription drugs and, in addition, display the appropriate CSA control symbol.

FDA ACTIONS FROM 1972 TO THE PRESENT: THE ANORECTIC REVIEW

Mr. Chairman, as you know, the Kefauver-Harris amendments required that FDA review for effectiveness all drugs previously approved on the basis of safety between 1938 and 1962. For the anorectic drugs the Agency elected to review the whole class at one time so that the same standards would be applied to each drug. The amphetamines were included in the review even though they had been marketed prior to 1938.

The overall review included not only a detailed statistical analysis of all of the controlled studies in our files relating to the effectiveness of these drugs in obesity, but also meetings with consultants and advisory groups.

An obviously important consideration in reviewing this class of drugs was the general standard to be applied in determining effectiveness. It was well recognized then, as it is today, that permanent weight loss over the long term is the desired goal of any treatment program for obesity and that proof of such long-term effectiveness is lacking for any of the adjunctive measures used in treating patients with obesity. This does not imply that all adjunctive measures are necessarily ineffective—only that proof of long-term effectiveness is not available from adequate and well-controlled trials. In the case of anorectic drugs, long-term trials would be very expensive and difficult to perform in view of the many other factors relating to patient motivation which would have to be controlled, or at least measured and accounted for in the statistical analysis of the results.

The problem of the standard of effectiveness to be required for marketing has been discussed repeatedly within the FDA and with our consultants. The standard we have adopted is that a demonstration of effectiveness should depend upon a finding in adequate and

well-controlled trials that patients taking the drug sustain a statistically significant greater degree of weight loss than patients taking a placebo. While it would obviously be of value to know with certainty the effect of the drug on the natural history of the disease, we have considered this to be a public health question which an individual drug firm cannot reasonably be expected to answer in the context of evaluating its particular product.

The approach taken in conducting the anorectic review was discussed by Dr. Henry E. Simmons, the former Director of the Bureau of Drugs, in his testimony before this subcommittee on December 13, 1972, and I would like to restate his description of its magnitude:

> The scope of the program was ambitious, and involved over 1,000 volumes of data concerned with twelve single entities. The drug products in which these entities were present, either alone or in combination, were marketed by 40 firms. Over 200 double-blind and controlled studies of efficacy which had been carried out on almost 10,000 subjects were included in the review.
>
> Individual patient data sheets were coded and key punched to facilitate computer analysis. This produced over 70,000 computer cards, representing over 70,000 patient visits of the 10,000 subjects. Each card included certain patient characteristics as well as changes in weight, blood pressure, pulse, and other possible adverse effects from visit to visit. The cards contained over 4 million units of information. Programs were then written to permit automatic statistical analysis in order to determine what effect the active drug had when compared with the placebo under "double-blind" controlled conditions.

These studies were then evaluated by our medical staff to determine whether there was, for each drug entity, substantial evidence that patients taking the drug sustained on the average a greater degree of weight loss over a 12-week period than patients on a placebo. The 12-week period was selected because it was the longest period for which there was reasonably comparable data on all of the drug entities in the review.

The results of this review were presented to FDA consultants during two meetings in 1972. This group was chaired by Dr. Thaddeus E. Prout, professor of medicine at Johns Hopkins University School of Medicine. Their recommendations were, among others, as follows:

1. The single-entity anorectic drugs including the amphetamines should "be permitted to be labeled for restricted use in obesity provided that they are used in association with a specific weight reduction program and that the clinically trivial contribution of these drugs to the overall weight reduction is properly emphasized."
2. The future approval of anorectic drugs should be "based on demonstration of efficacy or measured by statistical superiority of the drug over placebo in trials using FDA recommended protocols." The group did not recommend that demonstration of a long-term effect on the natural history of obesity be necessary for marketing.
3. All drugs in the anorectic class except fenfluramine should "be placed in schedule II on the basis of abuse potential."

As a result of this review, the following actions were taken by FDA in 1972–73:

1. FDA required that the anorectic drugs be relabeled to emphasize necessary warning information about their potential for abuse, and also to reflect accurately the indications for which they

were judged to be effective and to have an acceptable benefit-to-risk ratio, that is, narcolepsy, minimal brain dysfunction, and short-term adjunctive therapy in obesity. These conclusions were published in the December 1972 issue of the FDA Drug Bulletin which was distributed to some 600,000 health professionals.

2. We determined there was no place for parenteral amphetamines in medical practice and these products were removed from the market in 1973.

3. We took the position that preparations containing amphetamines in combination with other drugs—such as barbiturates, vitamins, and tranquilizers—failed to meet FDA's combination drug policy and were, therefore, ineffective as fixed combinations. Beginning in March 1973, procedures were begun to remove these from the market. A group of small manufacturers brought legal action to contest this action, but on December 28, 1973, the U.S. Court of Appeals for the Eighth Circuit upheld FDA's order. (*North American Pharmacal* v. *Department of Health, Education, and Welfare;* 491 F2d 546.) At the same time, several other manufacturers sought formal hearings on the withdrawal of their products from the market. Two products in this category remain unresolved at the present time. The agency has denied a hearing on one of them, Dexamyl, but this denial is stayed pending judicial review. The hearing request on the other product, Eskatrol, is still under review.

4. We recommended to DEA in 1973 that all of the drugs in the anorectic class be scheduled under the CSA. Previous to this recommendation, only the amphetamines and phenmetrazine were under the CSA; these were in schedule II. The advisory group headed by Dr. Prout had recommended, as I mentioned, that all of the anorectics, with the exception of fenfluramine, also be controlled in schedule II. After reviewing all of the information, however, we felt that the medical and scientific facts available at that time could not support this position since evidence of significant street abuse was not available for all drugs in the anorectic class. Consequently, the agency recommended that seven of the anorectics be controlled in schedule III on the basis of abuse potential even in the absence of clear evidence of significant abuse. These drugs were chlorphentamine, benzphetamine, phendimetrazine, chlortermine, mazindol, diethylpropion, and phentermine. Ultimately, the latter two drugs were placed by DEA along with fenfluramine in schedule IV. Given the nature of the data available at that time, we believe our scheduling recommendations were medically proper and responsible. Additional information has, of course, been steadily accruing since that time, some of which, for example, Dr. Jasinski's studies at NIDA's Addiction Research Center, have been discussed in recent testimony before this subcommittee. DEA is in the process of analyzing this new information on the anorectics and we look forward to their report.

Since 1973, the FDA has developed a mechanism—through the use of the National Prescription Audit and National Disease and Therapeutic Index—for monitoring the utilization of certain drugs

at the retail pharmacy level and in the offices of selected physicians. The trend analyses reports from this system are used for making production quota recommendations on schedule II drugs and for following prescribing patterns. In addition, we follow the data from the Drug Abuse Warning Network—DAWN—which is operated under joint contract from DEA and NIDA. FDA depends on DEA for special reports to identify abuse problems with specific drugs. Such problems may be recognized by DEA agents in the field or through their regional laboratory analyses or through monitoring the output of the DAWN system. Furthermore, NIDA has a substantial program to monitor licit and illicit drug use through general household surveys and through surveys of special populations—for example, high school students—monitoring hepatitis rates, and compiling drug use data on patients in treatment programs. Special demonstration projects or indepth reviews are also the subject of studies at various times. Information from all of these sources can be extremely useful in evaluating the extent of abuse associated with any given drug.

CURRENT STATUS OF ANORECTIC DRUGS

Mr. Chairman, 5 years have passed since the amphetamines and phenmetrazine were placed in schedule II, and 3 years have passed since the FDA's anorectic review and the placing of the remainder of these drugs in schedules III or IV. It is appropriate that we review at this time the effect of these important Federal actions on the use and abuse of these drugs and ask ourselves whether progress has been made, whether that progress is sufficient, and, if not, what further might be done in the future.

I would first like to discuss the effect of these actions on the prescribing of anorectic drugs as measured by the number of prescriptions filled in pharmacies. Appendix I shows the prescribing trends for anorectic drugs from 1964 to 1976. During the period from 1971 through 1973 there was a particularly dramatic decline in the prescribing of amphetamines.

Senator NELSON. Let me interrupt you for 1 minute.

Did we settle the fenfluramine question?

Dr. CROUT. Its effectiveness is essentially equal to all of the other drugs in the class.

Senator NELSON. You said that you would rely on the DEA to determine whether it is addictive, or whether it is being used in the streets?

Dr. CROUT. Yes.

This was a major period of Federal action. The number of manufacturers of these drugs also dropped considerably during that period. Since 1973 the usage of amphetamines has remained fairly constant at a rate of about one-fifth that of the peak year in 1965. The nonamphetamine anorectic drugs have increased in popularity since 1971 and are now prescribed roughly twice as often as the amphetamines. The rate of prescribing of the whole class of anorectic drugs is today approximately 60 percent of the peak rate in the mid-1960's.

Senator NELSON. Are not a number of those anorectics in schedules III and IV just as addictive as the amphetamines?

Dr. CROUT. Potentially so, although perhaps not so much.

I think when you get to schedules III and IV, you will see some interesting data on that point.

Senator NELSON. All right.

Dr. CROUT. I think the answer is that we are hopeful over the long term it will turn out to be true that there are members of this class that are substantially less addictive and less attractive to abusers than amphetamines.

Senator NELSON. Have some studies been done on that?

Dr. CROUT. Yes; that was the philosophy behind putting them in schedules III and IV instead of in II originally.

Senator NELSON. It had been my impression from some of the testimony that there were serious questions about these drugs being addictive.

Are they all central nervous system stimulants?

Dr. CROUT. All potentially, yes, but drug abuse is a funny business, where you frequently have to find out what happens in the street to know the answer to the question.

It turns out there are consumer preferences, if you will, among those who abuse drugs, and in a real sense that test is more useful than some of the laboratory data we get in smaller studies. Again, these are among the issues we are discussing with DEA.

Senator NELSON. But there are some differences between some drugs, perhaps like fenfluramine, which may not be addictive and which is a depressant. According to the physician from Canada, patients did not like it, and when you have two drugs that are competing, or three or four in the street, and one is highly preferred, it is just a difference between one ordinary brand and another that has more appeal.

And then if the other three are no longer on the street, what happens about this one that has the less appeal?

Mr. VODRA. There are side effects that make them more or less attractive. When we surveyed in 1973 about anorectic control, we talked to street users, and they termed one of the congeners "raunchy speed," "stuff you use only when you run out of good stuff," and "it is really the dregs." They do not like some of these things. They will use them only if nothing else is available.

Senator NELSON. That is the point I am asking. You are impressed by the figures that amphetamine use has gone down, and the congeners have gone up. My question is not whether amphetamines are preferable to the use of congeners, but whether or not they are addictive. If, in fact, that is the only one, that is the question that has to be answered, because if that is the only one available, and it is addictive, it will be used.

Dr. CROUT. Yes; let's go on perhaps to the next paragraph, which I think will be of interest to this question.

I would now like to turn to the issue of abuse of the anorectic drugs.

Before doing so, however, I must emphasize the limitations of the data currently available for presentation. As I previously noted, an analysis of the abuse potential and actual abuse of the anorectics is underway by DEA, and we look forward to receiving their findings.

My comments today are, therefore, based only on gross data from the DAWN system. By the way of background, the DAWN system

lists "mentions" of a drug during the contact of an individual at certain crisis centers—including "Hot Lines"—emergency rooms, and medical examiners or coroners offices throughout the country.

The "mention" of a drug can thus range from a telephone call to an overdose death. It should also be noted that "mentions" of drugs frequently occur in combination. A specific drug is not necessarily the cause of the episode. For example, if amphetamine is mentioned in an emergency room contact, the person may have, as his primary problem, an overdose of heroin but may also have taken an amphetamine.

More sophisticated analysis is thus necessary before a full picture is available of the societal problems associated with anorectic abuse.

With these limitations in mind, I would like to refer to appendixes II and III to make two basic points.

Appendix II is a bar graph which shows the ratio of total mentions of anorectic drugs in the DAWN system from July 1973 to December 1975, divided by the number of prescriptions for these drugs during this period.

Senator NELSON. What are the years?

Dr. CROUT. That is the total. We took all years lumped together, 1973 to 1975. The bar graph for amphetamines is the total number of DAWN mentions during the years 1973, 1974, 1975, all lumped together, divided by the number of prescriptions for these drugs during this 3-year period.

You can see the left bar graph relates to amphetamines, the next one to Preludin, and then at the bottom, the other drugs in the class.

This ratio can be considered as a crude index of the degree of abuse, that is, total DAWN mentions, per given amount of drug dispensed through legitimate sales at the pharmacy level.

Mr. GORDON. Dr. Crout, DAWN includes only the people who appear in clinics or emergency rooms, and that does not necessarily reflect who is abusing the drug; that is, how many people are abusing the drug.

Many people who abuse drugs do not go to these places. They abuse them in their homes, and they do not go to clinics afterward.

Dr. CROUT. This is again the only quantitative index of drug abuse going on in the country today on a national basis. It is not meant to include all episodes, but it ought to be a reasonable index of the amount of drug abuse activity going on.

Mr. VODRA. I think there is another point about DAWN data. If you look at the population of abusers and users of the central stimulant nervous system drugs, and assume that only a portion will go to points that will get them into DAWN collecting network, this is no reason to suspect a higher proportion of amphetamine users over other stimulant drug users will go into the DAWN system. Thus, if a proportionate number of people who are abusing each of the anorectics are coming in, then at least DAWN does give you from among that sample, a relative difference of levels of abuse among the various preparations which is shown in bar graph 2.

Mr. GORDON. It only tells us about those who get sick enough to go to clinics?

Mr. VODRA. That is right, but this is no reason to suspect an amphetamine user will get more sick than a user of diethylpropion or any other anorectic, if the pharmacology is fairly similar.

Dr. CROUT. There are other sensing systems in our society that provide estimates of the degree of drug abuse.

The National Institute on Drug Abuse has information on data from household surveys, and surveys in schools, and that is among the information we want to gather.

I cannot present those data today. In any event, I think it is fair to say, having pointed out the limitations, that the total number of DAWN mentions is an index of abuse, street abuse in our society.

Senator NELSON. Just one second.

What do the ratios mean on that chart?

Dr. CROUT. These are total mentions of abuse divided by total distribution of drugs during that period.

Senator NELSON. Total distribution?

Dr. CROUT. Total DAWN mentions, total incidence related to abuse, divided by sales of drugs during that period, so a tall bar means for any given amount of sales, more drug abuse.

Senator NELSON. I see, but that would not tell you anything about one, if there were one, that was smuggled into the country from Mexico, you would not know, would you?

Dr. CROUT. No; that is one of the variables not reflected in this figure.

I believe DFA will tell you, however, that today most of the domestic amphetamines do not come from across our borders.

It is legally manufactured and prescribed.

Senator NELSON. OK.

Dr. CROUT. Both the numerator and denominator of this index are subject to considerable error, as I mentioned.

Nevertheless, even this rough approach is revealing.

Appendix II clearly shows that the amphetamines, including methamphetamines, and, to a lesser extent, phenmetrazine, are associated with more contacts with the DAWN system per amount of sales than are other anorectics.

Here you can see all of the other drugs clustered together.

This graph in appendix III illustrates the second point I wish to make. The graph again shows the ratio of total DAWN mentions, this time by quarter years, divided by the number of prescriptions for these drugs in the comparable quarter.

The anorectic drugs in this appendix have been grouped somewhat differently—that is, by their schedules under the Controlled Substances Act.

I point out along the bottom line, this is a time trend during 1973 through 1975.

The main conclusion suggested by this graph is that abuse problems are greater with the schedule II drugs than with the other anorectics, as shown by the line at the top, and that the rate of such problems appears relatively unchanged over the past 3 years.

Senator NELSON. And you are saying at the same time that the studies indicate that the nonamphetamine anorectics and the amphetamine anorectics are about equally efficacious?

Dr. CROUT. Yes.

Senator NELSON. Roughly as trivially efficacious, I will put it, and that the abuser——

Dr. CROUT. Fair enough, sir.

Senator NELSON. All right. We will leave it in the record.

We have got to win one once in a while, and so your chart shows there is a much higher abuse-potential of the amphetamines used for the same purpose?

Dr. CROUT. Yes, sir.

Senator NELSON. This is a very convincing case. If they are roughly equivalent in terms of their trivial effectiveness, then it would appear that something ought to be done about the amphetamines?

Dr. CROUT. Yes, sir.

Mr. VODRA. It also indicates, Senator, that there is, for whatever reason, a significant difference in the response of the "abuse community."

Senator NELSON. Roughly what?

Mr. VODRA. A major difference in response of abusers to the schedule II anorectics, that is amphetamines and phendimetrazine, over the other drugs. This is the point I was suggesting earlier: For some reason we have not determined, the abusers prefer amphetamines by a wide margin. They have stated this preference in the illicit market for the scheduled anorectics. Amphetamines remain the problem area.

Dr. CROUT. [Reading.]

CONCLUSIONS AND PLANNED ACTIONS

Mr. Chairman, I would like now to state our present regulatory position in regard to the anorectics and to indicate our plans for future actions regarding these drugs.

The anorectic review of 1972 demonstrated that all these currently marketed drugs meet appropriate standards of effectiveness under the Federal Food, Drug, and Cosmetic Act. On the basis of the information available at that time, FDA also determined that this class of drugs meets the safety requirements of the act and are, on a benefit-risk basis, appropriate for marketing for the indication of obesity on a short-term basis as adjunctive therapy. The most stringent controls possible under Federal law have been in place for 5 years on those drugs which demonstrate greater abuse risk than the others, and the remainder of the class of anorectic drugs has been controlled under other schedules of the CSA for 3 years.

Recent information indicates, however, that the schedule II anorectics—amphetamine, dextroamphetamine, methamphetamine, and perhaps phenmetrazine—have continued to be abused at a relatively unchanging rate over the past 3 years. While there is considerable opinion that the current rate of abuse of amphetamines is well below that of the late 1960's, there is also evidence that the regulatory measures taken in the 1971–73 period may have accomplished as much as they are going to accomplish. It also appears that the major residual problems of abuse and misuse involving anorectic drugs lie with those already in schedule II and not those in schedules III and IV.

If the information currently being developed by DEA clearly indicates, as we anticipate it will, that amphetamines remain a major cause of abuse in spite of being in schedule II of the CSA, FDA will move ahead vigorously to withdraw the indication for obesity from amphetamines. We need to be sensitive to the other indications for which these drugs are used—narcolepsy and minimal brain dysfunc-

tion in children—but we must also recognize there are alternative drugs for these indications. I cannot predict at the present time whether any new regulatory action in regard to amphetamines would involve simply removal of the indication for obesity or complete withdrawal of the drugs from the market. Neither can I predict whether phenmetrazine might be involved in any such action. Answers to these questions will depend on the extent of documented diversion and abuse with these agents found by DEA and the judgments of those on our scientific staff and advisory committees who will review the data.

I would again emphasize that a report from DEA and additional data from the National Institute on Drug Abuse are necessary for FDA to take a strong legal position, and our staffs are working together on this matter.

The withdrawal from the market of a previously approved drug on the basis of its risk to society, as well as to the patient, is an innovative position on which there is little legal precedent. But we believe such a position is legal and are prepared to defend it.

While the preliminary data available to us do not appear to indicate an important public health problem with the schedule III and IV anorectics, we will, as part of our review consider these drugs also. Again, on the basis of careful consideration of data from our sister Federal agencies and the medical research community, we will take whatever action on these drugs is indicated. Such action might range from recommendations for rescheduling to improvements in the labeling. I do not anticipate at the present time, however, any new review for effectiveness comparable to the anorectic review of 1972. In view of the importance of obesity as a national nutritional problem and the lack of any widely accepted, universally effective alternative therapy, we do not think it medically appropriate to question at this time the marketing status of those anorectic drugs now in schedules III or IV.

I would also point out that the Food and Drug Administration has underway two major programs which will ultimately affect many prescription drugs including the anorectic drugs: The prescription drug labeling review and the patient package insert proposal. In the very near future, we will issue final regulations on the format and context of package inserts for the physician and, over the next several years, all prescription drug labeling will come into compliance with these regulations. Various drug categories will be taken on a priority basis under this program, and we consider anorectic drugs as properly among the priority drugs.

We also anticipate issuing in 1977 proposed regulations relating to patient package inserts for prescription drugs. This proposal will undoubtedly stimulate extensive public comment and may well require another year or more for development of a final order. It is our intent to develop patient package inserts for specific drugs only in the context of this general statement on policy and procedure. In specific cases in which the public health requires a patient package insert on a prescription drug, for important safety reasons, we will take such action on an ad hoc basis as we have for oral contraceptives and estrogens. For most drugs, however, we believe it is wiser to develop general policy ahead of specific patient labeling. We, therefore, anticipate at the present time that specific patient labeling for anorectic drugs will not be developed in the near term.

Finally, I would comment that whatever future action we in FDA might take in regard to this class of drugs, some degree of abuse may well continue. Clandestine manufacture and smuggling across international borders will remain a problem. Even if amphetamines are removed from the market, other stimulant drugs will remain available and abuse of these agents may grow. The abuse of stimulant drugs will thus remain a matter of continuing concern, and its control will require sustained vigilance from all of us. Drugs of this type are intrinsically attractive to a segment of our population and, at least for the foreseeable future, will remain so.

Control of the abuse problem in our society will require the continuing effort of many parties, as these hearings have made clear—physicians, pharmacists, the drug industry, education, and law enforcement agencies. FDA is proud of its record in the past in handling the anorectic drugs, and we look forward to maintaining that record in the future.

Thank you, Mr. Chairman; this concludes my formal statement. My staff and I would be most willing to answer any questions you may have.

Senator NELSON. Thank you very much.

What does the FDA plan to do about these drugs; whether to leave the amphetamines on the market as they are, whether to remove them entirely; or change the labeling so the indicated use may not include obesity?

Dr. CROUT. I think we will have to be imprecise on that.

The DEA is helping us, and we are dependent on that information. I think we will have to review with our advisory committees, or at least with our consultants, the two indications of narcolepsy and hyperkinesis due to minimal brain dysfunction in children, because much depends on whether amphetamines are needed for those uses. I think we can get our opinions in order on that within a number of weeks certainly. We expect it will be several weeks before we hear from DEA, and I am sure it will be a number of weeks after that before we go through an advisory committee procedure on those issues.

How soon an action can be taken would depend on the industry response and the legal processes, what hearings are required, whether there is court review, and so on.

That is simply impossible to predict.

Senator NELSON. The court review would not occur until sometime after a ruling has been made.

My question is in regard to the time when a conclusion is expected to be reached.

Dr. CROUT. I think with this, we can reach a conclusion within a matter of some weeks, as I mentioned.

I think a regulatory action is impossible to predict. Whether hearings are required or not I do not know.

Senator NELSON. Chart 3, shows the much higher incidence of drug abuse of amphetamines than the anorectic congeners. Given the conclusion which, I understand to have been reached by Dr. Crout's testimony, that they have about the same amount of effectiveness, what is the legal problem in saying that since in the marketplace there are available a number of nonamphetamine congeners which are as effective for purposes of controlling obesity, and which are not as addictive,

what is the legal problem in saying that we will remove the indication for obesity? What is the legal question?

Mr. MERRILL. If we assume the state of facts as you assume them, I think we would remove that indication of the drug on the ground it is not shown to be safe in relation to its benefits.

I would suspect when we proceed to do that, the manufacturers will probably begin to cross-examine in somewhat the same way Mr. Gordon did a moment ago. We want to have in hand the backup evidence that makes the facts real. In terms of legal authority we should have no problem; the problem is the procedure.

Senator NELSON. I will submit for the record some letters, two from Delco Chemical Co. to doctors.

It is pretty clear to see that the promotion is very strong.

I would just like to read these:

The enigma confronting the practitioner today is his inability to substantially increase his income from a level which is determined by the number of hours in a day and his physical stamina. Extend himself as he will, the added monetary rewards are discouragingly small.

There is a means of coping with this seemingly hopeless situation which has been instrumental in doubling, tripling and quadrupling many practices formerly bogged down in lethargy.

The products offered by Delco Chemical Company have made of many physicians key men in the anti-obesity field. Their practices have been built rapidly and either have augmented or supplanted entirely former specialties. The rise in income is almost unbelievable and the added effort minimal.

The most important factor responsible for this is a therapeutically efficacious product which has been used successfully in combatting obesity, a growing problem in our affluent society.

If you are interested in a substantial increase of income may we suggest that you return the self-addressed stamped post card to us and our representative will be happy to call upon you at your convenience.

We are the prime suppliers of obesity products which have been proven highly successful to the key men in your area as well as throughout the entire country from New York to Hollywood. These physicians enjoy incomes of $100,000.00 to $300,000.00 yearly.

Also, we supply Obstetricians, Gynecologists, Internists and General Practitioners who have incorporated weight control into their practices and have added $25,000.00 to $100,000.00 to their incomes yearly.

The products offered by Delco Chemical Company have made of many physicians key men in the anti-obesity field. The most important factor responsible for this is a therapeutically efficacious product which has been used successfully in combatting obesity, a growing problem in our affluent society.

If you are interested in a substantial increase of income, may we suggest that you return the self-addressed no postage required post card to us and our representative will be happy to call upon you at your convenience.

We have a number of other letters along this line which we will put in the record.[1]

Thank you, Dr. Crout, for taking your time.

Dr. CROUT. I should like to share your nausea listening to those letters.

Senator NELSON. Thank you. Mr. Gordon, please proceed.

Mr. GORDON. Doctor Crout, with respect to Eskatrol and Dexamyl, why are they still on the market?

Eskatrol should have been taken off the market a long time ago. What is the problem?

Dr. CROUT. Those two drugs are part of our whole DESI review, and the issues with those two drugs relate to their effectiveness.

[1] See materials supplied for the record by Senator Nelson beginning at p. 14975.

We have more than a hundred hearing requests on drugs like that, and these are two of them.

Perhaps the hardest job we have to do from the standpoint of just plain slow work is to handle hearing requests, and particularly when safety issues are not at stake, we treat them with a low priority. That is the reason for the delays.

These two drugs are not delayed any longer than any others in that whole group.

Senator NELSON. When do you estimate you will be acting on these?

Dr. CROUT. On Dexamyl we have denied a hearing, but have stayed the final order pending judicial review. Perhaps Mr. Merrill can comment on that, I think a final order on Eskatrol, we are hopeful of getting out reasonably soon.

I think I would rather put our work on the amphetamines in general. Obviously, if amphetamines, in general are removed from the market, that would overtake these two actions.

Mr. GORDON. Thank you.

Senator NELSON. Thank you very much. We appreciate your taking time to come.

Dr. CROUT. Thank you.

Senator NELSON. I have a long-distance telephone call that I have to make before noon.

Since I am on a diet myself, we will adjourn for 10 minutes and resume the hearings.

We will recess for 10 minutes.

[Whereupon, the subcommittee was in short recess.]

AETER RECESS

Senator NELSON. The subcommittee will resume its hearings.

Our next witness is Mr. Frederick A. Rody, Acting Deputy Director, Drug Enforcement Administration, Department of Justice, Washington, D.C.

Mr. Rody, you are welcome here, and I appreciate your taking time to come.

Your statement will be printed in full in the record.

You may present it however you desire, please identify for the reporter your associates, so that whatever comments they have to make will be accurately attributed in the record.

STATEMENT OF FREDERICK A. RODY, JR., ACTING DEPUTY DIRECTOR, U.S. DEPARTMENT OF JUSTICE, WASHINGTON, D.C., ACCOMPANIED BY ROBERT J. ROSTHAL, DEPUTY CHIEF COUNSEL; KENNETH A. DURRIN, ACTING DIRECTOR, OFFICE OF COMPLIANCE AND REGULATORY AFFAIRS; ERNEST A. CARABILLO, JR., CHIEF, REGULATORY SUPPORT DIVISION; AND GERALD VOYLES, SPECIAL AGENT IN CHARGE, LUBBOCK, TEX.

Mr. RODY. Thank you very much, Mr. Chairman.

Mr. Chairman and distinguished members of the subcommittee, my name is Frederick A. Rody, Jr., and I am the Acting Deputy Administrator of the Drug Enforcement Administration within the Department of Justice.

Today, I am appearing before you on behalf of Mr. Peter B. Bensinger, our Administrator, who is presently out of the country on official travel.

Appearing with me are Mr. Robert J. Rosthal, Deputy Chief Counsel; Mr. Kenneth A. Durrin, Acting Director of our Office of Compliance and Regulatory Affairs; and Mr. Ernest A. Carabillo, Jr., Chief of our Regulatory Support Division.

The Controlled Substances Act creates a partnership between the Attorney General and the Secretary of Health, Education, and Welfare.

The Attorney General is empowered to place a drug under control of the act, to remove a drug from control or to move a drug from one schedule to another schedule. To exercise this power, however, the Attorney General must have the concurrence of the Secretary that the contemplated action is medically and scientifically correct. The law states that the recommendations of the Secretary on medical and scientific matters are "binding" on the Attorney General and if the Secretary recommends that a drug not be controlled, the Attorney General cannot control it.

As the subcommittee has requested, I will briefly outline how that partnership has worked in the area of stimulant drugs.

The Controlled Substances Act, as it related to the stimulants, represented a congressional compromise under which Congress originally placed liquid injectable methamphetamine "speed" in schedule II and the amphetamine and methamphetamine in schedule III. However, it was clearly understood by the managers of the legislation for the House and the Senate that "proceedings will be initiated—by the Attorney General—involving a number of drugs containing amphetamines after the legislation has become law."

DEA's predecessor agency began a study of the abuse potential and actual abuse of the amphetamines and methamphetamine then in schedule III and in February 1971, forward the results of its study to HEW. In April, HEW agreed that the amphetamines and methamphetamine belong in schedule II and on May 25, 1971, we proposed in the Federal Register that the rescheduling take place. Thirty days were given for objections by interested parties.

Three major manufacturers filed objections: (1) Smith, Kline & French Laboratories requested a hearing on the transfer of its product, Eskatrol; (2) Mission Pharmacal Co. requested a hearing on the transfer of its product, Fetamin; (3) Pennwalt Corp. requested a hearing on the transfer of its product, Biphetamine.

On July 7, 1971, all amphetamines and methamphetamine, with the exception of the three drugs for which hearings had been requested, were ordered transferred from schedule III to schedule II. As to these three, application of the order was reserved pending a review of each drug and subsequent administrative hearings. Our review began with service of a subpena on Smith, Kline & French which in effect called for every piece of relevant information the company possessed on Eskatrol. Subsequent to that service, SKF, Mission, and Pennwalt withdrew their objections and requests for hearings and by Federal Register notice of August 19, 1971, their drugs joined the other amphetamines in schedule II.

Mr. Chairman, let me digress for a moment to note a fact important to the purposes of this subcommittee. In our efforts at that time to place the most rigorous controls on the amphetamines we received the support of the American Medical Association. Through its house of delegates, the AMA expressed approval of the rescheduling and urged "all physicians to limit their use of amphetamines and other stimulant drugs to specific, well-recognized medical indications."

It was early recognized that if our efforts to place the amphetamines in schedule II succeeded, a new danger to the public might arise. Two drugs—phenmetrazine—Preludin—and methylphenidate—Ritalin—had been placed in schedule III by the Congress. These drugs, while not true amphetamines, have been described as "amphetamine-like." It was considered highly possible that should amphetamines be moved to schedule II with its stringent controls, there could be a movement by drug abusers from the amphetamines to Ritalin and Preludin. Accordingly in April 1971, we sought the position of HEW on whether we could properly place these drugs in schedule II.

On July 29, 1971, HEW approved that rescheduling and negotiations began with representatives of the Ciba-Geigy Corp., then manufacturer of both products, and Boehringer-Ingelheim Ltd., owner of the U.S. patent on Preludin. It was the purpose of these negotiations to reach an agreement on placement of Ritalin and Preludin in schedule II without the need for lengthy hearings. The companies ultimately agreed and, on October 28, 1971, Ritalin and Preludin were placed in schedule II.

Turning now to the nonamphetamine anorectics—on February 15, 1973, HEW recommended that seven of these drugs be placed in schedule III of the Controlled Substances Act and one, fenfluramine, be placed in schedule IV. In Federal Register notices on May 9 and May 10, 1973, we proposed the precise scheduling recommended by HEW.

Mr. GORDON. What constraints resulted from placing the drug in schedule III and schedule IV?

Mr. RODY. Basically there is little difference in the constraints between schedules III and IV.

There are some criminal sanctions as to trafficking that are greater in schedule III; however, the significant difference is that schedule IV drugs are considered to be less dangerous than schedule III, and therefore this type of subtle difference certainly dictates to a certain degree the prescription and dispensing practices of doctors.

Mr. GORDON. Dr. Crout, not in today's testimony, but in a document we are going to put in the record, says that schedules III and IV have little but psychological impact on the practice of medicine, requiring only a special symbol on the labels and labeling and a practitioner's BNDD number on the prescription.

Do you agree with Dr. Crout that it does not have much effect on medical practice?

Mr. RODY. Certainly not as much as those drugs in schedule II. However, DEA believes that NIDA and the medical associations should establish guidelines on prescriptions and dispensing practices.

Senator NELSON. What does that mean?

Mr. RODY. Well, I think it would be to our advantage, in the enforcement of the Controlled Substances Act, to have established guidelines for use of doctors who dispense and prescribe drugs in their practices.

This would provide a peer influence within the professional community, and also it would serve as a reasonable base for DEA's enforcement efforts to be initiated wherever doctors fail to comply with recognized dispensing and prescription guidelines of the medical profession. It would serve as a basis to prove abusive drug dispensing and prescribing practices.

Senator NELSON. Is it not the responsibility of the FDA to establish the indicated uses of the drugs, and does it not have the authority to approve or disapprove them? Whom are you talking about other than the FDA?

Mr. RODY. I am not referring to the FDA regulatory responsibilities. FDA determines the medical and science value and safety of drugs, not dispensing and prescription practices. I am referring to the practices of doctors and the suggested need for guidelines by the profession as to what are medically recognized standards of application and how much or amount of drugs the patient should be given, and in what drug category.

Senator NELSON. I guess I do not follow that. You are saying the medical associations establish these guidelines?

Mr. RODY. I am suggesting that guidelines be established by NIDA in cooperation with the medical associations. They have the professional and medical experts, while DEA certainly has no regulatory authority on medical practice.

We are suggesting self-discipline standards among those professions.

Senator NELSON. That is what I am trying to identify precisely. The indicated uses of the drug have to be demonstrated under the law.

The FDA approves indicated usage of the drug. The indicated use of the amphetamine now is narcolepsy and the hyperkinetic syndrome, and control of obesity. The principal use of these drugs is for obesity.

As I understand it what you are saying is that the doctors who are using it more extensively than the approved indications warrant or are using it for none of the indicated uses, are practicing bad medicine, or violating the law, or doing something.

I am trying to get clear in my mind, what are you saying in addition to that?

Mr. RODY. I am having difficulty making myself understood.

What we are suggesting is a professional forum, both in NIDA and in the medical associations, that they establish the type of standards that are acceptable to those people that practice medicine, as to the degree of dispensing the drugs, and what type of drugs are to be used for those types of illnesses.

Senator NELSON. Are you talking only about addictive or abused drugs?

Mr. RODY. I think it would be applicable in all drugs, that have any bad side effects.

It would be certainly for those that are addictive or habit forming.

Senator NELSON. But all the prescription drugs have side effects of some kind or other, I suppose. What I am trying to get clear in my mind, are you suggesting that something beyond the Food and Drug Administration now has authority to do these things, that this be done by the National Institute of Drug Abuse.

Mr. RODY. Yes, I am.

Senator NELSON. Why, if the Food and Drug Administration is performing its function in approving the indicated uses of that drug, what in addition are you suggesting to that?

Mr. RODY. Sir, I am not an attorney, and if I may, could I refer this question to Mr. Durrin?

Senator NELSON. Certainly.

Mr. DURRIN. Senator, doctors have a fairly wide discretion and latitude with regard to indications for use on labeling for a particular drug.

What the Drug Enforcement Administration is intending to do with regard to controlled substances, controlled substances only——

Senator NELSON. You are only talking of controlled substances?

Mr. DURRIN. That is correct.

It is to get the leadership in the medical community, and in the medical associations to set firm guidelines, perhaps analogous to what is done in Suffolk County to set guidelines with regard to the discretionary uses for controlled substances among physicians, and we feel this kind of cautionary guideline from their peers will have a decided influence upon the prescribing practices of the vast majority of physicians in the country who want to do the right thing, who want to prescribe in the best interest of the public.

Senator NELSON. All of that is within the authority of the FDA now, is it not?

Mr. DURRIN. The Food and Drug Administration of course establishes indications for use, but even beyond that in terms of the number of doses prescribed in given cases, in terms of whether or not the condition of the patient in a particular situation necessitates the use of the drug, there are many discretionary areas that go far beyond indications of the use on the labeling of the drug, this is the kind of thing we have asked the medical community to give priority to in terms of guidelines.

Senator NELSON. Why wouldn't they work that out with the FDA, and then the State societies, the medical associations, and all of the rest of them would help enforce it?

Mr. DURRIN. Of course, we cannot dictate FDA's role, but it is our hope that all of these groups you are speaking of will engage in developing these kinds of guidelines.

Senator NELSON. Go ahead.

Mr. RODY. All right.

No objections were received from such major manufactures of the anorectics proposed for schedule III as the Upjohn Co.—Didrex—Warner/Chilcott—Pre-State—USV Pharmaceutical—Voranil—Sandoz Pharmaceuticals—Sanorex—or Ayerst Laboratories—Plegine. No objection to the proposed scheduling of fenfluramine—Pondimin—in schedule IV was received from the A. H. Robins Co.

Two maior manufacturers filed objections:

1. Merrell-National Laboratories requested a hearing on the scheduling of its product, Tenuate, in schedule III.

2. Pennwalt Corp., on the scheduling of its product, Ionamin, in schedule III.

The Merrell and Pennwalt hearing requests presented a grave policy issue involving fundamental fairness. All but these two companies had agreed to the HEW–DEA scheduling proposals. If the products

of the cooperating companies were scheduled by DEA while the Merrell and Pennwalt products remained uncontrolled during lengthy hearings, the economic inequity to the cooperating manufacturers and the danger that Tenuate and Ionamin would become abuse drugs of choice was obvious. Further, three of the anorectics, Voranil, Sanorex, and Pondimin, had never been on the U.S. market and had no domestic history of efficacy or abuse upon which scheduling comparisons with the Merrell or Pennwalt products could be made.

Merrell and Pennwalt finally agreed to placement of Tenuate and Ionamin in schedule IV pending the outcome of their hearings. This enabled us, on June 10, 1973, to place five of the anorectics in schedule III and fenfluramine in schedule IV as originally recommended by HEW. On July 6, 1973, Tenuate and Ionamin were added to schedule IV.

Clearly the resolution of the immediate problem did not resolve the permanent problem. We needed to know more about all the nonamphetamine anorectics and recognized we could find less than satisfactory answers in isolated, fragmented hearings concerned with Tenuate and Ionamin. It was decided, therefore, to monitor the manufacture, distribution, and use in the United States of all anorectics controlled in June and July 1973, paying special attention to indications of diversion and to chemical research on the abusability and dependence-forming characteristics of these substances.

Senator NELSON. You mentioned the anorectics controlled in June and July 1973. Do you mean all of them that were under some schedule of control including III and IV, or those that were placed on a schedule in June and July of 1973?

Mr. RODY. All those that are under schedules III and IV, sir.

Senator NELSON. Go ahead.

Mr. RODY. DEA, after discussions with the National Institute on Drug Abuse and the Food and Drug Administration, began its rereview as scheduled.

In addition to employing our own resources on the monitoring program, DEA contracted in March 1975 with the Stanford Research Institute to assist in the development of a method to schedule drugs objectively.

That study concentrated on the anorectics as models. We received the results of the Stanford study in April of this year. We have also received, under contract with the Research Planning Corp., the results of a study devoted in major part to identifying and quantitating abuse levels of the drugs in question.

On May 13, 1975, DEA forwarded a letter to each major manufacturer of a nonamphetamine anorectic drug asking information concerning the abuse potential of its particular product. On December 9, 1975 another letter to these companies requested manufacturing and distribution data. This massive amount of information has been received and is under review.

Thus, the hearings of this subcommittee have come at a fortuitous time. The testimony given by the witnesses who have appeared here and the conclusions the subcommittee draws from that testimony, together with the information we have been reviewing, will be closely considered by DEA in reaching our judgments on the drugs in question. Then, as contemplated by the Controlled Substances Act, those

judgments and the supporting data will be forwarded to HEW through the Food and Drug Administration for the definitive medical and scientific evaluation. Mr. Chairman, it should be said at this point that HEW and FDA have always cooperated fully with DEA in those areas in which our responsibilities are joined. We could not ask for better partners.

Mr. GORDON. When are you going to make that judgment you just mentioned?

Mr. RODY. The judgment would be made by HEW.

We cannot give you a firm date at this time. Hopefully by mid-December we will be able to provide FDA with information on diversion and drug abuse.

Mr. GORDON. When will that be?

Mr. RODY. Hopefully by mid-December, and we would also like to have benefit of the hearings, and if we may ask for an expeditious copy of the hearings.

Senator NELSON. The hearings will not be printed.

Mr. RODY. Certainly that is what we seek.

Senator NELSON. But the transcripts are available, if your department can afford it.

Now, let me get your role straight. You will supply to the FDA all of the information that your Agency has gathered respecting abuse of these drugs, is that roughly it?

Mr. RODY. Diversion and abuse, yes, sir.

Senator NELSON. Diversion refers to what?

Mr. RODY. Well, that would be diversion of legally produced drugs, where they are either stolen or otherwise illegally acquired from manufacturers, wholesalers or procurement.

Senator NELSON. We have had testimony by a witness who was himself a drug abuser at one time, and he stated that without having been involved directly, or having firsthand knowledge, drugs were stolen by employees at the manufacturing level, and brought out in the market. In other cases employees in a physician's office diverted drugs. Does your agency have any information about how extensive diversion might be, for example, out of the manufacturing plant by employees, or from physician's offices?

Mr. RODY. Yes, sir, we maintain data, both from our investigative actions and from the diversion investigatory units we have established. Diversion and abuse information is referred to the State regulatory agencies in that State to take action whenever it seems to be appropriate.

We also conduct an audit as to accountability at the manufacturing level, and wholesale distributor, and at the dispensing level.

Senator NELSON. How good are those controls? Do all of the manufacturers make their own basic compound, the active ingredients, or do they buy it from a supplier, from other manufacturers? What kind of controls do you have right from the source of production of the actual compound itself?

Mr. RODY. We have more accountability in schedule II, the controls are more restrictive, but if you would like more detail, Senator may we refer this question to Mr. Durrin?

Mr. DURRIN. We register the material down to the prescribing physician, we have about 535,000 annual registrants on our computerized system at this time.

In addition to the computer system, we maintain an investigative program whereby we inspect each manufacturer and distributor at least once every 3 years.

If we find violations, we take action up to and including removal of registration, and we also take appropriate civil or criminal prosecution.

We have seen over a period of time since the effective date of the controlled substances act in May 1971, a very significant tightening up at the manufacturer-distributor level of the handling of drugs.

I am not saying there is no employee diversion, but it is a much lesser factor in the total diversion picture than for example at the retail level at this point.

Senator NELSON. As I recollect, Dr. Crout said that he would be relying upon your agency to supply evidence respecting abuse of the amphetamines, the anorectic congeners, is that correct?

Mr. DURRIN. That is correct.

Mr. RODY. That is correct, and the next portion of my testimony goes right into that.

Senator NELSON. All right.

Go ahead.

Mr. RODY. This subcommittee has requested information on the current patterns of abuse and diversion of antiobesity drugs. Three sources have been employed to gather the information I will summarize:

First. The drug abuse warning network—DAWN—jointly sponsored by DEA and the National Institute on Drug Abuse, receives all drug mentions from selected emergency rooms, crisis centers, and medical examiners throughout the Nation and publishes this information on monthly basis.

Second. The system to retrieve information from drug evidence—STRIDE—constitutes a compilation of reports on all drugs received for examination by all DEA domestic and foreign laboratories.

Third. A recent telephone survey of DEA's domestic regions, which includes information on audits, sales, and so forth.

Mr. Chairman, there has been a 28 percent increase in DAWN mentions of amphetamines in the last 12 months. The increase of chronic effects as the reason for seeking emergency help strongly suggests that ever greater numbers of abusers have access to a continuing supply of amphetamines. At the same time, our laboratories report the appearance of less illicitly manufactured amphetamines and there are fewer reports of amphetamines being diverted from legal distribution systems. Accordingly, it must be concluded that increasing amounts of abused amphetamines come from home supplies and that these supplies are created largely by prescriptions and direct dispensing by physicians. The suggestion is implicit that significant numbers of physicians are prescribing and dispensing well over their patients' actual medical needs.

Phenmetrazine—Preludin—has become a serious problem as a street drug in areas of the United States ranging from Pennsylvania in the east to Nebraska in the west. Pockets of heavy abuse appear in Texas. The District of Columbia and surrounding States have been particularly hard hit. In the District, for example, we find Preludin trafficked under the street name "Bam" at $10 for a single 75 milligram

dosage unit. Since Preludin is water-soluable it is frequently injected intravenously and used in conjunction with heroin.

Senator NELSON. Is that one tablet?

Mr. RODY. That is one tablet, sir, and right now I believe the price is about 19 cents.

Senator NELSON. From the pharmacy on prescription, wholesale or retail?

Mr. RODY. The 19 cents figure is the wholesale figure, but it is being trafficked on the street at $10 a unit.

Senator NELSON. What is the price of a 75 milligram tablet, average price on a prescription from the pharmacy?

Mr. RODY. About 25 cents, so I am told.

Senator NELSON. About 25 cents a tablet in the pharmacy, and in the street it is $10?

Mr. RODY. That is correct.

Senator NELSON. Where, here in the District of Columbia?

Mr. RODY. That is the indication we have from our investigation in the District.

Senator NELSON. Is it similarly priced elsewhere in the country?

Mr. RODY. We do not have that much indication of this particular drug being available in all of the other areas of the country; it has been confined to Pennsylvania, westerly out to Nebraska, but particularly here in the District we have had a large indication of usage.

Mr. DURRIN. We have seen a price of as high as $15 for the 75 milligram dosage.

Senator NELSON. That is one of the congeners, one of the amphetamine-related tablets?

Mr. RODY. That is correct, sir.

Senator NELSON. Is this one especially expensive, or is it the same price prevailing for the amphetamines on the street?

Mr. RODY. Sir, I would have to defer the question to Mr. Durrin.

Mr. DURRIN. Let me just say it is a drug of choice among abusers. They particularly like this. It helps increase the effect of the heroin, and it is more popular than some of the other amphetamine-type drugs by comparison.

Pricewise, it is certainly one of the higher priced, legitimate street products.

Senator NELSON. Now, Preludin is in schedule II?

Mr. RODY. That is correct.

Senator NELSON. Why did that go to schedule II, since it is one of the congeners?

Mr. RODY. That was the result of our previous studies on diversion and abuse, and the data that we submitted to FDA. They in turn made that medical and scientific determination that Preludin should be placed in schedule II.

Senator NELSON. Do you somewhere in your testimony, or do some of your associates have any statistics on the cost in the street of the amphetamines?

Mr. RODY. We could certainly provide that to this committee. I am not sure if we have it with us at this time.

Mr. ROSTHAL. We will make it available, sir.

[Subsequent information was received and follows:]

STREET PRICES FOR AMPHETAMINE TABLETS

The following is a breakdown of amphetamine tablet prices on the illicit market. Each listing is a range of prices for varying tablet sizes broken down by Domestic Regions.

Region 1	Boston	.30 - 1.00/3-15 mg. tablet
Region 2	New York	.50 - 3.00/3-20 mg. tablet
Region 3	Philadelphia	.75 - 1.50/3-15 mg. tablet
Region 4	Baltimore	.25 - 1.50/3-25 mg. tablet
Region 5	Miami	.50 - 2.00/5-25 mg. tablet
Region 6	Detroit	.25 - 2.00/5-25 mg. tablet
Region 7	Chicago	.25 - 3.00/3-25 mg. tablet
Region 8	New Orleans	.50 - 3.00/5-25 mg. tablet
Region 10	Kansas City	.20 - .50/3-10 mg. tablet
Region 11	Dallas	.30 - 3.00/5-25 mg. tablet
Region 12	Denver	.25 - 2.00/5-25 mg. tablet
Region 13	Seattle	.25 - .60/3-10 mg. tablet
Region 14	San Francisco	.25 - 1.00/5-15 mg. tablet

Senator NELSON. Please proceed.

Mr. RODY. The U.S. attorney for the District of Columbia has focused public attention on the Preludin problem here by highly successful criminal and civil cases involving physicians and pharmacies. Continuing investigations by DEA indicate the existence of sophisticated criminal enterprises employing prescriptions obtained from doctors and forged prescriptions to build street supplies. Thefts from pharmacies also play a part in supplying the illicit traffic in Preludin.

In 1975 Western Fehr Laboratories, manufacturers of the basic ingredient in Preludin, Ciba-Geigy Corp., the sole manufacturer of Preludin in dosage form, and Boehringer-Ingelheim Ltd., the sole distributors of Preludin to wholesalers, petitioned DEA for an increase in the 1975 manufacturing and procurement quotas for Preludin previously set by DEA. That petition was rejected by DEA and it was again rejected by an administrative law judge following a lengthy hearing demanded by the companies. This resulted in an appeal by the companies to the U.S. Court of Appeals for the First Circuit which, on January 28, 1976, issued the final rejection.

In a unanimous opinion, the court found in part that, "DEA had the obligation when it found substantial evidence of broadscale diversion to achieve a more Spartan pipeline, even though this might cause inconveniences to manufacturer and distributor."

Mr. Chairman, just 3 weeks ago, on October 29, 1976, attorneys for Western Fehr Laboratories and Boehringer-Ingelheim Ltd., filed with Administrator Bensinger objections to DEA's proposed 1977 production quota for Preludin. Once again an administrative hearing has been demanded by the companies.

Mr. GORDON. On what basis are they demanding higher production quota? Did they come up with evidence to show the medical need for these higher quotas?

Mr. RODY. Sir, I believe that question would have to be answered by those companies.

Mr. GORDON. Don't they have to give a reason when they ask for higher quotas?

Mr. DURRIN. The request is based on projected sales, and, of course, we have our own yardstick in terms of measuring legitimate medical need, and sometimes we feel that the firms are a little bit optimistic in terms of projected sales of their product.

Mr. GORDON. Projected sales, as we saw, do not necessarily equal medical needs?

Mr. DURRIN. That is correct, and that is why we have a different opinion.

Mr. ROSTHAL. May I speak to that? I conducted the hearing and the argument in the court of appeals.

The significant thing I found at the hearing was that the company in projecting its sales for the future years at no time ever considered how much diversion there was.

They told us how much they sold to doctors, and how much was prescribed.

When they were asked on appeal, "Well, what about the diversion you know about, it is in the streets," they said diversion is DEA's business.

Making the drugs is ours they said. Now, that is a paraphrase, but very close.

Mr. RODY. Methylphenidate—Ritalin—differs from the other substances under consideration here today.

It is not indicated as an antiobesity drug. Ritalin is described as "effective" in the treatment of minimal brain dysfunction in children and in the treatment of narcolepsy, a form of sleeping sickness.

It is considered "possibly effective" for mild depression. It is ironic that under the heading "Adverse Reactions" in the Physicians' Desk Reference the manufacturer of Ritalin warns against loss of appetite in children leading to "weight loss during prolonged therapy."

Between July 1, 1973, and July 31, 1976, there were more Ritalin related abuse episodes reported in DAWN than any one of the 10 brandname amphetamines or nonamphetamine antiobesity products surveyed. The profile of Ritalin abuse is unlike the others. The great majority of the amphetamine and nonamphetamine anorectic reports come from crisis centers, the usual haven for street abusers in various phases of illness. Two-thirds of the Ritalin episodes were reported from hospital emergency rooms to which the more seriously ill are most often taken. Illicit sources such as street buys, forged prescriptions, stolen dosage units or gifts were listed in over half the episodes.

Mr. Chairman, before summarizing the information on the nonamphetamine anorectics, let me say that one of them, fenfluramine—Pondimin—may possibly be improperly described as a stimulant. Since coming on the market in 1973 fenfluramine has been reported as showing the indicia of a depressant causing some of the responses of an hallucinogen such as PCP.

The nonamphetamine, antiobesity products have received far fewer mentions in DAWN than the amphetamines, Ritalin, or Preludin. The anorectics are reported primarily from crisis centers as opposed to emergency rooms or medical examiners. Over 75 percent of the incidents involve legal prescriptions as the source. As with the amphetamines, the suggestion is implicit that significant numbers of physicians are prescribing and dispensing well over their patients' actual medical needs.

Mr. Chairman, Benjamin Gordon of the subcommittee staff has asked DEA for a more detailed report on one nonamphetamine anorectic, Ionamin. I have been told that Mr. Gordon's concern with this substance is not based on any known significant differences between Ionamin and most of the other nonamphetamine anorectics. Rather, Mr. Gorden's concern is predicated on the past history of the Pennwalt Corp., manufacturer and distributor of Ionamin.

In May 1971, as earlier noted, Pennwalt requested a hearing on the proposed transfer of its amphetamine product, Biphetamine, from schedule III to schedule II. That request was subsequently withdrawn and on August 19, 1971, the drug became subject to the Attorney General's power to limit manufacture by setting production quotas.

Mr. Chairman, the dates in this matter are most important. Until some time in June 1971, Pennwalt exported to Mexico City large quantities of the resin complex from which Biphetamine is manufactured. In Mexico City at a Pennwalt subsidiary, the resin complex was encapsulated and sold under the Mexican trade name Bifetamina.

Within months, Bifetamina appeared on the illicit market in the United States. A special task force working under the code name "Operation Blackjack" established that the southeastern and southwestern States were being flooded with Bifetamina and that the drug was being smuggled into the United States at six principal points along the Texas-Mexico border.

Pennwalt was ordered to show cause why its registration to export amphetamine products should not be revoked. The company chose not to contest the order and is now barred from exporting its amphetamine products to any part of the world.

Mr. Chairman, the order to show cause in that case said in part, "the illicit importation of Bifetamina from Mexico and the subsequent illegal sale of Bifetamina in the United States substantially subverts the purpose of placing all amphetamines in schedule II."

Senator NELSON. Who are the manufacturers in Mexico?

Mr. RODY. Strasenburg, which is Pennwalt's subsidiary in Mexico.

Senator NELSON. So Pennwalt was under court order?

Mr. ROSTHAL. We served them with an order to show cause as to why their registration with us to export amphetamine products should not be revoked, and why the total quota for all amphetamines should not be reduced by the amount of what we would take from them.

We conferred with them, I think they knew we had the evidence, because they withdrew, so the order to show cause was withdrawn, and the company, as Mr. Rody has said cannot ship amphetamines from the United States to any part of the world.

Senator NELSON. What was the legal basis of the Government in attacking the question of exportation.

Mr. ROSTHAL. There was a myriad of criminal cases made all over the South and the Southwest. This stuff showed up at truck stops, and many criminal cases were made.

The basis for the order to show cause was, Mr. Rody had said in citing from the order, that they were subverting the entire purpose of the Controlled Substances Act.

What they were doing in effect, Mr. Chairman, was conducting an end run.

They had quotas in the United States, but they could make as much as they wanted in Mexico City.

Senator NELSON. But the quota in the United States at that time prior to the court order did not apply to exports?

Mr. ROSTHAL. No; the quotas applied, I should have gone back on that.

The quotas applied to what they could manufacture for everything, but what they had done in the 2 years previous to our placing amphetamines in schedule II, a move which everyone in the industry knew was going to happen, was to ship large quantities, large quantities of the basic resin complex from their plant in Rochester, N.Y. to their plant in Mexico City.

Senator NELSON. Was the product made at that time in Mexico City, too?

Mr. ROSTHAL. No, the basic product, the complex was made in New York State, and shipped to Mexico City.

As Mr. Rody's testimony will develop, this was incapsulated, and they changed the name in Mexico to Biphetamina.

Senator NELSON. Although they may not export, are they manufacturing the compound?

Mr. ROSTHAL. I do not think so, because I think the only thing that they are making now in Mexico City, or encapsulating in Mexico City is Ionamin, with the name of Ionaminas.

Mr. Chairman, I think Mr. Rody's testimony does develop this.

Senator NELSON. Fine. Go ahead.

I did not get a chance to read it in advance.

Mr. RODY. The history of Pennwalt and Ionamin has a similar beginning. In May 1973, as earlier noted, Pennwalt requested a hearing on the proposed placement of its anorectic product, Ionamin, in schedule III.

Whether that hearing takes place will depend in large part on the results of DEA's comprehensive review of all the anorectics which will include the report of this subcommittee. Meanwhile, Ionamin remains in schedule IV.

In 1975, Pennwalt exported to Mexico City 300 kilograms of the bulk powder from which Ionamin is manufactured.

Mr. GORDON. May I interrupt for just a second?

You said 300 kilograms. As I understand it, Ionamin is made in two strengths, 30 and 15 milligrams; is that correct?

Mr. RODY. That is correct.

Mr. GORDON. If these 300 milligrams are manufactured in, say 30 milligram tablets, which is the strongest strength, that comes out to about 10 million pills, does it not?

Mr. DURRIN. That is correct.

Mr. GORDON. And if they manufacture it in 15 milligram grain tablets, it would come out to 20 million tablets?

Mr. RODY. That is correct.

Mr. GORDON. Are those pills for the obese people of Mexico?

Mr. RODY. We would have to speculate on that. We do know from some of our investigative activities, it is a bit more than that.

Thus far in 1976, another 300 kilograms of that same bulk powder has been exported to Mexico City.

In Mexico City, at the same Pennwalt subsidiary where Bifetamina was once produced the bulk powder is encapsulated and sold under the Mexican trade name, Ionamina.

Mr. Chairman, a report on the most recent survey of illicit sales of Ionamin and Ionamina will be forwarded to the subcommittee.

[Subsequent information was received and follows:]

INTRODUCTION

Ionamin is the brand name of a generic drug known as phentermine, which is manufactured and marketed by Pennwalt Prescription Products, a Division of the Pennwalt Corporation, Rochester, New York.

On February 15, 1973, HEW originally recommended to BNDD that phentermine should be made a controlled substance in Schedule III. BNDD published such a recommendation in the Federal Register on May 9, 1973. However, in view of evidence which was presented in the resulting comments, DEA announced on July 6, 1973 that phentermine would be controlled in Schedule IV (not III) effective on July 6, 1973.

Ionamin is marketed in capsule form, in strengths of either 15 mg. or 30 mg. Cumulative Supplement 2 of the 1976 Red Book indicates that the wholesale prices of the different product sales units are as follows:

15 mg. Capsules	
Bottles of 100	$13.19
Bottles of 400	$48.01
30 mg. Capsules	
Bottles of 100	$14.55
Bottles of 400	$52.71

Ionamin has a pharmacologic activity similar to that of the prototype drug of this class used in obesity, amphetamine (both d and l amphetamine). Actions include central nervous system stimulation and elevation of blood pressure. Tackyphylaxis and tolerance have been demonstrated with all drugs of this class in which these phenomena have been looked for.

Drugs of this class used in obesity are commonly known as "anorectics" or "anorexigenics". It has not been established, however, that the action of such drugs in treating obesity is primarily one of appetite suppression. Other central nervous system actions, or metabolic effects may be involved.

Whereas the natural history of obesity is measured in years, the available studies involving anorectic drugs are restricted to a few weeks or months in duration. Thus, the total impact of drug-induced weight loss over that of diet alone must be considered clinically limited.

Ionamin is indicated in the management of exogenous obesity as a short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors inherent in their use. The following contraindications should be looked for before prescribing Ionamin:

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glucoma.

Agitated states.

Patients with a history of drug abuse.

If tolerance to the anorectic effect develops, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Ionamin may impair the ability of an individual to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle.

The 1976 edition of the "Physicians' Desk Reference" (PDR) warns that Ionamin is related chemically and pharmacologically to amphetamines and other stimulant drugs which have been extensively abused. The possibility of abuse of Ionamin should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program.

Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

STREET AVAILABILITY

In an attempt to determine whether or not Ionamin is available on the street, ECI has collected information from the following sources; telephone survey of the Domestic Regions, STRIDE, DAWN, DIU's, the Import/Export Unit, and the Statistical and Data Services Section.

TELEPHONE SURVEY

The Compliance Program Manager at each of the Domestic Regional Offices was contacted on Wednesday, October 6, 1976, and he was requested to supply ECI with any available information concerning the street availability of Ionamin (or of the product Ionamina, the brand name for the same product marketed in Mexico by Laboratorios Strasenburgh de Mexico). This data was to be collected from such sources as in-depth compliance investigations, theft reports, seizures, street intelligence, and local enforcement agencies.

During the past twenty months, the total number of dosage units of both strengths of Ionamin which have been reported to DEA as having been stolen or lost intransit is about 153,000 (or about 7,650 d.u. per month). This figure does not include the intransit losses reported by Pennwalt before January 1976.

In reviewing the audit portions of those in-depth compliance investigations which included Ionamin as one of the drugs which were selected for audit, only five Regions reported any cases in which there was a deviation of more than ±5%. The largest single deviation was reported in a case in Region 6 (115-74-0043, dated February 18, 1975) in which a shortage of 36,300 d.u. of Ionamin (30 mg.) was uncovered. The total number of such investigations was twenty-seven.

The most significant Compliance case to date is an ongoing investigation in Region 5 (G3-76-2020) in which a pharmacist in a small town in Georgia is believed to have diverted approximately 96,000 dosage units of Ionamin since January 1975 (all of which were the 30 mg. strength).

In their conversations with the criminal groups within each Region, the Compliance Program Managers found that there is little demand for Ionamin on the street. Indications are that current street prices range from a low of twenty cents a capsule in Georgia, to a high of seventy cents and $1.10 per capsule in Texas.

The only significant seizures involving Ionamin (or Ionamina) occurred in Texas where approximately 90% of the 104,155 dosage units of anorectic drugs seized between July 1973 and September 1976 were the Pennwalt products.

STRIDE/Ballistics

During Fiscal Year 1976, DEA Laboratories analyzed a total of 68 exhibits of phentermine that could be identified to presumptive manufacturers or distributors. Of this total 85% (or 58 exhibits) were presumed to have been manufactured by Pennwalt.

DAWN

Of the five anorectics analyzed (Preludin, Tenuate, Ionamin, Tepanil and Pondamin), Ionamin ranks third in frequency. Of the 110 episodes purported to have involved Ionamin taken for psychic effect or dependence, during July 1973 to July 1976, 70% of the reports showed legal prescriptions as the source.

DIVERSION INVESTIGATIVE UNITS

On October 6, 7, and 8, 1976, a limited survey of abuse of Ionamin and its generic equivalents was conducted by contacting each of the nine operating Diversion Investigative Units. The following comments reflect the recent experience of each of the nine DIU states.

New Jersey DIU reports general, if somewhat limited abuse of Ionamin, Phentercot, and Fastin, in that order, but far less than the problem with Phenmetrazine (Preludin) and Phendimetrazine.

Massachusetts DIU reports very limited minor abuse, probably because Massachusetts' law classified phentermine as "an isomer of Methamphetamine" (leaving out the word "optical" in the definition); and so Ionamin is already classified by the state in Schedule "B", the highest available schedule for legitimately manufactured drugs for penalty purposes.

Michigan DIU reports no instances of Ionamin use or availability in the state. This of course also applies to generic equivalents of Ionamin/phentermine as well. DIU officials report heavy abuse of similar drugs, Phenmetrazine and Phendimetrazine.

Illinois DIU reports very limited minor abuse and availability of Ionamin; however Preludin (Phenmetrazine) and Ritalin (Methylphenidate) are heavily abused there and readily available.

California DIU reports a complete absence of traffic in Ionamin and in Ionamina (the Mexican version of the same product) in both Northern and Southern California. The stimulant drugs of choice in that state are Desoxyn, Preludin and Eskatrol, in that order.

North Carolina DIU reports moderate abuse of both Ionamin and Fastin (a generic). DIU cases related to these drugs tend to be confined to prescription writing doctors "who feel more comfortable" writing for these rather than for more well known stimulants.

Pennsylvania DIU reports heavy abuse of both Ionamin and Fastin, probably because phentermine was not controlled under state law until August 21, 1976. DIU officials predict a gradual falling off in the popularity of these two drugs since they are now controlled.

Texas DIU reports heavy trafficking and abuse of Ionamina, the Mexican equivalent of Ionamin, in all areas of the state adjacent to the Mexican border, and relatively common abuse elsewhere in the state. Except in the border areas, other stimulant drugs still lead in terms of abuse. Since July, 1973 and through at least April 1976, over 25 cases have been made involving Ionamina, with seizures and purchases totaling over 104,000 dosage units.

Alabama DIU reports exceptionally heavy trafficking and abuse in both Ionamin of U.S. manufacture and Fastin. In calendar year 1975, 99% of all drugs purchased or seized by the DIU were Ionamin. This phenomenal figure can be traced to a single DEA cooperation case (J4-75-0016) where 500,000 dosage units were seized. In a related case (same source) the Georgia Bureau of Investigation seized 100,000 more. The responsible distributor (in Miami) surrendered his registration in lieu of prosecution.

When the above case is removed from the figures, Ionamin still accounts for 35% of the total drugs obtained by the DIU that year.

During calendar year 1976 (to date), 22% of the drugs obtained by the DIU were phentermine, which broke down further to 73% Ionamin and 27% Fastin (a generic).

The Alabama DIU considers phentermine to be readily available and heavily abused, although amphetamine (when available) is still the drug of choice for abusers.

IMPORT/EXPORT

The following data reflects the volume of Ionamin (in its various forms) which has been exported by Pennwalt during calendar year 1975, and thusfar during calendar year 1976:

Dosage Form	Destination	Total Quantity
	1975	
15 mg. Capsules	El Salvador, Guatemala, Panama, Costa Rica, Nicaragua	214;810
30 mg. Capsules	About the same countries	508,800
Bulk Powder	*Mexico	300 kilograms
	1976	
15 mg. Capsules	El Salvador, Guatemala, Panama, Costa Rica, Nicaragua	161,010
30 mg. Capsules	About the same countries	353,870
Bulk Powder	*Mexico Argentina	300 kilograms 250 kilograms

*Mexico shipments to: Laboratorios Strasenburgh
de Mexico, S.A. de C.V.
Division del Norte 3442
Mexico 21, D.F. Mexico

Mr. RODY. For the purposes of today's hearing, I will say that Ionamin is a relatively minor problem in most of the United States.

However, in Texas we find heavy trafficking and abuse of Ionamina in all areas of the State adjacent to the Mexican border.

Since July 1973 through April 1976, some 25 cases have been made involving Ionamina, with seizures and purchases totaling over 104,000 dosage units.

Mr. Chairman, that concludes my formal testimony; however, I have with me Mr. Gerry Voyles, our special agent in charge, of Lubbock, Tex., who can provide an update on the status of Ionamina.

Senator NELSON. One question first.

Concerning these 25 cases between July 1973 and April 1976, involving 104,000 doses or units of Ionamina—you are saying that these drugs came illegally into the country?

Mr. RODY. That is correct, smuggled into the country.

Ionamina as opposed to Ionamin, which is domestically manufactured, that is correct.

Senator NELSON. Now, in 1972, the FDA testified before this committee that there was no difference between Ionamin and the amphetamines with respect to benefit, risks and addiction. Is that correct?

Mr. RODY. Sir, I do not have benefit of that testimony.

Mr. ROSTHAL. Yes, sir, that is correct.

Senator NELSON. All right. Go ahead.

Mr. GORDON. I want to ask one question.

Since Ionamin is now being illegally imported from Mexico, and illegally sold in the United States as in the case of the amphetamines, why not do for Ionamina what you did for the amphetamines?

Mr. RODY. Sir, we have had discussions with Pennwalt, and as recent as October 6, the president of Pennwalt communicated with DEA, and he offered full cooperation, even to the extent, if necessary of removing Ionamina from the market in Mexico, and today we would be pleased to accept that offer.

Mr. GORDON. That they will no longer ship to Mexico?

Mr. RODY. That was the offer that was made, and we would be pleased to accept it.

Senator NELSON. Do go ahead.

Do you have another witness?

Mr. RODY. Special agent Gerry Voyles. He is from Lubbock, Tex., office, and he adds significant insight due to his experience during Operation Blackjack, which I mentioned in my earlier testimony.

Senator NELSON. Could you give the reporter your full name?

Mr. VOYLES. Yes, sir.

Gerald Voyles.

Mr. Chairman, I was the field supervisor during Operation Blackjack during the years, part of the year 1971 and 1972.

During that time we were making cases, criminal cases against illicit traffickers in Bifetamina, which is a product manufactured by Pennwalt.

During that time, and during that investigation of Operation Blackjack as previous testimony has brought out, Pennwalt manufactured in the United States, and exported the bulk material to Mexico.

It was then encapsulated in Mexico City, in Strassenburg, a subsidiary of Pennwalt.

It was then sold, presumably through legitimate channels to pharmacias on the Mexican side of the Mexican border.

At that time, it was sold in the illicit traffic, smuggled into the United States through the South, the Southeast, and Southwest, primarily, it appeared at truck stops.

The pharmacias were identified during Operation Blackjack, the truck stops were identified, and many of the traffickers that were not apprehended were identified.

It is at this point with Ionamina, that we see a very deadly parallel.

Ionamina is manufactured in the United States, it is exported to Mexico, it is encapusulated in their plant in Mexico, recent investigations show that it has gone to the same pharmacias which we identified in 1971 and 1972, being brought into the United States, through the Southeast, the Southwest, and, again, we have very, very similar circumstances, as we had with Biphetamina in regards to Ionamina, and at this time, we also brought with us Mr. John Myer, from our Chicago laboratory.

Mr. Myer has brought an exhibit which he must maintain custody of due to the fact that this is still a criminal investigation, so at this time, we would like to show the chairman one exhibit from one case made in the Midwest United States, which is still under investigation.

We have a suspected source identified, so if we could at this time——

Senator NELSON. And these are all Mexican manufactured?

Mr. VOYLES. Mexican manufactured, yes.

Senator NELSON. It is all Ionamina?

Mr. VOYLES. Yes, sir, and if you would like to have some comparison between domestic manufacture and U.S. manufacture——

Senator NELSON. They look identical.

Mr. VOYLES. The only difference that we have on the Mexican manufacture, on the capsule, it has RJS.

On the U.S. manufacture, it has the Pennwalt logo.

Senator NELSON. How many tablets are involved?

Mr. VOYLES. This is one exhibit in a case. It is not the only exhibit.

Senator NELSON. But this came in what way into the country?

Mr. VOYLES. This is a criminal investigation that was conducted by our office in Indiana.

Senator NELSON. And this is all picked up in one batch?

Mr. VOYLES. Yes, sir.

Senator NELSON. What is the street value of these?

Mr. VOYLES. Sir, the street value runs approximately $1 to $1.50.

Senator NELSON. A tablet?

Mr. VOYLES. Yes, sir, and we have roughly 20,000 dosage units here.

Senator NELSON. And how much of this product has been picked up moving illicitly in this country in a particular period?

Mr. VOYLES. I cannot give you a definite answer on that.

We have several exhibits, which have come into our laboratories of this product.

I just cannot give you a figure.

Senator NELSON. You do not have a total?

Mr. VOYLES. No, sir.

Senator NELSON. And this is all Ionamina?

Mr. VOYLES. Yes, sir.

Senator NELSON. Where does the compound start out?

Mr. VOYLES. In the United States.

Senator NELSON. And then it is sent in bulk?

Mr. VOYLES. In bulk, and in Mr. Rody's testimony, he said I believe there were 300 kilos shipped this year.

Senator NELSON. And that is about 600 some pounds, I think a kilo is 2.2 pounds.

Mr. VOYLES. A kilo is 2.2 pounds; yes.

Senator NELSON. And that is how many, 300 kilos is how many tablets?

Mr. VOYLES. Approximately 10 million dosage units.

Senator NELSON. You would make about 10 million?

Mr. VOYLES. Yes, sir.

Also, there is a couple of other points I would like to make.

Where I come from, I have seen an example of Ionamina in Lubbock. A very well-to-do, very respected woman was arrested in the latter part of September with 60 dosage units of Ionamina.

I cannot give you the details of the case other than I know it is still pending, the charges she was arrested on by the local police, but the point is this, that it is being abused.

She would never think of going out into the street and buying a drug, yet she would go through the trouble to get a prescription.

Senator NELSON. She had used it?

Mr. VOYLES. Yes, sir.

Thank you.

Senator NELSON. Thank you very much.

Mr. VOYLES. We would like to seal this up now if we could.

Senator NELSON. Certainly.

Mr. VOYLES. This exhibit in Operation Blackjack, we identified a pharmacia in Mexico.

Our intelligence information in the case is that this exhibit here of Ionamina came from the same pharmacia as many of the exhibits we got of Biphetamina during Operation Blackjack.

Senator NELSON. The same pharmacia?

Mr. VOYLES. The same pharmacia.

Mr. GORDON. Would you care to guess how it gets from Pennwalt up to Indiana?

Mr. VOYLES. As far as getting from Pennwalt up to Indiana, it is manufactured in bulk in the United States, sent forward to Mexico City, encapsulated, sold ostensibly in the legitimate chain in Mexico.

I do not have that information. I do not know, but at that point it is diverted from the legitimate chain.

Mr. GORDON. Don't you think it is rather suspicious for so many tablets to be used in Mexico?

Mr. VOYLES. I would think so.

Senator NELSON. Thank you very much.

Mr. RODY. Yes, sir. Thank you.

Senator NELSON. Anybody on the panel have anything to add to the testimony?

Mr. RODY. No, sir, Mr. Chairman, that concludes our testimony.

Senator NELSON. Thank you very much.

Mr. GORDON. Mr. Rosthal, did you want to say something?

Mr. ROSTHAL. No, sir.

Well, all I ask is, I understand that Mr. McGraw of Pennwalt is going to testify. I do not suppose that there is any objection if I remained to hear it?

Senator NELSON. You are free to remain and can comment on the testimony of Pennwalt's testimony, and if they have any rebuttal to your comment, we are willing to accept that.

We will give everybody a chance for a full presentation, and full response in the record.

Somebody better take those amphetamines away from in front of us.

Mr. ROSTHAL. Simple possession, Mr. Chairman. It is only a misdemeanor. [Laughter.]

Mr. GORDON. Mr. Rosthal, will you remain in the room?

Mr. ROSTHAL. Yes, sir.

Senator NELSON. One more question.

For clarification—you do have a substantial amount of testimony or evidence as to diversion and abuse of amphetamines and the congeners; is that correct?

Mr. RODY. That is correct, Mr. Chairman.

Senator NELSON. And that will be presented at some early stage to the FDA?

Mr. RODY. That is correct.

Senator NELSON. And you say sometime in December?

Mr. RODY. Hopefully, I cannot give you an exact date, hopefully in December. We certainly would like to review, of course, some of the testimony that has occurred here.

Senator NELSON. Yes; and how would you describe the evidence you have, substantial, not substantial, overwhelming?

Do you have a description of the evidence of the abuse, of the use of amphetamines, and the congeners that are on the marketplace?

Mr. RODY. Sir, I think it would have to be described as very substantial.

Senator NELSON. Does that apply to those amphetamines and congeners which are being "legally prescribed" in this country through legal channels?

Mr. RODY. That is correct.

Senator NELSON. As well as diversion or illicit introduction into this country, is that evidence substantial too?

Mr. RODY. Yes, sir. Not to the same degree as it is on the amphetamines.

Senator NELSON. And do you have evidence showing widespread use and abuse?

Mr. RODY. Yes; we have data from our DAWN system which would reflect the number of episodes reported over the last 3 years in various categories of drugs.

Senator NELSON. And you consider that to be substantial?

Mr. RODY. It is reflective as being substantial, yes, sir.

Senator NELSON. Thank you very much.

Mr. RODY. Thank you.

Senator NELSON. Our next witness is Mr. Isaac McGraw, president of the pharmaceutical division of the Pennwalt Corp.

Mr. McGraw, could you please identify your associate for the record?

Mr. McGRAW. Yes, sir.

I have with me Mr. Matthew Broderick.

Senator NELSON. All right.

Go ahead, Mr. McGraw. You may present your testimony however you desire.

STATEMENT OF ISAAC R. McGRAW, PRESIDENT, PHARMACEUTICAL DIVISION OF PENNWALT CORP., ACCOMPANIED BY MATTHEW BRODERICK

Mr. BRODERICK. Mr. Chairman, I would like to state at the start that Mr. McGraw will be Pennwalt's witness.

Mr. Head will not testify. I think I have so advised Mr. Gordon.

Senator NELSON. All right.

Mr. McGRAW. Mr. Chairman, at the request of your committee, I am appearing on behalf of Pennwalt Corp. pharmaceutical division in order to provide the committee with our comments on the subject of antiobesity drugs.

As an introduction, in my appearance today on behalf of Pennwalt and its pharmaceutical division, I will review those major considerations which we believe to be responsive to this committee's invitation.

In order that you may readily comprehend our views, I should like to summarize them at the outset and then deal with them more fully by major category.

As part of Pennwalt Corp., a 126-year-old firm founded and still headquartered in Philadelphia, Pa., with annual sales of approximately $750 million, we share its pride in our collective integrity.

I should note that our division represents less than 10 percent of the company's total sales, and that our antiobestiy products represent less than 3 percent of total sales, with less than 1 percent in anorectic amphetamine products.

Senator NELSON. Gross sales?

Mr. McGRAW. Net sales.

Senator NELSON. How do you define net sales?

Mr. McGRAW. Sale less cash discount and shipping cost to the customer.

Antiobesity prescription medicine is the only federally recognized effective medicinal aid available in a course of medically supervised antiobesity treatment available to the 30 to 40 million Americans who are obese, namely, those who are at least 20 percent overweight.

Obesity is a recognized illness, in medical terms, as well as an emotional burden. It also complicates other quite serious medical problems.

Our pharmaceutical division clearly recognizes that its anorectic products should not be used unless prescribed by a physician. We firmly believe that our marketing program fully reflects this recognition and contains no suggestion that we seek to sell the patient *any* use of our anorectic products.

As this committee is aware, the Food and Drug Administration has found our anorectic products to be safe and effective and, in our judgment, we have continued to achieve very satisfactory compliance with the regulatory standards and programs which are the responsibility of the Drug Enforcement Administration.

We believe that you should find the factual evidence on the prescription dosage units of our products, per patient, to be consistent with their use as a short-term aid to the medically supervised obese patient.

We do not believe there is any probative evidence that our antiobesity products show any meaningful statistical or other factual evidence of abuse.

We recognize that in a population of 215 million Americans there is a very small but highly visible segment who are troubled and who may be determined to misuse or abuse legitimate products.

We believe, however, that the safety, effectiveness, and judicious prescription of antiobesity products cannot reasonably be condemned by the very limited factual evidence of their statistically quite infrequent misuse.

The Congress and 42 State legislatures have created, and the FDA, DEA, and State agencies administer, monitor, and enforce sophisticated and effective programs designed to insure proper medically supervised use of anorectic products.

We fully support these programs and cooperate readily with these agencies.

We believe that a scientific, technical or legal analysis fully and fairly considered, on the basis of factual rather than hearsay evidence, will continue to require the conclusion that our anorectic products serve a very worthwhile medical and human need—assistance to the physician who finds that his patient requires this medication.

I shall now turn to a more detailed review of the bases for the views I have just summarized.

CORPORATE HISTORY

Pennwalt Corp. was founded in 1850, in Philadelphia, where it continues to maintain its corporate headquarters. Pennwalt has more than 14,000 employees who are engaged in manufacture, sale, and distribution of its products in the United States, Europe, and elsewhere in the free world. Pennwalt's total annual sales are expected to exceed $750 million in 1976, derived from its operations in chemicals—approximately 50 percent—specialized equipment—approximately 25 percent—and health—including both dental and pharmaceutical operations—approximately 25 percent. The pharmaceutical division has annual sales of approximately $70 million and employs approximately 1,100 people.

PENNWALT'S PHARMACEUTICAL DIVISION

The pharmaceutical division manufactures and makes available to the medical profession a variety of therapeutic agents including antihypertensives, diuretics, antianxiety drugs, local anesthetics, antifungals, antispasmodics, antitussives, and antihistaminics as well as anorectics.

The total sales of Pennwalt's only amphetamine product, Biphetamine, are less than 1 percent of Pennwalt's annual sales, and the total sales of both Biphetamine and Pennwalt's nonamphetamine anorectic, Ionamin, are less than 3 percent of Pennwalt's annual sales.

Mr. GORDON. Mr. McGraw, according to the national prescription audit, the 1975 manufacture of sales of Biphetamines was $5,847,000, and Ionamine was $11,712,000.

These two drugs then account for about 26 percent of the annual sales of your pharmaceutical division, is not that correct?

Mr. MCGRAW. Yes, sir.

Mr. GORDON. In other words, these two drugs are very, very important to the total sales of your pharmaceutical division, and when you talk in terms of 1, 2, or 3 percent, it sounds small, but to the pharmaceutical division, these two drugs are very important; I want to bring that out.

Mr. MCGRAW. Yes, sir.

Our pharmaceutical division is headquartered in Rochester, N.Y., where it maintains its production, research, and marketing organizations. Our business was founded by the Strasenburgh family in Rochester, and was privately owned until 1960, at which time it was acquired by Wallace & Tiernan, Inc., headquartered in East Orange, N.J., with plants located in several areas of the United States and abroad. On March 31, 1969, we became part of the Pennwalt Corp., by virtue of its acquisition of Wallace & Tiernan on that date.

Biphetamine is scheduled by the Drug Enforcement Administration—DEA—as a controlled substance under schedule II. As such, the manufacture of this product is specifically limited in terms of quantity and is strictly regulated at every stage in its chain of distribution by the DEA, as I will discuss more fully later. Ionamin is scheduled by the DEA as a schedule IV substance. It, too, is strictly controlled and regulated at each level of distribution. Both products have been approved by the Food and Drug Administration—FDA—as safe and effective, as recently as 1974.

Senator NELSON. You heard the testimony of Mr. Rody, in which he said your company had offered to stop exporting Ionamine to Mexico; is that correct?

Mr. MCGRAW. I had a conversation with Mr. Durrin along those lines; yes.

Senator NELSON. Well——

Mr. MCGRAW. I will be more specific, Senator. I called Mr. Durrin when——

Senator NELSON. Mr. Durrin?

Mr. MCGRAW. Mr. Ken Durrin.

I first wrote a letter to the Administrator, Mr. Bensinger, calling his attention to information I had become aware of concerning an alleged confiscation of 250,000 capsules of Ionamine on the Southwest border of the United States.

This was not factual evidence. I called his attention to the report, and said I would be very happy to discuss it with him.

The letter was written on Friday, I have forgotten the exact date. It was in October.

In the letter I said I would call him Monday. Unfortunately, Mr. Bensinger was out of the office on Monday.

I was in a meeting, that I was unable to get free on Tuesday, I talked to Mr. Durrin on Wednesday, and asked him if he had any information about this unsubstantiated evidence which I was aware of.

Mr. Durrin said he knew there had been one confiscation on the

border. He did not know what the size was, as he was not working in that area, but he had heard that a number of capsules contained in one box had been sugared.

I offered my cooperation to come down to discuss the situation with him. I went over the controls that we had put in effect voluntarily on the drug in Mexico City. There are no such controls in Mexico as we have in the United States. In Mexico City, as you know, there are no such controls.

We had put in our own quota system, and I said I would offer 100-percent cooperation, and if it need be, I will take the product off the market.

That was my conversation.

Senator NELSON. What was the last sentence?

Mr. MCGRAW. If need be, I will take it off the market down there—Mexico.

That is not a quote, Senator. I was not expecting to hear this information this morning, because this is the first time I had any knowledge of it.

Senator NELSON. Mr. Rody said testimony—well, his testimony will speak for itself.

Of course, we do have the recorded record, but as I listened to it, I thought it was unequivocal that Mr. Rody in testifying said that Pennwalt had offered to stop shipping Ionamine to Mexico, and that he said we accept that offer, is that correct or not?

Mr. MCGRAW. That was not the offer made, sir.

I offered to take the product off the market in Mexico if we could not control it there.

I offered to cooperate with the DEA in anyway possible, offered to come to Washington at their convenience.

Senator NELSON. All of the Ionamine that your company sells in Mexico is shipped from the United States, or is so fabricated elsewhere?

Mr. MCGRAW. No, sir, we ship.

It is a resin compound of phentermine.

We ship the resin from Rochester, N.Y., to Mexico City, where it is mixed with other ingredients, and it is encapsulated, bottled, and distributed through legal channels in Mexico.

Senator NELSON. Just so I have it clear in my mind, so far as your company is concerned, is all of the material sold in Mexico the same sort of compound sold here in the United States?

Mr. MCGRAW. That is correct, Senator.

Senator NELSON. What did you exactly mean when you said a few moments ago that you had this conversation, and that you would take it off the market, if necessary, what does that mean.

Mr. MCGRAW. Well, at that time, Senator, we had no factual evidence.

I was working without factual evidence. I was offering to cooperate.

I was asking if it was fact. Mr. Durrin said he had heard, the figures he gave me of the number of capsules, were in line with the figures I had seen, and the article I had read, and thus I offered to come down to Washington at his convenience to check into the matter with him.

I told him of the controls we had in Mexico, if it was stolen, there was a possibility of tracing it, sir.

Senator NELSON. I still do not understand what you meant by saying you would take it off. You would stop shipping it to Mexico if necessary?

Mr. MCGRAW. Senator, I think I made myself very clear.

If we could not control it, if I had factual evidence that the product was being diverted, which we did not have at that time, and if that diversion could not be stopped, and depending upon the size of such diversion, offered to, if it came to that, to Mr. Durrin, if it came to that, I would take it off the market.

Senator NELSON. Do you have in your own mind any judgment about whether a substantial amount has been diverted? You saw the evidence in this one case, involving just in Indiana 20,000 tablets.

Would evidence repeated of that size batch several times constitute——

Mr. MCGRAW. I would have to see, Senator. I think it is unfair for you to ask me to quantify.

Senator NELSON. You intend to talk to the representatives of DEA?

Mr. MCGRAW. I certainly do.

Senator NELSON. On this precise question?

Mr. MCGRAW. I certainly do.

Senator NELSON. All right.

Go ahead.

Mr. MCGRAW. In our pharmaceutical operations at Rochester, we maintain a research and development facility, manned with qualified professionals including four doctors of medicine, 23 doctors of pharmacology and doctors of chemistry, and other related disciplines.

This staff and our administrative staff—quality control, governmental compliance, finance, personnel, and so forth—perform the various functions which these titles suggest.

THE PROBLEM OF OBESITY AND THE USE OF ANORECTICS

Internationally known medical and nutritional experts in the United States are generally agreed that there are approximately 30 to 40 million Americans between the ages of 21 and 65 who are at least 20 percent overweight.

To be 20 percent overweight is to be "obese," a condition that seriously affects the individual's well-being and life expectancy. Obesity also compounds other diseases. Medically, obesity is correlated with considerable increase in cardiovascular diseases, diabetes, liver and kidney diseases, and even accidents.

Indeed, to be obese is to be ill. The problem was defined by one reputable physician, Dr. Halberstam, as follows: [1]

> Fatness may be the single most important illness in America. It is certainly the most important form of malnutrition. Fat people have higher incidence of stroke, of high blood pressure, and, to a less marked degree, heart attacks. On all life insurance tables fat people live shorter lives than normals. [Emphasis supplied.]

In addition to physical disability, the obese frequently carry an additional burden, which Dr. Halberstam has described in these terms:

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[1] Dr. Michael Halberstam, "The Pills in Your Life," Ace Books, 1972, pp. 141–142.

Worse, the fat middle-class person lives not only with a physical burden, but with a psychologic stigma. The sociologist, David Riesman, has said that America is a "physionomic democracy." That is, we increasingly will accept into our social circles and business lives people of any race, creed, or color—so long as they are attractive. The other side of this is that we shun the ugly, the crippled, the fat. The next time you are at a gathering of strangers or getting on a bus or sitting down at a lunch counter, check your own reluctance to sit down alongside a fat person.

In discussing the proper role of anorectics in the treatment of obesity, we are confident that while this committee will consider the testimony of the experts, the layman, and others who have their respective and differing views, the committee will continue to be most interested in that which can be established factually.

We are equally confident this committee will examine the question of antiobesity medication in the context in which it arises—a population containing 30 to 40 million obese citizens who are entitled to medical and other therapeutic assistance in obtaining relief from their physical and emotional disabilities.

These disabilities cannot be dismissed with the notion that "willpower" or "self-discipline" or "counseling" are all that are needed. We can tell the sinners, the alcoholics, the chain smokers or the obese how to behave and turn our backs on them if they do not. But quite clearly preachment is not the cure for any serious disability.

We think it noteworthy that despite great medical progress in this country, the treatment of obesity is one of the few areas of preventive medicine being practiced today. Most other medical practice today remains remedia or post-traumatic. Medical attention *is* available to help the obese patient in his efforts to attain a more satisfactory level of physical condition by supervised weight loss.

Indeed, there seems to be general agreement in the technical as well as popular literature that the obese *should* seek a doctor's advice before undertaking any serious program of individual dieting.

If we have approximately 30 to 40 million obese individuals in the United States, and if we and they recognize that wishing "won't make it so," what remedies are appropriate?

Our pharmaceutical division believes that the obese individual has a medical problem which is best treated by a physician and aided by counseling and supportive techniques which will motivate the patient to attain his goals.

Pennwalt has acted on this belief in educational programs directed to both physician and patient. We believe that prescription of anorectic medication—ours or that supplied by other reputable pharmaceutical companies—is entirely the prerogative of the physician.

Senator NELSON. Do you really stick to that unqualifiably?

We had testimony this week from Suffolk County in Huntington Township of two doctors averaging 800 to 1,200 patients a week. Observation of the lines of people indicated that most of them did not have any obesity problem at all. Is it your view that it is solely the responsibility of the physicians in that kind of case, to issue prescriptions of the anorectic medication, that it is entirely the prerogative of the physicians?

Mr. MCGRAW. The physician is the only one, Senator, who can prescribe, yes.

Senator NELSON. You are not endorsing the widespread illegal use?

Mr. MCGRAW. I am not.

Senator NELSON. Go ahead.

Mr. MCGRAW. For more than 15 years, we have provided the patient, through his doctor, with literature intended to educate the patient—not sell him our products. Indeed, our products are not mentioned in this literature.

More than 10 million copies of our long-established and free booklet, "Are You Really Serious About Losing Weight?", have been distributed. It contains over 70 pages of highly useful information for the patient and no reference to Pennwalt products.

The educational value of our booklet was described by the internationally renowned Dr. Jean Mayer of the Harvard University School of Public Health, who said:

> There have been so many popular books and articles on obesity which make the most unreasonable promises to patients that it is pleasant to see a booklet taking the reasonable and truthful position that weight reduction is dependent on maintaining a negative energy balance—preferably based both on decreasing food intake and increasing energy expenditure.
>
> It is even more gratifying to see that the booklet is sponsored by an enlightened pharmaceutical company which realizes that while anorexigenic drugs can, in the hands of competent and well-informed physicians, make an important contribution to treatment during the initial period of weight reduction, they cannot substitute for reeducation of the patient as regards eating and living habits. They can gain time and make it easier for the obese individual to become used to smaller food portions. But a great deal of information and motivation also need to be given to the patient.
>
> Because the doctor's time is not unlimited, he needs teaching material, which this booklet quite adequately conveys. Reading the booklet should give the patient the chance for a more informed dialogue with his doctor.

In this same booklet, the patient is advised to "Count your facts before you count your calories" and then asked to take a True-False quiz on basic propositions alleged to relate to dieting, with 28 questions and answers.

I call your attention specifically to question No. 26 and our answer to it—at pages 3 and 5 of the booklet:

> Proposition: 26. A diet "pill" is an easier way of losing weight than dieting.
>
> Answer: 26. False. No pill can take the place of dieting. A diet pill is only a "training" aid to help cut down appetite for food while learning to adjust to eating less. It takes time to correct faulty eating habits—the real cause of overweight. Do not use any dieting drug unless it is prescribed by your physician for you.

In summary, our educational program is specifically addressed to a four-part theme: (1) Dietary counseling by the physician; (2) individualized dietary control addressed to the specific patient: (3) prescribed exercise; and (4) if necessary, antiobesity prescription.

THE REGULATORY SYSTEM

As this committee is fully aware, amphetamines and nonamphetamine anorectics are scheduled drugs which are regulated and controlled by the Food and Drug Administration, the Drug Enforcement Administration, and State authorities.

In 1970, the Congress passed the Drug Abuse Prevention and Control Act—"Controlled Substances Act"—at which time the Food and Drug Administration Bureau of Drug Abuse Control and the Depart-