

ment of Narcotics within the U.S. Treasury Department were assigned to the Department of Justice. This Justice Department enforcement agency is now known as the Drug Enforcement Administration.

The 1970 Controlled Substances Act established categories of drugs in five schedules of gradation, and the FDA and DEA cooperate with respect to specific scheduling thereunder. The FDA's role under the Federal statutory and regulatory scheme is to make a determination of the benefit-risk status and the effectiveness of particular drugs. The FDA has determined that Pennwalt's Biphethamine is safe and effective as an adjunct in the short-term management of obesity. As you know, the DEA has assigned it to schedule II. Similarly, the FDA has determined that Pennwalt's Ionamin is safe and effective. The DEA has assigned it to schedule IV.

The 1970 law also imposes stringent accounting, reporting and production requirements, extensive labeling requirements, registration of manufacturers, distributors and dispensing entities, elaborate requirements for safekeeping of controlled substances, and establishes other procedures for the control and supervision of controlled substances.

With respect to the manufacture of our schedule II product, Biphethamine, we must receive a quota allocation from the DEA, annually. That quota establishes the amount of amphetamine base (our raw material) which will be available to us for the relevant calendar year. In this process, Pennwalt:

1. Must have submitted before the close of each year a formal quota application for the forthcoming year, setting forth our raw material utilization for the preceding 3 years.

2. Upon receipt from the DEA, early in the new year, of a quota allocation—which generally does not afford a full calendar year of supply—we operate thereunder.

3. Several months later, as our inventory diminishes, we must make a further formal request for an additional quota allocation.

4. That request must contain:

- (1) a statement of current total plant inventory;
- (2) projected utilization to yearend at our current usage rate;
- (3) a resultant computation of the additional allocation we require; and

- (4) such other information as is appropriate to aid the DEA in its evaluation, including, for example, the following: (a) Comparisons of our distribution, stated in terms of kilos; (b) International Marketing Service—TMS—audits of drugstore purchases and prescription utilization; and (c) Wholesale distribution inventory level analysis.

As a result of the quota process I have described, we are supplied with a raw material base generally sufficient to meet our actual annual demand. However, we do not receive a quota allocation adequate to guarantee us that in fact we will be able to complete production for that calendar year.

As is evident, this rigorous quota control program is an essential part of the regulatory design to insure that the product originates and remains in legitimate channels of manufacture and distribution.

The proper scheduling of Ionamin—phentermine—has been under review by the DEA since early 1973. At that time, Pennwalt advised

the DEA that it would not oppose schedule III classification for Ionamin if related, competitive products were similarly scheduled. Pennwalt took this position in a spirit of cooperation, although Pennwalt remains unaware of any evidence that would support the schedule III classification proposed by the DEA. The matter remains pending, with Ionamin in schedule IV awaiting further action by the DEA, following its receipt of Pennwalt's lengthy documentation of the scientific and other facts we deemed relevant to the question.

In this connection, it should be noted that Pennwalt advised the DEA on November 17, 1975, that:

Phentermine, that is Pennwalt's Ionamin, has been marketed in the United States since approximately 1959. During the 16 (now 17) years since then, approximately 500 million dosage units of Ionamin have been prescribed by physicians for use by a diverse patient population, ranging from young adults to the aging, a population necessarily including a broad spectrum of emotional, mental and physical characteristics.

In all of those 16 years, Pennwalt has learned of no deaths or any serious physical or mental injury or damage attributable to the drug. In addition, Pennwalt is not aware of any significant instances of phentermine abuse, and its product liability experience with the drug Ionamin reflects but one payment, in the amount of \$3,500, to settle one suit brought by a patient who alleged she had used Ionamin (on prescription) as well as several other drugs manufactured by other defendants in her case.

THE DEA MONITORS AND AUDITS THE DISTRIBUTION OF ANTI-OBESITY DRUGS

The Drug Enforcement Administration plays a very active role in monitoring and auditing our scheduled substances. It requires that all manufacturers of all schedule II products submit monthly DEA-222-C forms. These reports require Pennwalt; for example, to list each purchase or sales transaction involving Biphedamine, as a schedule II substance, by date, amount, and identity and location of purchase.

The DEA also requires the quarterly filing of ARCOS computer tapes recording each controlled substance transaction under schedule II and all transactions involving narcotic drugs in any schedule exclusive of those on schedule V. These computer tapes show the movement of the drug both within the plant and in distribution, again showing date, amount, and recipient.

For Ionamin, a schedule IV product, the DEA requires that we record the name and location of each purchaser, its registration number, and the quantity, identity, and strength of the product by package unit. These same standards apply to our purchase of Ionamin's raw material, phentermine.

In addition, the DEA requires a separate listing of all controlled substance transactions, segregated from all other company records, to facilitate ready inspection by DEA representatives.

Separate reports of any suspected loss in transit, whether or not confirmed, and any other significant loss of any scheduled drug, are reported to the DEA immediately. If any suspected loss is not accounted for, followup reports are made.

The DEA also conducts periodic, formal audit inspections of Pennwalt's entire system of accountability for all schedules of controlled substances. Apart from these audits, DEA representatives are on our premises on a regular basis in the routine performance of their duties,

including monitoring, distribution, and reviewing our security programs for scheduled products.

In addition to Federal regulation, 42 States, including New York, California, Pennsylvania, Illinois, and Florida, have adopted the Uniform Controlled Substances Act, which contains controls similar to the Federal act.

EFFECT OF CONTROLS ON PRESCRIPTION EXPERIENCE: 1971 COMPARED TO 1975

Since the passage of the Controlled Substances Act of 1970, there has been a marked change in the prescription experience for anorectic products.

These changes may be summarized as follows:¹

	1971	1975
1. Total patient visits for obesity	23,668,000	20,601,000
2. Prescription usage:		
Medical prescriptions of anorectics (initial)	18,373,000	12,413,000
Total 2d or subsequent prescriptions	7,707,000	7,213,000
Total anorectic prescriptions	26,080,000	19,626,000
3. Total anorectic prescriptions:		
(1) Amphetamines	16,232,000	5,504,000
(initial prescriptions)	(13,201,000)	(2,745,000)
(2) Nonamphetamines	9,848,000	14,122,000
(initial prescriptions)	(5,172,000)	(9,668,000)
Total anorectic prescriptions	26,080,000	19,626,000
4. Reduction in total anorectic prescriptions from 1971 to 1975		-6,454,000

These figures demonstrate that the Controlled Substances Act has accomplished a dramatic reduction in the prescription of amphetamine anorectic products, but that a continuing medical requirement for those products remains.

The figures also demonstrate that while there has been an overall reduction in the total prescriptions of anorectic products, there also remains a very sizable patient population, consisting of millions of Americans, among the 30 to 40 million obese, who are receiving medically supervised treatment for their condition.

PENNWALT'S MANUFACTURE, DISTRIBUTION, AND SALES

All of the Federal regulations I described previously are complied with by Pennwalt in its manufacture, distribution, and sales. In addition, at the plant, production and shipping are monitored closely by management to assure the absence of loss and the detection of any attempted theft. As noted earlier, detailed records and monthly and quarterly reports to the DEA show each transaction both intraplant and to customers, its size and the identity of the customer.

At the present time, Pennwalt sells its prescription products, including Biphethamine and Ionamin, only to nonprofit hospitals and to approximately 450 wholesale distributors.

These wholesalers handle the complete line of Pennwalt products and all of them are also registered and regulated in their handling of scheduled drugs by the Drug Enforcement Administration. In addi-

¹ These data are based upon the National Disease and Therapeutic Drug Index (Non-Endocrine Obesity) and its National Prescription Audit.

tion to registration, the wholesalers are subject to the same stringent reporting requirements by the DEA as is required of manufacturers.

Using 1973 as a base, Pennwalt's direct sales of both Biphedamine and Ionamin to physicians have decreased.

By 1975, approximately 7 percent of Pennwalt's sales of Biphedamine, and approximately 4 percent of Pennwalt's sales of Ionamin, were made directly to physicians. Effective in the fall of this year, Pennwalt ceased all such sales.

Pennwalt has not promoted or advertised Biphedamine since 1971. Since that date, we have not detailed or sampled Biphedamine to physicians. Pennwalt advertises Ionamin, but only in journals addressed to the medical profession.

It also samples Ionamin in accordance with prevailing competitive practices and existing law.

Senator NELSON. You said your firm advertises only in journals addressed to the medical profession.

Is there any prescription drug advertised in this country to the general public?

Mr. McGRAW. Not that I know of, sir.

Senator NELSON. Please proceed.

Mr. McGRAW. In August 1976, the DEA proposed that sampling of all controlled products be prohibited. In that same month, Pennwalt wrote to the DEA to express our agreement with their proposal, and will comply immediately should this proposal become applicable to all competitors.

Senator NELSON. This occurred in August of this year, and concerns the supplying of free samples to physicians?

Mr. McGRAW. That is correct.

Senator NELSON. Did you agree to comply as soon as all other competitors agreed?

Mr. McGRAW. We agreed it should be prohibited, and we would cooperate with such a decision.

Senator NELSON. Has that decision been made yet?

Mr. ROSTHAL. No, sir.

Senator NELSON. Go ahead.

Mr. McGRAW. Pennwalt's 1975 promotional expenditures for Ionamin were approximately 6 percent of total Ionamin sales. Otherwise stated, our total promotional expenditures were approximately 4 percent of our total antiobesity drug sales. As noted, we have no promotional expenditures for Biphedamine.

These figures may be compared to the promotional expenditures for the most popular over-the-counter antiobesity product, which has an estimated 60 percent of the market. The total promotional expenditures for that product for the last available year have been reported to be more than 20 percent of its sales, on a sales volume of approximately \$15 million.

PHARMACY SALES OF PRESCRIBED ANORECTIC PRODUCTS

Before turning to the subject of alleged abuse of anorectics, we believe it useful to review briefly the total market for prescribed anorectics at the pharmacy level.¹

¹ The data cited are based upon IMS reports of pharmacy purchases for the years 1971 and 1975.

The sales figures just reviewed are in current dollars. If expressed in constant dollars, you would note a significant decrease in dollar volume for the sale of all prescription anorectic products.

PURCHASES BY RETAIL PHARMACIES: 1971 COMPARED TO 1975

	1971		1975	
	Amount	Percent	Amount	Percent
Total pharmacy purchases.....	\$78,636,000		\$83,247,000	
Amphetamine anorectics.....	46,670,000	59.0	23,237,000	27.0
(Pennwalt sales).....	(8,394,000)	19.0	(6,761,000)	29.0
Nonamphetamine anorectics.....	31,966,000	41.0	60,010,000	73.0
(Pennwalt sales).....	(3,244,000)	10.0	(11,920,000)	20.0
Total Pennwalt anorectic sales.....	11,638,000	14.8	18,681,000	22.4
Total anorectic sales of:				
(1) Other 2 major manufacturers.....	34,213,000		28,381,000	
(2) Pennwalt.....	11,638,000		18,681,000	
(3) All other.....	32,785,000		36,185,000	
Total pharmacy purchases.....	78,636,000		83,247,000	

ALLEGED ABUSE OF PENNWALT'S ANTI-OBESITY PRODUCTS

The IMS analysis of the relevant data on individual prescription size, for the most recent complete calendar year, 1975, shows that:

Average number of capsules per physician's prescription:	<i>Capsules</i>
Ionamin	31.1
Biphetamine	33.5

We believe it appropriate to conclude that the average obese patient therefore receives a prescription for enough Biphetamine or Ionamin capsules to provide one-per-day treatment up to a maximum of but 4 to 5 weeks, for short-term support. We therefore continue to believe that the IMS analysis demonstrates that pharmacies and the medical profession are providing a necessary service and that the patients are not afforded, by that process, the opportunity for any meaningful abuse. Thus, regardless of anecdotes relating to the alleged high volume of capsules per prescription, in actuality the prescription data reported by IMS is consistent with judicious prescription by the medical profession.

We should also note that Pennwalt regularly compares its actual factory shipments of both amphetamine—Biphetamine—and phentermine—Ionamin—containing products with IMS audits of drugstore purchases. In addition, our actual factory shipments and the drugstore purchases can be correlated with the quantity of either Biphetamine or Ionamin prescribed and dispensed, as shown by the IMS National Prescription Audit for the same period. Pennwalt regularly undertakes such analyses and remains satisfied that its products are prescribed within legitimate medical channels.

In short, our products are moving through the distribution chain in a proper fashion.

Pennwalt is not aware of any significant illegal use of its anti-obesity products. During the period January 1, 1972, to the present time, we have received from the DEA and other enforcement agencies but nine reports of alleged diversion from all sources—five for Biphetamine and four for Ionamin. When claims of either attempted or actual illegal use or diversion have been brought to our attention, Pennwalt has

cooperated fully with the enforcement authorities in the investigation, apprehension, and prosecution of those responsible.

Our experience also confirms an observation of Mr. Peter Bensinger, Administrator of the DEA, at the annual meeting of the top executives belonging to the Pharmaceutical Manufacturers Association, held in May of 1976. He noted that there is no reason to believe that industry is responsible for illegal trafficking in amphetamine. Pennwalt knows of no evidence to the contrary.

As this committee may know, allegations were made in January of 1972 that Pennwalt's antiobesity drug product Bifetamina—Biphetamine—in Mexico, was being illegally diverted by purchasers of that drug. Pennwalt was never given evidence of where and how this diversion occurred, nor has Pennwalt been advised of any prosecution with respect to those alleged diversions. Nevertheless, in January of 1972, Pennwalt ceased production and sale of amphetamine products in Mexico and at the same time decided to cease any further export of amphetamine products. These decisions were made to limit our Biphetamine sales to the United States and Canada, in reliance on strict regulatory practices which exist in those two countries. As this committee knows, in 1973 Canada withdrew its approval of amphetamine products.

Senator NELSON. For obesity reasons?

Mr. McGRAW. That is correct, sir.

Mr. BRODERICK. If I may interject, we indicate that we continue to export to Canada, that is wrong.

We should have referred to the fact that we continue to sell to Canada. We did not export to Canada.

Senator NELSON. All right. The record will stand corrected.

Mr. McGRAW. [Reading:]

COMBINATION AMPHETAMINE ANORECTICS

In February of 1973, the FDA published in the Federal Register a finding that all fixed combination amphetamine products were ineffective and unsafe. As a fixed combination, this finding included Biphetamine-T. Although the initial National Academy of Science—National Research Council—"NAS/NRC"—finding with respect to Biphetamine-T was that it was "possible effective", Pennwalt elected not to exercise its right to contest the FDA's 1973 redetermination. Pennwalt therefore discontinued further manufacture of the product and recalled all stocks from the distribution chain, at a cost of approximately \$1 million.

CONCLUSION

On the basis of the evidence which we have summarized today, Pennwalt believes that there is an established medical and social need for its antiobesity products.

We think it important that this committee differentiate between hearsay testimony, utterly unsubstantiated by factual support, and the testimony and documentary evidence available from sources which are recognized to be technically qualified to deal with a complex scientific, social, and medical question.

There remains a population, estimated to be between 30 and 40 million obese Americans, many of whom wish to avail themselves of

medical treatment in order to alleviate or eliminate this unfortunate condition. Our antiobesity products, and those of other responsible manufacturers, remain recognized as the only effective prescription medicinal aid available in a course of antiobesity treatment.

Moreover, as we have discussed today, the manufacture and distribution of those products is closely regulated by competent Federal agencies, which have the requisite expertise to evaluate the quality of our products and the legitimacy of their use.

The regulatory processes established by the Congress, over the years, have created a framework within which the serious questions which concern this committee have long been the subject of professional concern, both within the regulatory agencies and within the pharmaceutical industry. That process affords all of its participants due process, from investigatory, scientific, and legal perspectives.

Pennwalt appreciates the opportunity to appear before this committee in order to state the bases upon which its products are manufactured and distributed. Pennwalt remains confident that it can continue its 126-year-old reputation for integrity while engaged in this part of its enterprise.

I am ready to answer any questions you may have.

Senator NELSON. Thank you very much.

Do you have any well-controlled studies of your own, or are you aware of any well-controlled studies that would produce substantial evidence to refute the conclusion of the report to the Director of the Bureau of Drugs by the panel of consultants on anorectics headed by Dr. Prout in 1972, when that panel in its conclusions stated 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 alone must be considered clinically trivial?

Do you have any studies, or any evidence that would refute that conclusion, that this impact is clinically trivial?

Mr. McGRAW. I can show in the studies we submitted to the FDA, they were done over a 16-week period of time.

Senator NELSON. Were these studies submitted to the consultants on anorectic drugs?

Mr. McGRAW. No, sir.

Senator NELSON. When were they submitted?

Mr. McGRAW. They were submitted in 1971 to the FDA.

Senator NELSON. The report I am referring to is dated 1972.

Mr. McGRAW. As a result of the report of NAS/NRC, these products were ruled possibly effective, and we had to submit efficacy studies to the FDA.

Senator NELSON. The NAS/NRC panel was concluded in 1972. I was wondering if your studies were well-controlled and if they produced substantial evidence to refute the conclusions of the panel that the effects of these drugs were "clinically trivial." We would like to have those.

Mr. McGRAW. As I was saying, Senator, the studies we submitted for our efficacy studies were done over a 16-week period of time, and on a week-to-week basis, there was a fractional difference in weight loss, let us say a half a pound.

At the end of the 16 weeks, that was sometimes double as compared to a placebo, and I think that is significant as a statistical evaluation.

Senator NELSON. Sixteen weeks, half a pound a week, it would be 8 pounds, and twice that of placebo, that would be 4 pounds differential?

Mr. McGRAW. You could go 4 to 10 to 16, any multiples.

I was going to further say these studies were submitted to the FDA for their evaluation, all of the raw data, and so forth.

Senator NELSON. Thank you very much for taking the time to come to testify today.

Did Mr. Rosthal have anything to add?

Mr. BRODERICK. If I may, it was not until today, when I read Mr. Rody's statement, and I am particularly referring to the bottom of page 17 and the top of page 18, that we were aware that the DEA had evidence as the DEA put it, of the seizure of 104,000 capsules.

I know that Mr. Rody has offered to submit to this subcommittee the most recent survey relating to Ionamine on the Southwest border, and I would request, sir, with your permission, that such surveys be submitted to Pennwalt, so that we may review it, and cooperate with the DEA, sir.

Senator NELSON. I am assuming, based upon the testimony of Mr. McGraw, and Mr. Rody, that you are going to be discussing this question anyway, and whatever they submit to this committee would be a matter of public record, so it will be available to everyone.

Mr. BRODERICK. I would hope they would submit it.

Senator NELSON. Mr. Rosthal?

Mr. ROSTHAL. I will be very brief. The statement says Pennwalt was never given evidence of where and how this evidence came about, referring to Blackjack.

That insults me. I have pride of authorship to show cause, and I cite the cases.

If you have not read it since 1971, I will read it to you now.

Mr. BRODERICK. I would like to say in response, I do not want to get involved in a dispute with Mr. Rosthal, as I have great respect for him, but, as you know, in 1972, I believe, we appeared, Pennwalt appeared before Rogers' committee, when the Mexican situation was discussed.

At that time we were requested to submit supplemental information to the Rogers' committee, which we did.

One of the items of information which the Rogers' committee requested was the sales from the Mexican facility to pharmacies along the Mexican border.

We advised Congressman Rogers we had not be told by the DEA the names and locations of those pharmacies. The Congressman said he would ask the DEA to submit them to us. They never did.

Senator NELSON. Do you have anything further?

Mr. ROSTHAL. I do not remember that. I was at the hearing, and there is difficulty in supplying information to some people.

I do not say it directly about these two witnesses here today, but where we do have a case which might in the opinion of the Criminal Division, or a criminal lawyer, amount to a conspiracy, you usually do not tell it to the people who might possibly be conspiring.

Mr. BRODERICK. Please do not let my silence be an indication of any agreement.

Senator NELSON. All right. Thank you very much.

The subcommittee stands adjourned.

[Whereupon, the subcommittee was adjourned at 2:15 p.m.]

APPENDIX

PREPARED STATEMENTS

STATEMENT
BY

Carl D. Chambers, Ph.D.
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and
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Presented Before

Monopoly Subcommittee
Senate Select Committee on Small Business

Thursday
November 18, 1976

Mr. Chairman, 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. 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, non-prescription 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% of everyone who uses amphetamines as "pep pills" are males even though males represent only 46% of our population above the age of 13. Correspondingly, persons age 14 through 24 represent only about 26% of our total population but contribute some 55% 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. 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 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. 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 non-prescription 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 non-prescription 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 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 6,000,000 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 12,000,000 people above the age of 13 have used amphetamine "diet pills" with some 3,000,000 having done so recently and some 1,500,000 being current regular users of these drugs.
- Some 16,000,000 people above the age of 13 have used non-prescription stimulants of whom as many as 3,000,000 having done so recently. Probably as many as 500,000 people use one of the non-prescription 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 abusers 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 non-medical 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 non-narcotic drugs who were undergoing treatment for this abuse in nine cities. Records were reviewed and drug abusers were interviewed in the following cities:

Miami, Florida

Greensboro, North Carolina

Washington, D. C.

Atlantic City, New Jersey

New York City, New York

Des Moines, Iowa

Kansas City, Kansas

Phoenix, Arizona

San Francisco, California

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.

- 62% 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%. Of interest, 63% of all abusers of amphetamines had been introduced to the drugs by their friends or peers and only 23% had been introduced to amphetamines by a drug dealer.
- 15% 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 their 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 1966-1971 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 probably 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.

STATEMENT

OF

J. RICHARD CROUT, M.D.

DIRECTOR, BUREAU OF DRUGS
FOOD AND DRUG ADMINISTRATION

BEFORE THE

SUBCOMMITTEE ON MONOPOLY

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

NOVEMBER 19, 1976

Mr. Chairman and Members of the Subcommittee:

I appreciate the opportunity to appear here today to discuss the activities of the Food and Drug Administration (FDA) 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 DEA 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.

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 number one 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

14644 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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, i.e., loss of appetite, and thereby to assist the patient in restructuring his or her dietary habits.

There are currently twelve 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, clortermine 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

14646 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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 two 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.

14648 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

Concurrent with these actions, FDA has carried out an active program of surveillance over the advertising of these drugs. Since May 1966, thirty-eight legal, regulatory, and advisory actions related to their promotion have occurred. Of these actions, twenty-seven have been initiated in the last four 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

14650 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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 1,100 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 twelve-week period than patients on a placebo. The twelve-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.

14652 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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 1972-1973:

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, i.e., 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 United States 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, Dexamy1, 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 pherimetrazine 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

14654 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

absence of clear evidence of significant abuse. These drugs were chlorphentamine, benzphetamine, phendimetrazine, clortermine, 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, e.g., 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 (e.g., high school students), monitoring hepatitis rates, and compiling drug use data on patients in treatment programs. Special demonstration projects or in-depth 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, five years have passed since the amphetamines and phenmetrazine were placed in Schedule II, and three 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

14656 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

1971 through 1973 there was a particularly dramatic decline in the prescribing of amphetamines. 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 about one-fifth that of the peak year in 1965. The non-amphetamine 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.

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 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. This ratio can be considered as a crude index of the degree of abuse (i.e., total DAWN mentions) per given amount of drug dispensed (i.e., through legitimate sales at the pharmacy level). 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.

The 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. The main conclusion suggested by this graph is that abuse problems are greater with the Schedule II drugs, that with the other anorectics, and that the rate of such problems appears relatively unchanged over the past three years.

14658 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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 five 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 three 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 three 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 1971-1973 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 dysfunction 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.

14660 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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 re-scheduling 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 under way 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

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY 14661

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

14662 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

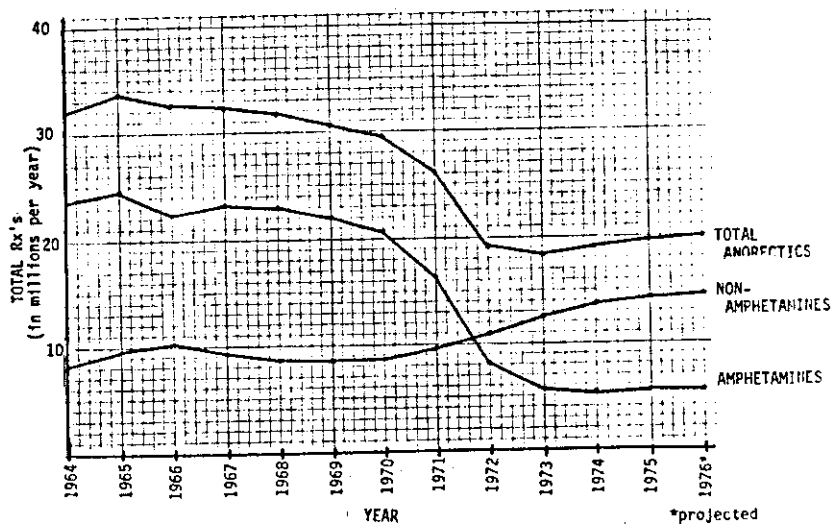
sustained vigilance from all of us. Drugs of this type are intrinsically attractive to a segment of our population and, at least for the foreseeable future, will remain so.

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.

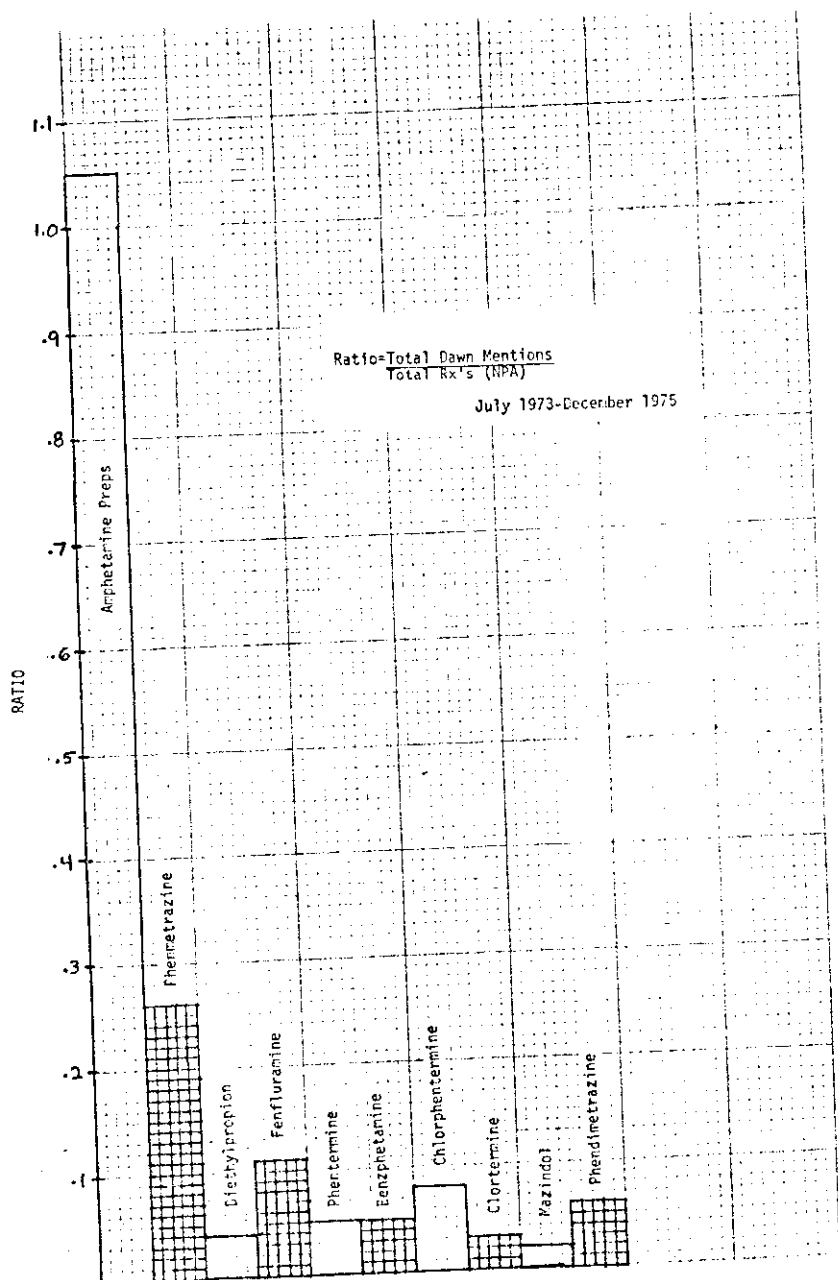
Thank you, Mr. Chairman; this concludes my statement. My staff and I would be most willing to answer any questions you may have.

APPENDIX I

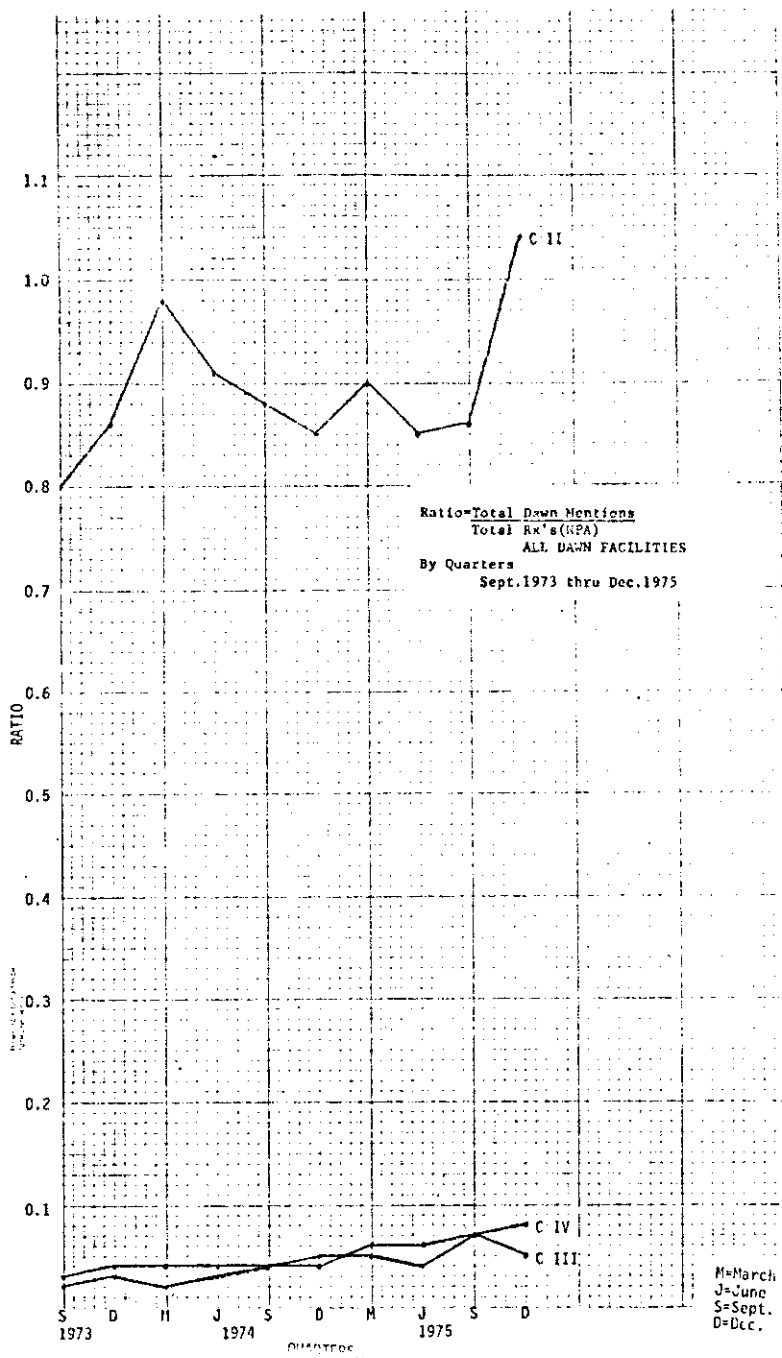
Figure 1
TOTAL NUMBER OF Rx's FOR ANORECTIC
AGENTS, 1964-1976



APPENDIX II



APPENDIX III



14666 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

STATEMENT FOR SENATE SMALL BUSINESS SUBCOMMITTEE ON MONOPOLY

Everett H. Ellinwood, Jr., M. D.

STIMULANT AND ANORECTIC DRUGS

Introduction

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 (See Table I for a listing of anorectic and stimulant drugs). 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 for 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

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY 14667

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	<u>Amphetamines</u>	
	d amphetamine	.Dexedrine, Obotan
	d,l amphetamine isomers.	.Benzedrine, Biphetamine, Delcobese, Obetrol
	methamphetamine	.Desoxyn, Fetamin
	d amphetamine + amobarbital	.Dexamyl
	d,l amphetamine + prochlorperazine .	.Eskatrol
	<u>Other Stimulant Drugs</u>	
II	methylphenidate	.Ritalin
II	phenmetrazine	.Preludin
III	benzphetamine	.Didrex
III	chlorphentermine	.Pre-Sate
III	clortermine	.Voramil
III	mazindol	.Sanorex
III	phendimetrazine	.Bontril, Melfiat, Obe-Nil, Stratobex, Bacarate
IV	diethylpropion	.Tenuate, Tepanil [®]
IV	fenfluramine	.Pondimin
IV	phentermine	.Ionamin, Fastin

- 2 -

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 six to twenty times a day, and at times and conditions that would be compromising and dangerous.

There is 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 two- to three-week start-up period to allow the individual to gradually cut down his food intake patterns then discontinue the medication, needs also to be questioned. Several authors (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

- 3 -

Usually, the weight loss amounted to one 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 three- and six-week studies. The one-year studies were not well-controlled and did not have good follow-up. A word of caution is needed in that these studies are based on the 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 McLaren-hume, 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.

Therapeutic Effects Weighed Against Abuse Potential

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

- 4 -

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 non-abused anorectics emerging; that is, the ring-substituted amphetamine analogues. 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 (for example, 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

- 5 -

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. 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 1/20 as potent as amphetamine in elevating blood pressure in rats, and has no effect on body temperature (Bizzi, et al., 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, et al., 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, phenmetrazine, and diethylpropion (Baxter, et al.,

- 6 -

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, et al., 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.

Recommendations

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 trade-off 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^R and Fastin^R) and diethylpropion (Tenuate^R and Tepanil^R) at least into Schedule III. 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

- 7 -

Schedule II would require that the physician explicitly write these prescriptions without refills. This would place considerably more emphasis on re-evaluation 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. 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.

Impact of Stimulant Abuse on the Individual and 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 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

- 8 -

for at least 3 to 6 months following high dose amphetamine maintenance (Seiden, et al., 1976). Thus, there are clinical descriptions as well as basic research indicating that there may be long-term changes following chronic amphetamine intoxication.

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 consensus 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, et al., 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 aggression 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

- 9 -

volatile state and is the one not infrequently implicated in violent or assualtive 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, et al., 1971; Greene, et al., 1973; Tinklenberg, et al., 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 lability 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) impulsiveness or reactiveness, and 2) a lability of mood in which the user abruptly vacillates from a warm congeniality to fiercly 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) seven of the thirteen subjects were acutely psychotic

- 10 -

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 thirteen 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 persecutors 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 two-month

- 11 -

period 31 of 60 convicted murderers had some connection with the misuse of amphetamines; Rylander (1969) reports that there had been three murders, one 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% of the subjects included in his series from England.

In a recent study by the Kalants (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); 7 to suicide; and 3 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: 1) chronic amphetamine abuse, 2) an acute change in the individual's state of emotional arousal, 3) 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

- 12 -

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 become 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

- 13 -

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. It tends to wax and wane depending on the drug cycle and dosage level. Hallucinations tend to dissipate two to three days after cessation of amphetamine use, yet delusions continue up to two weeks and have been noted in some patients for as long as a 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 re-trigger the psychosis rather rapidly in individuals who may have been abstinent from amphetamines for over a period of a year (Kramer, 1969; Bell, 1973; Ellinwood, 1973). The Japanese (Utena, 1966) also described 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 doses (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.

CONCLUSIONS AND RECOMMENDATIONS

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 neuropharmacology 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 non-abused 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 non-abused 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 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.

14682 ~~COMPETITIVE~~ PROBLEMS IN THE DRUG INDUSTRY

- 16 -

Finally, it would be helpful to have some means of monitoring and restricting physicians and/or obesity clinics that overprescribe the stimulant anorectics.

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Assault and Homicide Associated with Amphetamine Abuse

BY EVERETT H. ELLINWOOD, JR., M.D.

The author describes the histories of 13 persons who committed homicide while intoxicated with amphetamines. In most of these cases, the events leading to the homicidal act were directly related to amphetamine-induced paranoid thinking, panic, emotional lability, or lowered impulse control. The most important variables associated with these cases included predisposing personality, environmental circumstances, and the use of other drugs.

RECENT STORIES in the news media have linked the use of drugs with a series of bizarre murders. Often it is not clearly stated what type of drug is in question, and in many cases several types of drugs have been used. There is a need to distinguish as clearly as possible the specific types of drugs associated with aggression and violence.

The consensus among those who work closely with problems of drug abuse is that the opiates do not tend to induce unwarranted violence (1). For years, alcohol and sedatives have been associated by most investigators with an increased incidence of violence that is thought to be secondary to a lowering of impulse control (2). Reports from law-enforcement personnel and psychiatrists, as well as from drug abusers themselves, have indicated that amphetamines may also be related to aggressive behavior,

perhaps more specifically than any other group of drugs (3,4).

I recently examined four persons who committed murder after taking large doses of amphetamines. The interviews were held after the court proceedings were over. I have outlined below three of these cases to illustrate the direct effect of amphetamine-induced paranoid ideation or emotional lability leading to the violent act. These three cases were chosen because of the absence of other variables that often play a part in the violence associated with drug abuse.

Case Reports

The first case illustrates the rapid evolution of paranoid thinking after acute high-dose use (repeated drug use over several hours) of amphetamines in an effort to combat the effects of sleep deprivation.

Case 1. This 27-year-old truck driver shot his boss in the back of the head because he thought the boss was trying to release poison gas into the back seat of the car in which he was riding. "I thought they had gassed me. My boss kept reaching down beside him and pulling on something. I rolled the window down to let the gas out. I got nauseated and passed out due to the gas; I then got up on my elbow and shot my boss, who was driving."

Over the previous 20 hours, in order to make a nonstop 1,600-mile trip, Mr. A had ingested 180 mg. of amphetamine; he had not slept for 48 hours. Mr. A usually used less than 40 mg. of amphetamine on long trips. Six to eight hours before the murder, he had become increasingly suspicious that someone had planted drugs on his truck. At this point, Mr. A called a highway patrolman, related his suspicions in a bizarre manner, and was taken to the local jail for safekeeping.

While at the jail, he kept seeing a man hiding and watching him from across the street. "Then there were muffled voices in the next room and they tried to gas me. I could hear the hissing. I got down and locked under the door; I saw feet there! I still remember them. Both the jailer and

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the truck-stop people acted peculiar; I thought they were out to get me."

Soon afterward, his boss arrived to take him home and Mr. A's delusions about the boss gradually evolved. "I tried to tell the boss that those men were waiting on us and would kill us. He said something, and I knew then he was in on it." When Mr. A arrived at the car, there were bottles on the floor and he attributed a sinister significance to them. Because of this clue, he knew that his boss and the other rider were going to harm him. Mr. A checked his handbag for the pistol he carried with him when trucking. After several minutes he panicked when he again smelled the "poison gas."

An interview 18 months after the shooting revealed that Mr. A still believed that many of the above events had taken place. "I'm convinced that those things happened; I did see the man hiding.... It was just too real not to be true. I know it sounds crazy and I wouldn't believe it if someone else told me." There was no other evidence of psychotic thinking or delusions. In fact, I was struck by Mr. A's clarity of thought and judgment in other spheres. Mr. A had previously been judged to be sane by two other psychiatrists. His past history indicated that he was an impulsive individual with strong, dependent family attachments. There was no previous history of psychiatric difficulty or treatment.

More often chronic amphetamine users learn to take paranoid thoughts in their stride. They only partially believe their thoughts and do not act on them; they appear to be playing games with the "persecutor-victim." A factor that may contribute to the loss of this awareness of the paranoid nature of their thinking is the solitary life-style of some drug users, which does not give them an opportunity to cross-validate their ideas with others. Case 2 illustrates the gradual development of paranoid delusions in a man who lived an isolated life and was a chronic amphetamine abuser.

Case 2. Mr. B was a 26-year-old man who had used amphetamines for more than two years and had gradually increased his dose to 500-800 mg. per day. Often he used barbiturates or alcohol to calm him down but he had had neither prior to the homicide. Although he obtained amphetamines from people in the drug subculture and obtained money for drugs illegally, Mr. B was not extensively involved in the drug subculture. Essentially he was a loner who spent most of his time in his apartment.

"During the last three months, I got more and more fearful and suspicious." At first he knew he was "thinking crazy." "Then it became real, and

it still feels so at times. I thought my neighbor was plotting with the feds to get me." He took his apartment apart, including his furniture, trying to find microphones and "listening devices."

During the last three or four days before the homicide, Mr. B did not sleep at all. He described a panic state over his ill-defined tormentors, who were sometimes thought to be federal agents and sometimes a gang that was after him because he had stolen drugs from one of its members. Thinking that his neighbor was one of "them" he waited and watched one evening until his neighbor returned. "I went to his door to listen. He heard me and opened the door, and I shot him."

At the time of his interview, three years after the homicide, Mr. B was a very hostile, sullen man with little evidence of any close personal contacts. He had an early history of remarkable deprivation, material as well as emotional.

In addition to causing paranoid delusions, amphetamines also appear to facilitate acting on aggressive impulses. Case 3 illustrates the intense ambivalence combine with emotional lability to which the individual may be reacting, while appearing to others to be bizarrely unconcerned about the violent act.

Case 3. During an argument with her paramour, this 32-year-old woman pulled a pistol out of her waistband, stuck it in his stomach, and calmly fired. When the victim got out of the car, she followed him and stated, "You wanted to die; I showed you." She then shot the victim twice more. She turned to a bystander and said, "Turn him over and take a picture of his pretty face." Mrs. C felt that she must have been crazy, because she later got in the back seat of the patrol car, propped her feet up, and tickled the sheriff on the ear, asking him if it felt good. After interrogation at police headquarters, Mrs. C got up saying, "Well, I've got to go; I've got a hair appointment."

Originally, amphetamines were prescribed for Mrs. C to help her lose weight. However, she soon discovered that they relieved her loneliness and depression; gradually, over a period of 18 months, she increased the dose to 400-600 mg. per day. Hallucinations were not infrequent. She became suspicious. "Even the people who were helping me were against me." Six months before the shooting, she bought a pistol to protect herself and her children at night. "Someone would come in the window at night; I almost shot at times, it was so real."

"I hated the people I loved the most." Mrs. C became very involved with another man while her husband was away in Viet Nam. As the time for her husband's return drew near, she became panic-stricken over how to end their affair. "Yet

TABLE 1
Some Characteristics of 13 Amphetamine Abusers Who Committed Homicide

CASE NUMBER	AGE	AMPHETAMINE USE	USE OF OTHER DRUGS	PRIMARY CONDITION DURING HOMICIDE	SCHIZOPHRENIC AFTER WITHDRAWAL
1	27	Acute	None	Paranoid	No
2	26	Chronic	None	Paranoid	No
3	32	Chronic/acute	None	Emotionally labile	No
4	72	Chronic	Barbiturates and heroin	Panic (during robbery)	No
5	27	Chronic/acute	Alcohol	Impulsive	No
6	30	Chronic	Alcohol	Paranoid	No
7	25	Acute	Alcohol	Impulsive	No
8	42	Acute	None	Paranoid	No
9	20	Chronic	LSD	Paranoid	Yes
10	21	Chronic	LSD	Panic (during robbery)	Yes
11	18	Chronic/acute	LSD	Impulsive/paranoid	Yes
12	22	Chronic	Frequent	Paranoid	Yes
13	23	Chronic	LSD	Paranoid	Yes

I was fantastically jealous if he even mentioned another woman. First, I would tell him he had to leave me alone; then I would play games by following him to see if he was meeting another woman. I would rifle his wallet and car for letters or clues. Then I would try to irritate him or flirt with others to make him jealous."

Mrs. C was in this type of emotionally labile state at the time of the shooting. "I hadn't slept for four days, was constantly active, and was taking pills like a chicken with its head cut off." (She was taking 600-1200 mg. per day.) Just before the incident, she told her paramour that she was going to leave for good. Teasingly, he said that he would bring his new girl friend by. "I was wild inside like a caged animal, but calmly told him that he never would. He asked how I would stop him and I told him I'd kill him and I did."

At the time of the interview, 13 months after the shooting, Mrs. C was completely lucid, without any psychotic manifestations. Both the interview and psychological testing revealed a woman with low impulse control, especially in regard to anger. There was a preoccupation and warm concern about her family and children. Mrs. C had been described by most interviewers as an outgoing, gregarious woman who was rather engaging in her conversation.

Factors Leading to Violence

Because amphetamine abuse in the four cases I examined appeared to be directly related to the induction of violence, I sent letters to six forensic psychiatrists asking if they had examined people with similar histories. It proved difficult to find such cases. Only nine additional cases were reported by these six psychiatrists (see table 1). The rest of this report is based on histories from these 13 cases but it is complemented by a larger background of information from

similar cases involving assault, rape, kidnapping, attempted homicide, and "near misses."

A review of the histories of these 13 persons who committed homicide after taking amphetamines makes it abundantly evident that many other variables were involved in the evolution of behavior leading to the violent act. Probably, the most important of these are: 1) predisposing personality, 2) environmental conditions, and 3) the use of other drugs. The most pronounced environmental factors leading to violence were found in those who were actively involved in the drug subculture. The concomitant use of other drugs, especially sedatives and alcohol, with their known capacity to lower impulse control, was indeed pertinent.

Perhaps the most interesting variable, but the one that is most difficult to assess, is personality predisposition, especially in cases where the individual is judged to be psychotic after withdrawal of amphetamines. In the three cases described above, neither involvement in the drug subculture nor concomitant use of other drugs was a factor. These three were not judged to be psychotic after the withdrawal of amphetamines, but predisposing personality was a definite factor, especially in the second and third cases. Both Mr. B and Mrs. C were quite impulsive and aggressive, even after the withdrawal of amphetamines.

Two others among the 13 included in this review were noted to have similar impulsive personalities. Five of the 13 were judged, by the original examining psychiatrist, to be schizophrenic after complete withdrawal of amphetamines. In three of these five persons, it was evident from the histories that am-

EVERETT H. ELLINGWOOD, JR.

1173

phetamine abuse had contributed to the precipitation of the more florid schizophrenic process. These three had neurological schizoid or latent schizophrenic adaptations prior to the use of amphetamines, but after initiation of drug use they deteriorated rapidly. Four out of the five who were diagnosed as schizophrenic repeatedly used LSD in conjunction with amphetamines--a factor that further complicates the picture. In general, the five diagnosed to be schizophrenic were younger (average age: 21) than the other eight persons, whose average age was 29.

Some Other Factors

In addition to the predisposing personality, several other recurrent factors were apparent in these histories. These factors included: 1) an acute (repeated drug use over several hours) large dose of amphetamines or a dramatic increase in the amount used; 2) loss of intellectual awareness of the delusional nature of thought, precipitated either by sleep deprivation or by alcohol and sedatives--in some cases, psychotic thinking appeared to be potentiated by LSD and other psychotomimetics; 3) amphetamine-induced suspiciousness, delusions, fear, and panic, as well as emotional lability and impulsiveness; 4) a solitary life-style with little chance for cross-validation of delusional thinking; 5) mutual enhancement of suspiciousness and paranoid ideas with other "speed freaks" (often, however, individuals in a "crash pad" will act as a check on one another, pointing out to an individual that he is becoming too paranoid); 6) carrying a concealed weapon; 7) armed robbery as a means of supporting drug use; and 8) conflict over drug dealings.

The acute nature of the amphetamine abuse was a significant factor in six cases. Three persons with low tolerance took large amounts of amphetamines over a period of a few hours; all three developed paranoid panic states. Two other persons who had been chronically abusing amphetamines dramatically increased the dosage for the two to three days prior to the homicide. (Thus absolute amphetamine intake was not as important as its relationship to the level of tolerance.) It was noted that in these states of acute panic the individual often attached his paranoid thought to almost

anyone. More specifically, the amphetamine abuser might attack a total stranger, who just happened to be passing by on the street, because of a sudden, intense, delusional feeling about the person.

In the cases of assault, robbery, and attempted homicide, as well as those of homicide, the use of alcohol or sedatives appeared to be a significant factor in at least a third of the individuals. The main problem appeared to be a loss of intellectual awareness of the nature of the drug-induced paranoid thinking and a lowering of impulse control. 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. In contrast to usual amphetamine use, most of these high-dose combination users have little, if any, memory of the events associated with the assault. Sleep deprivation was also a major factor leading to decreased intellectual awareness. In several cases, there was a gradual evolution of a paranoid system involving the victim; then, following a period of alcohol intoxication or chronic loss of sleep, the amphetamine abuser acted on his delusions.

Failure to maintain intellectual awareness of the nature of the drug-induced paranoia is a common denominator involved in many of the factors listed. For instance, several of these subjects appeared to have lost intellectual awareness because they lived alone and had little chance to cross-check their delusional thinking. A long-term solitary life-style seems particularly significant in fostering this effect. Quite often, such people become fearful and hallucinatory at night. Many of them were actually loners and outsiders, even though they were actively involved in the drug scene. Scapegoating of these outsiders is not unusual. One 27-year-old Caucasian man who used large doses of speed intravenously, along with LSD, developed an acute state of paranoid panic, which was potentiated by his group of Negro companions. Although he overinterpreted the gestures and behavior of those around him, it was a fact that the group of "speed freaks" he was running with did treat him as an outsider and often threat-

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. (This happened to Mr. A several times.) On the other hand, it may be a very gross misinterpretation of the entire environment; strangers suddenly become sources of persecution. Often the person mistakes a stranger for a persecutor or, alternately, for a friend (11, 12). 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 descriptions (4), nonfatal pursuits are not uncommon; Kramer and others (9) 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 change in sensibilities that is actually associated with misinterpretation and the violent act.

Conclusion

Until there are figures available for comparing the incidence of homicide associated

with amphetamines and that associated with such drugs as barbiturates and narcotics, the most definitive answer to questions about the relationship between violence and amphetamine usage may come from such case reports as the three reported here. In these cases, homicide was clearly related to an amphetamine-induced delusional process and/or state of emotional lability. I recently reviewed several cases of amphetamine-induced assaults in which the history of amphetamine abuse was not even considered in the initial evaluation. One wonders whether the reported incidence of amphetamine-induced assault and homicide would not be much higher if physicians were more fully aware of the problem. Indeed, we have no data showing the number of assaults and homicides committed by people under the influence of amphetamines or other drugs. Routine urine examinations to detect the presence of drugs in the system of every person arrested for a violent crime would be of great help in evaluating the incidence of this problem.

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(STATEMENT BY
(THOMAS M. GELLERT, M. D., 150 MAIN STREET, HUNTINGTON, NEW YORK
(BEFORE SUBCOMMITTEE ON MONOPOLY
(SENATE SMALL BUSINESS COMMITTEE
(NOVEMBER 18, 1976

Mr. Chairman, distinguished members of the Committee, I appear today as a representative of some 250 physicians who decided to attack a problem of drug abuse among their patients without waiting for governmental guidelines, prohibitions, or coercion. We are proud of our efforts and we are gratified by the results. But now, five 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, New York, a township of some 200,000 people on the Eastern end of Long Island. The drug we have attempted to control is the amphetamine, its immediate family, and its cousins the anti-obesity medications.

Five years ago, in the face of a rapidly increasing problem of drug abuse, Huntington physicians decided to stop writing amphetamine prescriptions. We hoped that by this voluntary act we would remove a sizeable 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.

14692 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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 anti-obesity drugs and an expected increase in the writing for non-amphetamine 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 five years. The new physicians in town have been quick to learn of our amphetamine ban and their cooperation has been exemplary.

If we've 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% of the practicing physicians in our community, some duly licensed doctors have decided to confine their practices to the drug treatment of obesity. 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. 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.

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 readymade parade of victims in any community. They are the tired, overweight housewives; the self-conscious overweight teenagers; or, for that matter, any obese 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. Undoubtedly, in our community his practice is assisted by the unavailability of amphetamines elsewhere. Therefore, 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 anti-obesity 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 ^{long-term} that amphetamines have no 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 five 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~~ ^{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. The facts do not support this conclusion.

As a physician whose practice of internal medicine includes large numbers of desperately ill cardiac patients, I have had considerable experience

14694 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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.

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 anti-obesity 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. It was pointed out that a special permit was necessary to use methadone for any purpose other than analgesia. This is a unique situation. Apparently, 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 one-month supply which is not refillable and which is dispensed in a specially-marked container. I also recommend that the continued use of the non-amphetamine 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.

14696 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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Before Monopoly Subcommittee of the Senate Small Business Committee

November 9, 1976

Distinguished Senators, Ladies, and Gentlemen:

I am glad to learn that the Subcommittee is studying various problems of prescription drugs, and I am particularly glad that the committee has asked me to give my views on the possible teratogenicity of the anti-obesity drugs, since the opportunity allows me to act in what I consider a most important role as an advocate for the unborn child. Before I discuss the possible teratogenicity of the anti-obesity drugs specifically, I would like to give a brief overview of the problem of drugs and teratogenicity in general. Teratogenicity is the capacity of an agent to malform the embryo and the agent is called a teratogen.

The thalidomide tragedy has focused attention on the effects of drugs in early pregnancy. Currently, according to the March of Dimes, 250,000 American babies are born each year with mental or physical defects. 500,000 defective fetuses are lost each year in spontaneous abortions and stillbirths. Birth defects cause additionally about 560,000 deaths annually. The survivors are afflicted with blindness, hearing impairments, heart or circulatory defects, mental retardation,

bone or muscle disease, digestive, endocrine or urinary impairments. Although few drugs have been definitely linked to human birth defects, many are under suspicion. Even aspirin, readily available and massively consumed, has been associated with congenital malformation in experimental animals and with an increased stillbirth rate and a significantly reduced birth weight in humans.

Several alarming studies of the use of drugs by pregnant women suggest that the problem is that drug-taking is our cultural pattern. According to two prospective studies published in 1963 and 1964 pregnant American women took on the average of four different drugs per woman during the first trimester of pregnancy. In a more recent Scottish survey of 911 pregnant women, 65% took over-the-counter drugs, 2.2 on the average per woman. Eighty-two per cent took drugs prescribed by their physicians, each woman taking an average of four different drugs including iron, analgesics, vitamins, barbiturates, diuretics, antiemetics, antibiotics, sulfonamides, cough medicines, antihistamines, hormones, tranquilizers, bronchodilators, hypnotics and appetite suppressants. Unfortunately, the situation with American women has worsened in the last decade. A recent study of middle and upper class Texas women indicated that they took from 3 to 29 different drugs with the mean increased to 10.3 drugs per woman. Pediatricians used to be terribly concerned that the child was to be delivered into a sea of bacteria. I am concerned that the fetus is being incubated in a sea of drugs.

Since most of these drugs were not prescribed to support or save the pregnancy or to save the mother's life and since the effects of so many drugs on the fetus are poorly understood, administration of

any drug to the mother during pregnancy should be greatly justified and, at least, an agonizing decision made in each case. The physician is confronted with two medical imperatives: alleviating suffering and doing no harm. I think that it is time in considering pregnant women that the balance be shifted to doing no harm. It is here that I feel that I am an advocate of the unborn child when I say that the use of drugs should be extremely limited during pregnancy, and then only when the medical indication is compelling. There should be a clear advantage of benefit over risk in each case.

The first principle that applies to human fetal malformation which I would like to mention is that the kind of fetal effect an agent produces is dependent upon the time of its action during development. Fertilization of the egg by the father's sperm occurs within 24 to 36 hours after ovulation. Implantation of the early embryo in the uterus occurs in the human around the 9th day of pregnancy. The differentiation of the embryo proceeds in this site until the 8th or 9th week of pregnancy at which time almost all organs are fully formed. From the end of the 3rd month when differentiation is virtually complete, the embryo becomes a fetus whose main function thereafter is growth. The critical period for malformations then is during the first 3 months of pregnancy. Thus, the most severe damage caused by a drug in the embryo can occur before the woman in many cases is even aware that she is pregnant.

The drugs known to cause human malformation fall into four main categories: The first group of drugs consists of the anticancer agents consisting primarily of folic acid antagonists and antimitotics. These drugs are highly toxic to the embryo and produce malfor-

mations in a high percentage of exposed fetuses. The types of malformations observed in these infants are varied and multiple with no basic pattern of syndrome recognizable.

The second group of known human teratogens are the steroidal sex hormones, androgens, estrogens, and progestins. It is heartening to note that recent prospective studies of drugs taken by pregnant women suggest that the use of steroids in the first trimester of human pregnancy has been virtually eliminated. The decline in the use of steroids during pregnancy probably came about as the result of physician education that androgens and progestins masculinized females, while estrogens and progestins feminize males. Moreover, the primary use of progestins and estrogens to maintain pregnancies in threatened abortions has not proved to be effective. Thus, the benefits to risk ratio of these drugs for this purpose is quite low. The anomalies of sex differentiation caused by the sex hormones occur in a large per cent of fetuses exposed to these agents in the uterus.

The third teratogen known to affect the human is maternal alcoholism which produces malformations of a variety of organ systems in exposed fetuses. The risk of the fetal alcohol syndrome in exposed fetuses is only about 30%.

The last drug known to malform the fetus and perhaps the best known one is thalidomide. This drug illustrates the second principle of malformations applicable to humans. This principle is that a drug which is virtually harmless to the mother can be devastating to the development of the fetus. Thalidomide again is an example of a drug that is a very strong teratogen affecting nearly 80 to 90% of exposed fetuses. It causes a specific syndrome of absence of various joints and bones

14700 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

called phocomelia. I think because of the widespread publicity concerning thalidomide, I need not dwell on the lessons learned from the use of this drug in humans.

The thalidomide experience has led to the establishment of four criteria for the detection of a new teratogenic agent in man. The criteria for detection require: (1) an abrupt increase in the incidence of a particular defect or association of defects or syndrome, (2) coincidence of this increase with a known environmental change, for example, widespread use of a new drug, (3) known exposure to the environmental change early in pregnancy at the critical period yielding characteristically defective infants, and (4) absence of other factors common to all pregnancies yielding infants with the characteristic defect. It can be seen that these criteria for detection of new teratogenic agents will be useful only if the teratogen is effective in a majority of exposed fetuses. In this case any of the above mentioned drugs already known to be effective human teratogens would have fulfilled these criteria. I call a teratogen which has the capacity to affect above 30% of exposed fetuses a "hard" teratogen. However, most of the other drugs suspected to play a teratogenic role in man are not of the hard variety but are "soft" teratogens. A soft teratogen has a low level of effectiveness that is, it has the capacity to raise the incidence of a defect by a factor of 2 to 4 times over background level. I believe that the data on the anti-obesity drugs, which Dr. Nora probably will present in greater detail, suggest that these drugs fall into the category of soft teratogens.

The history of the studies suggesting possible teratogenicity of anti-obesity drugs is typical of that of detection of soft teratogens.

In 1965 Dr. Nora and his associates had noted that 3 mothers of children born with the congenital heart defect of transposition of the great vessels had taken an anti-obesity drug, dexamphetamine sulphate, during the early weeks of pregnancy. They then determined whether dexamphetamine sulphate could produce in pregnant mice congenital malformations especially congenital heart defects. They administered the drug in approximately 20 to 50 times the human dose to the mice in order to maximize the chances of detecting malformations. They found that in addition to cleft lip and eye abnormalities cardiac malformations were produced in the experimental animals and not in the controls. Thus, a single very large dose of dexamphetamine sulphate can produce congenital cardiac and other malformations in mice. Moreover, another appetite suppressant, phenmetrazine, has also been shown to produce congenital defects in animals. In 1967 Dr. Nora's group in a retrospective analysis of 219 cases and a prospective study of 52 cases involving use of dexamphetamine sulphate during human pregnancy yielded no teratogenic effects. The question was reconsidered in 1970 however, when a subsequent study of 184 mothers of infants with heart malformations showed a higher incidence of amphetamine ingestion than a controlled group. Another study has found an elevated incidence of biliary tract atresia among offspring of mothers taking amphetamines. Some confirmation of these suspicions comes from the retrospective survey of Scottish mothers which showed a higher proportion of children with various malformations including congenital heart defects from mothers who had taken dexamphetamine for suppression of appetite during the early part of pregnancy than the control mothers of normal infants. Two studies also show that phenmetrazine was associated with

14702 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

the birth of defective children, but it was not confirmed by a third report.

These studies cannot be considered at the moment to be more than tentative evidence, since the numbers of cases in all of the surveys of congenital heart disease associated with exposure to anti-obesity drugs are too small to be able to detect a three to four fold increase over the background level of congenital heart defects. The background incidence of congenital heart defects in humans is approximately 8 per 1000. To detect a teratogen which sufficiently raises this background level one would need a minimum of 18 cases of congenital heart disease occurring per 1000 exposed fetuses to demonstrate significant soft teratogenicity. However, I think the fact that these associations consistently turn up in a variety of studies makes the anti-obesity drugs a highly suspect drug for producing defects in humans at a low level.

We have been talking to this point about the teratogenicity of an agent which is only manifest as anatomic malformation recognizable at birth. I would like to raise the possibility that the anti-obesity drugs when administered in the critical period may be able to produce functional malformations not observable at birth but only at later stages. These so-called latent effects raise another hazard of prenatal drugs. Work published this year has shown that the administration of dexamphetamine sulphate to rats at the critical period in the same dosage as given to humans did not produce recognizable anatomic defects in the rat pups at birth. However, it was found that the experimental offspring showed a marked reduction in the ability to accommodate to new surroundings and this effect persisted for at least

3 months after birth. The effect was associated with a persistent depression of brain autonomic nervous system transmitters. This kind of defect is called "behavioral teratogenesis". It appears to be due to a teratogenic effect of a drug on the fetus causing chemical malfunctioning of the brain which is manifest in abnormal behavior and which may not become apparent long after birth.

Concerning the use of anti-obesity drugs in the pregnant woman I again resort to the medical imperative that the physician do no harm. The effectiveness of the anti-obesity drugs is questionable and this area will be discussed by Dr. Yaffe. Thus, the benefits to risk ratio is exceptionally low. At any rate, I feel that the use of anti-obesity drugs during pregnancy should at least be carefully regulated.

Before I close I would like to make one last point on a positive note, I believe that it is reasonable to expect or perhaps to hope that certain drugs may be found that will benefit the fetus as well as the mother. As the fetus becomes accessible to medical probing, through amniocentesis and other techniques, it is conceivable that drugs could be administered to treat the fetus within the uterus. Recently, one of the first such successes in treating a defective fetus has been reported. The child was shown to have an inherited disease known as methylmalonic acidemia by amniocentesis. The fetus was treated within the uterus with vitamin B12 which is known to benefit this disease. The child was born normal. Thus, I believe that fetal therapy with drugs may become very important. I would like to say that this area of fetal therapy is a promising one where drugs should be of great benefit to the unborn child. I would like to take this opportunity to make a plea that research in this area should be greatly supported.

Thank you for your attention.

STATEMENT BY

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BEFORE THE MONOPOLY SUBCOMMITTEE OF THE SENATE
SMALL BUSINESS COMMITTEE

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Historically, there is ample evidence that drug abuse antedated drug therapy, just as toxicology paved the way for pharmacology. Primitive man seems to have been more interested in poisons than medicines; even Hippocrates, although he recommended natural salicylates from willow trees for eye disease and childbirth, considered most drugs essentially useless. But when the Greeks wished to dispose of Socrates, they had a most effective herb. Today, in the case of amphetamines, this tape is being run backwards with increasing speed. Pharmacology is reverting to toxicology. We are now compelled to examine the consequences of the fact that the use and abuse of this truly addicting and dangerous drug is now quite widespread.

In 1887 the German pharmacologist L. Edeleano first synthesized phenylisopronylamine, but he was uninterested in exploring the pharmacological properties of the drug which would eventually become famous as "Penzedrine," and put this extraordinary stimulant back on the shelf. Not until 1910 did G. Pargess and Sir H. H. Dale investigate the effects on experimental animals of this and a series of closely related chemical compounds, which they called "sympathomimetic amines." However, no one in America or England grasped the implications of their findings for another 17 years. George Piness, who was seeking a synthetic ephedrine substitute was aware of Edeleano's discovery and suggested to Gordon Alles that he look for a synthetic amine substitute for ephedrine. Alles confirmed Piness' hunch in 1927 by concluding that the most effective such substitute was the original amphetamine synthesized by Edeleano.

14706 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

Because of his willingness to use himself as a human guinea pig, Alles not only discovered very quickly that amphetamine was active whether inhaled or taken orally, but he also found that "Benzedrine" was surpassed by its dextro (right-handed) isomer (eventually marketed as "Dexedrine" or dextro-amphetamine) in its ability to alleviate fatigue, increase or intensify his alertness, and make him feel euphorically confident even when it kept him awake long into the night.

In some way F. P. Nabenhauer, the chief chemist at the drug house of Smith, Kline & French, found out about Alles' work, and began to experiment with various commercial applications of amphetamine in conjunction with his firm's patented inhaling device. The executives at Smith, Kline & French realized the potential bonanza this "new" class of synthetic "ephedrine substitute" represented, and persuaded Alles to sell them all his patent rights. In 1932 their "Benzedrine" inhaler was first made available to the public by non-prescription, over-the-counter sale in drug stores across the country. The American Medical Association gave this new drug the generic name "amphetamine," and in a mild parenthetical warning note, it cautioned that "continued over-dosage" might cause "restlessness and sleeplessness," but assured physicians that "no serious reactions have been observed." In late 1937 the American Medical Association approved the new drug in tablet form recognizing it as an acceptable therapeutic medication for the treatment of narcolepsy and also post-encephalitic parkinsonism. The American Medical Association further stated that "Benzedrine" was "useful" in the treatment of "certain depressive psychopathic conditions," and even that persons "under the strict supervision of a physician" could take amphetamine in order to capture "a sense of increased energy or capacity for work, or a feeling of ex-

hilation."

Soon the national media, and especially Time magazine, which called the new drug "poisonous," were giving amphetamine a tremendous amount of sensational publicity, which did nothing to discourage use. Quite to the contrary, the numerous references to these "brain," "ben," and "super-man" pills in popular press "news" stories and feature articles, even when ostensibly phrased as warnings, acted mainly to arouse the curiosity and interest of the American people. But the most important factor was the quick and amazingly enthusiastic reception accorded these inhalers and pills by the medical profession.

Public attitudes toward the amphetamines were initially and for many years either positive, neutral, or merely humorous, and the people who used them did not, in the tremendous majority of cases, fit into any traditional stereotypes of "drug fiends." As long as the medical community was willing to accent the manufacturers' claims, no one was going to question why in 1932 practically any new psychoactive "medicine" could be marketed without any proof of either safety or efficacy. Nor did the American Medical Association, the Food and Drug Administration, or the Federal Bureau of Narcotics have any legal or sub-legal authority to deny a drug company the right to sell practically any chemical not specifically forbidden by the Harrison Act of 1914. All the Food and Drug Administration could do was recommend appropriate therapeutic indications; it had absolutely no power to limit or warn against consumer purchasing of drugs for which prescriptions were not required; and the last non-prescription amphetamine inhaler was not removed from the market until 1971. Furthermore, the amphetamines clearly demonstrated the ease with which drug manufacturers

14708 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

could expand claims for their products and advertise their usefulness in an unlimited range of areas. Some drug firms obtained patents for their amphetamine congeners and combinations on the basis of these drugs' alleged "antidepressant" actions, and then expanded their advertising claims to include the "treatment" of conditions as disparate as obesity, alcoholism, enuresis, and so on; others took different tacks, starting from the claim that their product was "uniquely effective" in the treatment of obesity, but proceeded to employ the same basic tactics. Somehow, supporting articles and thinly disguised testimonials invariably appeared in "reputable" medical organs like the Journal of the American Medical Association just prior to the publication of advertisements extending the reasons for prescribing amphetamines. Although only a few of these reports were exposed as fraudulent, most of them were clearly biased, did not use random sampling or double-blind techniques, and frequently arrived at conclusions which were dubious.

Complementing the enthusiastic over-prescribing of amphetamines by physicians is the fact that since the 1930's there have been several ways in which the public could procure these euphoriants with little or no assistance or interference from organized medicine, the Food and Drug Administration, or any state or federal drug abuse control authorities. First, of course, there were the inhalers. Although Smith, Kline & French held the patent on the "Benzedrine" inhaler until 1960, other drug companies quickly realized that they could sell their own imitations without fear of patent-infringement suit because "Benzedrine" was only one of an almost unlimited variety of equally stimulating, euphorigenic, and toxic amphetamine congeners. By the end of World War II, there were at least seven different inhalers on the market containing large amounts of these drugs, and all

of them could be purchased at drug or grocery stores without a prescription. All of these products were very easy to break open, and the number of different techniques of ingestion was limited only by the ingenuity of the abusers. Although dissolving the fillers in alcohol or coffee produced the desired effects, a much stronger kick could be obtained by chewing these bits of cotton, or simply swallowing them whole. The extent of inhaler abuse was finally documented in the medical literature by the now classic study conducted by R. R. Monroe and H. H. Drell in late 1947. They found that about 25 per cent of more than 1,000 military prisoners openly admitted to abuse of amphetamine inhalers. Monroe and Drell stressed that their figures were "deceptively low," because amphetamine intoxication was considered a grave offense by the military prison authorities. Prison life could not be blamed for this outbreak of drug abuse and addiction; more than 95 per cent of the men had begun to take amphetamines after induction into the Army, but before incarceration. It was apparent that these men resorted to inhalers because, unlike their fellows outside the barracks, they did not have access to "Benzedrine" in pill form. Monroe and Drell were also careful to point out that most of these prisoners were not criminals, but "essentially normal persons who were merely victims of circumstances or severe situational stress."

In the years following the Monroe report the abuse of amphetamine inhalers became such an obvious socio-medical problem that many drug firms withdrew their products from the market. The remaining drug firms were supposedly forced to drop their inhalers in 1959, when these amphetamine sources were finally banned by the Food and Drug Administration except as prescription items. However, this ban was almost totally ineffective, because it applied only to devices containing "Benzedrine" and dextro-

14710 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

amphetamine. This left a major loophole that was seized upon by a number of the drug houses; in fact, one small Midwest drug house began to market its "Valo" inhaler, containing 150 mg of methamphetamine after the Food and Drug Administration ban had gone into effect. The ultimate inhaler abuse -- intravenous injection of the contents -- was first reported in 1959, and was soon fairly widespread. As late as March of 1970, B. M. Angrist and his co-workers reported four cases of amphetamine psychosis resulting from abuse of the "Vyamine" inhaler, which contained 250 mg of mephentermine, even though 250 mg represents 10-20 times the usually prescribed central nervous system stimulating dose. The "Vyamine" inhaler was finally withdrawn from the market on July 22, 1971, because of pressure from the Justice Department.

But even though the inhalers did introduce millions of young people to the amphetamines, most users found that it was just as easy to procure the pills. In the first three years after "Benzedrine" was introduced in tablet form, sales rose to over 50 million units. The outbreak of World War II gave perhaps the greatest impetus to date to both the legal, medically authorized use and the illegal, black market abuse of these drugs. By 1958 the annual legal United States production of amphetamines had risen to 75,000 pounds, or 3.5 billion tablets -- enough to supply every man, woman, and child with about 20 standard (5 mg) doses. Less than 10 years later, the drug industry admitted it was pouring out 160,000 pounds -- about 8 billion amphetamine tablets -- per year, or enough for 35 to 50 pills for every living American. By 1970 reported legal amphetamine production had risen to over 10 billion tablets and in 1971 it rose again to over 12 billion.

By 1946 Smith, Kline & French had been so successful in its amphet-

mine promotion campaign that a paper by W. R. Bett listed 39 generally accepted "clinical uses" for the drug, including treatments of schizophrenia, morphine and codeine addictions, "nicotism" (tobacco smoking), heart block, head injuries, infantile cerebral palsy, irradiation sickness and hypotension. Bett, who further recommended the drug for ailments like sea sickness, persistent hiccup, and even "caffeine mania," was only one of a huge number of physicians who regarded amphetamines as "versatile remedies" which were second only to a few other extraordinary drugs like aspirin in terms of the scope, efficacy and safety of their effects.

Since the therapeutic heyday of the amphetamines at the end of World War II, the list of "accented" medical indications for these drugs has shrunk, even though per capita consumption has risen dramatically. Even the American Medical Association is slowly realizing that the amphetamines are at best ineffective or minimally effective in the treatment of nearly all the conditions for which they are still prescribed, and that in the relatively uncommon cases where drug therapy is definitely indicated, a safer and more appropriate medication is often available.

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 amphetamines.

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. This is not surprising; almost every drug which is now condemned as addictive was vouchsafed by the official medical establishment as extremely useful and non-addicting when it was first introduced. For example, when morphine was acetylated in 1898 the

14712 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

new drug was heralded as a non-addictive 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 eunhorogenic. 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 "philon"). 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 disorientation and loss of self-control may lead to violent acting out of aggressive impulses. His head aches, 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 mg) of "Benzedrine" to 20 "physically fit" and "normal" subjects in a controlled laboratory experiment. Almost without exception their subjects exhibited pallor and flushing, palpitations, and changes (usually marked increases) in pulse rate and blood pressure. 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.

14714 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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 five 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 ten 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, hemorrhage or other "vascular accidents," nausea, vomiting, difficulty in breathing, tremor, ataxia, or loss of sensory abilities, twitchings, tetany, convulsions, loss of consciousness, and coma.

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 two-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 angitis," 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. Furthermore, they pointed out that they had found no evidence of necrotizing angitis 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 et al. found that 14 of their 19 patients showed moderate to severe occlusion, and the other five 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 factor. Accordingly, Rumbaugh et al. administered methamphetamine by needle to five monkeys at dosages roughly equivalent to 50 to 100 mg for humans.

14716 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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 two 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), insomnia, 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 re-evaluation 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 1940s 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 three-year investigation of patients admitted to five London hospitals, and discovered 42 unmistakable 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 five 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.

Prior to Connell's work, it had usually been assumed that only persons who were in some peculiar way "latent schizophrenics" or "pre-psychotics" would ever develop psychoses after even massive and prolonged doses of amphetamines. But Connell strongly opposed this assumption. At least six 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

14718 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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 dextro-amphetamine, 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-producing effects of amphetamine for five 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 afterwards 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 (non-schizoid and non-paranoid) 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 for the other five ranged from 120 mg (one day)

to 700 mg (five 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 dextro-amphetamine to persons who were non-psychotic could precipitate a paranoid psychosis, and that their experiments definitely ruled out the up till then widely accepted hypothesis that only "previously borderline psychotics" would sustain an amphetamine psychosis.

Unlike heroin and cannabis, amphetamines appear to be uniquely criminogenic as a result of distinct psychopharmacological properties. The only other widely used drugs that have similar properties even approaching the strength of amphetamines are alcohol and, in some cases, barbiturates. But because amphetamine-related crime occurs primarily within speed cultures where it is largely ignored by the police, and because speed freaks rarely attempt any large-scale external crime, "official" crime rates for speed users are deceptively low. Moreover, the low level of "criminal skill" within speed cultures may reflect that amphetamines are more available and therefore less costly than heroin, or perhaps even reflect the amphetamines' ego-disruptive properties, which make it difficult for the speed freak to acquire more than a bare minimum of any skills, criminal or otherwise.

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 semi-humorous 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)

14720 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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 ninety-six 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 will-power. But the wisdom of such a solution must be examined. Do clinical and experimental studies reliably establish that amphetamine and its congeners have a measurable anorectic

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

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.

In 1938 a research group led by Poul Bahnsen compared one hundred normal subjects receiving amphetamine with an equal number receiving placebo. Nineteen of the active drug group and one 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. Rosenherg 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 one and two, the students received no medication, and during weeks three and four, they received placebo. During this control period totaling twenty-six 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 five to thirteen, half of the students received 10 mg of dl-amphetamine before each meal, and the other half received 5 mg. During week five, the subjects in both groups lost an average of one 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. Adlerstern and M. E. Mavor 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 two to five months oral thyroid medication (2-3 grains desiccated thyroid daily) was added; and Group C, after three months of dietary restriction, received amphetamine sulphate (5 to 10 mg twice daily, one to two 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 one or two 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 twenty-seven obese patients attending the Welfare Island Dispensary. They took an initial dose of 15 mg Dexedrine per day (rapidly increased to a maximum of 30 mg) and were permitted to eat as they pleased. After eight weeks, 47 percent were maintaining a weight loss of one pound per week; after twelve 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 mg d-amphetamine sulfate) to dogs one hour before feeding, with the result that food intake was substantially decreased. In the case of one dog (16 kg in weight) who was given injections of 10 mg per day, food consumption was reduced by 87 percent and body weight by 27.4 percent within thirty-two days. After thirty 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 1950s, 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 1950s 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 sulfate, 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. Kuipersmith conducted what he termed a "comparative clinical investigation" in which he employed ephedrine-ethylenediamine complex, d-amphetamine sulfate, d-amphetamine sulfate 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 eager-

ness 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 thirty-five 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 sixty patients treated with fairly high (30 mg daily) doses of Ionamin lost an average of less than seven pounds over the one-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 their patients "reported a wakefulness which was not unpleasant, 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 Hays 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, 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 sulfate is a nontoxic safe drug which may safely be used in obstetric patients to aid them in preventing excessive gain of weight." Studies like his 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 anorectic 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 'pen pills' and invite abuse. Past experience leads to scepticism when claims are made that a new anorectic-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" notion 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.

14728 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

I doubt the wisdom of using amphetamines for weight reduction under any circumstances. Although they can cause a three to four-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 seem 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. Individual physicians -- not only psychiatrists, but specialists in all areas, as well as general practitioners -- who have over-prescribed 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.

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY 14729

STATEMENT BY

JOHN W.D. HENDERSON, M.D. 365 Laurier Avenue, OTTAWA, CANADA

BEFORE SUBCOMMITTEE ON MONOPOLY

SENATE SMALL BUSINESS COMMITTEE

NOVEMBER 18, 1976

14730 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

STATEMENT TO THE U.S. SENATE: SENATOR GAYLORD NELSON

18 November 1976 - 0010 hours

JOHN W.D. HENDERSON, M.D., OTTAWA, CANADA

Gentleman:

It is a pleasure to appear before you today to explain (as best I can) the history and the rationale of the changes in amphetamine controls imposed within the borders of Canada, and the effect they have had on amphetamine use in our country - at least in terms of amphetamines of legal origin.

As outlined in Table I Designated drugs in Canada: manufactured or imported 1967-1976 and Designated drugs: exported 1967-1976 you may see that amphetamine (which covers both the racemic form sometimes known as benzedrine and dextroamphetamine sometimes known as dexedrine) were previously imported into Canada in fairly large amounts. For example in 1969 nearly 750 kilograms or nearly 1630 pounds of amphetamine were imported. None of this particular group was manufactured.

In the year 1970 the amount imported had dropped to 536.7 kilograms. One would like to think that this modest drop was the result of the beginning realization among physicians - as the result of an educational program that the use of amphetamines in medicine needed some degree of discrimination, and that attempts were being made to discourage the prescribing of these substances for other than genuine medical conditions. By 1971 however the importations had risen again. Whether this was because of stock-piling in the light of "rumblings" that control measures were about to be taken, or whether because of a return to more liberal prescribing, or a combination of both, remains uncertain.

However in the Spring of the year 1972, the then Minister of National Health and Welfare Mr. John Munro rather unexpectedly declared in Parliament that amphetamines and a number of related drugs defined specifically as

- 2 -

benzphetamine and its salts; methamphetamine and its salts; phenmetrazine and its salts; and phendimetrazine and its salts would be made "designated drugs" under the Canadian Food and Drugs Act, and be subjected to strict controls in terms of valid diagnoses for prescribing them.

I well remember the stunned reaction within the medical community of Canada over this unprecedented degree of control, and the distress felt by many physicians that the two stated conditions narcolepsy and hyperkinetic disorders of children, which our Minister had described as the only two valid indications for the use of these drugs, was not in accordance with actual medical needs.

By a process which is operative and functional within the Canadian Department of National Health and Welfare, a Canadian Medical Association delegation was invited to discuss the proposed regulation which would be delayed for a period of six months so that full consultation with all interested parties could take place. During this process I was asked to chair a study committee of approximately 12 physicians from both inside and outside of our Federal Department of Health and Welfare.

In a series of discussions this committee was found to be divided in its opinion regarding the usefulness of amphetamines or amphetamines plus barbiturates in providing a "short-cut" method of diagnosis of psychiatric illness (especially depression), although a minority felt strongly that these drugs as used by psychiatrists often increase the degree of communication which is essential to successful psychotherapy.

There was unanimous agreement that amphetamines have little or no place in the treatment of depression and that there is little or no evidence that the fast action of amphetamines is actually useful in determining prognosis regarding a response to tricyclic antidepressants. Whereas it was formerly believed that amphetamines beneficially increased the activity of depressed persons, more recent opinion seems to suggest that an increase of activity in acutely depressed individuals may lead to an even higher incidence of suicidal attempts.

Our committee as a whole rejected the concept that amphetamines should be used as a form of maintenance therapy for the treatment of amphetamines dependence. In this regard there was thought to be a problem regarding separation of the diagnosis of "dependence" against "dependence with depression" in view of the fact that withdrawal of amphetamines almost invariably cause a period of rebound depression.

It was agreed that in virtually every diagnosis for which amphetamines are indicated the drug is adjunctive to other measures. Although gentleman your present interest concerns the use of amphetamines and amphetamine derived drugs as anti-obesity agents, it may interest you to know that our committee attempted to carry out a systematic review of the medical literature, and within this discussed a number of conditions in addition to obesity where some authorities have recommended the use of amphetamines.

For example our committee was of the opinion that the use of amphetamines for neuromuscular disorders was unjustified. Hypothalamic or post traumatic brain syndrome which is, at best, an ill-defined condition may on very rare occasions be an indication for amphetamines. The condition however is sufficiently rare in Canada, that it was a unanimous opinion of our committee not to include it as an approved indication.

Reports of idiopathic edema which proved responsive to amphetamines engendered considerable skepticism on the part of our members. While the committee was unanimous in believing that there was no rationale for this use, it is recognized that there have been a few anecdotal accounts of improvement in idiopathic edema after empirical use of amphetamines. Whether there is any specific pharmacological reason for this, or it is simply the result of increased physical mobility was quite unclear. We agreed that this condition should not be added to the list of approved medical conditions for which amphetamines are indicated, but remain a condition for which special authority from time to time could perhaps be given.

- 4 -

Non-narcoleptic hypersomnia may not be as rare as formerly believed. Active research is presently being carried out in several countries. Many of these patients cannot be diagnosed as true narcolepsy but yet the hypersomnia is sufficiently overpowering to make work and normal living impossible without the use of an analeptic agent, usually of the amphetamine class. At the time of our deliberations we chose not to include this diagnosis as a specified condition for amphetamine use, but agreed to await the results of further research.

Enuresis in childhood has been shown to respond to nightly amphetamines. In the opinion of some physicians it may at times respond better to an amphetamine than to methylphenidate (Ritalin) or a tricyclic antidepressant. The subject however has been incompletely researched, but there remains a general reluctance on the part of Canadian physicians to encourage amphetamines for young persons who can become dependent upon them, although it is well recognized that this does not always happen. There was also worry that amphetamine-altered sleep could result in undesirable changes in pituitary growth hormone release. It was thus our recommendation that any special authorization for the use of amphetamines for the treatment of enuresis in childhood should be for a short, temporary period only.

The use of amphetamines combined with analgesic drugs for the treatment of dysmenorrhea has been common practice in the past. The removal of dysmenorrhea as an approved indication for the use of amphetamines resulted in a number of letters of enquiry from both general practitioners and few obstetricians and gynecologists. While it is true that amphetamines because of their effect on mood, do change the quality of pain, and therefore can be said to be synergistic with analgesics, it is likely that easy availability of amphetamines to young women might just be one of the prime conditions that can eventually result in dependence. We were agreed that the question of amphetamine use in primary dysmenorrhea is one which relates strictly to a risk-benefit ratio.

Shortly thereafter the Canadian Society for Obstetrics and Gynecology informed us that it too felt that the danger of habituation to amphetamines in young women should not be ignored, and that this danger is perhaps greater than any possible benefit from the drug. It thus appeared to us that the inclusion of dysmenorrhea on the list of approved medical conditions would be unwise.

We reached consensus about acceptable conditions for which amphetamines (meaning at this time gentleman, dl-amphetamine, dextroamphetamine, benzphetamine, methamphetamine, phenmetrazine and phendimetrazine) should be prescribed by licenced practitioners in Canada. These are as follows:

- 1) Narcolepsy. This was entirely acceptable as an indication for judicious use of amphetamine compounds. The problem is one of diagnosis, for there are no water-tight diagnostic features, and the symptomatology is highly subjective. If there is any diagnosis which I personally feel may be overused at the present time as an indication for amphetamines since the time of our legislation, it is this particular condition.
- 2) Hyperkinetic disorders in children. This also may be an acceptable indication, provided that the diagnosis is not merely one of hyperactivity, which occasionally can be familial. In many ways the true hyperkinetic disorder in children which responds to amphetamines may be the result of a minimal brain dysfunction of organic nature. We recognized of course that drugs other than amphetamines of the designated variety, including methylphenidate and imipramine, a tricyclic antidepressant, can also be used for these children. Even more recently it has been suggested that caffeine may be the safest of all stimulants to help these particular children whose behaviour improves under drug therapy.

- 6 -

- 3) Mental retardation (minimal brain dysfunction). The committee continued to have a problem with this particular designation specifically because mental retardation must be carefully defined. It is not an equivalent to "minimal brain dysfunction". The committee however was also dissatisfied with the term minimal brain dysfunction in view of the fact that it is not a recognized diagnostic term, and means nothing in terms of pathophysiology. However it was accepted that it may be difficult to define an acceptable alternative name which would be well understood by medical practitioners. The real concept here is perhaps given by the clumsy term "organic mental behavioural or learning disorder". As this is what we chose to define by the term minimal brain dysfunction, our members felt that as such it should be retained on our approved list.
- 4) Epilepsy. Some forms of epilepsy are perhaps benefited by amphetamines although the indication is by no means universal.
- 5) Parkinsonism. While many neurologists find no use for amphetamines in this condition, there are others who feel that the drugs may increase mobility and can decrease some of the side effects of other compounds which are used to ameliorate tremor and muscle rigidity.

One further special use is in the combatting of hypotensive states associated with anaesthesia. Amphetamines are of course sympathomimetic agents, and have been used as vasopressor agents to increase blood pressure. In recent years there has been a movement away from the use of vasopressors in shock and shock-like states. Nevertheless it would appear that in the hands of skilled physicians who prefer an amphetamine over other vasopressors, there may still be a valid reason to have it available.

Our only other accepted condition is in veterinary practice where the drug may be used in the depression of cardiac and respiratory centers. I refer here specifically to I.V. methamphetamine commonly known as "speed".

You will note, of course, that I have up until now not discussed the question of amphetamines and obesity, although I know this to be your main point of present interest. There are indeed a number of compounds on the market in North America based on amphetamine which have as their primary medical indication the depression of appetite. Many of the names are probably well known to you: phentermine, sold under the trade name of Ionamin; chlorphentermine under the trade name of Presate; diethylpropion under the name of Tenuate; more recently the drug fenfluramine known variously as Pondamin or Ponderex has been introduced, and most recently maxindol or Sanorex has been made available in Canada. Another is Phacetoperane known as Lidepran in Canada. All but one of these are amphetamine based. All have as their primary target the obese patient. They are not identical in terms of their stimulation of the central nervous system because changes in the molecule can decrease the actual amount of stimulation and thus euphoria. However all of them demonstrate some stimulation, and probably because of this the psychological phenomenon of positive reinforcement is produced. This simply means that unless the effect of a drug is perceived as pleasurable, we usually do not develop a hankering to use it again. The effects of amphetamines and most amphetamine-derived drugs for most humans results in a pleasurablely altered state of consciousness (if one wants to employ that term).

In honest I must make some exception for the drug Fenfluramine. Although there is no argument that pharmacologically or chemically, one has to classify this as an amphetamine, it does have very little potential for abuse. In my opinion after employing it as a physician in a number of patients, I was impressed quite early how much it differed in terms of the expected appeals for another prescription. The drug probably effects more than one area of the brain, and has a side effect a tired, drowsy feeling rather than stimulation. Neurophysiological testing of the brain however shows some degree of subcortical stimulation. The point is that the drowsiness effect area is greater than the stimulant effect. In addition Fenfluramine seems to cause some nausea and sometimes diarrhea, and this

- 8 -

in working persons is quite unwelcome.

I have little or no indication about the abuse potential or the new drug mazindol but I have a suspicion that this unique formula, quite unlike that of the main family of amphetamines, and which may have its effect on a different site (septum) of the brain, will nonetheless become a drug of dependence. The manufacturers themselves state that this imidazo-iso-indole anorectic agent shares many pharmacological properties with the amphetamines and their congeners. They clearly admit the effects of mazindole include some central nervous system stimulation.

In general terms, and I fully admit that I cannot regard myself not as an authority about obesity, but as one who has been faced with many patients who want to lose weight and find it difficult to remain on any form of suitable diet, I think that a rationale for the anti-obesity pill is faulty. Obese people whose problem has arisen not from some very rare glandular problem, is one of faulty eating habits. At times it is nothing more than lack of good information about the question of energy, calories, the meaning of carbohydrates, and even the nutritional content of many natural foods. Perhaps even more important is the non-realization by many persons who are having trouble losing weight, that alcoholic beverages contain very large number of calories and often are the basis of the difficulty that they are having in losing their excess poundage and then keeping it off. The concept of giving chemical agents in an attempt to lower appetite (which they do for only a limited period of time, such as 3 to 5 or maybe 6 weeks, after which tolerance occurs and there is then little or no appetite depression) is surely not the logical way to combat the underlying problem. I suspect that what really happens in most patients who are given amphetamine-like compounds, is that they have an initial weight loss of 4 or 5 pounds and are thus encouraged. If however they have not in fact changed their eating habits during that period of time, and the anorexiant properties begin to wear off at the previous dosage level, then they begin to eat more and so no further loss occurs. Psychological stimulation or euphoria however may continue to some extent, and if the drug is taken away, then this effect is missed. The repeat prescription is really for the psychic effects rather than anorexiant effects. This possibly is unfair as a generalization, but it is hard to justify amphetamines as appetite

depressants over any length of time. Tolerance has one other danger - the dose has to be increased to overcome it.

To be honest I must say that I have employed Fenfluramine for a few patients who have assured me that they have tried diets, regimes, and exercise but they have not lost weight. They are unhappy and depressed. Three weeks therapy with Fenfluramine can demonstrate to patients that adherence to a suitable diet will result in some weight loss, and proves to them that a long-term re-education program is the only thing that will in fact help them in the long run.

My own impression is that the "Weight watchers" type organization is the best kind of program for most obese people, because it involves group therapy and mutual support and peer-counselling. Indeed some reputable Canadian physicians have said openly that physicians probably should not be involved to any great extent in anti-obesity programs for simple diet-induced overweight conditions, because the Weight watcher type program does so very much better in both the short and long term. The concept is not to use drugs, but to re-educate people not only about eating habits, but buying habits and cooking habits at the same time.

I have deliberately again not spoken about one other member of the amphetamine class, methylphenidate known commercially as Ritalin. It is hard to know why we have not regarded this in much the same light as other amphetamines. Indeed if you have studied the proposed Convention on Psychotropic Substances (1971) of the World Health Organization you will see that methylphenidate is regarded by that organization as a true amphetamine. Signing the Convention would entail in my country a move of methylphenidate from essentially a non-controlled prescription drug schedule (F) to the controlled status known in Canada as schedule (G). Whether or not it should be subject to the specific stringencies of the five "designated amphetamines" that were brought under control by the special restricted legislation of 1973, I am not prepared to forecast. I have no way of presenting you with proof that methylphenidate is not prescribed as an anti-obesity drug but the indications for it in Canada as outlined in our Compendium of Pharmaceuticals and Specialties (1976) a volume which is comparable to your Physician's Desk Reference does not include obesity.

- 10 -

Ritalin as a central nervous system stimulant may produce a number of adverse effects that include nervousness, insomnia, dizziness, nausea palpitation, headaches and occasionally blood pressure and pulse rate changes. Abdominal pain and weight loss during prolonged therapy have been reported and apparently occur more frequently in children than in adults. Overt psychotic behaviour and psychic dependence have occurred especially with chronic high dose use. For most of the amphetamines the psychosis is paranoid in nature and there is actually little difference between this mental disorder and that associated with the drug cocaine.

Overdose of these drugs will cause central nervous system overstimulation and excessive sympathomimetic effects resulting in vomiting, agitation, tremor, muscle twitching and convulsions that are sometimes followed by coma. Mental confusion and even hallucinations have been reported. Other symptoms includes sweating, headache, a rise in temperature, tachycardia, palpitations, and even cardiac arrhythmias.

I would like to leave with you the thought that those of us who are in legislation over drugs, those involved in the prescribing of drugs that have an effect on the brain and our emotions those who dispense them, and those who develop and market them need some common understanding about the dependence potential and liability of all drugs that are made widely available within our society. I have tried for myself to devise a system of thinking about drugs in terms of benefits as contrasted with risks. I have included for you some of the questions that I ask of all drugs whether of legal or illegal origin, and because these stray far from traditional pharmacology, I have tentatively called this the social profile of psychotropic drugs.

Questions are included under the heading of Benefits of its availability. The same number but different questions relate to the risk of the substance to individual and public health. There are also risks of the substance to safety in this includes the whole area of increased risk-taking behaviour, loss of psychomotor control. There are risks to our dominant social order and the culture of our people. Finally, I want to know something about its dependence liability. If one answers these various questions and providing a numerical value in terms of 0 to plus 10 of

"goodness" or 0 to minus 10 of "badness", one can contrive a series of curves such as I have outlined as an example for the drug methylphenidate. Unfortunately I have not yet tried to construct similar types of curves nor an analysis for the specific amphetamine derivatives presently used for the treatment of obesity.

Finally, you may from my original table see that our imports of amphetamines into Canada are now very very low. Indeed we have wondered whether or not our stringent regulations have resulted in an overkill and that some patients who might benefit from amphetamines are not being prescribed them because of the concerns about long-term effects which we have engendered in our physician population. The phendimetrazine being manufactured is not marketed in our country, and is available only for export purposes. The manufacturers of Benzphetamine have not imported any into Canada since 1967 and have now decided to abandon the entire market.

Questions that still remain include the fundamental one which concerns the correctness of designating certain illness, as valid for the long-term prescribing of amphetamines while leaving the door open for physicians who need to use the drugs for extraordinary cases. In Canada since the beginning of our regulations has amounted to about 240 per year. The number is quite stable. I may say in passing that no reasonable request has ever been refused by our Department of National Health and Welfare.

Some increase in congener sales when one part of the amphetamine spectrum is squeezed is only to be expected, and it is a question of judgement whether or not the increase is acceptable. I shall present some group figures for certain congeners during my statement. In Canada however, there is quite recent evidence of illicit manufacture of diethylpropion - and this would not be taking place if there was not a street market for it. It is thus a potential threat and cannot be ignored. There is no reason for me to believe that the same phenomenon could not occur with some of the others too.

- 12 -

If Canada becomes a signatory to the Convention on Psychotropic Substances it surely does not make sense to include Amfepramone (the European name for diethylpropion) and not include all the others of the same class with it.

Finally, could medicine really live and flourish without hardship to any patient without amphetamines at all? The answer is probably affirmative but I would forecast that the transition would need to be reasonably slow rather than abrupt for there are many patients presently dependent on this class of drugs and who would suffer withdrawal and become depressed if these drugs are all suddenly unavailable. To leave what experts may regard as the least harmful of the family for a specified period of time would seem to be a human but nonetheless logical step in ultimate elimination of this family with its potential hazards.

For obesity itself, I believe that there is no real indication for amphetamine type drugs. Whether or not there is indeed any rational even for a safe non amphetamine, non habituating chemical to try to depress over a period of time the appetite in those who require re-education of eating habits is quite uncertain. Personally I would regard even this as quite irrational.

14742 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

Part, impose such conditions as in his opinion may be desirable in the public interest on the right of the pharmacist to purchase a controlled drug.

nonobstant toutes les dispositions de la présente Partie, imposer telles conditions qu'il juge désirables dans l'intérêt du public au droit dudit pharmacien d'acheter une drogue contrôlée.

DIVISION 4

Practitioners

Rev. & new
P.C. 1972-
3049
Dec. 19, 1972

"G.04.001. (1) In this section

(a) "administer" includes prescribe, give, sell, furnish, distribute or deliver; and
(b) "designated drug" means any of the following controlled drugs:

- (i) amphetamine and its salts;
- (ii) benzphetamine and its salts;
- (iii) methamphetamine and its salts;
- (iv) phenmetrazine and its salts; or
- (v) phendimetrazine and its salts.

Rev. & new
P.C. 1972-
3049
Dec. 19, 1972

(2) Subject to subsections (3) and (4) and section G.06.001, no practitioner shall administer a controlled drug to any person or animal.

Rev. & new
P.C. 1972-
3049
Dec. 19, 1972

(3) A practitioner may administer a controlled drug, other than a designated drug, to a person or to an animal, if

- (a) that person or animal is a patient under his professional treatment; and
- (b) the controlled drug is required for the condition for which the patient is receiving treatment.

Rev. & new
P.C. 1973-382
Dec. 11, 1973

(4) A practitioner may administer a designated drug to an animal or a person who is a patient under his professional treatment where the designated drug is for the treatment of any of the following conditions:

- (a) in humans
 - (i) narcolepsy,
 - (ii) hyperkinetic disorders in children,
 - (iii) mental retardation (minimal brain dysfunction),
 - (iv) epilepsy,
 - (v) parkinsonism, or

TITRE 4

Praticiens

G.04.001. (1) Dans le présent article,

Ab. et remp.
C.P. 1972-
3049
19 déc. 1972

a) «administrer» comprend prescrire, donner, vendre, fournir, distribuer ou remettre; et

b) «drogue désignée» signifie l'une des drogues contrôlées suivantes:

- (i) amphetamine et ses sels,
- (ii) benzphetamine et ses sels,
- (iii) méthamphetamine et ses sels,
- (iv) phénmetrazine et ses sels, ou
- (v) phémidimétrazine et ses sels.

(2) Sous réserve des dispositions des paragraphes (3) et (4) et de l'article G.06.001, il est interdit à tout praticien d'administrer une drogue contrôlée à une personne ou un animal.

Ab. et remp.
C.P. 1972-
3049
19 déc. 1972

(3) Un praticien peut administrer, à une personne ou à un animal, une drogue contrôlée, autre qu'une drogue désignée, si

Ab. et remp.
C.P. 1972-
3049
19 déc. 1972

a) ladite personne ou ledit animal sont des sujets qu'il traite à titre professionnel; et si

b) l'état de ladite personne ou dudit animal traités commande l'emploi de ladite drogue contrôlée.

(4) Un praticien peut administrer une drogue désignée à un animal ou à une personne qu'il traite à titre professionnel, lorsque la drogue désignée est destinée au traitement de l'un des états suivants:

Ab. et remp.
C.P. 1973-
3823
11 déc. 1973

- a) chez l'homme,
 - (i) narcolepsie,
 - (ii) troubles hypercinétiques chez l'enfant,
 - (iii) arriération mentale (dysfonction cérébrale minimale),
 - (iv) épilepsie,
 - (v) syndrome parkinsonien, ou

1. BENEFITS OF ITS AVAILABILITY

- is it curative of illness
- does it provide good palliation of symptoms
- is it effective for severe (or only trivial) illnesses or disorders
- how well is it non-interfering with the action of other drugs or food
- does it lack idiosyncratic (unpredictable) reactions
- how good is its therapeutic index (ratio of therapeutic effects over toxic effects)
- is it reasonably priced on the market
- are there any social benefits (or only intoxication) when used in a recreational manner

2. RISKS OF THE SUBSTANCE TO INDIVIDUAL AND PUBLIC HEALTH

- does it impair learning ability (life skills and formal education):
i.e. brain function
- does it lead to the undesirable consequences of chronic sensory deprivation
- does it cause brain damage

14744 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

- does it cause any other organic damage
- is its use associated with states of malnutrition
- does it lead to a high accident rate (falls; drownings; auto accidents etc)
- is it likely to be lethal in overdose
- what are the health risks when used recreationally over any length of time

3. RISKS OF THE SUBSTANCE TO PUBLIC SAFETY

- does it lead to deviant (potentially destructive) behaviour
- does it lead to aggressive behaviour (including sexual aggression)
- does it lead to violent behaviour
- is it associated with loss of psychomotor and judgemental control
- is the criminal element in society involved in obtaining the substance (guns, thefts, assaults, blackmail etc.)
- does it lead to increased risk-taking behaviour
- does it lead to flattening of affect (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

4. RISKS OF THE SUBSTANCE TO THE DOMINANT SOCIAL ORDER AND CULTURE

- does it lead to non-coping behaviour (low self-reliance)
- does it lead to loss of productivity and creativeness
- is it associated with recruitment of non-users
- does it lead to degradation of ethical and moral values
- does it lead to socially unacceptable standards of behaviour, dress, cleanliness etc.
- is it associated with amotivational states
- is it associated with economic losses to the community
- does it lead to anarchic inclinations when used non-medically (no one is going to tell me what I can and I can't do)

5. DEPENDENCE LIABILITIES OF THE SUBSTANCE

- is a state of dependence likely after experimental use
- will dependence occur after regular low-dose use
- will dependence occur after only heavy use
- is psychological dependence problematic in terms of quitting
- does use result in physical addiction
- is recidivism high after periods of abstinence
- how great are its reinforcing properties
- how great is the likelihood of abuse in Canada

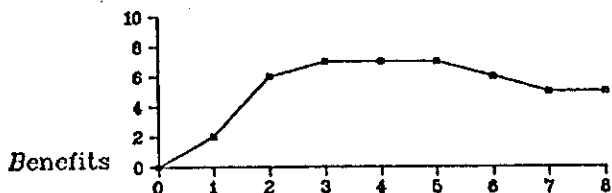
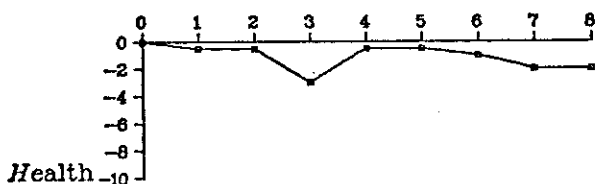
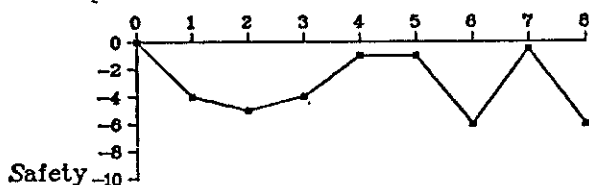
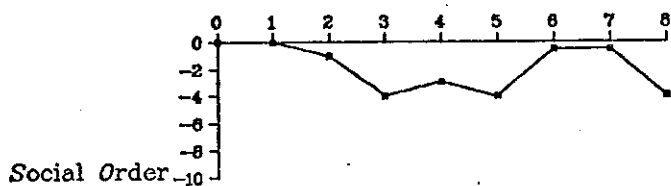
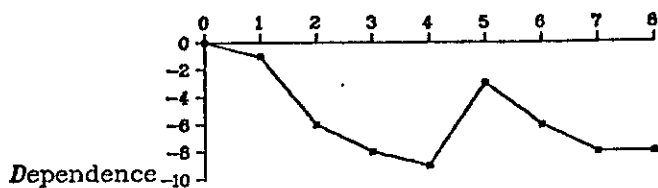
Methylphenidate

Table I
DESIGNATED DRUGS IN CANADA - MANUFACTURED OR IMPORTED 1967 - 1976

	AMPHETAMINE	BENZPHETAMINE	METHAMPHETAMINE	PHENOMETHAZINE	PHENMETRAZINE
1967	669.817	NIL	101.302	NIL	NIL
1968	495.759	NIL	89.895	NIL	NIL
1969	740.395	NIL	69.979	NIL	NIL
1970	536.754	NIL	55.130	NIL	NIL
1971	756.175	NIL	44.746	NIL	NIL
1972	32.457	NIL	41.795	4907.75	** 155.8
1973	1.395	NIL	23.000	5821.12	115.20
1974	1.550	NIL	.0006	3025.5	111.30
1975	0.475	NIL	0.550	1544.5	41.01
* 1976	*** 176.137	NIL	0.125	1654.8	40.0

DESIGNATED DRUGS - EXPORTED 1967 - 1976

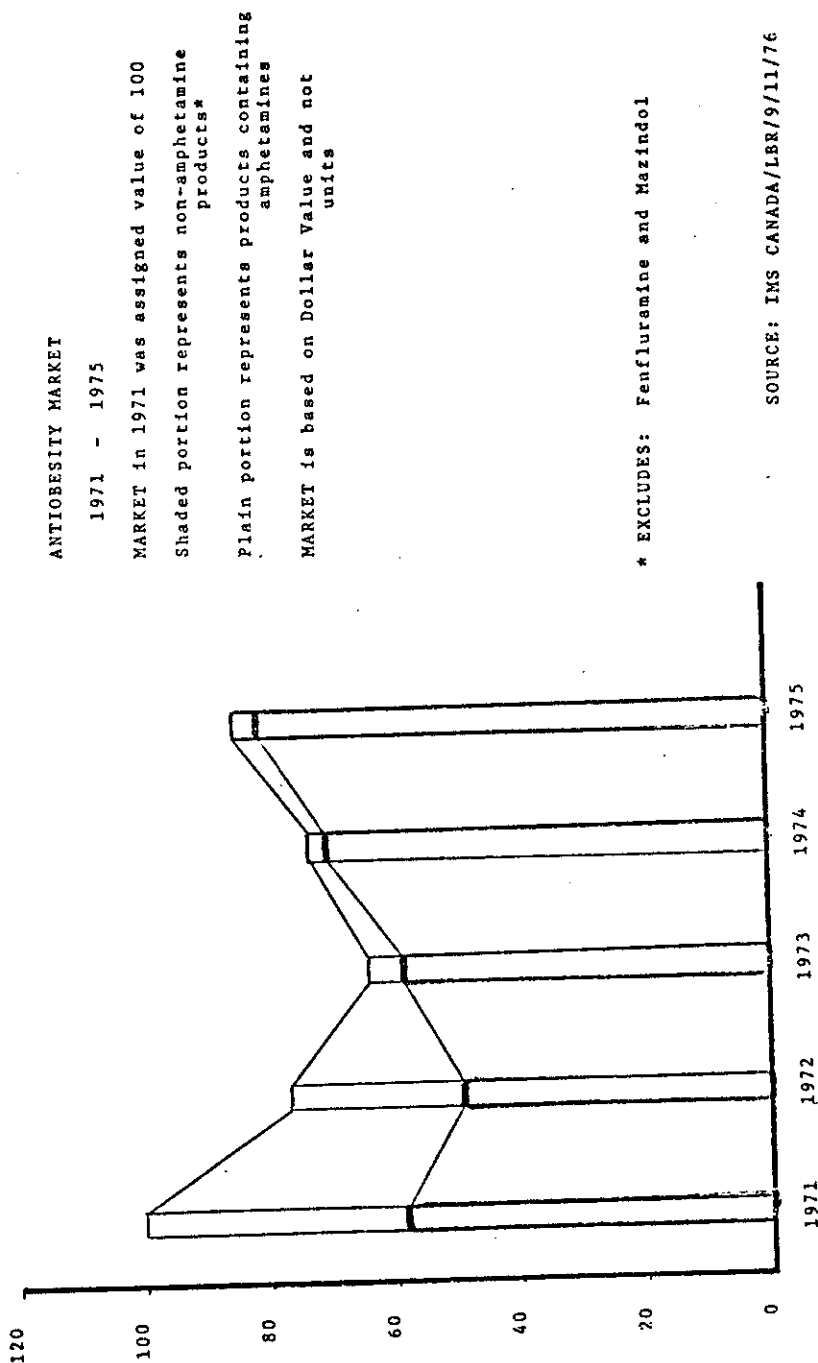
1967	9.972	NIL	0.800	NIL	NIL
1968	29.485	NIL	NIL	NIL	NIL
1969	20.990	NIL	0.027	NIL	NIL
1970	32.587	NIL	NIL	NIL	NIL
1971	26.182	NIL	0.006	NIL	NIL
1972	1.517	2.500	28.610	1407.757	59.775
1973	2.159	NIL	NIL	5013.744	43.558
1974	2.974	NIL	NIL	1923.193	2.190
1975	1.084	NIL	0.006	1899.588	3.285
* 1976	.525	NIL	NIL	1300.699	5.175

* Up to and including October 28, 1976

** Drugs not controlled prior to 1972

*** Imported for conversion to an uncontrolled substance not utilized for medical purposes

UNIT OF WEIGHT - KGS.





DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

STATEMENT

BY

DR. DONALD R. JASINSKI

Chief,
Clinical Pharmacology Section

NATIONAL INSTITUTE ON DRUG ABUSE
ADDICTION RESEARCH CENTER

Lexington, Kentucky

ON

COMPARATIVE CLINICAL PHARMACOLOGY

OF THE ANTI-OBESITY DRUGS

BEFORE THE

SUBCOMMITTEE ON MONOPOLY OF THE
SENATE SELECT COMMITTEE ON SMALL BUSINESS

NOVEMBER 10, 1976

TESTIMONY BEFORE U. S. SENATE

SMALL BUSINESS COMMITTEE

November 10, 1976

Mr. Chairman and members of the Subcommittee, my name is Donald R. Jasinski. I am a physician who is a Commissioned Officer in the United States Public Health Service. I hold the position of Chief, Clinical Pharmacology Section, of the National Institute on Drug Abuse Addiction Research Center, Lexington, Kentucky.

For over forty 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 six 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 prototypic 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 anti-obesity 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 drug-taking. 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, diethylpropion, phentermine and benzphetamine all produce typical amphetamine-like effects. These drugs differ from one another in milligram for milligram potencies (see attached table). In sufficient doses, however, all can produce the same degree of effects.

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. 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, phenmetrazine and methylphenidate are three of the drugs pharmacologically equivalent to amphetamine. At times all have had a high incidence of abuse equalling that of amphetamine. On the other hand, three anti-obesity 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 co-sponsored 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% 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% 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% of those for amphetamine, while the number of new

prescriptions are 6% of those for amphetamine. 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 non-medical use of stimulant drugs. The specific stimulant drugs reported were amphetamine, methamphetamine, methylphenidate, phenmetrazine and biphphetamine. There were no mentions of diethylpropion, benzphetamine, or phentermine. Similar considerations also indicate a relatively low incidence of abuse of both fenfluramine and clorphenentermine, 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.

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 anti-obesity 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 consequence 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 anti-obesity 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.

EQUIVALENT EUPHOROGENIC DOSESSubcutaneous Studies

<u>d</u> -amphetamine	10 mg
<u>d</u> -methamphetamine	10 mg
Methylphenidate	20 mg
Phenmetrazine	40 mg
Ephedrine	50 mg
Diethylpropion	140 mg
<u>d</u> -amphetamine (oral)	10 mg

Oral Studies

<u>d</u> -amphetamine	10 mg
Phentermine	20 mg
Benzphetamine	50 mg
<u>l</u> -Ephedrine	50 mg
Diethylpropion	70 mg

PHYSIOLOGIC, SUBJECTIVE, AND
BEHAVIORAL EFFECTS OF
AMPHETAMINE,
METHAMPHETAMINE,
EPHEDRINE,
PHENMETRAZINE, AND
METHYLPHENIDATE IN MAN

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Lexington, Ky.

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ment of Health, Education, and Welfare,
Public Health Service, Health Services and
Mental Health Administration

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**Physiologic, subjective, and behavioral effects of
amphetamine, methamphetamine, ephedrine,
phenmetrazine, and methylphenidate in man**

Five centrally acting sympathomimetic amines, d-amphetamine, d-methamphetamine, ephedrine, phenmetrazine, and methylphenidate, were studied in man. All of these agents increased blood pressure and respiratory rate, produced similar types of subjective changes, and increased the excretion of epinephrine. With regard to these parameters, there was a high concordance between estimates of their relative potencies. The concordance between the potency estimates for the different parameters suggests, but does not prove, that these five agents share a common mode of central action. Further, if the peripheral modes of action as elucidated by animal studies are true for man, this study suggests that it is unlikely that their central actions in man are a consequence of the release of norepinephrine in the brain.

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Services and Mental Health Administration*

Several central nervous system stimulants, including d-amphetamine, d-methamphetamine, methylphenidate, and phenmetrazine, have been increasingly abused and their abuse seems to share many features in common. Patients taking these drugs to obtain feelings of well-being and euphoria frequently escalate the dose to the extent that a toxic psychosis is produced. On the basis of animal experi-

ments, these drugs have several known modes of action including release of catecholamines, blockade of uptake of catecholamines, inhibition of monoamine oxidase, a serotonergic action, and cocaine-like effects. Our experiments were conducted in man comparing the effects of d-amphetamine, d-methamphetamine, phenmetrazine, methylphenidate, and ephedrine (Fig. 1) on several physiologic, behavioral, and neurochemical measures to delineate their mode or modes of action in producing subjective effects. Closely related to this end was the goal of validating meth-

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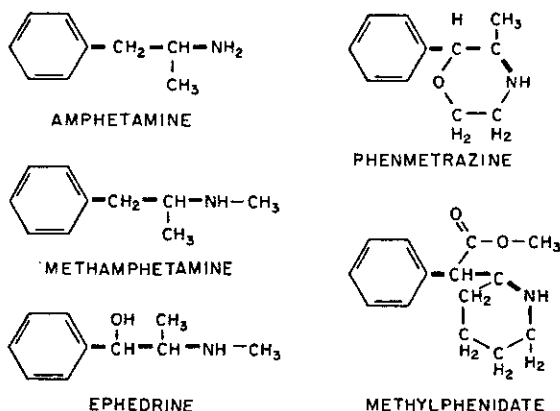


Fig. 1. Chemical structures of amphetamine-like drugs.

ods for assessing amphetamine-like subjective effects which are related to their abuse and abuse potentiality.

Methods

Physiological and behavioral measures.

Subjects participating in these studies were male prisoners serving sentences at the Clinical Research Center, Lexington, Kentucky, for Federal crimes committed in connection with narcotic use. All subjects volunteered for the study and were examined to ensure their mental and physical suitability. Studies were conducted on the wards of the Addiction Research Center. At weekly intervals the subjects were admitted to the Addiction Research Center ward the evening prior to the test day. All were interviewed, and blood pressure, pulse rate, and body temperature were determined in order to detect intercurrent minor illnesses. After dinner was served, the patients engaged in various ward activities (table games, television, reading) until they retired. The patients were awakened at 0600, and breakfast was served on the ward. Base-line physiologic observations were obtained at 0700 and 0730. Medication was administered subcutaneously in a 2 ml. volume at 0800 on a double-blind basis, and physiologic ob-

servations were made and questionnaires completed by both subjects and observers at 0830, 0900, 1000, 1100, 1200, 1300, and 2000.

The following physiological observations were made: (1) indirect blood pressure (always determined on the same arm by the same observer with the patient supine; mean blood pressure calculated as the diastolic pressure plus one third of the pulse pressure; blood pressure determinations repeated until 3 consecutive mean pressures fell within a 5 mm. range); (2) pulse rate; (3) respiratory rate; (4) rectal temperature; and (5) pupil diameter (determined photographically in 30 foot candles of light with an accommodation distance of 26 inches). The food chosen by the patients at lunch, which was served at 1130, was weighed and the caloric content calculated from standard tables. The caloric content of uneaten food was not measured. This measure then is an index of the appetite of the patient at the time that he went through the food line.

The questionnaires completed include the single dose questionnaire for both subjects and observers⁶ and a psychological test completed by the subjects which consisted of questions from the following scales

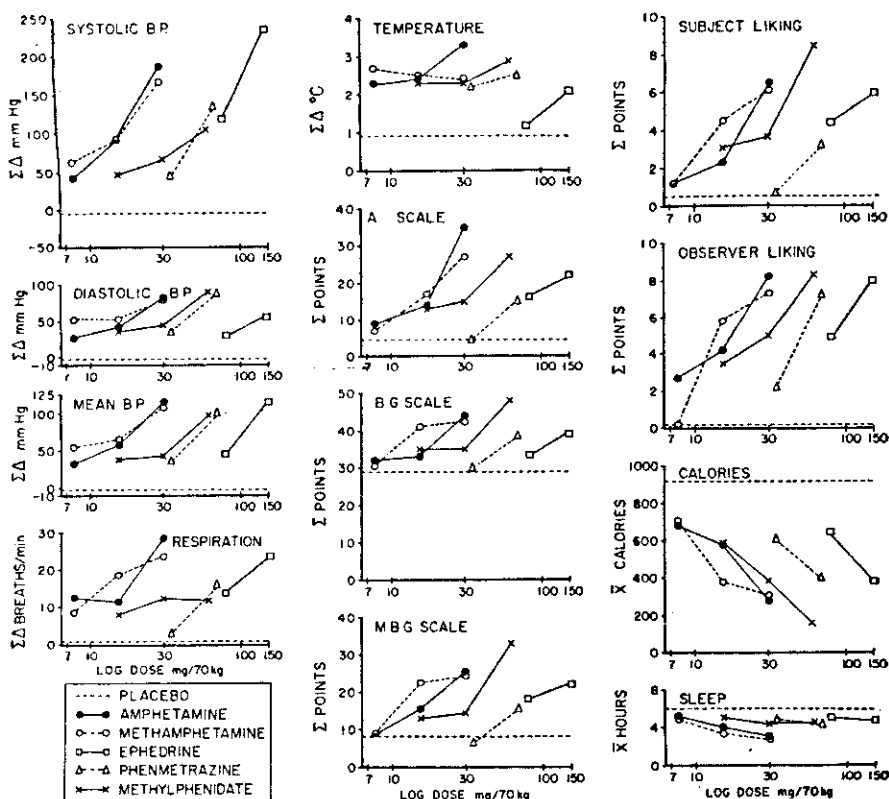


Fig. 2. A summary of dose-response relationships obtained for several physiologic and subjective parameters with amphetamine-like drugs. These data provided the basis on which relative potency data presented in Table I were calculated.

of the Addiction Research Center Inventory⁹: PCAG (pentobarbital, chlorpromazine, alcohol group scale), which is a measure of sedation; MBG (morphine-benzedrine group scale), a measure of euphoria; LSD (lysergic acid diethylamide group scale), which estimates dysphoric and psychotomimetic changes; and BG (benzedrine group scale), an empiric amphetamine scale. In addition, a new 11 item amphetamine (A) scale was constructed for those items for which there was a significant regression of response against dose for the 3 doses of *d*-amphet-

amine and a nonsignificant deviation from linearity. The items of the various scales are presented in Appendix 1.

On the morning following the test day, subjects were asked to estimate, to the nearest ½ hour, the amount of time they had slept the previous night. No attempt was made to verify this subjective estimate.

Dose levels of the drugs to be compared were selected on the basis of results obtained in the preliminary dose run-up study. The comparison was done in two parts. In the first part, *d*-amphetamine (7.5, 15, and 30 mg. per 70 Kg.), *d*-meth-

Table I. Potencies of methamphetamine, phenmetrazine, methylphenidate, and ephedrine relative excretion

Drugs	Systolic blood pressure	Diastolic blood pressure	Mean blood pressure	Respiratory rate	Amphetamine scale
d-Methamphetamine	0.92* (0.76-1.13)	1.49† (0.98-2.56)	0.99* (0.78-1.25)	0.92‡ (0.52-1.59)	0.93‡ (0.67-1.26)
Phenmetrazine	0.26‡ (0.22-0.32)	0.41* (0.31-0.53)	0.31‡ (0.25-0.38)	0.32* (0.21-0.42)	0.21* (0.12-0.38)
Methylphenidate	0.31* (0.24-0.43)	0.57‡ (0.41-0.82)	0.44‡ (0.34-0.58)		0.48* (0.33-0.67)
L-Ephedrine	0.27* (0.22-0.34)	0.11‡ (0.08-0.16)	0.19* (0.15-0.24)	0.24* (0.15-0.45)	0.17* (0.11-0.24)

Potency estimates are expressed as number of milligrams of d-amphetamine equivalent to 1 mg. of the drug. Figures in least one of the criteria for a valid bioassay was not fulfilled.

*Based on a 5 point assay.

‡Based on a 6 point assay.

†Based on a 4 point assay.

amphetamine (15 and 30 mg. per 70 Kg.), and a placebo condition were compared. Twelve subjects participated and were assigned to one of two 6 × 6 latin square blocks for which dose ordering was randomized. The second part of the study was initially planned to compare ephedrine (75 and 150 mg. per 70 Kg.), phenmetrazine (35 and 70 mg. per 70 Kg.), and methylphenidate (15 and 30 mg. per 70 Kg.) also using a 6 × 6 latin square design.

Eleven subjects participated in both experiments. Because one subject who had participated in Part 1 could not participate in Part 2, a placebo condition and the three amphetamine doses were added for the twelfth subject in Part 2. In addition, because some of the bioassays were not completely satisfactory, a 7.5 mg. per 70 Kg. dose of methamphetamine and 60 mg. per 70 Kg. dose of methylphenidate were administered at weekly intervals at the end of the second part of the experiment to the 12 subjects participating in Part 2.

Analysis of variance was done to determine if there were any significant across-weeks effects which could indicate the development of tolerance or adaptation for the first part of the experiment, as well as to segregate the variance due to regression (dose effect), between-preparations

differences, linearity, and parallelism for both parts. Depending on the particular experiment and the particular parameter, either a 4, 5, or 6 point assay was used. A valid bioassay was one in which there was a significant regression, no significant deviation from linearity, no significant difference in preparations, and a significant treatment effect. Relative potency and confidence limits were calculated according to the method of Cox and Ruhl.⁴

Urinary catecholamine methods and procedures. Patients voided immediately before receiving medication or a placebo at 0800 and then drank 500 ml. of water. Urine samples were collected from 0800 to 1100 in bottles containing 10 ml. of 6N HCl. During this time, the patients remained in bed, except when physiologic observations were made, to minimize variability in catecholamine excretion by partially controlling for the influence of exercise.

The urine specimens were frozen and stored at -15° C. until analyzed. Specimens whose volume was less than 500 ml. were diluted to this volume prior to being frozen. Urinary epinephrine, norepinephrine, and dopamine were analyzed using a modification of the method of Weil-Malherbe.²⁵ Duplicate samples were used

to amphetamine for physiologic and subjective measures as well as enhanced epinephrine

BC scale	Subjects' liking	Observers' liking	Caloric intake	Sleep time	Urinary epinephrine
1.68* (1.14-2.30)	1.16† (0.77-1.82)	1.22† (0.89-1.12)	1.19† (0.80-1.83)	1.45† (0.93-2.58)	2.34† (0.99-54.8)
0.31* (0.21-0.42)	0.22* (0.08-0.65)	0.33* (0.26-0.41)	0.43* (0.23-0.81)	0.25† (0.12-0.44)	0.21† (0.04-0.46)
0.58* (0.45-0.80)	0.59* (0.46-0.82)	0.58† (0.42-0.80)	1.05* (0.64-1.83)	0.52* (0.22-1.39)	0.75† (0.38-2.16)
0.17* (0.11-0.24)	0.21* (0.15-0.33)	0.21* (0.15-0.29)	0.19* (0.12-0.29)	0.07* (0.00-0.14)	0.22† (0.00-0.46)

parentheses are the 95 per cent confidence limits of the estimate. The omission of 95 per cent confidence limits indicates that at

for determining endogenous catecholamine content. Determinations on duplicate samples to which a mixed standard of epinephrine, norepinephrine, and dopamine were added prior to the hydrolysis were made to determine the efficiency of recovery of the method and to permit values to be corrected for standard recovery. Centrifugation of the specimens which is frequently necessary before the urine is applied to the alumina column was omitted in this experiment because a heavy precipitate was not produced in the dilute specimen; hence, there was no impediment to flow through the column due to this factor. Urinary creatinine was estimated according to the method of Peters.²¹

Results

Physiological changes. All drugs produced a dose-related increase in blood pressure (Fig. 2), and as can be seen from Table I there is good concordance between the potency estimates for systolic, diastolic, and mean blood pressures for all drugs. With one exception, the potency estimates were not significantly different from one another. The effects of ephedrine on diastolic blood pressure and systolic blood pressure were relatively less and greater, respectively, than the effects of

amphetamine on these same parameters (Table I and Fig. 2).

Amphetamine, methamphetamine, ephedrine, and phenmetrazine had about the same relative potency in increasing respiratory rate as they had in elevating mean blood pressures. Although methylphenidate also produced a significant increase in respiratory rate, the slope of the dose-response relationship over the dose range studied was not statistically significant. The maximum increase in respiratory rate was significantly less than that seen following the highest doses of amphetamine, methamphetamine, and ephedrine.

All drugs produced significant increases in body temperature. The relative potencies and 95 per cent confidence limits for the three drugs in comparison to amphetamine in which the criteria for a valid assay were met are: ephedrine, 0.06 (0.00 to 0.11); phenmetrazine, 0.33 (0.01 to 0.51); and methylphenidate, 0.41 (0.20 to 0.65). As can be seen from Fig. 2, ephedrine was less potent in increasing body temperature than in increasing mean blood pressure and respiratory rate and in producing subjective changes. Although methamphetamine was quite effective at all dose levels studied in elevating body temperature,

Table II. Analysis of correlation coefficients between blood pressure and pulse rate for the five centrally acting drugs

Drugs	Correlation between cells	Correlation within cells	Correlation between subjects	Total correlation
Amphetamine	-0.702* (20)	-0.134 (231)	-0.223* (11)	-0.281* (251)
Methamphetamine	-0.565* (20)	-0.144 (231)	-0.370* (11)	-0.278* (251)
Ephedrine	-0.734* (13)	-0.136 (154)	-0.003 (11)	-0.277* (167)
Phenmetrazine	-0.147* (13)	-0.485 (154)	-0.612* (11)	-0.367* (167)
Methylphenidate	0.679* (20)	0.111 (231)	0.179* (11)	0.238* (251)

Between-cells correlation represents that attributable to the different observation periods (I) and the dose (D) as well as $I \times D$. Within-cells correlations include between-subjects and the interactions involving subjects (S , $S \times I$, $S \times D$, and $S \times I \times D$). The figures in parentheses represent the degrees of freedom. The between-cells correlation coefficients were all significant when they were tested with the $S \times I \times D$ interaction term, thus demonstrating conclusively that these correlations were due to drug effects and not to a relationship between pulse rate and blood pressure that could have existed in the population.³

* $p < 0.01$.

the slope of the regression line was not statistically significant (Fig. 2).

All drugs except ephedrine produced a significant degree of pupillary dilation; however, a valid assay was obtained only when amphetamine was compared with methamphetamine (0.92 [0.05 to 6.62]).

The effects of all drugs on pulse rate were quite complex. All drugs produced tachycardia; however, for amphetamine, methamphetamine, ephedrine, and phenmetrazine there was an over-all negative correlation between pulse rate and blood pressure (Table II). The time-action curves of amphetamine on blood pressure and pulse rate are presented in Fig. 3 and illustrate typical relationships between these variables that have also been seen with methamphetamine, ephedrine, and phenmetrazine. Both the 7.5 mg. per 70 Kg. and 15 mg. per 70 Kg. doses produced a modest increase in blood pressure and a tachycardia during the first 5 hours after administration. In contrast, the 30 mg. per 70 Kg. dose level produced a greater increase in blood pressure, and, during the time when blood pressure was maximally elevated, the mean pulse rate was not significantly different from placebo value. However, 5 hours after administration of the high dose of amphetamine, when the pressor response was decreasing, a marked tachycardia was observed. The relative bradycardia seen

with the greater pressor responses was undoubtedly reflex in origin and accounts for the negative correlation between blood pressure and pulse rate. In contrast to these drugs, as can be seen from Fig. 3, all doses of methylphenidate produced a marked tachycardia, and a positive correlation was found between blood pressure and pulse rate for methylphenidate (Table II).

All drugs reduced appetite as assessed by the caloric value of food selected from the serving cart, and valid assays were obtained for all drugs. Potency estimates were not significantly different from potency estimates obtained using blood pressure for methamphetamine, phenmetrazine, and ephedrine. Methylphenidate was somewhat more potent in suppressing caloric intake than it was in elevating blood pressure but not in producing amphetamine-like subjective effects (Table I).

All drugs decreased the patients' estimates of sleep time, and valid assays were obtained for this measure for all drugs except ephedrine. The potency estimates were in good agreement with the potency estimates obtained with the physiologic measures and subjective rating scales (Table I).

Subjective effects. All drugs increased in a dose-related manner the scores on A, BG, and MBG scales (Fig. 2); however, the usefulness of these scales in calculating

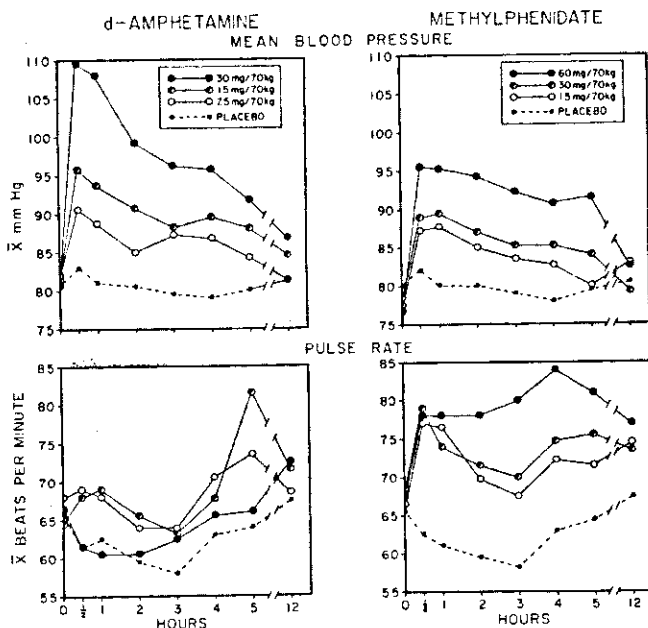


Fig. 3. Mean blood pressure and pulse rate time-action curves for d-amphetamine, methylphenidate, and a saline placebo.

relative potencies differed for different drug comparisons. Valid potency estimates were obtained for all drugs except ephedrine when using the A scale and for all drugs except phenmetrazine when using the BG scale. None of the assays were valid using the MBG scale.

All drugs decreased PCAG scale scores below placebo levels. The largest doses of all drugs increased LSD scale scores above the placebo level.

By and large, relative potencies obtained using the A and BG scales were in good agreement with each other, as well as potency estimates obtained for blood pressure.

Subjects indicated that they liked the effects of all drugs, and the observers felt that the patients liked all drugs. The "liking" scores were dose related (Fig. 2), and potency estimates for all agents showed

a good agreement with potency estimates obtained using the A and BG scales (Table I).

Patients' and observers' identifications of the various drugs and doses are presented in Table III. The frequency that drugs were identified as "benzedrine" increased with dose levels for all drugs; however, even at the highest levels less than 30 per cent of the identifications made by patients were that of benzedrine for any of the drugs studied. It is particularly interesting, especially in view of the similarities of the subjective effects of these drugs to morphine,⁹ that not a single patient identified any dose of any drug as an opiate. The identifications by the observers were quite similar to those of the patients, except that the percentage of benzedrine or ephedrine identifications for the high doses of amphetamine and methamphetamine

Table III. Drug identification by subjects and observers (single dose questionnaires)

Drugs	Placebo	d-Amphetamine			d-Methamphetamine			l-Ephedrine		dl-Phenmetrazine		Methylphenidate		
		7.5	15	30	7.5	15	30	75	150	35	70	15	30	60
Subjects														
Benzedrine	—	—	7	29	4	15	20	11	15	—	22	17	15	24
Cocaine	—	—	4	7	—	—	—	6	4	—	—	6	10	12
Marihuana	—	1	—	—	5	5	4	—	8	6	6	—	5	8
Goofballs (barbiturate)	—	—	—	2	—	—	—	4	6	—	—	4	1	—
Other	7	13	38	46	21	41	43	49	54	6	35	15	24	42
Blank	93	86	51	16	70	39	33	30	13	88	37	58	45	14
Observers														
Benzedrine	—	—	15	57	—	27	57	13	20	—	25	11	7	22
Cocaine	—	—	—	—	—	—	—	—	—	—	5	—	—	—
Ephedrine	—	2	13	—	—	11	7	—	7	—	—	7	2	7
Goofballs (barbiturate)	4	—	—	—	—	—	1	—	—	—	—	—	1	2
Other	4	37	31	34	56	43	17	53	59	32	56	30	54	58
Blank	92	61	41	9	44	19	18	34	14	68	14	52	36	11

For each treatment there were seven opportunities (times) for each subject to identify the drug. The numbers in each column are percentage identifications and were calculated using the total possible responses (84). Some observers identified the agent as "ephedrine" on several occasions.

Table IV. Summary of symptoms and signs (single dose questionnaires)

Symptoms and signs	Pla- cebo	d-Ampheta- mine			d-Methamephata- mine			l-Ephedrine		dl-Phen- metrazine		Methylphenidate		
		7.5	15	30	7.5	15	30	75	150	35	70	15	30	60
Symptoms														
Relaxed	7	13	24	40	18	36	31	15	38	18	21	20	18	23
Nervous	—	—	2	20	10	27	29	15	29	—	30	18	5	36
"Drive"	—	—	2	12	—	4	15	5	11	—	2	5	14	21
Gastric sensa- tion	1	—	2	4	—	4	12	2	4	—	10	1	5	17
Sleepy	4	—	—	—	—	—	—	—	—	—	—	—	—	—
Other	6	8	12	26	—	21	14	33	23	2	2	2	19	32
Signs														
Relaxed	4	35	69	83	55	65	65	52	69	32	76	40	56	75
Nervous	—	—	2	8	—	12	14	15	21	—	11	7	6	7
"Drive"	—	—	—	12	—	10	18	4	14	—	7	4	6	29
Sleepy	11	—	—	—	—	—	—	—	—	—	—	—	—	—
Nausea and vomiting	—	—	—	—	—	4	—	—	—	—	—	—	2	2
Other	4	5	7	2	1	5	7	11	13	1	5	—	4	10

Percentages were calculated in the same manner as that for Table III, except that the symptoms listed were not mutually exclusive. For purposes of tabulation, "Nervous" also includes the response "irritable"; "Drive" includes the response "excited"; "Gastric sensation" includes the responses nausea, "pleasant sick," "nervous stomach," and turning of the stomach.

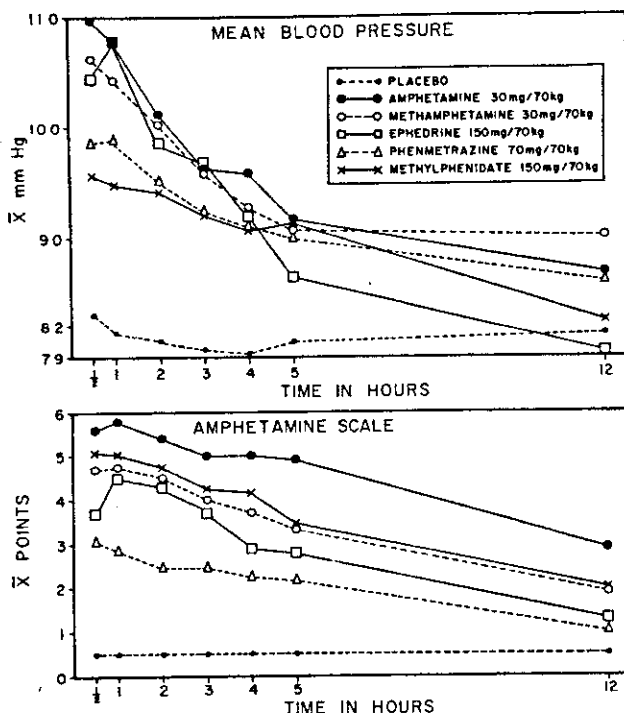


Fig. 4. The time-action curves for approximately equipotent doses of the amphetamine-like drugs.

was much greater than that for ephedrine, methylphenidate, and phenmetrazine.

Table IV summarizes the frequency with which various signs and symptoms were reported on the single dose questionnaires by both patients and observers. "Relaxed" was the most commonly reported sign and symptom. The incidence of feelings of nervousness increased with dose of the drugs, and nervousness was more commonly reported by subjects than observers.

Time course. Fig. 4 shows the time-action course of approximately equipotent doses of all drugs for mean blood pressure and subjective changes as assessed by the amphetamine scale (A). The duration of action of ephedrine on mean blood pressure seemed to be shorter than that of the

other drugs; however, the subjective effects of all drugs persisted for 12 hours, being above placebo level at this time.

Catecholamine excretion. Tables I and V summarize the effects of the drugs on urinary catecholamine excretion. As can be seen, none of the drugs significantly affected the quantity of creatinine excreted. Only the 30 mg. dose level of methamphetamine significantly increased the volume of urine excreted. All drugs increased the excretion of epinephrine in a dose-related manner, and valid potency estimates were obtained for all agents except ephedrine. As can be seen from Table I, the potency estimates for all drugs based on epinephrine excretion were not significantly different from those obtained for the other

Table V. The effects of single doses of *d*-amphetamine, *d*-methamphetamine, ephedrine, methylphenidate, and phenmetrazine on urinary epinephrine, norepinephrine, dopamine, creatinine, and urine volume during the first 3 hours after the drugs were administered

Treatment	No. Subjects	Epinephrine (μ g per 3 hr.)	Norepi- nephrine (μ g per 3 hr.)	Dopa- mine (μ g per 3 hr.)	Creati- nine (mg. per 3 hr.)	Urine volume (ml. per 3 hr.)
Placebo	13	1.90 $\pm$ 0.26	9.1 $\pm$ 1.4	96 $\pm$ 25	262 $\pm$ 53	539 $\pm$ 48
<i>d</i> -Amphetamine, 7.5 mg. per 70 Kg.	13	3.01 $\pm$ 0.39*	12.9 $\pm$ 2.9	346 $\pm$ 262	263 $\pm$ 22	553 $\pm$ 86
<i>d</i> -Amphetamine, 15.0 mg. per 70 Kg.	13	3.66 $\pm$ 0.44*	12.2 $\pm$ 1.7	180 $\pm$ 113	251 $\pm$ 24	699 $\pm$ 72
<i>d</i> -Amphetamine, 30.0 mg. per 70 Kg.	13	3.85 $\pm$ 0.42†	10.6 $\pm$ 1.4	74 $\pm$ 12	221 $\pm$ 20	679 $\pm$ 86
Placebo	12	1.95 $\pm$ 0.28	9.4 $\pm$ 1.5	101 $\pm$ 26	274 $\pm$ 56	563 $\pm$ 45
<i>d</i> -Methamphetamine, 7.5 mg. per 70 Kg.	12	3.41 $\pm$ 0.37†	13.3 $\pm$ 2.3	153 $\pm$ 45	242 $\pm$ 28	647 $\pm$ 83
<i>d</i> -Methamphetamine, 15.0 mg. per 70 Kg.	12	3.80 $\pm$ 0.46†	8.8 $\pm$ 0.6	94 $\pm$ 20	225 $\pm$ 13	730 $\pm$ 113
<i>d</i> -Methamphetamine, 30.0 mg. per 70 Kg.	12	4.35 $\pm$ 0.67†	10.2 $\pm$ 1.2	75 $\pm$ 11	225 $\pm$ 26	767 $\pm$ 101†
Placebo	12	1.70 $\pm$ 0.18	9.0 $\pm$ 1.5	99 $\pm$ 27	267 $\pm$ 57	528 $\pm$ 53
Ephedrine, 75 mg. per 70 Kg.	12	3.03 $\pm$ 1.01	8.8 $\pm$ 0.6	79 $\pm$ 15	246 $\pm$ 16	489 $\pm$ 83
Ephedrine, 150 mg. per 70 Kg.	12	3.94 $\pm$ 0.46†	13.3 $\pm$ 1.5	103 $\pm$ 17	249 $\pm$ 17	559 $\pm$ 82
Placebo	12	1.70 $\pm$ 0.18	9.0 $\pm$ 1.5	99 $\pm$ 57	267 $\pm$ 57	528 $\pm$ 53
Methylphenidate, 15 mg. per 70 Kg.	12	2.99 $\pm$ 0.42†	10.7 $\pm$ 1.0	139 $\pm$ 45	256 $\pm$ 29	542 $\pm$ 69
Methylphenidate, 30 mg. per 70 Kg.	12	3.50 $\pm$ 0.43†	12.3 $\pm$ 0.2	77 $\pm$ 6	231 $\pm$ 17	572 $\pm$ 84
Methylphenidate, 60 mg. per 70 Kg.	12	4.62 $\pm$ 0.57†	10.9 $\pm$ 0.8	68 $\pm$ 5	252 $\pm$ 13	487 $\pm$ 66
Placebo	12	1.70 $\pm$ 0.18	9.0 $\pm$ 1.5	99 $\pm$ 27	267 $\pm$ 57	528 $\pm$ 53
Phenmetrazine, 35 mg. per 70 Kg.	12	2.55 $\pm$ 0.40†	9.7 $\pm$ 1.0	76 $\pm$ 10	245 $\pm$ 19	450 $\pm$ 55
Phenmetrazine, 70 mg. per 70 Kg.	12	3.57 $\pm$ 0.43†	8.4 $\pm$ 1.0	72 $\pm$ 10	244 $\pm$ 19	507 $\pm$ 70

The results are expressed as the mean plus or minus one standard error.

* $p < 0.005$: Different from placebo by a paired comparison *t* test.

† $p < 0.001$: Different from placebo by a paired comparison *t* test.

‡ $p < 0.05$: Different from placebo by a paired comparison *t* test.

parameters. The quantity of norepinephrine excreted under all drug conditions was not significantly different from the placebo condition, although the slope of the dose-response line for ephedrine was statistically significant. Dopamine excretion was not altered by any of the drug conditions when compared to the placebo condition; however, the regression coefficients for the dopamine dose-response relationship for methamphetamine and methylphenidate had a significant negative slope.

Discussion

The mode of action of amphetamine-like drugs in producing central nervous system effects is not known; therefore, at this time classifications of these drugs

must be based on similarities of drug syndromes.

On the basis of physiologic responses as well as subjective changes, amphetamine and methamphetamine were equipotent with respect to most parameters, and no evidence was obtained that supported the view that the central stimulatory actions of methamphetamine relative to its peripheral effects are greater than those of amphetamine in man when the two drugs are administered subcutaneously.

Aside from the fact that phenmetrazine was $\frac{1}{3}$ to $\frac{1}{4}$ as potent as either amphetamine or methamphetamine, it seemed to be qualitatively similar to amphetamine and methamphetamine.

Methylphenidate differed from amphet-

amine, methamphetamine, ephedrine, and phenmetrazine in that pulse rate was positively correlated with blood pressure; whereas, a negative correlation was seen with other drugs. The negative correlation between heart rate and blood pressure was probably a consequence of reflex inhibition of heart rate caused by hypertension. Methylphenidate has been shown to abolish reflex hypertension produced by carotid occlusion,¹⁸ and analysis has shown that the locus of this action is probably in the central nervous system.¹⁹ It is possible that methylphenidate also antagonizes centrally the baroreceptive reflex responsible for bradycardia.

The subjective effects of ephedrine were quite commensurate with its effects on mean blood pressure and did not support the commonly held position that its central effects are less marked than those of amphetamine. Ephedrine was disproportionately weaker than amphetamine in elevating diastolic blood pressure than in elevating systolic blood pressure. It is also noteworthy that ephedrine was the only drug that did not produce a significant degree of mydriasis and was the least effective agent in increasing body temperature.

Several drug effects that may reflect increased activity of central autonomic centers should be mentioned. Although the dose-response relationship for methylphenidate in increasing respiratory rate and rectal temperature and the dose response of methamphetamine in increasing body temperature were quite flat, both drugs induced significant increases of these variables. As previously mentioned, ephedrine did not cause mydriasis and was less effective than the other drugs in elevating body temperature. Interpretation of these disparities is difficult. If taken at face value, they would indicate that methamphetamine, ephedrine, and methylphenidate do differ from amphetamine and phenmetrazine, at least with regard to certain central actions. On the other hand, these discordant results stand by and large in contrast to an over-all concordance of

the potency estimates and may be attributable to sampling, despite the fact that these differences were statistically significant. These discordant results do deserve further investigation to determine if they are due to differences in selectivity of action, differences in intrinsic activity, or differences in modes of action of the drugs.

With regard to the subjective effects, the drugs were similar. Differences between potency estimates derived from the A, BG, and MBG scales should not be overly interpreted, since the items of all three scales assess affective states characterized by happiness, contentment, pleasantness, and feelings of proficiency. The predominant effect at low and intermediate dose levels was the production of feelings of relaxation, well-being, and contentment. Although these feelings were intensified by the largest doses, the largest doses also produced signs and symptoms of nervousness, as well as elevation of LSD scale scores. It is paradoxical that these drugs, which are classified as stimulants, produce symptoms and associated signs of contentment and relaxation; however, this is the most important aspect of their euphoriant actions.

In defining the abuse potentiality of a drug, a variety of factors are of importance including its ability to induce compulsive drug-seeking behavior, its organ and psychotoxicity, and its social toxicity.^{16, 17} As has been previously discussed, the five drugs studied produce similar types of subjective effects and peripheral effects, and because of these similarities it is probable that they have a similar mode of action in producing central changes that cause their abuse. Dependence of the amphetamine type is characterized by the production of compulsive drug use and by a toxic psychosis that is a consequence of intoxication.^{3, 6, 13} The abuse of amphetamine, methamphetamine, methylphenidate, and phenmetrazine is well recognized. Further, severe intoxication with methamphetamine,^{7, 11, 14} phenmetrazine,^{11, 2} and methylphenidate¹⁵ produces toxic psychoses that are in-

distinguishable from that produced by amphetamine. Ephedrine was selected for this study because it is a widely used sympathomimetic amine which, we thought, had not been abused and could therefore serve as a negative control in validating the methods. Review of the literature revealed several case reports of the abuse of ephedrine. Panse²⁰ in his review cites two cases of ephedrine abuse reported by Groenewald in his dissertation in medicine (Düsseldorf, 1960). Subsequently, Herridge and A'Brook¹² reported two cases and Prokop²² one case of ephedrine abuse. In these cases there was not only evidence of compulsive drug-seeking behavior, but all patients developed a toxic schizophrenia-like psychosis. It would thus appear that the constellation of subjective and physiological responses herein described provides a valid measure of the abuse potentiality of amphetamine-like drugs.

Epinephrine was the only catecholamine whose excretion was enhanced by the five sympathomimetic agents studied. The blood pressure changes are more characteristic of those produced by norepinephrine than epinephrine. These findings would be consistent with Vane's²⁴ observation and conclusions that the pressor effect of tyramine and amphetamine is caused by a local tissue release of norepinephrine which is not accompanied by an increase in circulating norepinephrine. The observations in man are difficult to reconcile with the observations of Harvey and associates¹⁰ who found that amphetamine increased blood norepinephrine levels in the anesthetized pithed cat with or without adrenal glands. It is possible that dose level and route of administration may be important differences between the experiments. In Harvey's and associates' study, all doses were administered intravenously, while in our study they were administered subcutaneously. Further, the lowest dose of amphetamine that they studied was 0.5 mg. per kilogram whereas, in the study in man it was 30 mg. per 70 Kg. It is quite certain that the peak levels of amphetamine obtained

in this study would be less than those obtained in Harvey's and associates' study. Of course, species differences may also be of importance.

Studies of Thomä and Wick²⁵ indicate that phenmetrazine is a directly acting sympathomimetic amine since its pressor effect and effect on the nictitating membrane were enhanced rather than antagonized by cocaine. The fact that phenmetrazine enhanced epinephrine excretion in man would therefore suggest that increased activity of the adrenal gland was due to the central activation of efferent sympathetic fibers. There is little evidence that methylphenidate causes the release of either epinephrine or norepinephrine from peripheral sympathetic neurons or that it has a significant direct sympathomimetic action^{18, 19}; therefore, it must be assumed that the peripheral autonomic changes must be a consequence of a central action of methylphenidate. One must further assume on the basis of methylphenidate's peripheral effects that either the central norepinephrine receptors differ from those in the periphery or that methylphenidate interacts with another type of receptor.

If this line of reasoning is correct, and it is based on the assumption that the pharmacology of these agents elucidated in animals is applicable to man, and one further assumes that the similarity of the syndromes of the five amines indicates that they have a similar mode of action, then one must conclude that the euphorogenic and psychotogenic effects of these agents must be due to activation of a receptor other than a noradrenergic receptor; however, these data do not completely rule out the noradrenergic hypothesis because methylphenidate may inhibit the uptake of centrally released norepinephrine since it has other cocaine-like activity^{18, 19} and therefore could increase the amount of norepinephrine available at central postsynaptic receptors.

The authors wish to thank Drs. C. A. Haertzen and R. Hoeldike for their help in the statistical analysis of the data.

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Appendix

My speech is slurred (PCAG).
 I am not as active as usual (PCAG).
 I have a feeling of just dragging along rather than coasting (PCAG).
 I feel sluggish (PCAG).
 My head feels heavy (PCAG).
 I feel like avoiding people although I usually do not feel this way (PCAG).
 I feel dizzy (PCAG).
 It seems harder than usual to move around (PCAG).
 I am moody (PCAG).
 People might say that I am a little dull today (PCAG, negative BG).
 I feel drowsy (PCAG, negative LSD).
 I am full of energy (negative PCAG).

Today I say things in the easiest possible way (MBG).
 Things around me seem more pleasing than usual (MBG).
 I have a pleasant feeling in my stomach (MBG).
 I feel I will lose the contentment that I have now (MBG).
 I feel in complete harmony with the world and those about me (MBG).
 I can completely appreciate what others are saying when I am in this mood (MBG).
 I would be happy all the time if I felt as I feel now (MBG).
 I feel so good that I know other people can tell it (MBG).
 I feel as if something pleasant had just happened to me (MBG).
 I would be happy all the time if I felt as I do now (MBG, negative LSD).
 I feel more clear headed than dreamy (MBG, BG, negative PCAG).
 I feel as if I would be more popular with people today (MBG, A).
 I feel a very pleasant emptiness (MBG, A).
 My thoughts come more easily than usual (MBG, A, BG).
 I feel less discouraged than usual (MBG, A).
 I am in the mood to talk about the feelings I have (MBG, BG).
 I feel more excited than dreamy (A, negative PCAG).

Answering these questions was very easy today (A, BG).
 My memory seems sharper to me than usual (A, BG).
 I feel as if I could write for hours (A, BG).
 I feel very patient (A, negative LSD).
 Some parts of my body are tingling (A, BG, LSD).
 I have a weird feeling (A, LSD).
 My movements seem faster than usual (BG).
 I have better control over myself than usual (BG).
 My movements seem slower than usual (negative BG).
 I find it hard to keep my mind on a task or job (negative BG).
 I don't feel like reading anything right now (negative BG).
 It seems I am spending longer than I should on each of these questions (LSD).
 My hand feels clumsy (LSD).
 I notice my hand shakes when I write (LSD).
 I have a disturbance in my stomach (LSD).
 I have an increasing awareness of bodily sensations (LSD).
 I feel anxious and upset (LSD).
 I have unusual weakness of my muscles (LSD).
 A thrill has gone through me one or more times since I started this test (LSD, negative PCAG).
 My movements are free, relaxed, and pleasurable (negative LSD).

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Effects of diethylpropion and d-amphetamine after subcutaneous and oral administration

The effects of diethylpropion were determined and compared with those of d-amphetamine in 9 subjects using a crossover design. Diethylpropion produced effects qualitatively similar to those of d-amphetamine, but significantly less potent. Orally diethylpropion was $\frac{1}{10}$ to $\frac{1}{11}$ as potent as d-amphetamine while subcutaneously diethylpropion was $\frac{1}{10}$ to $\frac{1}{20}$ as potent as d-amphetamine. A striking difference between diethylpropion and d-amphetamine was the relatively greater oral efficacy of diethylpropion. Diethylpropion was twice as potent orally as subcutaneously while oral and subcutaneous d-amphetamine were equipotent.

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The phenethylamine, diethylpropion (Tenuate, Tepanil), differs structurally from amphetamine (Fig. 1) and is claimed to be a more selective anorexiant than d-amphetamine.¹ The incidence of abuse of diethylpropion is reported to be relatively low.¹⁷

This study characterizes the actions of diethylpropion in man and compares these actions with those of d-amphetamine. It was undertaken to further validate methods established for measuring centrally active sympathomimetic amines in man¹⁸ as well

as to elucidate the modes of action of anorexiant and amphetamine-like stimulants.

Methods

Subjects were 9 federal prisoners with documented histories of narcotic abuse. All admitted prior abuse of amphetamine-like agents. Each was judged to be in good health.

Drugs were administered under double-blind conditions with at least 7 day intervals between drugs. Each of the 9 subjects received the following 13 treatments in random order: placebo condition; d-amphetamine 7.5, 15, and 30 mg administered subcutaneously; d-amphetamine 10, 20, and 40 mg administered orally; diethylpropion 150, 300, and 600 mg administered subcu-

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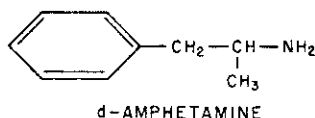
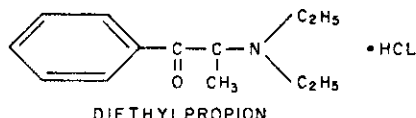


Fig. 1. Structure of diethylpropion and *d*-amphetamine.

taneously; and diethylpropion 100, 200, and 400 mg administered orally.

The methods used in studying these drugs, with some modifications as described below, have been previously reported.¹⁴

Subjective effects and euphoria were measured with drug identifications and "liking scores" from the subject's and observer's single-dose opiate questionnaires and scores on three scales administered as a subjective drug-effect questionnaire. These scales were the "Benzedrine Group" (BG), the "Morphine-Benzedrine Group" (MBG), and the "Amphetamine Scale."¹⁵ The MBG, containing euphoric items, and the BG, containing items relating to intellectual efficiency, were determined with factor-analytic techniques from items in the Addiction Research Center Inventory.¹⁵ The "Amphetamine Scale" is an 11 item subset from the MBG and BG scales demonstrated by Martin and his colleagues¹⁶ to show a significant regression of response against dose for subcutaneously administered *d*-amphetamine.

Physiologic effects measured were systolic and diastolic blood pressures, rectal temperature, pulse rate, and pupil size. Pupillary diameter was determined photographically with the eye 11 inches from a back-illuminated opal glass screen delivering 300 footlamberts of luminance.

The following protocol was followed each test day. At 7:00 and 7:30 A.M., control observations of systolic and diastolic

blood pressure (obtained in duplicate), respiratory rate, pulse rate, and rectal temperature were recorded after subjects had been in a supine position for 10 minutes. Pupils were photographed after each set of observations. At 8:00 A.M., medications were administered both subcutaneously and orally to maintain double-blind conditions. Placebo condition consisted of "blanks" by both routes of administration. At 8:30, 9:00, 10:00, 11:00, and 12:00 A.M., and 1:00, 2:00, and 8:00 P.M., physiologic observations and subjective effects were measured.

Anorexic effects were measured by estimates of the caloric value of food consumed at the noon and evening meals of the test day. Except for noncaloric beverages, subjects fasted from midnight until the noon meal (11:00 A.M.) and then again until the evening meal (5:00 P.M.). At each meal the portion of food chosen was weighed; after eating, the residual food was weighed and this weight was subtracted from the weights of the food chosen. Caloric value was determined from standard charts. Total caloric intake was the sum of the caloric intake for the two meals.

On the morning following the test day, subjects were asked to estimate to the nearest half hour the amount of time they had slept the previous night. From 6:00 P.M. of the test day until 6:00 A.M. the morning following the test day, observers would observe the subject and judge if he was sleeping. For each observation of sleeping, a half hour of sleep time was awarded.

The hydrochloride of diethylpropion and the sulfate of *d*-amphetamine were used. For subcutaneous injection, drugs were dissolved in normal saline. For oral administration, drugs were added to 30 ml of cherry syrup. Normal saline was the subcutaneous blank and 30 ml of cherry syrup was the oral blank.

Results

The four drug conditions—subcutaneously administered diethylpropion, orally

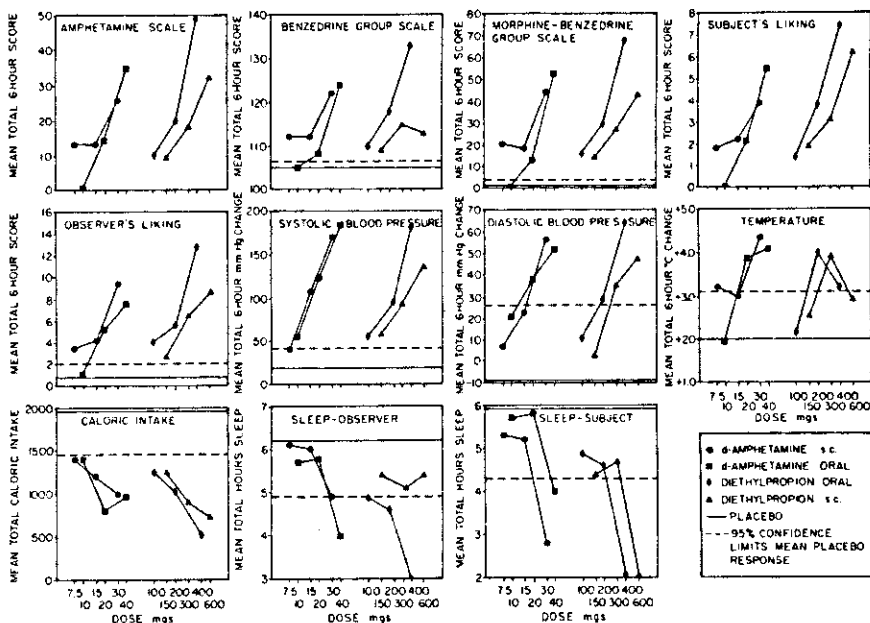


Fig. 2. Dose-response curves for placebo condition, and subcutaneously (s.c.) and orally administered diethylpropion and *d*-amphetamine. Each point represents the mean response of 9 subjects. Responses for subjective scales represent the sum of the scores for the first 7 observations (total 6 hour scores). For blood pressure and temperature, responses are calculated as the sum of the changes from the mean of the predrug controls for the first 7 observations (total 6 hour change). Total caloric intake and total sleep time calculations are described in the text. All subjects gave zero scores on the "amphetamine" and subject's "liking" scales for placebo administration.

administered diethylpropion, subcutaneously administered *d*-amphetamine, and orally administered *d*-amphetamine—produced qualitatively similar subjective effects and euphoria as evidenced by significant dose-related scores on the "Amphetamine Group," "Benzedrine Group," "Morphine-Benzedrine Group," and "liking" scales (Fig. 2). Furthermore, both subjects and observers predominantly identified the four drug conditions as "amphetamine" or "cocaine" (Table I).

By both routes diethylpropion and *d*-amphetamine increased systolic and diastolic blood pressure, increased rectal temperature, and decreased caloric intake (Fig. 2). As reported by observers (Fig.

2), subcutaneously administered diethylpropion and *d*-amphetamine did not produce significant sleep decreases, whereas when administered orally, both drugs decreased sleep. As reported by subjects (Fig. 2), the largest dose of each four drug conditions significantly decreased sleep.

Significant pupillary dilation was observed only with the 300 and 600 mg subcutaneous doses and the 400 mg oral doses of diethylpropion. Tachycardia occurred with all four drug conditions with a trend for pulse rate to be negatively correlated with blood pressure.

Although diethylpropion and *d*-amphetamine produced qualitatively similar syndromes, diethylpropion was less potent

Table I. Drug identification from the single-dose opiate questionnaire for the comparison of placebo condition, with d-amphetamine and diethylpropion*

	Pla- cebo	d-Amphetamine subcutaneous			d-Amphetamine oral			Diethylpropion subcutaneous			Diethylpropion oral		
		7.5	15	30	10	20	40	150	300	600	100	200	400
Subjects†:													
Blank	63	47	43	29	63	42	31	47	30	22	51	31	11
Benzedrine (am- phetamine)	0	14	15	25	0	19	16	10	17	27	12	23	33
Cocaine	0	2	5	8	0	0	7	6	0	7	0	7	10
Marijuana	0	0	0	0	0	0	0	0	0	0	0	0	7
Alcohol	0	0	0	0	0	0	0	0	0	0	0	0	2
Thorazine	0	0	0	1	0	0	0	0	0	0	0	0	0
Miltown or Librium	0	0	0	0	0	0	0	0	2	0	0	0	0
Other	0	0	0	0	0	0	9	0	0	7	0	0	0
Observers‡:													
Blank	58	33	28	10	56	25	13	46	21	9	36	22	2
Benzedrine (am- phetamine)	5	29	22	52	6	36	50	17	42	48	26	41	61
Barbiturates	0	0	13	0	0	0	0	0	0	0	0	0	0
Dope (opiates)	0	0	0	1	1	0	0	0	0	0	1	0	0
Thorazine	0	0	0	0	0	0	0	1	0	0	0	0	0
Other	0	0	0	0	0	0	0	1	0	0	0	1	0

*Numbers represent total responses by all subjects for the first 7 observations. Maximum responses in any category are 63.

†There were no subject identifications of barbiturates, dope (opiates), or LSD.

‡There were no observer identifications of marijuana, alcohol, LSD, Miltown, or Librium.

Table II. Relative potencies and 95% confidence limits from the dose-response curves in Fig. 2 for the comparison of diethylpropion and d-amphetamine*

Parameter†	d-Amphetamine oral equivalent to 1 mg of d-amphetamine subcutaneous (mg)	Diethylpropion oral equivalent to 1 mg of d-Amphetamine oral (mg)	Diethylpropion oral equivalent to 1 mg of diethylpropion subcutaneous (mg)
Amphetamine Scale	1.1 (0.2-3.1)‡	6.6 (3.0- 75.9)§	0.49 (0.20-0.83)‡
Benzedrine Group Scale	1.4 (0.8-4.4)‡	5.5 (2.6- 43.9)§	0.53 (0.19-0.90)‡
Morphine-Benzedrine Group Scale	1.3 (0.7-3.9)‡	6.3 (2.9- 68.5)§	0.48 (0.16-0.85)‡
Subject's liking	1.4 (0.8-3.1)‡	6.4 (3.2- 35.8)§	0.58 (0.31-0.90)‡
Observer's liking	1.4 (0.8-6.8)‡	11.3 (6.6- 26.4)‡	0.50 (0.28-0.74)‡
Systolic blood pressure	1.1 (0.9-1.5)‡	10.9 (3.8-573.1)‡	0.54 (0.34-0.74)‡
Diastolic blood pressure	1.0 (0.2-6.9)§	7.7 (3.0-244.9)§	0.55 (0.26-0.89)‡
Temperature	1.2 (0.6-3.0)§	7.3 (3.0-110.7)‡	0.68 (0.38-0.94)‡
Caloric intake	0.9 (0.1-3.4)‡	8.0 (3.5- 14.8)§	0.56 (0.13-1.2)‡
Sleep—observer	0.8 (0.0-3.9)‡	—¶	—¶
Sleep—subject	1.0 (0.6-1.6)‡	11.7 (5.2- 65.9)‡	0.85 (0.45-1.48)‡

Assays were calculated such that the statistical requirements were met for validity of parallel line bioassays from a randomized block analysis of variance.

†Confidence limits in parentheses.

‡4 point bioassay.

§5 point bioassay.

‡6 point bioassay.

¶Invalid assays.

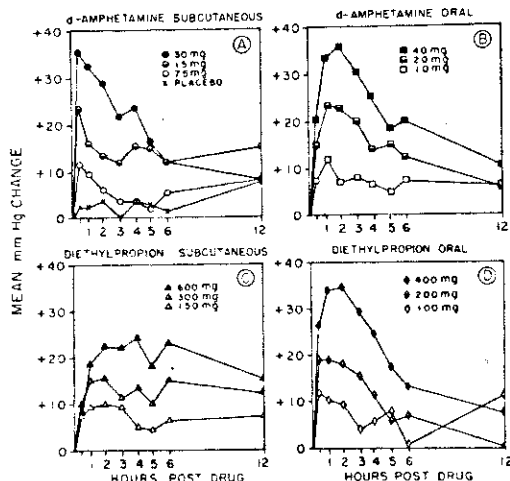


Fig. 3. Time-action curves for changes in systolic blood pressure from the mean of predrug controls following placebo condition and the administration of *d*-amphetamine subcutaneously (A), and orally (B), and diethylpropion subcutaneously (C), and orally (D). Each point represents the mean change from 9 subjects.

than *d*-amphetamine, as indicated by relative potencies (Table II) calculated from the dose-response curves shown in Fig. 2. Oral diethylpropion was $\frac{1}{6}$ to $\frac{1}{11}$ as potent as oral *d*-amphetamine. A striking contrast between diethylpropion and *d*-amphetamine was the potency difference between routes of administration for each drug. Oral *d*-amphetamine was equipotent to or slightly less potent than subcutaneous *d*-amphetamine whereas, in contrast, oral diethylpropion was twice as potent as subcutaneous diethylpropion. Subcutaneous diethylpropion can then be estimated to be $\frac{1}{10}$ to $\frac{1}{20}$ as potent as subcutaneous *d*-amphetamine.

Time-action curves for changes in systolic blood pressure (Fig. 3) indicated trends for differences in the onset of action of the four drug conditions. Subcutaneous *d*-amphetamine (Fig. 3, A) had a prompt onset of action with maximum effects at the half hour postdrug observation while subcutaneous diethylpropion (Fig. 3, C) had a slower onset of action. Relative to the

subcutaneous route, the onset of effects with oral *d*-amphetamine (Fig. 3, B) was slower with peak effects at 1 to 2 hours. Oral diethylpropion (Fig. 3, D) produced effects more promptly than subcutaneous diethylpropion (Fig. 3, C) and possibly more rapidly than oral *d*-amphetamine (Fig. 3, B).

Discussion

Diethylpropion produces a syndrome qualitatively similar to that of *d*-amphetamine as evidenced by identifications as "amphetamine" and "cocaine" responses on scales for subjective effects and euphoria, increases in blood pressure and body temperature, and decreases in caloric intake and sleep. On the other hand, relative potency calculations for these measures indicate that diethylpropion is $\frac{1}{6}$ to $\frac{1}{11}$ as potent as *d*-amphetamine when both are administered orally but $\frac{1}{10}$ to $\frac{1}{20}$ as potent when both are administered subcutaneously. Furthermore, relative potencies for concurrent measures indicate no significant

dissociation among acute anorexiant activity, vasopressor activity, or subjective effects. A significant contrast between diethylpropion and *d*-amphetamine is the oral-to-parenteral potency ratios where diethylpropion is twice as potent orally as subcutaneously, while, in contrast, oral and subcutaneous *d*-amphetamine were nearly equipotent.

The relative potency estimates in these studies correspond to those determined by other investigators. The relative potency of $\frac{1}{6}$ (diethylpropion as *d*-amphetamine) in man for decreases in caloric intake (Table II) corresponds to the acute anorexiant potency estimates of Gyls and his colleagues⁹ of $\frac{1}{5}$ in rats and $\frac{1}{9}$ in dogs for oral diethylpropion and *d*-amphetamine. Boxill and his colleagues² estimated diethylpropion $\frac{1}{10}$ as potent as *d*-amphetamine as a vasopressor in anesthetized dogs; they, too, observed differences in potency estimates for routes of administration in that diethylpropion may have been relatively more potent by intraduodenal administration than by intravenous administration. In man, Jonsson and colleagues¹³ estimated 50 mg of oral diethylpropion equal to 10 mg of oral *d*-amphetamine as a euphoriant.

Existing data suggest that the greater oral effectiveness of diethylpropion may be attributable to greater conversion of diethylpropion to an active metabolite. In man orally administered diethylpropion is metabolized through sequential *N*-deethylation, reduction of the ketone, parahydroxylation of the benzene ring, oxidative cleavage of the nitrogen, and conjugate formation resulting in 21 identified and 2 unidentified metabolites.¹⁴ Metabolites formed by *N*-deethylation or reduction of the ketone have been synthesized and demonstrated to have anorectic, stimulant, and vasopressor activity in animals.* Blood samples taken $\frac{1}{2}$, 2, and 4 hours after oral

administration of 400 mg. of diethylpropion and subcutaneous administration of 600 mg of diethylpropion in one subject not in the crossover study indicated that at these times the levels of diethylpropion were higher following subcutaneous than following oral administration.*

Demonstration of amphetamine-like subjective effects, euphoria, and physiologic effects coupled with reports^{3, 4, 11, 14, 15, 21} of compulsive drug-seeking behavior and psychoses indicate that diethylpropion is appropriately classified as an amphetamine-like drug. Relating the abuse potential of diethylpropion to amphetamine-like agents held to have high abuse potential is difficult since diethylpropion has been marketed for a decade and a half with extremely few reports of abuse. Relating the abuse potential of diethylpropion to centrally active sympathomimetic amines with little or no recognized abuse potential is even more difficult. Ephedrine, a centrally active sympathomimetic amine widely available with almost no abuse, clearly produces amphetamine-like subjective effects, euphoria, and physiologic effects,¹⁶ at least when administered subcutaneously.

Diethylpropion is available only as a 25 mg tablet or 75 mg Dospan (a mucilaginous gel in aqueous solution designed to retard release). As a parenteral euphoriant, the 25 mg tablet would be equivalent to 1 to 2 mg of *d*-amphetamine. It would be necessary to dissolve a large, if not impossible, number of tablets to achieve doses equieuphoric to doses of amphetamine reported for intravenous abuse. Comparatively, the standard 25 mg tablet of ephedrine administered parenterally would be equieuphoric to 5 mg of parenterally administered *d*-amphetamine.¹⁶ Similar considerations of the 75 mg Dospan preparation leads to a conclusion of low likelihood of parenteral abuse. This estimate of low parenteral abuse potential is supported by

*Unpublished data. Project Report D-84-05, Drug Metabolism Department, The William S. Merrell Co., Division of Richardson-Merrell, Inc., Cincinnati, Ohio.

*Plasma samples analyzed by Drs. G. Wright and J. Lang, Drug Metabolism Department, William S. Merrell Co.

lack of reports of sustained intravenous abuse of diethylpropion.

Diethylpropion could more easily be used as an oral euphoriant. The 25 mg diethylpropion tablet would then be equivalent to 2 to 4 mg of *d*-amphetamine. The euphorogenic potential of the 75 mg Dospan preparation cannot be estimated since plasma studies in man following administration of diethylpropion in this preparation indicate delayed absorption.²⁴ The absence of data on the euphorogenic properties following oral administration of other centrally active sympathomimetic amines, especially those of low abuse potential, such as ephedrine, prevent relative comparisons. Consequently, judging relative abuse potential of oral diethylpropion on the basis of relative euphoric properties remains moot. The low incidence of oral abuse may indicate a relatively lower abuse potential than *d*-amphetamine. This estimate is consistent with general experience with other psychoactive drugs pharmacologically equivalent to standard drugs of high abuse potential that are widely available with relatively low levels of abuse. This is especially true of narcotic analgesics with drugs such as codeine,^{11,12} *d*-propoxyphene,^{6,11} and diphenoxylate.⁷ The low abuse potential of these narcotic analgesics is generally held to be related to their availability exclusively or predominantly as oral preparations in low dosage units and to their physiochemical properties, which make intravenous abuse of the agent of preparation difficult or impossible.

On the basis of these studies, diethylpropion appears to be qualitatively similar to *d*-amphetamine in its action with a parental potency half that of ephedrine.

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A comparison of fenfluramine and amphetamine in man

dl-Fenfluramine hydrochloride (60, 120, 240 mg), d-amphetamine sulfate (20, 40 mg), and placebo were compared in 8 postaddict volunteers, each dose given orally in random sequence at weekly intervals using a double-blind crossover design. Fenfluramine had little effect on blood pressure and temperature, but caused a marked dilation of pupils, whereas amphetamine was a potent vasopressor and a weak mydriatic. While fenfluramine produced euphoria in some subjects, its overall effects were unpleasant, sedative, and qualitatively different from amphetamine. Three subjects given 240 mg of fenfluramine experienced brief but vivid hallucinogenic episodes characterized by olfactory, visual, and somatic hallucinations, abrupt polar changes in mood, time distortion, fleeting paranoia, and sexual ideation. These observations indicate that fenfluramine is a hallucinogenic agent with a pharmacologic profile in man that is not amphetamine-like.

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Human subjects given the anorexigenic drug, fenfluramine (N-ethyl-m-trifluoromethyl phenylisopropylamine, Pondimin), often report a sense of unpleasant lethargy from the drug rather than a euphoric "high,"⁸ and concomitant electroencephalographic patterns can be more characteristic of sedative agents than drugs of the amphetamine class.³⁻⁵ Moreover, with animal paradigms of human drug-seeking behavior, fenfluramine is not reinforcing²² and relatively devoid of amphetamine-like sympathomimetic properties.²

From these and other studies, one might conclude that fenfluramine is unique and not likely to lead to amphetamine-like psychotoxicity or

abuse—an estimate corroborated by the very few reports of fenfluramine abuse in Europe where the drug has been available clinically for some years.^{7, 20} On the other hand, Levin has reported descriptions of 60 young men from South Africa (where the drug could be obtained without prescription) who self-administered fenfluramine in doses of 80 to 400 mg on one or more occasions to obtain a euphoric effect.^{15, 16} The constellation of symptoms remembered by these men included hallucinogenic, sedative, and amphetamine-like effects. Of possible concern are still other reports of dysphoria and sleep disturbance after chronic fenfluramine use and abrupt withdrawal.^{12, 19} a like sequence also following amphetamine.

There is therefore the possibility that fenfluramine may have reinforcing properties (amphetamine-like or otherwise) not previously identified in controlled clinical studies. To explore this issue, the subjective and physio-

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logic effects of fenfluramine and amphetamine were compared by using methods previously described by Martin and associates¹⁸ and Jasinski, Nutt, and Griffith.¹³

Methods

Participants were 8 men detained for federal crimes committed in connection with their narcotic use. They ranged in age from 31 to 44 and were in good health, as evidenced by medical history, physical examination, and appropriate laboratory studies, and exhibited no psychiatric impairment beyond drug abuse and concomitant antisocial behavior. All had used narcotics for an average of 18 yr before incarceration; in addition, 7 had also used amphetamine or cocaine, and 4, LSD-like hallucinogens. Participation was voluntary.

The doses of *dl*-fenfluramine hydrochloride (60, 120, 240 mg) and *d*-amphetamine (20, 40 mg) were selected following a dose run-up and on the basis of prior studies,¹⁸ respectively. During dose run-up, 1 subject given 270 mg of fenfluramine reported transient, paranoid thoughts just prior to a euphoric episode. For this reason, and because a demonstration of psychotomimetic effects was not a purpose of this study, the largest dose of fenfluramine used in the crossover was 240 mg, an amount also well tolerated in toxicity studies done elsewhere. A cherry syrup with a trace of quinine added served as both the vehicle for the drugs and as a placebo. Each treatment was administered orally in random sequence at weekly intervals under double-blind conditions.

Subjects were admitted to the ward the evening before their test day and examined to rule out intercurrent illnesses. On the test day, they were awakened at 6:30 A.M., and baseline physiologic observations were made at 7:00 and 7:30 A.M. Treatments were given at 8:00 A.M. Physiologic observations would then be repeated at 0.5, 1, 2, 3, 4, 5, 6, 12, and 24 hr postdrug. These were: (1) duplicate 10-min supine blood pressures as determined by calibrated sphygmomanometer and auscultation; (2) pulse rate; (3) respiratory rate; (4) rectal temperature; and (5) pupil diameter (determined photographically; eye 11 inches from a back-

illuminated opal glass screen and target transilluminated to 300 ft-lamberts). Two-min standing blood pressures and pulse rates were obtained at 3 and 24 hr and compared to the immediately preceding supine values. Urine pH was not controlled in this acute study.

At these postdrug intervals, subjective effects were measured by a group of questionnaires completed by both subjects and observers. These were the Single Dose Opiate Questionnaire for subjects and observers⁶ and a special questionnaire for subjects that consisted of items from the following scales of the Addiction Research Center Inventory¹⁰: MBG (Morphine-Benzedrine Group Scale), a general measure of drug-induced euphoria; LSD (Lysergic Acid Diethylamide Group Scale), a measure of dysphoric and somatic symptoms elicited by graded doses of LSD and certain narcotic antagonists^{11, 12}; and an 11-item Amphetamine Scale, a measure specific for the dose-related effects of *d*-amphetamine.¹⁸ The Amphetamine Scale contains items that relate mainly to concepts of self-confidence and personal assertiveness.

The effects of drugs on food intake were estimated by calculating the caloric value of food actually eaten at the noon, evening, and breakfast meals (using weighed portions and standard tables). Except for noncaloric beverages, including coffee, subjects fasted from midnight until the noon meal and then again until the evening meal (5:00 P.M.).

The morning following the test day, subjects estimated their time asleep to the nearest half-hour. Sleep time was also estimated by observers who inspected subjects at half-hour intervals during the evening and night (6:00 P.M. to 6:00 A.M.).

Dose-effect relationships were determined by partitioning the treatment sums of squares from the analysis of variance for a randomized block design into components to test the significance of the regression mean square of measured total 6-hr response on each measure against dose of amphetamine and fenfluramine. In addition, mean placebo responses and 95% confidence limits of mean placebo response were calculated for each measure to allow dif-

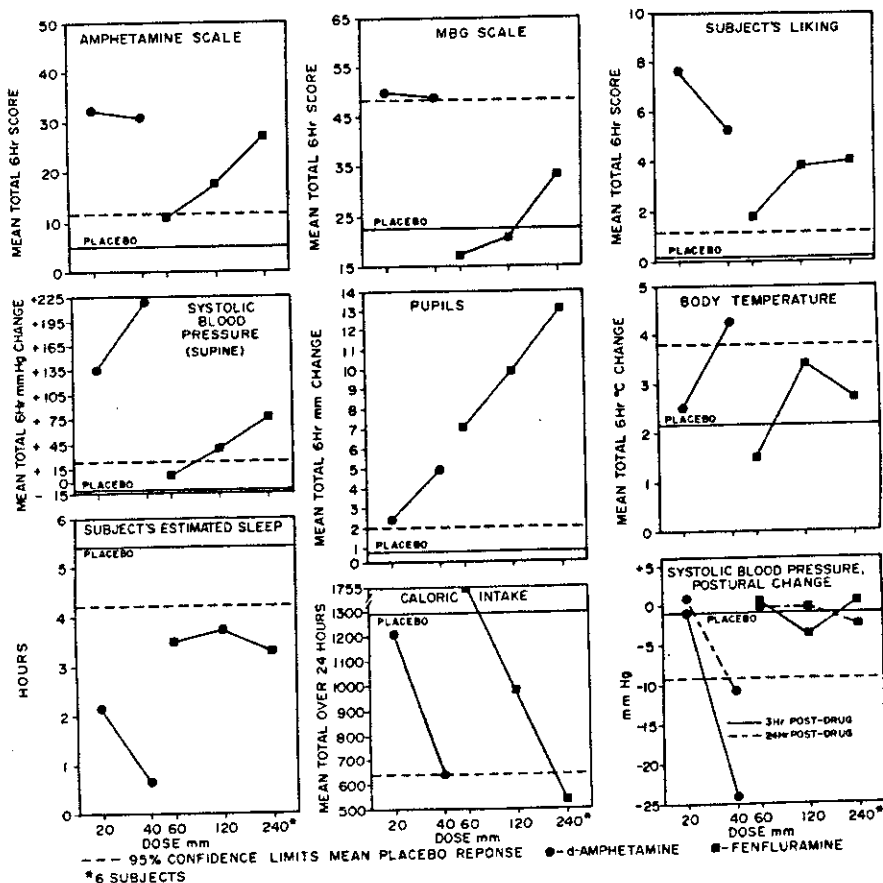


Fig. 1. Dose-response plots for placebo condition and orally administered *dl*-fenfluramine and *d*-amphetamine. Each point represents the mean group response of 8 subjects (6 subjects, 240 mg fenfluramine condition). Responses for subjective scales represent the sum of the scores for the first 7 observations (total 6-hr scores). Blood pressure and temperature responses are calculated as the sum of the changes from the mean of the predrug control for the first 7 observations (total 6-hr change). Caloric intake, sleep time, and postural blood pressure change are described in the text.

ferentiation of fenfluramine and amphetamine effects from placebo.

Results

To compare the effects of fenfluramine and amphetamine during the first few hours after administration, the responses with each mea-

sure for the first 7 observations (total 6-hr scores) were summed and the mean total 6-hr scores were used to construct dose-response as illustrated in Fig. 1. However, some effects persisted as long as 12-24 hr.

Physiological effects. The most prominent physiological effect of fenfluramine was a dose-

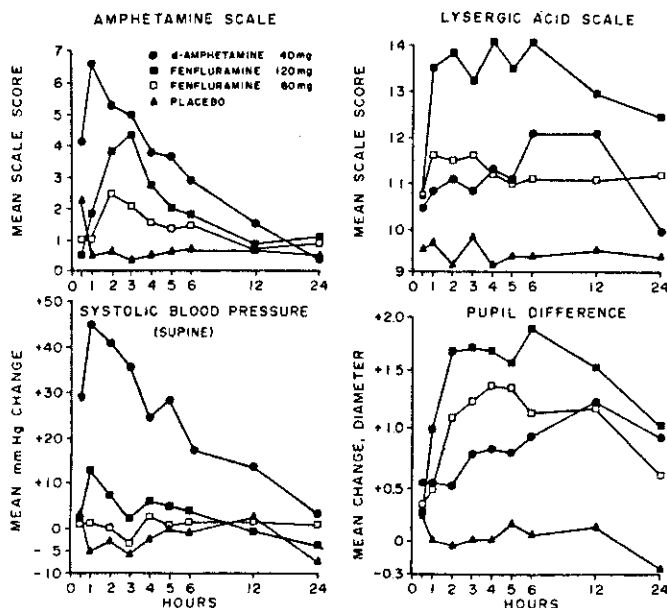


Fig. 2. Time-action curves for amphetamine and fenfluramine. Each point represents the mean change from 8 subjects. Euphoric effects (amphetamine scale) were paralleled by elevation of supine blood pressure while dysphoric effects (LSD scale) were accompanied by mydriasis.

related increase in pupil diameter; the effect of amphetamine by this measure during the first 6 hr was, by comparison, relatively slight (Fig. 1). Fenfluramine also elevated systolic and diastolic blood pressures, but less than did amphetamine. Although not statistically significant, there was a trend for pulse rate to increase with fenfluramine and to decrease with the larger dose of amphetamine. The larger dose of amphetamine caused hyperpyrexia and differences in standing and supine blood pressure, the latter being manifested 24 hr later (Fig. 1). As may be seen in Fig. 2, the pressor effects of amphetamine and fenfluramine generally assumed a time-course paralleled by the duration of euphorogenic effects (Amphetamine Scale). The mydriatic and LSD Scale responses were of much longer duration.

Appetite and sleep. Amphetamine, 40 mg, and fenfluramine, 120 and 240 mg, reduced caloric intake at the three meals following drug administration, but because of a large

variability, only the effects on the noon meal were statistically significant. Valid relative potency calculations for this effect indicate 4.2 mg of fenfluramine equivalent to 1 mg of amphetamine as an anorexiant, but with admittedly wide 95% confidence limits (2-412). Both fenfluramine and amphetamine caused significant reduction in self-estimated sleep time (Fig. 1); only amphetamine, however, reduced observed sleep time.

Subjective effects. Significant degrees of euphoria were produced by amphetamine as indicated by elevated Amphetamine, MBG, and Subjects' Liking Scale scores (Fig. 2). This euphoric response tended to change gradually in a stepwise fashion during the 6-hr interval. The dysphoric items (LSD Scale) elicited by amphetamine were not significantly different from placebo in this small series. Seven of 8 subjects rated the larger dose of amphetamine as more euphorogenic than the 20-mg dose, and a significant dose relationship could be shown

Table I. Drug identifications (single dose questionnaire) for comparison of placebo condition with d-amphetamine and fenfluramine*

Subjects	Placebo	d-amphetamine		Fenfluramine		
		20	40	60	120	240†
Blank	45	25	19	42	23	11
Dope	0	0	0	0	0	0
Cocaine	0	2	0	0	3	0
Marijuana	0	0	0	0	0	0
Barbiturate	0	0	0	0	0	12
Alcohol	0	0	0	0	0	0
Benzadrine (amphetamine)	3	29	36	0	5	8
LSD	0	0	0	6	10	5
Thorazine	0	0	0	0	0	0
Librium	0	0	0	0	0	0
Others	1	0	4	6	1	9

*Numbers represent total response by all subjects for the first 7 observations. Maximum response in any category, =56.

†Six subjects.

among these 7 by Amphetamine, MBG, and Liking Scale measures. One subject, however, denied both euphorogenic and dysphorogenic effects after the 40-mg dose (but not at 20 mg), which flattened the dose-response curve. These effects of amphetamine were generally categorized by subjects as "amphetamine" (Table I). Although subjective effects were accompanied by obvious behavioral changes, no relationship between behavioral change and drug condition or dose condition could be demonstrated.

The response to the 60 mg dose of fenfluramine was modest. Only 3 subjects identified this dose as psychoactive (subjects' liking, Fig. 1; Table I). The effect with the larger doses of fenfluramine was more definite; however, subjects varied considerably in their response to the same dose of fenfluramine and to different doses, and in terms of the manifestation of a particular effect over time. In contrast to amphetamine, the euphoric mood states elicited were of shorter duration, episodic, and accompanied by degrees of personal grandiosity. These euphoric changes would alternate (sometimes in a matter of minutes) with even more striking dysphoric episodes that eventually became the more prevailing and predominant effect. These polar opposites of mood and early psychotomimetic effects were reflected in simultaneous elevations of Amphetamine, Liking, and LSD Scale measures during the first 6 hr. The combined

6-hr MBG Scale response, a more general measure of drug-induced euphoria, was not different from placebo. However, a randomized block analysis of variance of peak MBG scores indicated significant dose-related increases with fenfluramine. These MBG Scale peaks were of short duration (1-2 hr) and associated with peak Amphetamine Scale and blood pressure elevations.

Five of the 8 subjects receiving the 240-mg dose of fenfluramine eventually were sedated and categorized the response as "barbiturate"-like (Table I), although their appearance more resembled that seen following a large dose of phenothiazines. Hallucinogenic phenomena were not observed in these 5. Three other subjects, however, experienced frank hallucinogenic episodes of sudden onset, but without sedative effects.

Hallucinogenic effects. Three subjects sustained clear-cut hallucinogenic syndromes during the crossover assay. This response was not expected and, except as noted, promptly antidoted with diazepam.

Only mild changes were noticed in 1 subject. Approximately 1½ hr postdrug, he became angry and demanded a conference to learn "why people were looking at his television set"—an inappropriate concern because the receiver was locked and secure in his room in another part of the building. In a matter of minutes, however, he experienced a "mellow high," denied being angry, and explained

that his preoccupation was without foundation. He thereafter continued with testing and identified other changes such as time compression and alterations of body image, which came in "waves" for about 5 hr. Because the patient was comfortable, in good contact with staff, and willing to continue, no attempts were made to terminate these symptoms.

With 2 other subjects, hallucinogenic effects were more pronounced. One man with considerable LSD experience became mute some 45 min after taking fenfluramine, and for the next half-hour communicated by making animal-like noises and gestures. Upon recovering his voice, he explained that he had been on a "beautiful trip," which began with his noticing that the shadows cast by the venetian blinds reminded him of a reptilian underbelly. Subjectively, he was very quickly transformed into a large and fearsome dinosaur, searching, during what seemed like a period of years, for his dinosaur wife and child—an experience that culminated in an ecstasy of reunion and closeness with his family group. The subject later explained that he was at all times aware that his experiences were drug-induced and unreal, but his decision to remain mute was to prolong the state as long as possible. The thematic content of his hallucinogenic state was connected by the subject to a troubled domestic relationship.

A second subject also experienced derealization, rapid, and polar alterations of mood, visual hallucinations, distortions of perspective, changes in body image, vivid sexual hallucinations and ideas, and transient paranoia. In contrast to the episodes described above, this subject evaluated his experience as mostly unpleasant, except for the sexual hallucinations. He and the above subject experienced infrequent, short-lived episodes of unreality for 3 days postdrug.

Discussion

Previous studies from the Addiction Research Center have shown the relationship between amphetamine structure and amphetamine activity in man or, more specifically, the pharmacologic profiles obtained by modifications of the isopropylamine side chain (meth-

amphetamine, phenmetrazine, methylphenidate, ephedrine, diethylpropion, benzphetamine). These structural configurations were observed to have a profound effect on weight potencies but pharmacologic profiles were essentially unchanged. In other words, for a given effect on appetite, all drugs produced equal degrees of euphoria and vasopressor change despite differences in physical potency ranging from 1:1 to 1:20.^{13, 18}

It was significant to learn whether a different type of structural modification (ring substitution), as exemplified by fenfluramine, would give qualitative alterations in pharmacologic responses and not merely qualitative differences in overall potencies. Our study indicates that the most conspicuous similarity between the effects of amphetamine and fenfluramine is an anorexigenic effect, fenfluramine being about $\frac{1}{4}$ as potent as amphetamine—an estimate in keeping with other efficacy studies in man²³ and inhibition of food intake by oral fenfluramine in the dog.¹ In rat assays, fenfluramine is relatively more potent,² perhaps because this animal can parahydroxylate the reference drug, amphetamine, more rapidly. This is a minor pathway in man. There is also good evidence that fenfluramine and amphetamine-induced anorexia may involve different pharmacologic mechanisms.^{9, 14, 21}

In most other respects, the effects of fenfluramine were quite different. Fenfluramine, unlike amphetamine, caused substantial and generally dose-related subjective expressions of lethargy, sedation, dysphoria, and unpleasant somatic symptomatology. While fenfluramine was to some degree euphorogenic, as evidenced by elevated Amphetamine and Subjects' Liking Scale scores, this response could be differentiated from amphetamine by the transitory MBG response, subjects' drug identifications, and clinical manifestations. The physiologic profiles were also different. Fenfluramine was a weak vasopressor and a potent mydriatic, whereas amphetamine caused substantial increases in blood pressure and mild pyrexia, but effects on pupils had a rather long latency. Only amphetamine induced significant postural differences in blood pressure. These data indicate that fenfluramine is not amphetamine-

like and probably would not substitute in amphetamine-like patterns of abuse.

In support of Levin's studies,^{15, 16} fenfluramine was observed to have hallucinogenic activity in 3 of 5 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 anorexiatic.

While 3 subjects experienced hallucinogenic phenomena (without sedation), 5 others were moderately sedated following the largest dose of fenfluramine and denied psychotomimetic symptoms. No reasons can be given for these differences. Preliminary data suggest that the hallucinatory response may result from a rapid absorption of oral fenfluramine or its conversion to norfenfluramine.

The similarity between the effects of fenfluramine and endogenous emotional depression, both characterized by symptoms of dysphoria, hypochondriasis, insomnia, emotional lability, and anorexia, is of interest, suggesting that ring-substituted phenethylamines may be used as tools to investigate these functional states.

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14788 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

PROGRESS REPORT ON STUDIES FROM THE CLINICAL PHARMACOLOGY SECTION
OF THE ADDICTION RESEARCH CENTER

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This report presents findings relative to the morphine-like properties of three drugs, d-propoxyphene napsylate, azidomorphine, and butorphanol and to the assessment of three amphetamine congeners, d-benzphetamine, dl-fenfluramine, and chlorphentermine. Brief reference will be made to a peculiar effect of amphetamine on blood pressure.

SECTION I: MORPHINE-LIKE DRUGS

d-Propoxyphene

This drug (Darvon[®]) is a morphine-like analgesic. In recent years, the napsylate salt of this agent has been utilized to maintain or detoxify heroin dependent patients^{1,2,3,4,5} where it was felt that the drug had certain advantages over methadone, i.e., 1) a lower abuse liability; 2) milder degree of physical dependence produced; and 3) greater acceptance by some patient categories. Fraser and Isbell⁶ demonstrated some years ago that the hydrochloride salt of d-propoxyphene had morphine-like effects in man, since the drug produced both miosis and morphine-like subjective effects and suppressed morphine abstinence. Moreover, in direct addiction studies, the hydrochloride produced morphine-like physical dependence. Although d-propoxyphene was less potent than morphine, it was relatively more toxic.

Oral doses of 800-1600 mg of d-propoxyphene napsylate have been recommended for detoxification and/or maintenance of heroin addicts. Larger doses produce untoward manifestations such as convulsions and a toxic psychosis. It is of interest, therefore, to determine the degree of morphine-like activity produced by d-propoxyphene napsylate in this dose range and to determine if this activity is sufficient to suppress abstinence in subjects physically dependent upon 60 mg of morphine/day.

Nine non-dependent subjects were administered the following conditions in random order at weekly intervals: morphine sulfate (10, 20 mg subcutaneously); d-propoxyphene hydrochloride (210, 420, and 600 mg, orally); d-propoxyphene napsylate (310, 620, and 700 mg orally); and placebo (oral capsule and saline, s.q.). To maintain double blind conditions, subjects received both the oral and subcutaneous conditions simultaneously with appropriate substitution of active drug.

One and one-half mg of d-propoxyphene napsylate and 1.0 mg of the hydrochloride contains equal amounts of d-propoxyphene base. Prior studies⁷ have shown that d-propoxyphene, 600 mg, orally, produces effects equivalent to a 20 mg subcutaneous injection of morphine sulfate; and this dose of d-propoxyphene hydrochloride is not convulsive in man. Therefore, 900 mg of the napsylate salt was presumed to be the maximum dose that should be studied. However, during a preliminary dose run-up, 750 mg of d-propoxyphene napsylate produced nervousness, anxiety, apprehension and hyperreflexia (effectively antagonized by naloxone in one subject). For this reason, the

maximum dose of d-propoxyphene napsylate was chosen as molar equivalents to d-propoxyphene hydrochloride (210 and 420 mg).

Drug effects were measured by change in pupil size (measured photographically⁸) and scores on scales from the Subjects' and Observers' Single Dose Opiate Questionnaire,¹⁰ and items from the Morphine-Benzdrine Group (MBG) Scale.¹¹

Subcutaneous morphine and oral d-propoxyphene hydrochloride produced a dose-related miosis and morphine-like subjective effects. d-Propoxyphene was 1/30 to 1/40 as potent as morphine but d-propoxyphene hydrochloride, 600 mg orally, and morphine, 20 mg subcutaneously, produced equivalent effects (Fig. 1). These findings, with the hydrochloride are similar to observations reported previously.

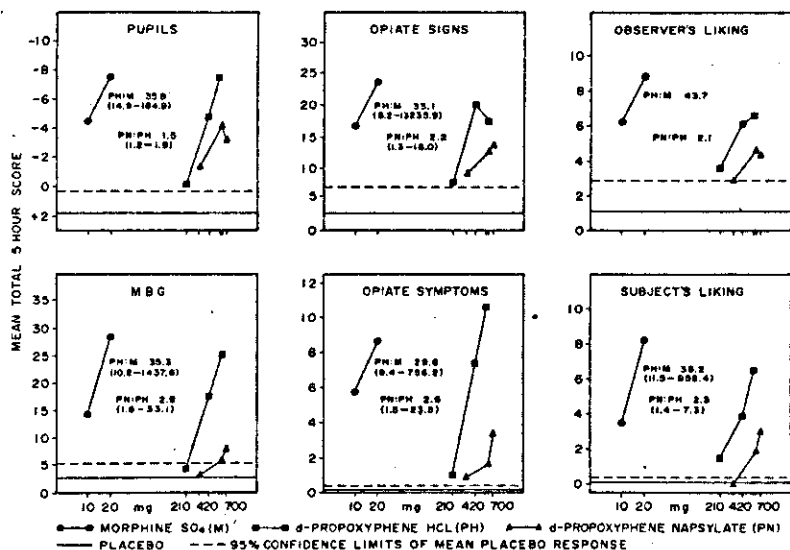


Figure 1. Dose response curves utilizing total 5 hour scores for the comparison of orally administered d-propoxyphene napsylate, orally administered d-propoxyphene hydrochloride and subcutaneously administered placebo. Potency estimates with 95% confidence limits in parentheses are expressed as mg of d-propoxyphene napsylate orally equivalent to 1 mg morphine sulfate subcutaneously (PH:M) and mg of d-propoxyphene napsylate orally equivalent to 1 mg d-propoxyphene hydrochloride orally (PN:PH):

No response to orally administered d-propoxyphene napsylate was greater than that observed with 10 mg of subcutaneous morphine (Fig. 1). For this reason, valid relative potencies could not be obtained using morphine (10 and 20 mg) as a reference drug. Potency estimates were then calculated between the d-propoxyphene napsylate and d-propoxyphene hydrochloride using the responses to the two lower doses of the d-propoxyphene hydrochloride as a standard. A valid relative potency estimate on pupils of 1.5 was obtained which would be expected for the two salts on the basis of equal base content. A tendency for the salt of the napsylate to be less potent was indicated by the various scale scores (Fig. 1); however, because of the wide confidence limits, these differences in potencies were not statistically significant.

The data was further analyzed to determine if there is any difference in the onset of action between d-propoxyphene napsylate and the hydrochloride since plasma concentration studies in dogs administered large toxic doses of d-propoxyphene indicate delayed absorption of the napsylate salt.¹² Time action curves for d-propoxyphene napsylate, 620 mg, and d-propoxyphene hydrochloride, 420 mg, (containing equal amounts of base) were compared and also to the response to d-propoxyphene napsylate, 700 mg orally, and placebo (Fig. 2). The napsylate, at these dose levels, appears to have a longer latency to onset.

The second group of experiments was conducted using subjects dependent upon 60 mg of morphine administered subcutaneously (15 mg q.i.d.). This level of dependence has been shown to be associated with a discomforting abstinence syndrome upon abrupt withdrawal¹³ and with sufficient dependence to conduct substitution and precipitation tests. The first series of experiments were 24 hour substitution tests,¹⁴ each subject being given, in place of regular doses of morphine, the following drugs: placebo (oral capsule plus subcutaneous injection); morphine 3 and 6 mg subcutaneously, d-propoxyphene hydrochloride 110 and 220 mg orally, and d-propoxyphene napsylate 165 and 330 mg orally. Each of these doses was administered double blind at weekly intervals 3 times for 3 consecutive 15 mg maintenance doses of morphine. Double blind conditions were maintained by administration of appropriate blank medications so that subjects received an oral capsule and an injection each time. From the 14th through the 24th hour after the last stabilization dose of morphine observations were made hourly for withdrawal sickness as 0 = not sick; 1 = slightly sick; 2 = moderately sick; 3 = severely sick.

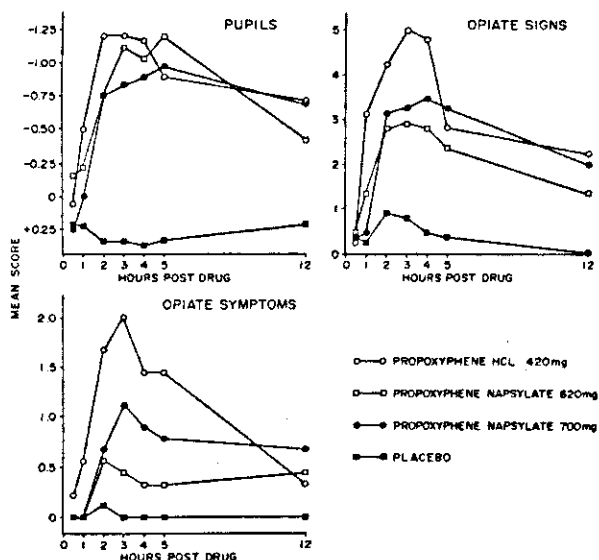


Figure 2. Time action curves from the comparison of orally administered d-propoxyphene napsylate, orally administered d-propoxyphene hydrochloride, and subcutaneously administered morphine sulfate. The 420 mg dose of d-propoxyphene hydrochloride and the 620 mg dose of d-propoxyphene napsylate represent approximately equal amounts of d-propoxyphene base.

Subcutaneous morphine, oral d-propoxyphene napsylate, and oral d-propoxyphene hydrochloride suppressed abstinence scores significantly as shown in Figure 3. In addition, all diminished sickness scores relative to the placebo condition. These results indicate that both d-propoxyphene napsylate and the hydrochloride salt are capable of suppressing abstinence signs and symptoms. Valid relative potencies were not obtained in these

studies because the statistical criteria were not met. However, it was estimated that d-propoxyphene hydrochloride is approximately 1/24 as potent as subcutaneous morphine in suppressing abstinence and d-propoxyphene napsylate is roughly about 1/49 as potent as morphine.

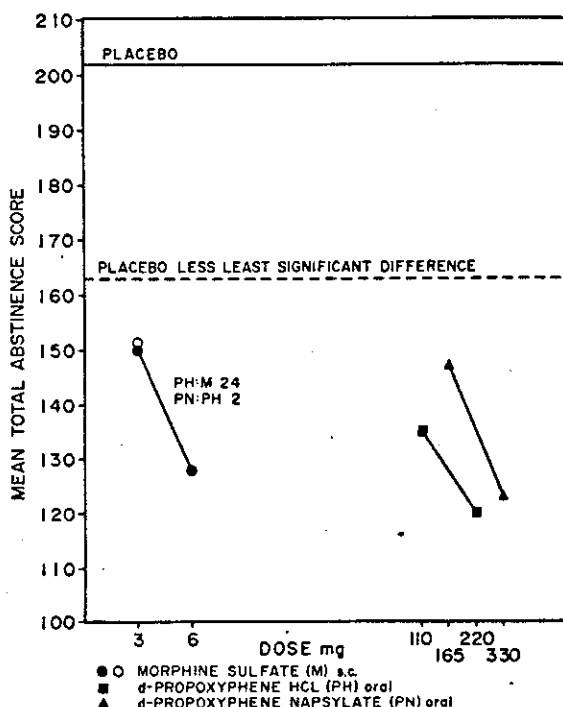


Figure 3. Total abstinence scores from 24 hour substitution studies in subjects dependent upon 60 mg morphine per day with morphine subcutaneously, d-propoxyphene napsylate orally, and d-propoxyphene hydrochloride orally. The least significant difference was determined from randomized blocks analysis of variance. The open circle for the morphine, 3 mg, represents a replication of that treatment one week following the completion of the other substitutions.

Following this, 2 of the 4 subjects participated in an additional experiment in which oral d-propoxyphene napsylate (300 mg q.i.d.) was completely substituted for chronic morphine. For 2 weeks subjects received a double blind injection of 15 mg morphine subcutaneously and a blank capsule (lactose). Daily observations were made which included observations for abstinence scores (daily Himmelsbach scores) as well as completion of a questionnaire¹⁰ designed to measure the chronic effects of opiates and the effects of abstinence. Capsules containing d-propoxyphene napsylate were gradually substituted for the morphine until after a period of 9 days subjects were maintained on 1200 mg/day of orally administered d-propoxyphene napsylate (Table 1). For the next 10 days this dose of d-propoxyphene napsylate was maintained as were all observations. During the transition phase, when the subjects were receiving both morphine and d-propoxyphene napsylate, there were significant Himmelsbach scores indicating mild abstinence with subjects reporting "kicking" (Table 1). However, the transition from morphine to d-propoxyphene was purposefully slow to minimize these abstinence symptoms so that subjects felt comfortable. During the period of maintenance on d-propoxyphene napsylate alone the demonstration of Himmelsbach scores suggested mild abstinence was present (Table 1). A number of symptoms were reported during this maintenance on d-propoxyphene napsylate which included feelings of persistent tiredness, weakness, lethargy; additionally there were initially, episodic feelings of elation, euphoria, palpitations and restlessness described by the subjects as effects most closely resembling those following amphetamine and cocaine. During this period of maintenance on d-propoxyphene, caloric intake was suppressed and the subjects lost body weight. The major source of points in the abstinence scores during this period of maintenance on d-propoxyphene were due to this decrease in caloric intake and continuing loss of body weight. On the 21st day of the experiment placebo capsules were substituted for the daily maintenance dose of d-propoxyphene napsylate (Table 1). Both subjects immediately perceived the substitution and reported withdrawal sickness (Table 1). During the next few days abstinence scores increased reaching a peak on the second or third days of substitution. Both subjects additionally identified this as mild abstinence and reported that the drug made them feel bad and were uncomfortable. On the eighth day a 2.5 mg dose of morphine was administered because of these feelings of uncomfortableness.

Table 1. Responses by subjects and observers to chronic opiate questionnaires, daily drug doses and daily Himmelsbach scores for the substitution of d-propoxyphene napsylate for morphine.

Day	Morphine	d-Propoxyphene Napsylate	Himmelsbach Score	SUBJECT #1		SUBJECT #2	
				Kicking+ Sub. Obs.	Feelst+ Sub. Obs.	Kicking+ Sub. Obs.	Feelst+ Sub. Obs.
1	45	250	6	N	0	Y	-1
2	30	500	5	Y	-3	Y	-3
3	30	600	11	N	0	Y	-1
4	32.5	600	12	N	0	Y	-1
5	25	900	12	N	-1	Y	-2
6	15	900	7	N	0	Y	-2
7	20	900	14	N	-1	Y	-2
8	5	1200	7	N	0	Y	-1
9	7.5	1200	13	N	-1	Y	-1
10	0	1200	8	N	-1	Y	0
11	0	1200	10	N	-1	Y	-1
12	0	1200	12	N	0	Y	-1
13	0	1200	15	N	0	N	-1
14	0	1200	14	N	0	N	-1
15	0	1200	11	N	0	N	0
16	0	1200	18	N	0	N	0
17	0	1200	20	N	0	N	0
18	0	1200	17	N	0	N	0
19	0	1200	17	N	-1	N	-1
20	0	1200	17	N	-1	N	-1
21	0	0	21	Y	-1	Y	-1
22	0	0	21	Y	-1	Y	-1
23	0	0	22	Y	-1	Y	-1
24	0	0	24	Y	-1	N	0
25	0	0	22	Y	-2	N	-1
26	0	0	21	Y	-2	N	-1
27	0	0	24	Y	-1	N	0
28	2.5	0	22	Y	-1	N	0
29	5	0	26	Y	-1	N	0
30	0	0	22	N	-1	N	0

† Responses (yes or no) to question, "Are you (is patient) kicking?"

‡ How do you (does patient) feel? Very good +2; Good +1; Average 0; Slightly bad -1; Moderately bad -2; bad -3; Very bad -4.

On the basis of these studies the following conclusions are made:

- 1) Single oral doses of d-propoxyphene napsylate can produce morphine-like activity equal to 10 mg of morphine subcutaneously
- 2) d-Propoxyphene napsylate orally can suppress the signs and symptoms of abstinence in subjects dependent upon 60 mg of morphine per day administered subcutaneously
- 3) Abrupt withdrawal of chronically administered d-propoxyphene napsylate, 1200 mg orally/day, is associated with a morphine-like abstinence syndrome
- 4) Daily oral doses of d-propoxyphene napsylate, 1200 mg, would be equivalent in morphine-like activity to 20 mg of subcutaneously administered morphine daily. By extrapolation, this level of morphine-like activity would be equivalent to that of 10 mg of heroin parenterally or 10 mg of methadone orally.

Evaluation of Azidomorphine for Morphine-like Effects

Azidomorphine (Fig. 4), a morphine derivative, is 40 to 300 times more potent than morphine as an analgesic in man and animals but in equianalgesic doses is reported to be less toxic and to produce lesser degrees of physical dependence than morphine.^{17,18,19}

The miotic and morphine-like subjective effects of azidomorphine as well as its ability to suppress abstinence was assessed.

Miosis and Subjective Effects

Seven, non-dependent subjects received the following drugs at weekly intervals: azidomorphine bitartrate, 0.35 mg, 0.70 mg, 1.40 mg and 1.80 mg; morphine sulfate 15 and 30 mg; and placebo (normal saline). All drugs were administered subcutaneously in random order under double-blind procedures. Drug effects were measured by changes in pupil size, measured photographically; Subjects' and Observers' Single Dose Opiate Questionnaires;^{9,10} and from the Morphine-Benzedrine Group Scale (MBG) of the Addiction Research Center Inventory.¹¹

Control photographs were obtained at 0700 and 0730. Drugs were administered at 0800 subcutaneously under double blind conditions and at 0830, 0900, 1000, 1100, 1200 and 1300 pupil photographs were repeated and questionnaires were completed.

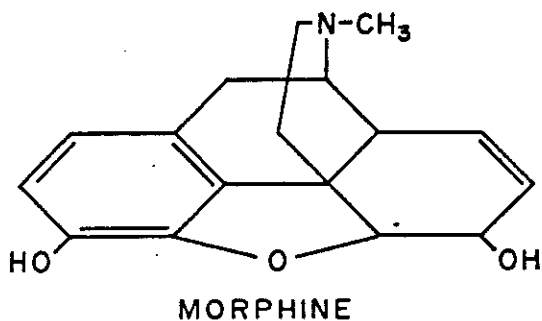
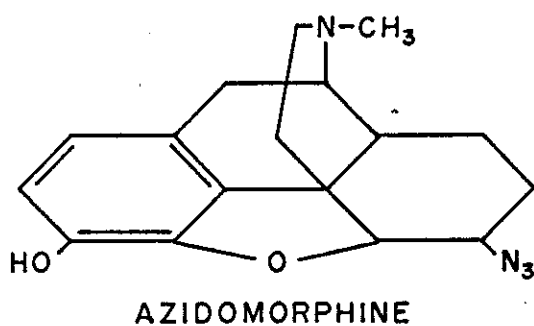


Figure 4. Structure diagrams of azidomorphine (6-deoxy-6-azido-dihydroisomorphine) and morphine.

Azidomorphine produced dose-related morphine-like subjective effects and miosis, as shown by the decreases in pupil size and elevated MBG Scale scores, Opiate Signs and Symptoms scores and Subjects' and Observers' "liking" scores (Fig. 5). Both azidomorphine and morphine had similar profiles (Table 2) and azidomorphine was consistently identified as an opiate (Table 3). Relative potency calculations, meeting the statistical criteria for valid bioassays, indicate that azidomorphine bitartrate is 10 to 50 times more potent than morphine sulfate (Table 4). Comparison of the time action curves for the effects of azidomorphine 1.8 mg; morphine 30 mg; and placebo on these same measures indicates that azidomorphine may have a more rapid onset and a shorter duration of action than morphine (Fig. 6).

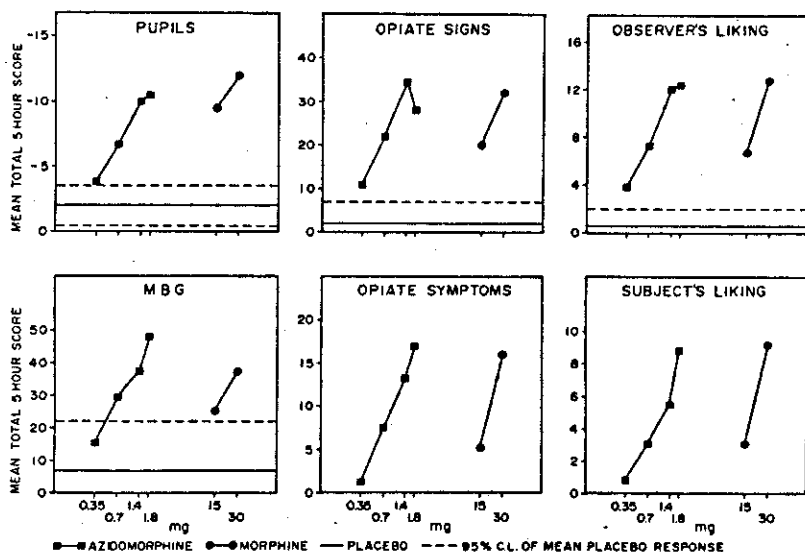


Figure 5. Dose-response curves utilizing total 5 hour sums from the comparison of azidomorphine, morphine and placebo.

Table 2. Opiate signs and symptoms: Responses to morphine and azidomorphine on the single dose opiate questionnaires.

Response	Placebo	Morphine		Azidomorphine			
		15 mg	30 mg	0.35 mg	0.7 mg	1.4 mg	1.8 mg
Opiate Signs							
Normal	38	9	0	20	7	2	3
Scratching	1	22	34	16	27	35	29
Red-eyed	3	12	19	0	12	20	15
Relaxed	4	33	42	20	36	39	39
Coasting	0	10	19	4	10	24	16
Soapboxing	1	16	18	9	13	19	19
Vomiting	0	0	7	0	0	2	1
Nodding	0	0	1	0	1	0	1
Sleepy	3	2	5	4	9	8	8
Nervous	0	2	15	1	1	8	14
Drunken	0	0	1	0	0	1	0
Other	1	5	11	1	9	27	5
Opiate Symptoms							
Normal	42	20	6	39	24	16	13
Turning of stomach	0	6	15	0	6	8	6
Skin itchy	0	2	14	2	7	16	23
Relaxed	0	6	17	3	14	18	15
Coasting	0	4	11	0	4	7	9
Soapboxing	0	0	7	2	4	7	9
Pleasant sick	0	11	11	0	5	5	7
Drive	0	0	1	0	0	2	5
Sleepy	0	2	6	0	0	2	2
Nervous	0	0	5	0	1	3	0
Drunken	0	0	0	0	0	0	6
Other	0	0	0	0	0	0	0

Each value represents the total number of responses obtained in the total 5 hour observation period for all patients. Maximum number of responses for any one category is 42.

Table 3. Drug identification patterns on the single dose opiate questionnaires.

Identification	Placebo	Morphine		Azidomorphine			
		15 mg	30 mg	0.35 mg	0.7 mg	1.4 mg	1.8 mg
By Observers							
Blank	38	9	0	20	8	2	3
Dope	4	33	42	22	35	40	39
By Subjects							
Blank	42	22	8	39	25	16	13
Dope	0	20	32	3	17	26	29
Barbiturate	0	0	1	0	0	0	0
Other	0	0	1	0	0	0	0

Each value represents the total number of responses obtained in the total 5 hour observation period for all patients. Maximum number of responses for any one category is 42. Cocaine, marihuana, alcohol, benzedrine, L.S.D., Thorazine^(R), and Miltown^(R) or Librium^(R) identifications were not reported by observers or subjects.

Table 4. Relative potencies of azidomorphine bitartrate and morphine sulfate.⁺

Parameter	Total 5 Hour Response	Peak Response
Pupils	0.09(0.000 to 0.246) ^{4,†}	0.07(0.002 to 0.185) ⁵
Opiate Signs	0.04(0.009 to 0.092) ⁵	0.04(0.006 to 0.105) ⁵
Observers' Liking	0.05(0.015 to 0.098) ⁶	0.04(0.008 to 0.097) ⁵
M.B.G.	0.04(0.004 to 0.109) ⁶	0.02(0.000 to 0.099) ^{4,†}
Opiate Symptoms	0.05(0.007 to 0.112) ⁶	0.03(0.002 to 0.096) ⁵
Subjects' Liking	0.06(0.011 to 0.131) ⁶	0.04(0.009 to 0.101) ⁶

⁺Potencies expressed as mg azidomorphine bitartrate equivalent to 1 mg morphine sulfate with 95% confidence limits in parenthesis. Superscripts following parenthesis indicate number of points used in parallel line bioassays.

[†]Values for confidence limits 0.0004 and lower are shown as 0.000.

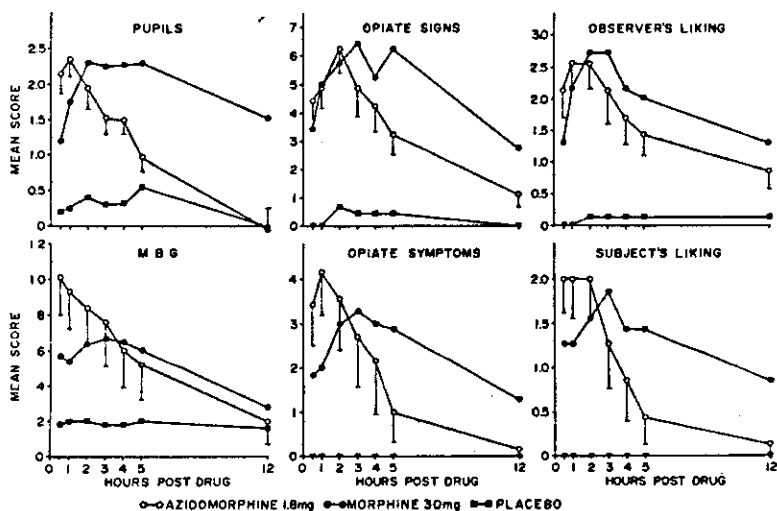


Figure 6. Time action curves for placebo, azidomorphine, 1.8 mg, and morphine, 30 mg. Brackets represent the standard error of the mean placebo response.

Substitution Studies

The ability of azidomorphine to substitute for morphine and suppress morphine abstinence was determined in 5 subjects dependent upon 60 mg of morphine administered subcutaneously daily (15 mg q.i.d.). The 24 hour substitution procedure^{13,14} was used in which each subject received 3 double blind medications in place of 3 consecutive doses of morphine and from the 14th to the 24th hour of substitution observations were made hourly for abstinence signs. At these same times subjects rated their degree of withdrawal sickness as 0 = not sick; 1+ = slightly sick; 2+ = moderately sick; and 3+ = very sick. Control responses to placebo, morphine, 3 mg, and morphine, 6 mg, were obtained initially. Each subject then received a dose of 1.8 mg of azidomorphine in the 24 hour substitution procedure (total dose 5.4 mg). In these studies azidomorphine effectively substituted for morphine and suppressed abstinence (Table 5).

Table 5. Total abstinence and sickness scores during the 24 hour substitution test.⁺

Drug	Abstinence Score	Sickness Score
Placebo	189.6 $\pm$ 24.9	10.6 $\pm$ 2.2
Morphine 3 mg	154.2 $\pm$ 24.4	10.0 $\pm$ 0.8
Morphine 6 mg	130.2 $\pm$ 20.0 [†]	4.6 $\pm$ 2.0 [†]
Azidomorphine 1.8 mg	106.4 $\pm$ 15.4 [‡]	1.8 $\pm$ 1.1 [‡]

⁺Total scores represent the means and standard errors for 11 observations in 5 subjects in which placebo, morphine and azidomorphine were substituted for 3 consecutive 15 mg doses of morphine.

[†]Significantly different from placebo as calculated using 2-way analysis of the variance and the method of least significant differences.

These present studies indicate that azidomorphine has morphine-like activity in man as indicated by its ability to produce morphine-like subjective effects, miosis and to suppress morphine abstinence. Azidomorphine is 10 to 50 times more potent than morphine and may have a somewhat more rapid onset and shorter duration of action.

Evaluation of Butorphanol for Morphine-like Effects

The morphinan derivative, butorphanol, (α -BC-2627) (Fig. 7) is a morphine antagonist having analgesic activity in man and animals.²⁰ Butorphanol does not substitute for morphine nor suppress abstinence in the morphine-dependent monkey.²⁰ Butorphanol is currently being evaluated for the ability to produce dependence of the morphine type in man.

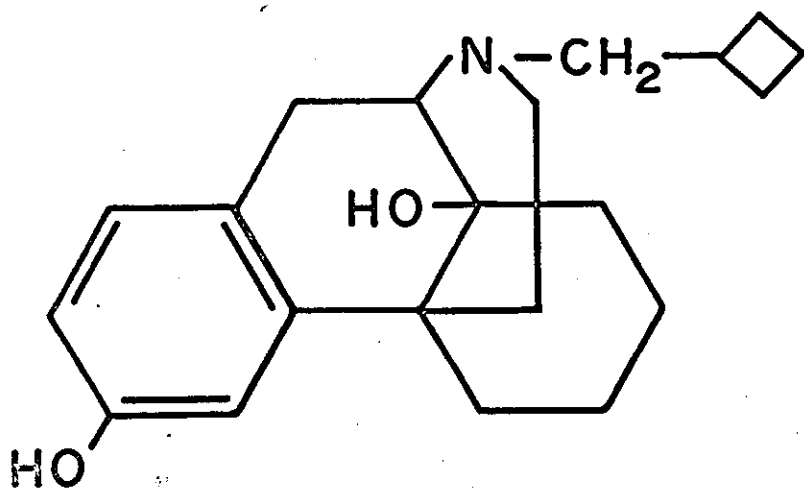


Figure 7. Structure diagrams of butorphanol (1-BC-2627, 1-N-cyclobutylmethyl-3, 14 8-dihydroxymorphinan).

Miosis and Subjective Effects

Initially, single doses of butorphanol, morphine and placebo were compared to determine the ability of butorphanol to produce morphine-like subjective effects and miosis. Ten subjects received at weekly intervals, placebo (normal saline), morphine sulfate, 7.5, 15 and 30 mg; and butorphanol tartrate, 2, 4, and 8 mg. Drug effects were measured by change in pupil size, measured photographically; Subjects' and Observers' Single Dose Opiate Questionnaires^{9,10} and items on the Morphine-Benzedrine Group (MBG) Scale, a general measure of drug induced euphoria; the LSD Scale, a measure of early psychotomimetic and dysphoric effects; and the Pentobarbital-Chlorpromazine-Alcohol Group (PCAG), a measure of apathetic sedation.¹¹ Control pupil observations were taken each day at 0800 and 0830. Drugs were administered subcutaneously under double-blind conditions at 0800. At 0830, 0900, 1000, 1100, 1200, 1300, 1400 and 2000 pupils were again photographed and questionnaires were

completed. Time action curves on changes in pupil size and the various scale scores indicate that the duration of action of butorphanol appears to be similar to that of morphine through the 12 hours (Fig. 8). Dose response curves (Fig. 9) were constructed on these same measures using the mean total 5 hour responses (sum of the first 6 responses). Compared to morphine (Fig. 9; Table 6, 7), butorphanol produced certain effects similar to morphine, including pupillary constriction, significant dose-related scores on Symptoms and Signs Scales, "Liking" Scales, and identification as an opiate by subjects and observers. Butorphanol, however, did not produce significant scores on the MBG Scale (a measure of drug-induced euphoria), but did produce significant LSD and PCAG Scale elevations (Fig. 9). Butorphanol was also identified as a barbiturate more frequently than morphine and produced "nervousness" and "drunkenness" more frequently than morphine (Table 6, 7). Thus, the overall profiles of butorphanol appear to resemble those produced by agents such as nalorphine and cyclazocine. Potency estimates meeting statistical criteria for validity were obtained on certain of the measures (Fig. 9) indicating butorphanol tartrate was 1/3 to 1/5 as potent as morphine sulfate.

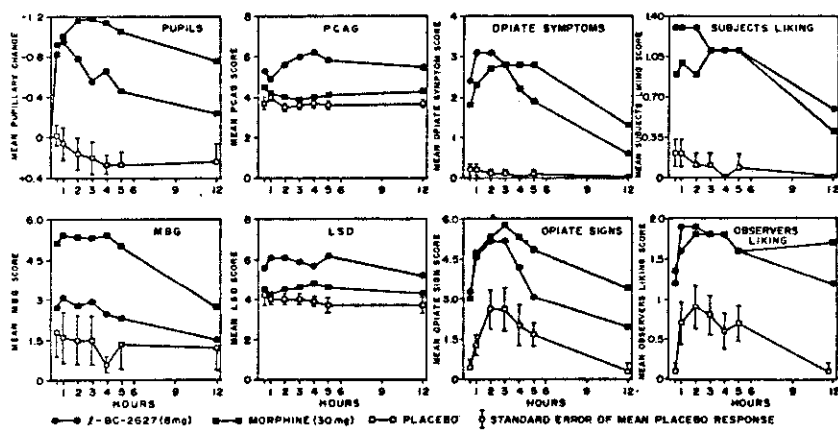


Figure 8. Time action curves for changes in pupil size and scores on scales for placebo, morphine, 30 mg, and butorphanol (1-BC-2627), 8 mg.

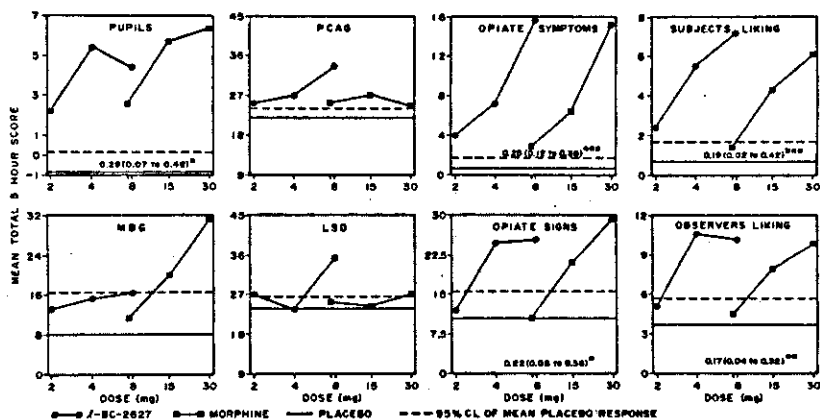


Figure 9. Dose response curves utilizing total 5 hour responses from the comparison of butorphanol, morphine and placebo. Numbers represent statistically valid relative potencies with 95% confidence limits in parentheses expressed as mg of butorphanol equivalent to 1 mg morphine. Four point assay*, five point assay**, six point assay***.

Table 6. Cumulative responses to symptoms and signs from the Single Dose Opiate Questionnaires. Maximum response in any category is 70.

Symptoms	Placebo	Butorphanol			Morphine		
		2.0	4.0	8.0	7.5	15	30
Normal	63	44	20	6	55	32	18
Turning of Stomach	---	5	3	4	5	1	18
Skin Itchy	---	4	4	15	---	6	23
Relaxed	5	7	24	23	9	24	37
Coasting	---	---	10	15	---	9	20
Soap Box	2	2	---	---	5	9	10
Pleasant Sick	---	---	---	1	4	2	4
Drive	---	---	---	1	---	---	---
Sleepy	---	1	10	16	---	3	4
Drunken	---	4	7	30	---	---	---
Nervous	---	10	4	16	---	1	1
Other	---	2	2	9	4	2	5
Signs							
Normal	40	29	9	3	31	15	8
Scratching	8	6	23	22	12	28	49
Red Eyes	46	7	26	13	2	20	42
Relaxed	28	34	60	56	37	18	62
Coasting	8	11	16	34	12	18	20
Soap Box	11	29	26	45	25	41	43
Vomiting	1	---	1	---	---	---	3
Nodding	---	3	10	2	---	1	3
Sleepy	10	5	15	16	2	1	9
Nervous	5	10	4	17	1	1	---
Drunken	---	1	9	17	---	6	6
Other	2	6	16	13	9	12	17

Table 7. Cumulative identifications by subjects and observers from the comparison of butorphanol, morphine and placebo. Maximum responses in any category is 70.

Subjects	Placebo	Butorphanol			Morphine		
		2.0	4.0	8.0	7.5	15	30
*Identified as: Blank	63	44	19	6	53	33	19
Dope	3	3	24	30	11	26	47
Barbiturate	2	14	24	22	---	6	1
Alcohol	---	---	---	7	---	---	---
Other	2	9	3	12	6	5	7
Observers							
*Identified as: Blank	40	29	9	5	31	15	8
Dope	21	34	14	50	39	48	62
Barbiturate	---	4	4	10	---	---	---
Alcohol	---	---	---	5	---	6	---
Amphetamine	---	1	7	1	---	---	---
Other	7	15	20	27	9	1	6

*The following choices were listed but were not chosen as identifications: cocaine, marihuana (pot), LSD (acid), Thorazine, Miltown or Librium.

Despite the unpleasant side-effects noted, subjects also evidenced "liking" scores which equalled those produced by 30 mg of morphine (Fig. 9). One interpretation of these "liking" scores is that butorphanol is more reliably euphorogenic than agents such as nalorphine or cyclazocine and suggests that there may be a difference in the profiles of subjective effects produced by agents such as pentazocine, cyclazocine and butorphanol.

An additional study was conducted to compare the subjective effects of pentazocine, butorphanol, cyclazocine and morphine. The same experimental procedures and methods were utilized as described above except that the last observation time was omitted. Nine subjects participated. Each received in random order at weekly intervals the following medication: placebo (normal saline); cyclazocine (base), 0.5 and 1.0 mg; pentazocine (base), 40 and 80 mg; butorphanol (salt), 2 and 4 mg; and morphine sulfate (salt), 10 and 20 mg. One subject did not complete the 1 mg cyclazocine treatment because he found this dose to be extremely disturbing. Consequently, the responses to cyclazocine, 1 mg, are based on 8 subjects.

The effects of butorphanol, cyclazocine and pentazocine could be differentiated from morphine by elevated PCAG and LSD Scale scores; greater responses on the symptoms and signs categories, "sleepy," "drunken," "nervous"; and a tendency to identify these effects as barbiturate-like (Fig. 10; Tables 8, 9). Relative potencies (Table 10) were similar to those obtained previously for butorphanol (Fig. 9), pentazocine,¹³ and cyclazocine²² relative to morphine. A second set of relative potencies calculated for comparison of cyclazocine with pentazocine and butorphanol with pentazocine (Table 10) indicate that butorphanol is approximately 15 to 25 times more potent than pentazocine and that cyclazocine is approximately 25 to 100 times more potent than pentazocine. Of interest was the observation that statistically valid relative potencies were not obtained with all measures for these comparisons with pentazocine because of significant "F" ratios for non-parallelism and preparation mean squares in the analysis of variance suggesting differences in the profile of subjective effects among these agents.

Precipitation Studies

The first studies conducted in 5 subjects dependent upon 60 mg of morphine per day (15 mg q.i.d., subcutaneously) involved precipitation tests using our standard procedure²³ in which each subject received placebo; 1.5 and 3 mg of nalorphine; and 4, 6 and 8 mg of butorphanol. Butorphanol, 4 mg, precipitated mild abstinence with abstinence scores equivalent to that produced by nalorphine 1.5 mg (Table 11). However, increased doses, 6 and 8 mg, did not increase abstinence scores. The precipitated abstinence scores for butorphanol were not significantly different from those produced by placebo. Larger doses of butorphanol were not given because the 8 mg of butorphanol produced nervousness, apprehension, and irritability, along with a mild degree of abstinence as would be expected from the single dose studies.

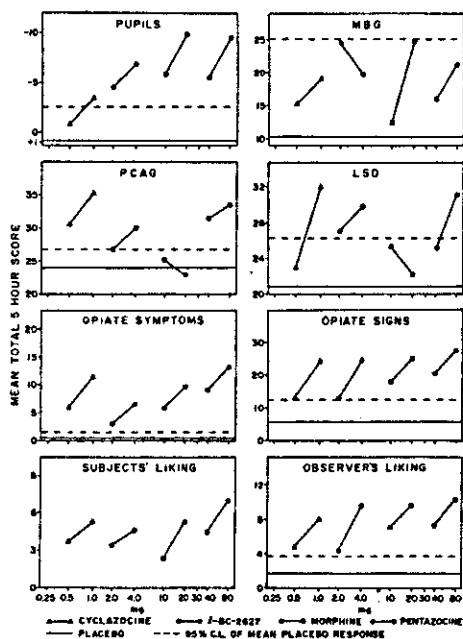


Figure 10. Dose response curves (total 5 hour responses) from the comparison of butorphanol, pentazocine, cyclazocine, morphine and placebo.

Table 8

Identification of drugs by subjects and observers from the comparison of butorphanol, pentazocine, cyclazocine and morphine. Maximum responses in any category is 54.

Subjects	Placebo	Butorphanol		Pentazocine		Cyclazocine		Morphine	
		2.0	4.0	40	80	0.5	1.0 *	10	20
BLANK	52	33	22	17	18	21	11	25	16
DOPE	0	10	12	14	18	13	8	6	14
Cocaine	0	0	0	0	0	0	0	0	0
Marihuana	0	0	0	0	8	5	2	0	0
Barbiturate	0	0	4	14	5	3	5	4	0
Alcohol	0	0	3	7	0	0	5	4	5
Amphetamine	0	1	0	0	4	6	0	4	6
LSD	0	0	0	0	2	0	9	0	0
Thorazine	0	0	0	2	0	0	1	0	0
Librium	0	0	2	0	0	0	0	0	0
Other	2	13	13	11	11	12	17	14	13
Observers									
Blank	38	23	6	8	6	20	11	5	5
Dope	6	23	47	38	47	15	27	48	49
Cocaine	0	0	0	0	0	0	0	0	0
Marihuana	0	0	0	0	0	0	0	0	0
Barbiturate	0	1	1	5	1	8	5	0	0
Alcohol	0	0	0	0	0	0	0	0	0
Amphetamine	1	0	0	0	0	0	0	1	0
LSD	0	0	2	0	1	0	0	0	0
Thorazine	0	0	0	0	0	0	0	0	0
Librium	0	0	0	0	0	0	0	0	0
Other	10	8	3	3	5	13	6	0	1

* Responses from 8 subjects

Table 9

Cumulated number of responses by subjects and observers to signs and symptoms of the Single Dose Opiate Questionnaires for the comparison of butorphanol, pentazocine, cyclazocine, morphine and placebo. Maximum responses in any category is 54.

Opiate Symptoms	Placebo	Butorphanol		Pentazocine		Cyclazocine		Morphine	
		2.0	4.0	40	80	0.5	1.0*	10	20
Turning of Stomach	2	0	4	4	13	8	5	11	7
Skin Itchy	0	1	5	7	7	0	5	4	14
Relaxed	0	6	8	11	18	10	9	8	14
Coasting	0	6	5	9	14	4	10	1	1
Soap-Boxing	0	0	0	3	0	0	4	4	5
Pleasant Sick	0	0	1	0	8	0	2	0	0
Drive	0	0	2	0	3	0	2	1	5
Sleepy	0	5	7	5	11	6	3	4	2
Nervous	2	0	0	5	9	0	3	0	2
Drunken	0	0	9	13	10	3	18	5	5
Other	0	3	8	8	4	5	12	9	10
Opiate Signs									
Scratching	4	9	23	12	27	5	21*	15	38
Red-Eye	4	4	15	14	23	13	15	21	17
Relaxed	15	32	47	43	47	33	37	48	47
Coasting	2	13	25	20	21	11	19	10	20
Soap-Boxing	6	13	18	23	21	6	17	21	22
Vomiting	0	0	1	0	3	0	0	1	0
Nodding	0	0	1	0	6	0	4	0	1
Sleepy	7	13	19	9	23	18	18	9	10
Nervous	6	1	5	20	6	6	5	5	8
Drunken	0	0	0	5	10	4	9	0	4
Other	2	10	16	9	8	17	3	6	17

* Responses from 8 subjects

Table 10

Potencies of butorphanol, cyclazocine and pentazocine relative to morphine (1 mg).

	<u>Butorphanol</u>	<u>Pentazocine</u>	<u>Cyclazocine</u>
Pupils	0.32(0.21-0.85) ⁺	4.23(2.96-6.22)	----- ⁺
Symptoms	0.35() [‡]	2.24() [‡]	0.04(0.02-0.07)
Signs	0.24(0.13-0.89)	3.01() [‡]	0.07(0.03-54.78)
S. Liking	0.18() [‡]	2.44(0.40-4.12)	0.04() [‡]
O. Liking	0.25(0.17-0.45)	3.62(1.33-7.38)	0.08() [‡]
MBG	----- ⁺	4.05(1.30-13.53)	0.04() [‡]
PCAG	----- ⁺	0.005() ^{+,‡}	----- ^{+,‡}
LSD	----- ⁺	----- ⁺	----- ^{+,‡}

Potencies of butorphanol and cyclazocine relative to pentazocine (1 mg).

	<u>Butorphanol</u>	<u>Cyclazocine</u>
Pupils	0.07(0.05-0.15) ⁺	0.04(0.02-556.66) ^{+,‡}
Symptoms	0.15() ^{+,‡}	0.01() [‡]
Signs	0.07(0.04-0.25)	0.01(0.01-0.11)
S. Liking	0.09() [‡]	0.01() [‡]
O. Liking	0.06(0.04-0.12)	0.02(0.01-0.14) ⁺
MBG	0.07() [‡]	0.01() [‡]
PCAG	0.15() [‡]	0.01() [‡]
LSD	0.04(0.007-0.21)	0.01(0.007-0.01) [‡]

- ⁺ Significant preparation difference
[‡] Nonsignificant regression coefficient
[±] Significant nonparallelism

Table 11. Means and standard errors for total modified Himmelsbach score obtained in precipitation tests. Total precipitation scores are the sums of scores from five observations.

<u>DRUG</u>	<u>PRECIPITATION SCORE</u>
Placebo	52.2 $\pm$ 11.8
Nalorphine 1.5 mg	64.0 $\pm$ 12.2
Nalorphine 3.0 mg	102.6 $\pm$ 21.39 ^{.025}
Butorphanol 4.0 mg	65.6 $\pm$ 21.8
Butorphanol 6.0 mg	59.8 $\pm$ 22.3
Butorphanol 8.0 mg	69.6 $\pm$ 10.3

The superscript is the level of significance for the difference from placebo as calculated using 2-way analysis of the variance (subjects X treatments) and the method of least significant differences.

Substitution Studies

Following precipitation tests, subjects also participated in 24 hour substitution tests¹⁴ to determine if butorphanol could substitute for morphine and suppress abstinence. On separate weeks, subjects were given, in lieu of regular doses of morphine, three consecutive doses of each of the following: saline placebo; morphine 3 and 6 mg; and butorphanol, 0.6 and 1.2 mg. Abstinence scores were assessed hourly from the 14th through the 24th hour of substitution. At these same times the degree of sickness was assessed as 0 = not sick; 1+ = slightly sick; 2+ = mildly sick; and 3+ = very sick. Partial maintenance doses of morphine suppressed both the symptoms and signs of abstinence (Table 12). Butorphanol, 0.6 and 1.2 mg, both suppressed the abstinence but this effect was slight and no significant dose relationship was found.

On the basis of preliminary studies it appears the pharmacologic profile produced by butorphanol is not morphine-like but more closely resembles that produced by agents such as nalorphine, cyclazocine and pentazocine. Morphine antagonist activity was not clearly demonstrated.

SECTION II: AMPHETAMINE-LIKE DRUGS

Side-Chain Modified Amphetamine Congeners

In 1971, Martin et al.²³ reported on the subjective and physiological effects of *d*-amphetamine and several related congeners (Fig. 11, #1-5). While these agents differed in terms of mg potencies, none seemed to have a selective effect on euphoria, blood pressure or appetite (Table 13). Martin²³ proposed that this profile of subjective and physiologic effects be used to classify agents as amphetamine-like in man for the purpose of assessing abuse potential. Since then, several more drugs have been assessed by these same methods. This program is directed by Dr. John Griffith.

The 5 agents originally studied by Martin et al.²³ were various side chain modified amphetamine congeners (Fig. 11). Two further examples of this class have been since studied, diethylpropion and benzphetamine (Fig. 11, #6, 7). Diethylpropion was reported last year as being "amphetamine-like." It is a relatively weak compound, however, as indicated by the potency estimates in Table 13.

Benzphetamine

This compound, also a side-chain modified derivative, was assessed more recently. Its profile of subjective and physical effects resembles that of amphetamine but its oral potency is of the same order as diethylpropion or subcutaneously administered *z*-ephedrine (Table 13).

Table 12. Means and standard errors for total abstinence scores and total sickness scores obtained in 24 hour substitution tests in 4 subjects where morphine, placebo and butorphanol were substituted for 3 consecutive 15 mg doses of morphine. Total abstinence or total sickness scores are the sum of scores from all 11 observations.

<u>DRUG</u>	<u>ABSTINENCE SCORE</u>	<u>SICKNESS SCORE</u>
Placebo	189.6 $\pm$ 25.0	10.4 $\pm$ 2.2
Morphine 3 mg	154.2 $\pm$ 24.4	10.0 $\pm$ 0.8
Morphine 6 mg	130.2 $\pm$ 19.0 ^{.025}	4.6 $\pm$ 2.0 ^{.025}
Butorphanol 0.6 mg	154.4 $\pm$ 8.2	6.2 $\pm$ 1.8 ^{.05}
Butorphanol 1.2 mg	163.2 $\pm$ 35.6	6.8 $\pm$ 2.0 ^{.1}

Superscripts are levels of significance for the difference from placebo as calculated using 2-way analysis of the variance (subjects X treatments) and the method of least significant differences.

SIDE-CHAIN MODIFIED AMPHETAMINE CONGENERS

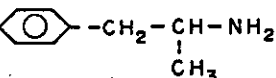
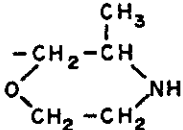
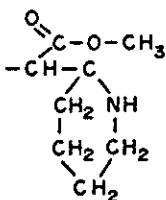
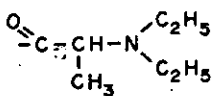
	SIDE CHAIN	GENERIC NAME
1.		d-AMPHETAMINE
2.	" $-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{NH}-\text{CH}_3$	d-METHAMPHETAMINE
3.	" $\begin{array}{c} -\text{CH}-\text{CH}-\text{NH}-\text{CH}_3 \\ \quad \\ \text{OH} \quad \text{CH}_3 \end{array}$	l-EPHEDRINE
4.	" 	PHENMETRAZINE
5.	" 	METHYLPHENIDATE
6.	" 	DIETHYLPROPION
7.	" $-\text{CH}_3-\text{CH}(\text{CH}_3)-\text{N}(\text{CH}_3)-\text{CH}_2-$ 	BENZPHETAMINE

Figure 11. Structure diagrams of side-chain modified amphetamine congeners.

Table 13. Relative potencies for the ability of benzphetamine to produce amphetamine-like subjective effects and comparison with relative potencies from previous studies.^{7,21-24} Expressed as mg of d-amphetamine equivalent to 1 mg of the test drug.

	MBG SCALE	AMPHETAMINE SCALE	BENZEDRINE SCALE	SYSTOLIC B.P.	DIASTOLIC B.P.	CALORIC INTAKE
d-Amphetamine	1	1	1	1	1	1
d-Methamphetamine ⁺	---	0.93	1.68	0.92	1.49	1.19
Methylphenidate ⁺	---	0.48	0.58	0.31	0.57	1.05
*Phenmetrazine ⁺	---	0.21	0.31	0.26	0.41	0.43
Ephedrine ⁺	---	0.17	0.17	0.27	0.11	0.19
Diethylpropion ⁺	0.15	0.15	0.18	0.09	0.12	0.16
Benzphetamine ⁺	.20	.22	.24	.13	.13	.17

⁺Comparison by the subcutaneous route

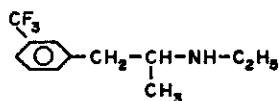
*Comparison by the oral route

Ring Substituted Amphetamines

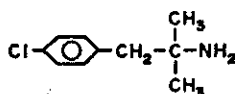
Of interest are studies of two ring-substituted amphetamine analogs, fenfluramine¹⁰ and chlorphentermine. Their structural formulae are given in Fig. 12.

FIGURE 12

RING-SUBSTITUTED AMPHETAMINE CONGENERS



FENFLURAMINE



CHLORPHENTERMINE

Figure 12. Structure diagrams of fenfluramine and chlorphentermine.

Fenfluramine

This drug (Pondamin[®]) is an appetite suppressant recently introduced into the United States. Clinical experience with this pharmaceutical in Europe is more extensive and indicates that fenfluramine is relatively devoid of amphetamine-like properties. Fenfluramine is not an important item of abuse. Levin, however, has identified clandestine abuse in South Africa but his report suggests that the subjective effects are not necessarily amphetamine-like.

In this study, d1-fenfluramine (60, 120, 240 mg); and d-amphetamine (20, 40 mg) and placebo were administered to 8 subjects at weekly intervals in single oral doses using a double-blind, randomly assigned, cross over design utilizing standard methods.

In this, as in other studies, fasting subjects were administered drug or placebo at 0800. Just prior to this time (0700 and 0730) control physiologic observations were made including: supine systolic and diastolic blood pressures, pupil size (determined photographically under bright light, near accommodation conditions), and rectal temperature. At intervals following drug or placebo (1/2, 1, 2, 3, 4, 5, 6, 12 and 24 hours) these physiologic observations were repeated. At these same intervals, a number of subjective tests and behavior checklist were administered; namely, the Subjects' and Observers' Single Dose Opiate Questionnaire which allows categorization of the drug effects as "amphetamine-like"; "barbiturate-like"; etc. and specification of the degree of "liking." Also administered were Addiction Research Center Inventory derived scales including the Amphetamine Scale;²³ the Morphine-Benzadrine Group Scale (MBG), a more general measure of drug-induced euphoria; and the LSD Scale. This last reflects the hypochondrical and despondent mood states triggered by a number of hallucinogenic drugs. Anorexia was measured by decreases in the estimated caloric content of food portions freely consumed at the noon, evening and breakfast (next morning) meals. Self estimations of sleep time was a measure of drug-induced insomnia. Additionally, two-minute standing blood pressures were obtained at 3 and 24 hours post-drug.

The profile of effects of fenfluramine were distinct from that of d-amphetamine (Fig. 13). Fenfluramine had little effect on blood pressure or temperature and was not particularly euphorogenic as indicated by minor MBG and "Liking" Scales. Unlike amphetamine, however, fenfluramine caused a marked dilation of pupils and elevation of the LSD Scale. On the other hand, both drugs interfered with sleep and appetite. Fenfluramine was identified by subjects more often as an "LSD" or "barbiturate"-like substance.

An unexpected response, despite the precaution of a preliminary dose run-up, was observed among 3 subjects who manifested hallucinatory states characterized by visual and olfactory hallucinations, rapid and polar changes of mood, distorted time sense, fleeting paranoia, and sexual hallucinations.

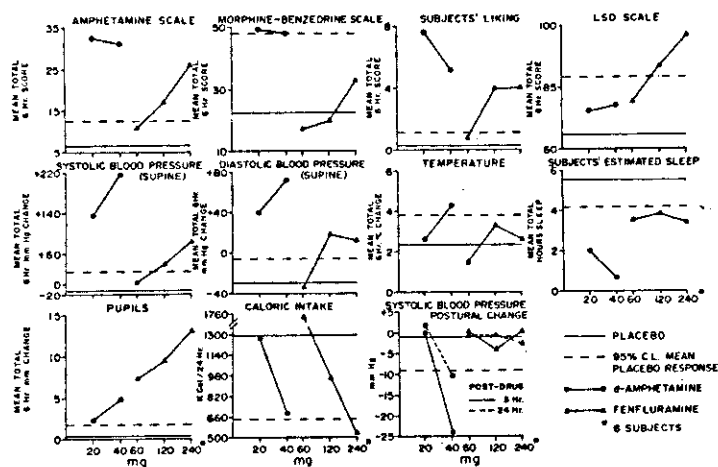


Figure 13. Dose response curves from the comparison of chlorphentermine, d-amphetamine and placebo.

Chlorphentermine

Chlorphentermine was assessed in a manner similar to that described for fenfluramine excepting that the Pentobarbital-Chlorpromazine-Alcohol Group Scale (PCAG) (apathetic sedation) was included as an additional measure. Nine subjects received chlorphentermine (50, 100, 200 mg); d-amphetamine (20, 40 mg) and placebo, each condition administered orally at weekly intervals.

Chlorphentermine produced a profile of effects distinct from that of d-amphetamine but similar to that of fenfluramine (Fig. 14). Chlorphentermine is mydriatic, dysphorogenic (LSD Scale), anorexigenic, and sedative while relatively devoid of vasopressor effects. Although some subjects were grossly sedated by chlorphentermine, no hallucinatory syndromes were observed.

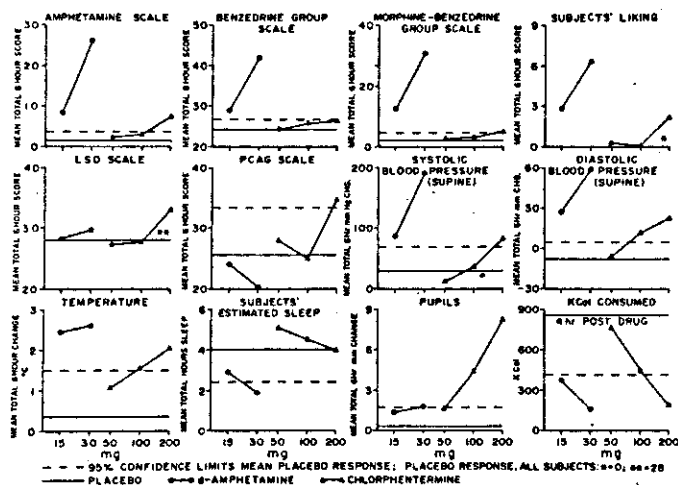


Figure 14. Dose response curves from the comparison of chlorphentermine, d-amphetamine and placebo.