Conclusions

Based on the compounds studied to date, two general relationships between amphetamine structure and activity appear to be emerging:

1) Modification of the isopropylamine side-chain has prominent effects on mg potencies but causes little dissociation among measures of appetite, blood pressure, or mood. It should be noted that the less potent amphetamine-like drugs (ephedrine, benzphetamine, diethylpropion) can generate a "high" equivalent to 40 mg of d-amphetamine, but apparently are rarely abused. The reasons for this relationship are not known.

2) Aromatic substitution may generate amphetamine congeners which are more selectively appetite depressants than euphoriants or vasopressors. The utility of this approach may be limited, however, by the emergence of certain side-effects such as dysphoria, sedation and/or hallucinations.

Differential Effects of d-Amphetamine on Supine and Standing Blood Pressures and Pulse Rates

In the studies just described, blood pressure and pulse changes were measured routinely with the subjects in a supine position (supine beforehand for 10 minutes). More recently 2 minute standing blood pressure and pulse rates have also been measured after the patient has gone from a supine to a standing position. These standing blood pressures and pulse rates measured 3 and 24 hours after amphetamine administration were observed to differ from those measured in the supine position.

A study was conducted to more systematically assess these changes. Placebo (saline) and d-amphetamine sulfate, 30 mg, were administered subcutaneously to 5 patients at 7-day intervals.

Blood pressures and pulse rates were measured in the supine (10 minutes rest) and standing (2 minutes erect) positions at 1 and 0.5 hours before drug administration and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 13 and 24 hours after drug administration.

Following placebo administration, there is little difference in the supine or standing systolic blood pressure (Fig. 15A and 15B) or pulse rate (Fig. 15C). Following d-amphetamine administration there is an increase

in the systolic blood pressure in the supine position (Fig. 15A) but the standing pressures are not very different from placebo (Fig. 15B). Accompanying this change in systolic blood pressure upon standing, there is a marked increase in pulse rate (Fig. 15C).

The time course of the fall in systolic blood pressure and increase in pulse rate following standing from the supine position was determined in two patients, the response of one is illustrated in Fig. 15D. Notice that the pulse and blood pressure changes are not a postural "bounce" but increase gradually over a period of several minutes.

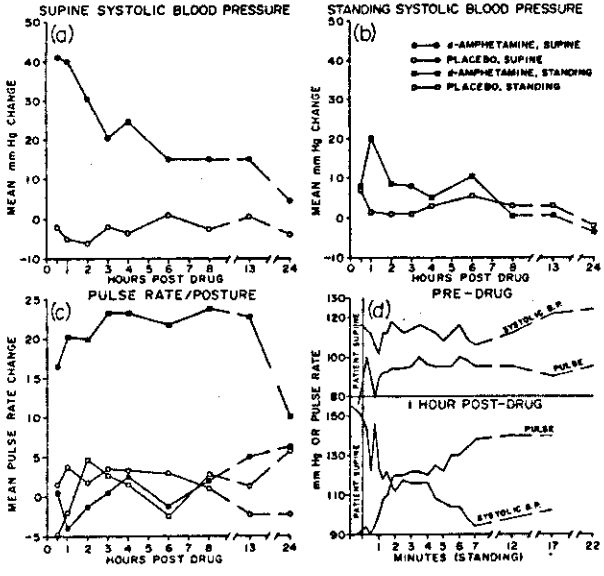

Figure 15. Changes in supine and standing systolic blood pressure and pulse rates following d-amphetamine and placebo administration. (A) Change in supine systolic blood pressure, (B) change in standing systolic blood pressure, (C) changes in supine and standing pulse rates, and (D) lower graph illustrates time course of decrease in blood pressure and increase in pulse rate following standing from the supine position in one patient receiving d-amphetamine. Pre-drug changes are shown in upper half.

These alterations of cardiovascular effects produced by d-amphetamine may be of some clinical and theoretical importance. They suggest that patients with acute amphetamine-induced hypertension should not be forced to lie supine during hospitalization. Moreover, the blood pressure difference might be used to diagnose amphetamine intoxication. Conventional explanations of amphetamine effects on blood pressure do not explain the postural difference observed.

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

by

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Direct Addiction Studies With Butorphanol

Single dose studies conducted previously indicated that butorphanol produced subjective effects resembling those produced by cyclazocine, pentazocine and nalorphine rather than morphine.[1] Further studies indicated that in subjects dependent upon 60 mg of morphine daily, butorphanol neither precipitated nor suppressed abstinence.[1]

A direct addiction study was initiated in 7 subjects to determine if butorphanol produced physical dependence. One subject withdrew from the study at a dose level of 24 mg for reasons unrelated to the study. In the other 6 subjects butorphanol was administered in increasing doses 4 times daily to a stabilization dose of 48 mg (12 mg q.i.d.). From single dose estimates of miotic, euphoric and analgesic potencies, this dose of butorphanol would be equivalent to approximately 240 mg of morphine daily.

During the first few days of drug administration subjects commonly complained of racing thoughts and "seeing my thoughts." Following this subjects began reporting drowsiness and increased awareness of body sensations. Some subjects also complained that the drug made them suspicious and paranoid. Subjects appeared sedated and spent most of their time in bed. Yet, when questioned they would complain of inability to sleep. Furthermore, even when subjects appeared to be sleeping soundly, they were easily aroused. Subjects reported a number of symptoms associated with opiates such as constipation, nausea and difficulty urinating. However, analysis of the chronic dose questionnaire[2] indicated that subjects most frequently identified the effects of butorphanol as a barbiturate with lesser identifications as an opiate, as marijuana or thorazine (Table 1). The observers identified butorphanol

as an opiate or as a barbiturate. During chronic administration subjects liked the effects of butorphanol as measured by the chronic opiate questionnaire[2] to a lesser extent than other groups of subjects reported for various doses of morphine (Fig. 1). The pattern of responses on the symptoms from the chronic opiate questionnaire did not show significant correlation with the patterns of symptoms for various levels of morphine administration.

Table 1. Identifications by 6 subjects and observers of butorphanol from chronic questionnaires administered once daily during the period of chronic butorphanol administration (35 days).

	Subjects	Observers
Drug effect	207	210
Identified as opiate	44	210
Identified as barbiturate	170	139
Identified as marijuana	14	0
Identified as speed	1	0
Identified as LSD	1	0
Identified as thorazine	24	0

The maximum number of responses possible was 210.

Chronically administered butorphanol decreased pupil size, increased diastolic blood pressure slightly, and increased body weight and caloric intake (Fig. 2 and Table 2).

Administration of naloxone, 4 mg, and nalorphine, 40 mg, to these subjects during the 4th week of chronic administration of butorphanol precipitated an abstinence syndrome with subjects reporting typically opiate-like withdrawal and a degree of sickness (Table 3). This 40 mg dose of nalorphine did not produce any discernible subjective effects including psychotomimetic effects indicating a degree of cross tolerance between butorphanol and nalorphine.

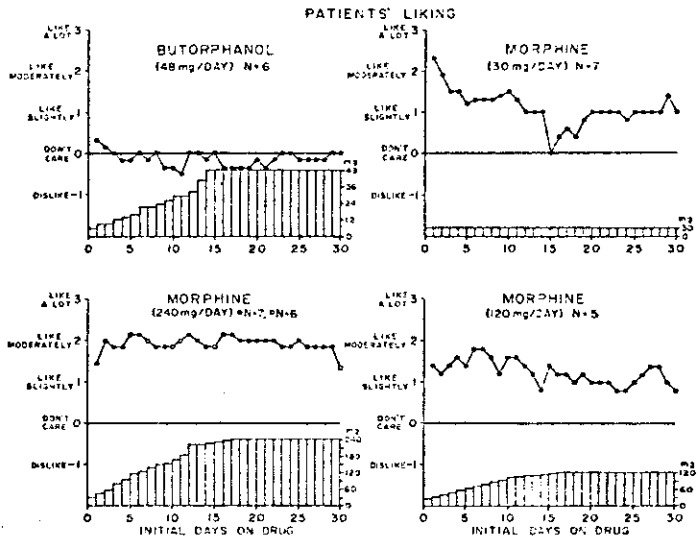


Figure 1. Liking scores from the chronic questionnaires completed by subjects during chronic butorphanol administration compared with liking scores obtained from three other groups of subjects receiving 30, 120 and 240 mg of morphine daily (unpublished data).

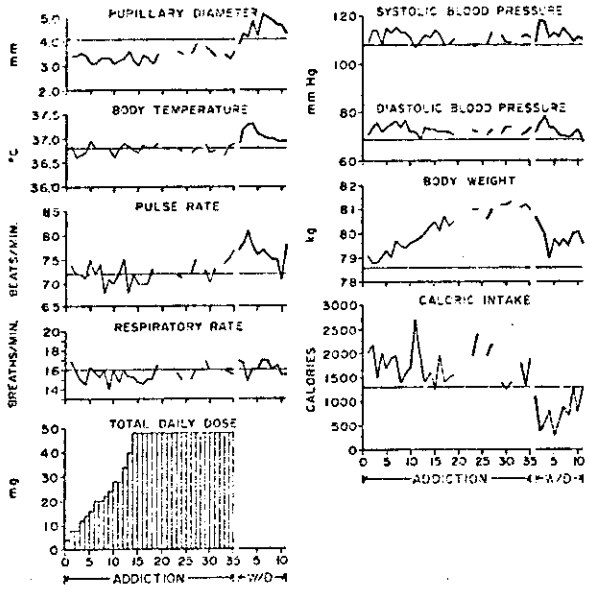


Figure 2. Time course of changes in physiological measures for the 6 subjects during the addiction cycle with butorphanol. The solid line represents the mean of 14 days of pre-drug observations. The addiction phase and withdrawal phase (heavy lines) represent daily means.

Table 2. Significant differences in physiologic measures for the addiction cycle with butorphanol. Each value represents the mean response for 6 subjects over all observations in the designated period.

Parameters	I 14 Days Pre-Drug	II 19 Days Butorphanol	III 7 Days Withdrawal
Pupil size	4.14**	3.30**	4.53*
Pulse rate	71.98	71.61*	77.65**
Rectal temperature	36.82	36.79**	37.13**
Systolic blood pressure	108.22	109.51	113.54*
Diastolic blood pressure	69.02*	73.12	73.75*
Respiratory rate	15.84	15.46	16.45
Body weight	78.60**	79.70	79.86**
Daily caloric intake	1321**	1770**	662**

The significance of differences between column I and column II are indicated by asterisks in column I. Differences between column I and III are indicated by asterisks in column III. Differences between column II and column III are indicated by asterisks in column II. The significance of these mean differences were determined with paired t tests.

*p <0.05

**p <0.01

Table 3. Means and standard errors for modified Himmelsbach scores and sickness scores obtained in precipitation tests utilizing standard methods.[3] These scores are the sums of scores from 5 observations.

Drug	Precipitation Score	Sickness Score
Placebo	51.5 ± 8.6	0.2 ± 0.2
Nalorphine 40 mg	82.0 ± 13.6$^{.05}$	1.0 ± 0.5
Naloxone 4 mg	132.2 ± 17.0$^{.01}$*	5.8 ± 1.8$^{.01}$*

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

*The precipitation and sickness scores for naloxone are significantly different from those for nalorphine at $p < .01$.

After 35 days of chronic butorphanol administration, saline placebo was substituted for butorphanol under double blind conditions. Within 24 hours, all subjects perceived the placebo substitution and reported withdrawal symptoms which increased in severity from the 24th through the 48th hour. Accompanying this were pupillary dilation, increases in body temperature and pulse, and decreased caloric intake (Fig. 2 and Table 2). Generally symptoms reported were those described for opiate withdrawal but in addition there were symptoms which have been described only with nalorphine or cyclazocine withdrawal syndromes. Four subjects reported electric shocks usually associated with faintness and two subjects reported itching. All subjects found this abstinence syndrome to be somewhat uncomfortable and asked for morphine to relieve their symptoms on the second night of withdrawal. They were consequently offered a small dose of butorphanol or a sedative. All subjects rejected the butorphanol and chose to receive a sedative. Five of the six received diazepam, 15 mg, and the other subject received pentobarbital, 100 mg. Analysis of the chronic opiate questionnaire[2] indicated that the subjects reported feeling bad through the first week of withdrawal with denial of discomfort by the 8th day of abstinence (Fig. 3).

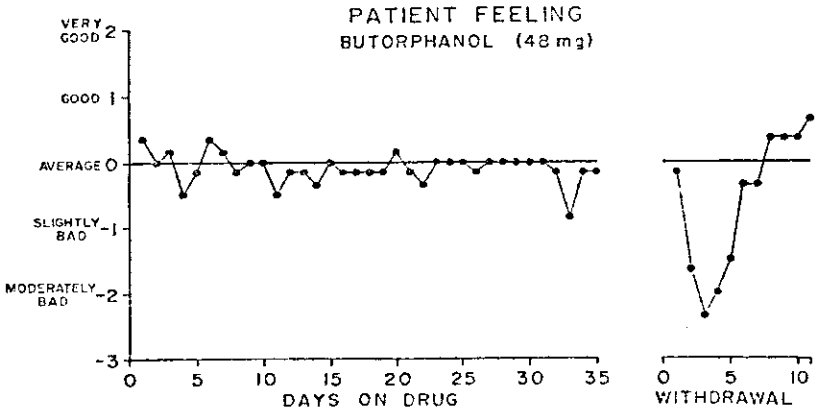


Figure 3. Mean daily responses by six subjects to the question "How do you feel?" during the chronic administration and withdrawal of butorphanol.

Significant Himmelsbach scores were obtained following butorphanol withdrawal reaching its peak on the 3rd day and subsiding (Fig. 4) with an intensity slightly greater than produced by pentazocine but less than morphine. Analysis of the sources of points in the Himmelsbach score indicated that butorphanol more closely resembled cyclazocine abstinence than morphine abstinence (Table 4).

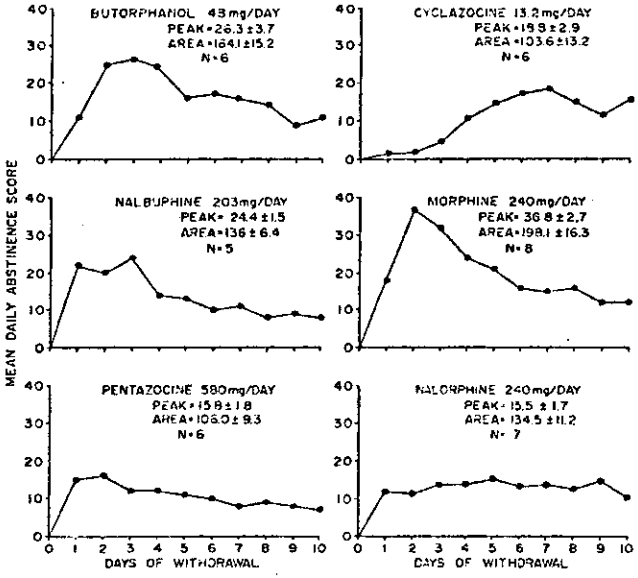


Figure 4. Mean daily Himmelsbach scores for the withdrawal of butorphanol in 6 subjects and comparison with withdrawal Himmelsbach scores for cyclazocine,[4] nalbuphine,[5] morphine,[6] pentazocine,[7] and nalorphine.[18] N represents the number of subjects. Also shown are the means and standard errors for the peak and total area Himmelsbach scores.

On the basis of these and previously reported studies,[1] butorphanol appears to produce effects which most closely resemble those produced by agents such as pentazocine,[7] cyclazocine,[4] and nalorphine[8] rather than morphine-like agents. Unlike these agents, butorphanol did not precipitate abstinence in morphine-dependent subjects.

Table 4. Comparison of mean sources of points in the Himmelsbach scores for butorphanol, morphine,[6] nalorphine,[8] pentazocine,[7] nalbuphine[5] and cyclazocine[4] abstinence for the 10 days following abrupt withdrawal.

Source of Points	Morphine (M)		Nalorphine (Nl)		Pentazocine (P)		Nalbuphine (Nb)		Cyclazocine (C)		Butorphanol	
	% Total Points	Rank	% Total Points	Rank	% Total Points	Rank	% Total Points	Rank	% Total Points	Rank	% Total Points	Rank
+Signs	4.4	6	11.0	3	9.4	4	17.3	3	12.8	4	11.1	6
++Signs	9.3	5	3.8	7	29.2	1	26.2	1	16.7	2	18.3	2
Caloric intake	1.9	8	6.7	6	3.2	8	4.8	7	5.5	6	13.0	5
Restlessness	0.8	9	1.1	8	0.0	9	0.8	8.5	0	9	0.5	9
Emesis	2.8	7	0.0	9	4.6	6	0.8	8.5	0.7	8	5.4	7
Fever	12.1	3	15.8	1	15.5	3	12.9	4	33.9	1	18.4	1
Hyperpnea	31.1	1	10.8	4	26.2	2	20.2	2	11.1	5	4.6	8
Systolic blood pressure	25.5	2	9.5	5	3.5	7	8.8	5	3.1	7	13.8	4
Weight loss	11.5	4	20.9	2	8.4	5	8.2	6	15.8	3	15.0	3
rs	M X Nl = 0.60		M X P = 0.60 Nl X P = 0.40		M X Nb = 0.64 Nl X Nb = 0.44 P X Nb = 0.88**		M X C = 0.47 Nl X C = 0.72* P X C = 0.78* Nb X C = 0.71*		M X B = 0.37 Nl X B = 0.52 P X B = 0.43 Nb X B = 0.40 C X B = 0.80*			
r	M X Nl = 0.27		M X P = 0.47 Nl X P = 0.18		M X Nb = 0.44 Nl X Nb = 0.19 P X Nb = 0.90**		M X C = 0.16 Nl X C = 0.87** P X C = 0.54 Nb X C = 0.53		M X B = 0.08 Nl X B = 0.57 P X B = 0.33 Nb X B = 0.45 C X B = 0.69*			

Comparisons are made with Spearman rank order correlation coefficients (rs) and product moment correlation coefficients (r).

**p <0.01

*p <0.05

Assessment of Oxilorphan

Oxilorphan is a narcotic antagonist proposed as a possible therapeutic agent in the treatment of opiate addiction. Previously[9] we had observed that subcutaneously administered oxilorphan is approximately equipotent to *dl*-cyclazocine in precipitating abstinence in morphine-dependent subjects. On the other hand, subcutaneous oxilorphan was only 1/4 as potent as subcutaneous *dl*-cyclazocine in producing increases on the LSD and PCAG Scale scores in non-tolerant, non-dependent subjects. Further, at 24 hours after administration of single doses, there were persistent LSD Scale scores, PCAG Scale scores and miosis with both oxilorphan and cyclazocine. Thus, oxilorphan appeared to have the duration of action of *dl*-cyclazocine with equal antagonist potency but a lesser ability to produce agonist effects. Two additional studies have been completed. First was a comparison of single doses of orally and subcutaneously administered oxilorphan in non-tolerant, non-dependent subjects, and second, an assessment of the duration of action of oxilorphan in blocking the effects of morphine in non-tolerant, non-dependent subjects.

In the first study oxilorphan, 1.5 mg and 3.0 mg, was administered both orally and subcutaneously to 8 subjects at weekly intervals under double blind conditions. Drug effects were measured with subjects' and observers' single dose questionnaires[6] and a subjective drug effects questionnaire[13] containing items from the LSD, PCAG and MBG Scales of the Addiction Research Center Inventory, as well as with photographs measuring change in pupillary size. Drug effects were assessed at 1/2, 1, 2, 3, 4, 5, and 6 hours after drug administration.

In these doses, orally administered oxilorphan did produce some effects which were distinguished from placebo; however, the onset of effects with orally administered oxilorphan were markedly slower than those with subcutaneously administered oxilorphan. Consequently, the responses at the 3rd, 4th, 5th and 6th hours which to an extent represents the mean peak response of both orally and subcutaneously administered oxilorphan were utilized to construct dose response curves (Fig. 5). Measures where valid bioassays were obtained indicated that orally administered oxilorphan was 1 to 1/2 times as potent as subcutaneously administered oxilorphan (Fig. 5).

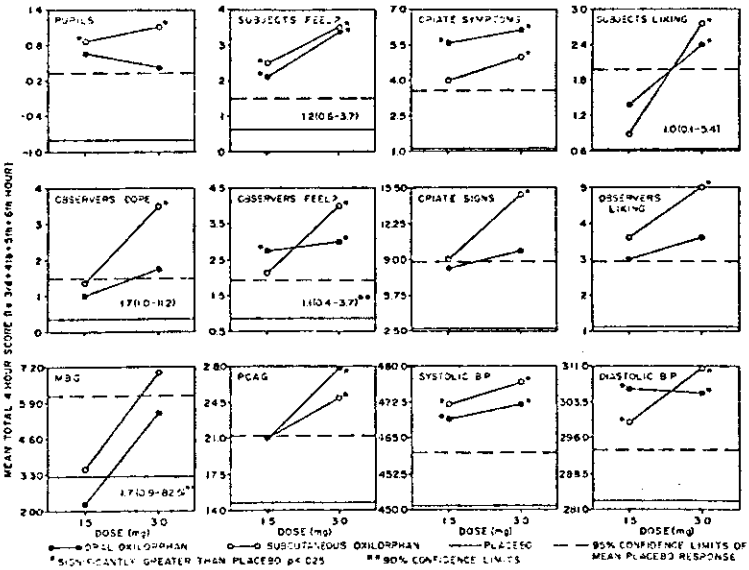


Figure 5. Dose response curves utilizing responses at 3rd, 4th, 5th and 6th hours for orally and subcutaneously administered oxilorphan.

In the second study, the blocking effects of subcutaneously administered oxilorphan, 0.6 mg/70 kg, on the effects of subcutaneously administered morphine sulfate, 25 mg/70 kg, was assessed in 6 subjects. Each subject received in random order at weekly intervals the following 5 treatments: 1) morphine alone; 2) oxilorphan alone; 3) morphine preceded by oxilorphan at 12 hours; and 5) morphine preceded by oxilorphan at 24 hours. The experimental design was similar to that used by Martin and his colleagues[10] to estimate the duration of blocking action of cyclazocine, 0.6 mg, on morphine, 25 mg/70 kg.

Oxilorphan administered 4 and 12 hours before morphine clearly blocked the miotic effects of morphine. At 24 hours there was still a blockade but to a lesser degree (Fig. 6). Similar results were obtained on the measures of subjective effects. Comparison of the data obtained with oxilorphan with that for cyclazocine obtained by Martin and his colleagues[10] suggests that even though oxilorphan has some degree of blocking activity at 24 hours, its blocking activity may decrease more rapidly than cyclazocine's from the 4th to the 24th hour.

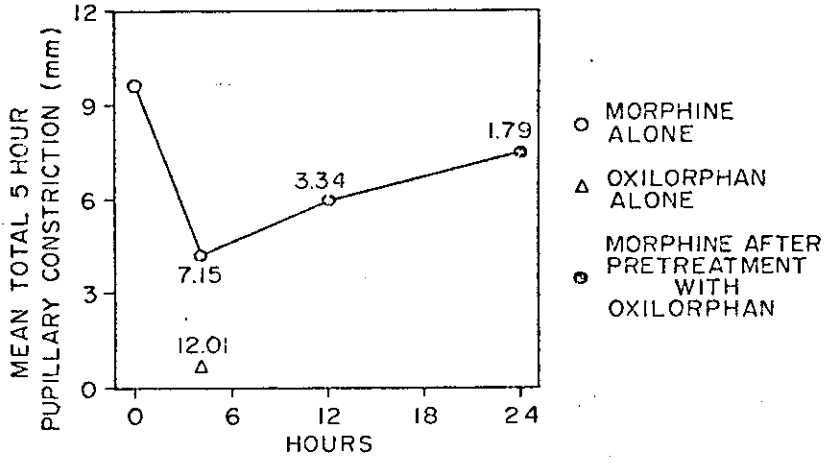
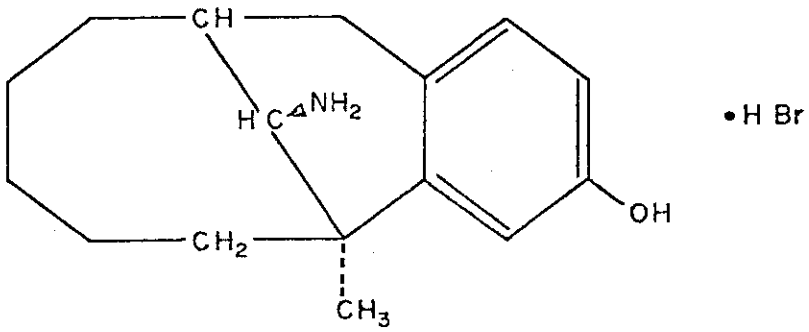


Figure 6. Blocking ability of oxilorphan (0.6 mg subcutaneously) on the miotic effects of morphine (25 mg/70 kg subcutaneously). Numbers represent the "t" values calculated for the comparison of the miotic response to that of morphine alone.

Assessment of Wy-16,225 for Morphine-Like Subjective Effects and Miosis

Wy-16,225 is a bridged aminotetralin (Fig. 7) which is an effective analgesic[11] but does not appear to be a morphine-like drug in studies in monkeys.[11] In morphine-dependent monkeys Wy-16,225 precipitated abstinence in non-withdrawn monkeys and did not suppress abstinence in withdrawn morphine-dependent monkeys. Further chronic administration of Wy-16,225 did not induce physical dependence.



Wy-16,225

Figure 7. Structure of Wy-16,225 [(-)-13β-amino-5,6,7,8,9,10, 11,12-octahydro-5 α-methyl-5,11-methanobenzocyclodecen-3l-ol]

A single dose study was conducted in which each of 10 subjects received Wy-16,225, 15, 30 and 60 mg; morphine, 15 and 30 mg; and placebo at weekly intervals under double blind conditions. Drug effects were assessed at 0.5, 1, 2, 3, 4, 5, 6, and 12 hours after drug administration with change in pupillary diameter,[6] subjects' and observers' single dose opiate questionnaires[6,12] and a subjective drug effects questionnaire.[13]

Examination of time action curves suggest that Wy-16,225 has a somewhat more rapid onset than morphine and shorter duration of action (Fig. 8). Wy-16,225 was identified predominantly as an opiate (Table 5), produced a typical pattern of opiate-like symptoms and signs (Table 6) and produced dose-related increases on the various scales measuring morphine-like effects (Fig. 9). Relative potencies from these dose response curves indicated that Wy-16,225 was approximately equipotent to morphine (Fig. 9).

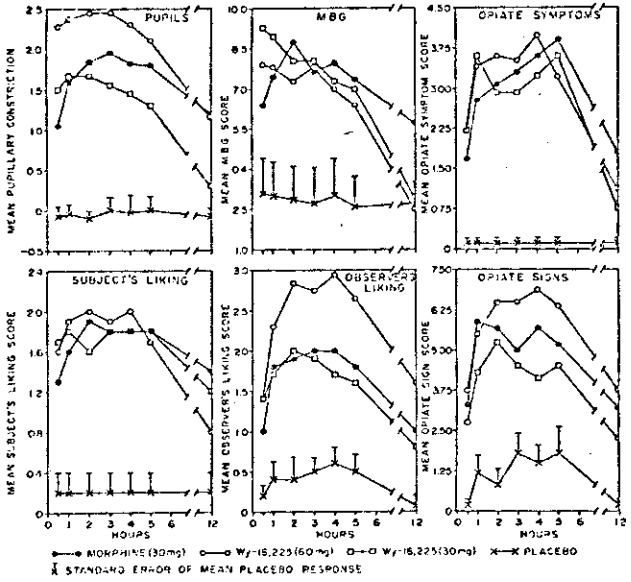


Figure 8. Time action curves for the comparison of Wy-16,225, morphine and placebo. Each point represents the mean response. The response to morphine, 15 mg, and Wy-16,225, 15 mg, doses were omitted.

Table 6. Cumulative responses on individual signs and symptoms from the Single Dose Opiate Questionnaire.*

Response		Morphine		Wy-16,225		
Opiate Symptoms	Placebo	15 mg	30 mg	15 mg	30 mg	60 mg
Normal	54	26	5	15	8	3
Turning of Stomach	0	20	22	3	10	15
Skin Itchy	0	7	28	9	26	27
Relaxed	6	20	32	19	40	31
Coasting	0	11	28	7	29	31
Soap Box	0	1	0	0	6	0
Pleasant Sick	0	0	8	4	2	11
Drive	0	0	0	0	1	2
Sleepy	0	3	5	1	3	0
Drunken	0	0	0	0	0	0
Nervous	0	9	9	3	11	11
Other	0	0	1	2	0	11
Totals	60	97	138	63	136	142
Opiate Signs						
Normal	39	5	2	3	0	2
Scratching	9	27	48	37	39	55
Red Eyes	3	27	30	12	19	38
Relaxed	20	55	57	57	60	56
Coasting	9	9	24	12	21	27
Soap Box	1	30	33	27	22	30
Vomiting	0	3	4	1	2	11
Nodding	0	1	0	2	0	2
Sleepy	8	2	5	5	8	5
Nervous	0	9	13	6	10	8
Drunken	1	1	3	1	1	7
Other	4	22	17	19	11	26
Totals	94	191	236	182	193	267

*Each value represents the total number of responses obtained for that sign or symptom category during the

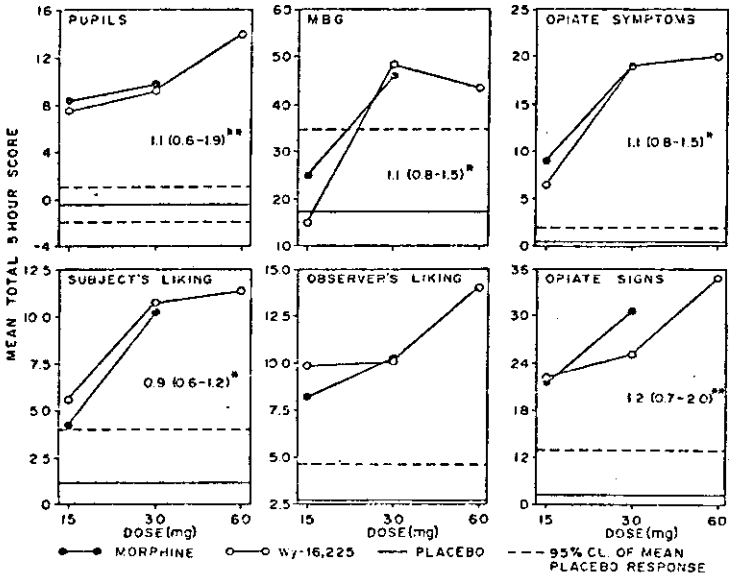


Figure 9. Dose response curves utilizing total 5 hour scores for the comparison of Wy-16,225, morphine and placebo. Numbers represent relative potencies and 95% confidence limits expressed as mg of Wy-16,225 equivalent to 1 mg of morphine.

Evaluation of Phentermine and *l*-Ephedrine for Amphetamine-like Effects

Phentermine (α,α-dimethyl phenethylamine, Ionamin®) and *l*-ephedrine were evaluated for their relative ability to produce amphetamine-like subjective and physiologic effects in man. Each of 10 subjects received at weekly intervals oral phentermine, 25, 50 and 100 mg; oral *l*-ephedrine, 75 and 150 mg; oral *d*-amphetamine, 15 and 30 mg; and placebo utilizing a double blind crossover design. Subjective and physiologic effects utilizing our standard procedures[14,15] were assessed at 0.5, 1, 2, 3, 4, 5, 12 and 24 hours after drug administration.

Both phentermine and *l*-ephedrine produced typical amphetamine-like subjective and physiologic effects. Potency estimates indicated that oral phentermine is 1/2 as potent and oral ephedrine is 1/3 to 1/7 as potent as oral *d*-amphetamine (Table 7). The potency of these two drugs in producing euphoria relative to previously studied drugs is shown in Table 8.

Table 7. Relative potencies and 95% confidence limits from the comparison of phentermine, *l*-ephedrine, *d*-amphetamine, and placebo. Potencies expressed as mg of phentermine or *d*-amphetamine equivalent to 1 mg *d*-amphetamine.

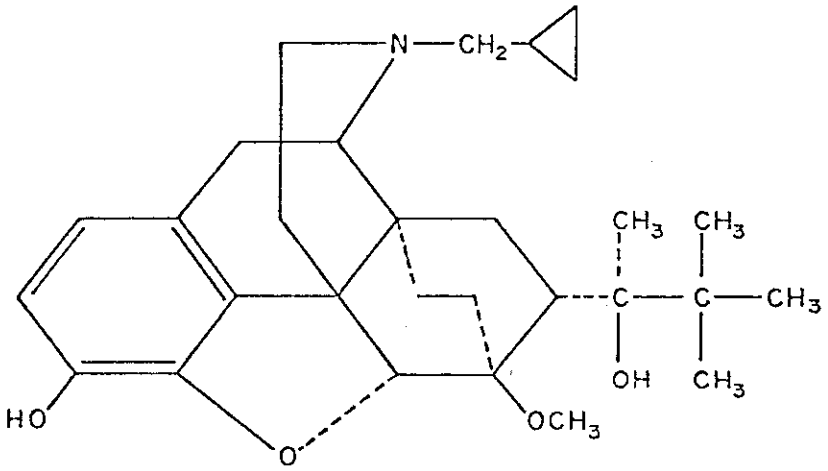
Subjective Measures	Phentermine	*l*-Ephedrine
Morphine-Benzedrine Group Scale	2.5(1.7-3.6)	6.7(3.6-41.2)
Amphetamine Scale	2.5(1.8-3.6)	5.2(3.2-8.5)
Physiologic Measures		
Systolic blood pressure	2.4(2.0-2.9)	3.4(2.6-4.1)
Diastolic blood pressure	1.8(1.0-2.9)	6.8(4.4-16.0)
Pulse decrease	-----	3.5(0.1-7.1)
Temperature increase	2.4(2.0-2.9)	-----

Table 8. Summary of estimates of relative potencies of various amphetamine-like drugs in producing

Subcutaneous Studies		Reference
d-Amphetamine	1	
d-Methamphetamine	1	14
Methylphenidate	2	14
Phenmetrazine	4	14
l-Ephedrine	5	14
Diethylpropion	14	15
d-Amphetamine (Oral)	1	15
Oral Studies		
d-Amphetamine	1	
Phentermine	2	
Benzphetamine	5	1
l-Ephedrine	5	
Diethylpropion	7	15

Assessment of Buprenorphine for Morphine-Like Effects in Man and Evaluation as a Maintenance Drug in the Treatment of Narcotic Addiction

Buprenorphine is an oripavine derivative (Fig. 10) which is an effective analgesic in man and animals. In monkeys, buprenorphine did not exacerbate or suppress morphine abstinence and did not produce physical dependence in direct addiction tests. In the chronic spinal dog,[16] buprenorphine 1) produced a profile of morphine-like effects in the non-dependent animals, 2) precipitated and suppressed abstinence in dependent animals, and 3) produced physical dependence with chronic administration. It was concluded from these studies that buprenorphine was a partial agonist of morphine.



BUPRENORPHINE

Figure 10. Structure of buprenorphine (N-cyclopropylmethyl-7 α-(1-(S)-hydroyl-1,2,2-trimethyl-propyl)-6,14-indoethano-6,7,8, 14-tetra-hydronororipavine).

The present studies were initiated to assess the abuse potential of buprenorphine in man. During the course of these studies, however, it became apparent that buprenorphine was a potent, long acting drug which suggested its possible utility as a maintenance drug in the treatment of opiate addiction and the studies were modified accordingly. It was thought that buprenorphine as a partial agonist of morphine with perhaps a greater affinity for the morphine receptor and a long duration of action would 1) be an effective blocker of morphine through the mechanism of cross tolerance and the mechanism of competitive dualism, 2) have some reinforcing effects, and 3) would produce only minimal physical dependence.

Three single dose studies were conducted. In each, drug effects were measured with change in pupillary diameter, subjects' and observers' single dose opiate questionnaires[6,12] and the subjective drug effects questionnaire[13] containing items from the MBG Scale and PCAG Scale and the LSD Specific Scale.

In the first study, subcutaneous buprenorphine, 0.2, 0.4 and 0.8 mg; subcutaneous morphine, 15 and 30 mg; and placebo were compared in 9 subjects utilizing the double blind crossover design. In these studies observations were made at 0.5, 1, 2, 3, 4, 5, 12, and 24 hours after drug administration. Buprenorphine produced typical morphine-like subjective effects and miosis but its effects were of slower onset than morphine and were longer lasting. There was a greater effect at 24 hours with all doses of buprenorphine than with the 30 mg dose of morphine. Subjects and observers identified buprenorphine predominantly as an opiate with a pattern of signs and symptoms similar to those for morphine. Because of the disparity in time action curves, dose response curves were constructed utilizing peak responses for each drug rather than total 5 hour scores. Buprenorphine produced dose-related increases in mean peak scores on miosis and all measures of morphine-like subjective effects and was estimated to be approximately 30 to 50 times more potent than morphine (Fig. 11). There is no evidence that buprenorphine produced elevations on the PCAG or LSD Scale scores greater than those produced by morphine (Figure 11). In these studies buprenorphine, like morphine, had emetic action but this emetic effect of buprenorphine would persist 8 to 12 hours after buprenorphine and was found disturbing by some of the subjects.

In the second study subcutaneous buprenorphine, 0.6 and 1.2 mg, and subcutaneous morphine, 20 and 40 mg, were compared to determine if the effects of buprenorphine plateaued on these measures as it did on certain measures in the non-tolerant, non-dependent chronic spinal dog.[16] On all measures the responses to 1.2 mg were less than responses to 40 mg of morphine. Relative potencies were obtained only on the miotic effects indicating again that buprenorphine was 1/25 to 1/30 as potent as

morphine (Fig. 12). The responses to the 1.2 mg dose of buprenorphine as measured by the MBG Scale scores and the opiate symptoms scores were less than that produced by 0.6 mg of buprenorphine. Again, buprenorphine did not produce significantly greater PCAG or LSD Scale scores than morphine. These results suggest that 1.0 mg of buprenorphine may produce maximum effects with these effects in the range of 30 mg of morphine.

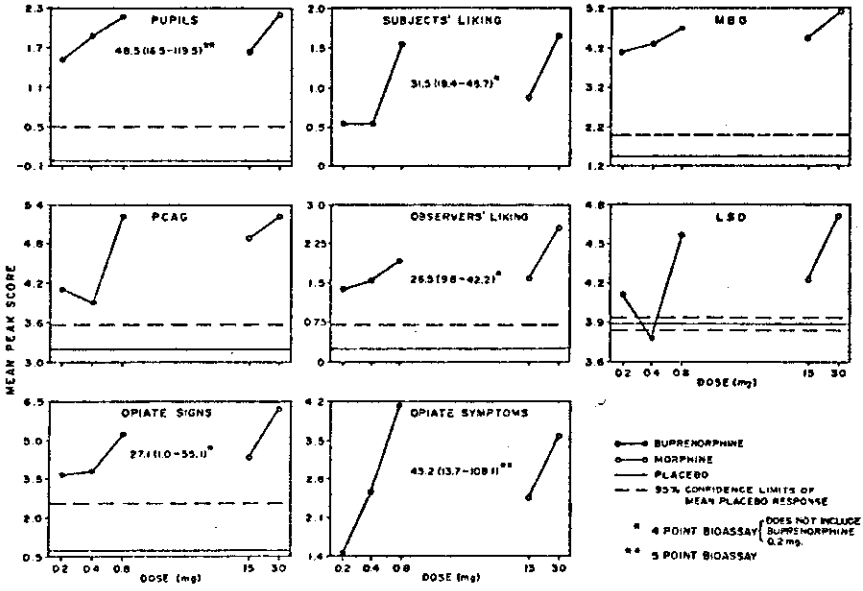


Figure 11. Dose response curves for the comparison of buprenorphine, morphine and placebo utilizing mean peak responses. Numbers represent relative potencies and 95% confidence limits expressed as mg of morphine equivalent to 1 mg of buprenorphine.

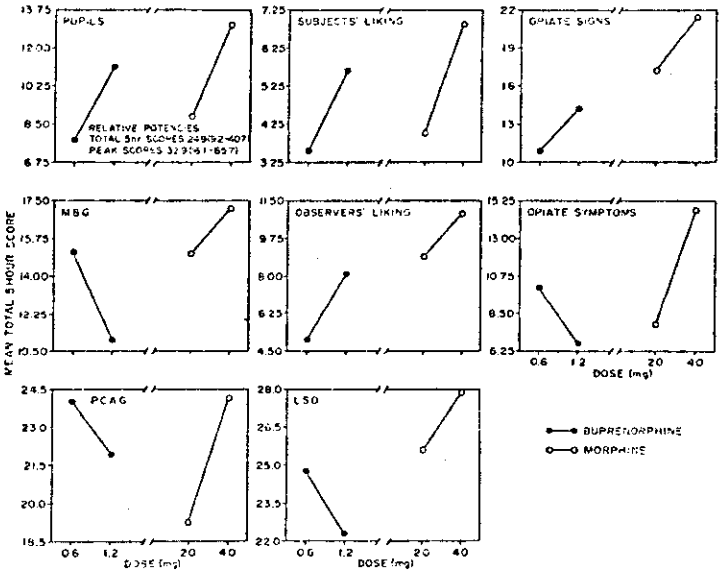


Figure 12. Dose response curves for the comparison of buprenorphine, morphine and placebo utilizing total 5 hour scores. Relative potencies expressed as mg or morphine equivalent to 1 mg of buprenorphine.

In the third single dose study buprenorphine, 1.0 mg; morphine, 30 mg; methadone, 30 mg; and placebo were administered intramuscularly at weekly intervals to 14 subjects utilizing a randomized crossover double blind design. Observations were made at 0.5, 1, 2, 3, 4, 5, 6, 12, 24, 30, 36, 48, 54, 60 and 72 hours after drug administration. Morphine produced significant miosis through the first 24 hours of drug administration (Fig. 13). Buprenorphine and methadone, however, produced persistent miosis which lasted through the observation at 72 hours (Fig. 13). Morphine produced subjective effects lasting through the second day while buprenorphine and methadone produced some degree of subjective effects which lasted at least 72 hours (Fig. 13 and 14). All three drug conditions

showed a characteristic time action of subjective effects. During the first 6 hours there were significant MBG elevations but concurrently measured PCAG scores were not elevated. From the 12th hour on, however, the PCAG scores became significantly elevated while the previously elevated MBG scores returned to control levels.

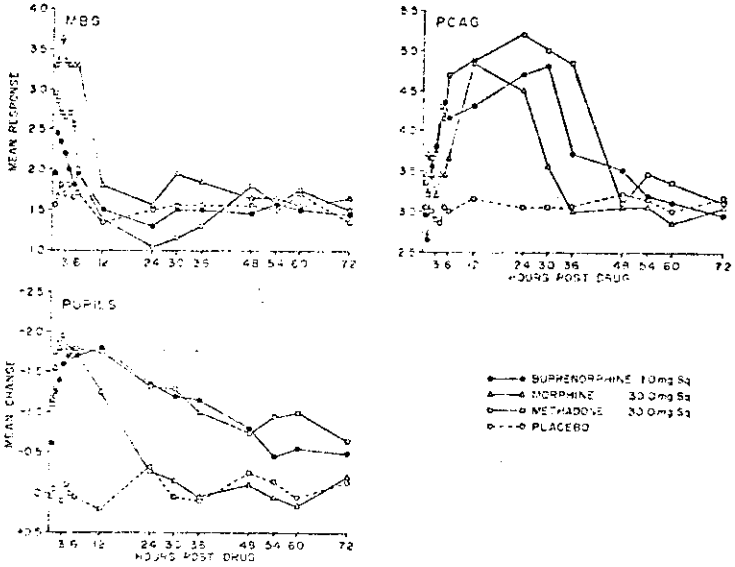


Figure 13. Comparison of the duration of action of buprenorphine, morphine, methadone and placebo in constricting pupils, producing PCAG and MBG Scale scores.

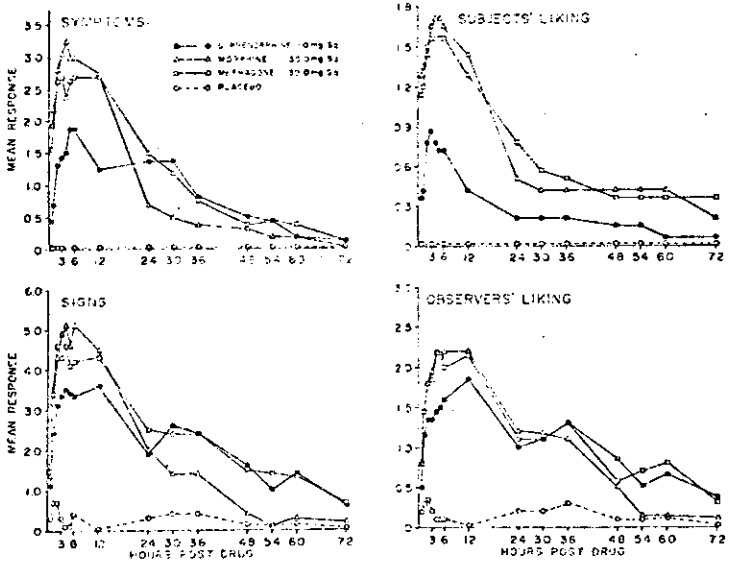


Figure 14. Comparison of the duration of action of buprenorphine, morphine, methadone and placebo in producing scores on the symptom, sign and liking scales.

The single dose studies indicate that buprenorphine produces typical morphine-like subjective effects and euphoria in man and is 25 to 50 times more potent than morphine. Further, there may be a plateau of maximum activity with 1.0 mg of buprenorphine.

A direct addiction study was conducted with subcutaneous buprenorphine to determine if 1) buprenorphine produced significant physical dependence, and 2) to determine if chronically administered buprenorphine would block the effects of morphine. Once daily at 8:30 a.m. five subjects received

a single subcutaneous injection. For 2 weeks this injection was saline. Then buprenorphine, 0.5 mg, was substituted for the saline injection. The dose of buprenorphine was progressively doubled until the 15th day when a dose of buprenorphine, 8.0 mg, was administered. This dose, which would be equivalent to approximately 240 mg of morphine, was then administered once daily through the remainder of the study. During the period of chronic administration, 2 sets of experiments were performed. Single doses of morphine and placebo were administered under double blind conditions and their effects compared with the effects of single doses of placebo; morphine, 15 mg; and morphine, 30 mg, administered during the control phase when subjects were receiving saline. These experiments were to determine if buprenorphine exerted a significant blocking action. The second set of experiments during chronic administration consisted of the administration of naloxone to precipitate morphine-like abstinence.

During chronic administration of buprenorphine, analysis of responses on the chronic questionnaire administered once daily indicated that subjects identified the drug predominantly as an opiate (dope) and liked the effects of buprenorphine (Fig. 15). The pattern of symptoms from the chronic opiate questionnaire were similar to those observed with morphine in other studies. During chronic administration, pupils constricted and diastolic blood pressure decreased slightly (Table 9). There were no changes in pulse rate, systolic blood pressure, respiratory rate, body weight or significant decrease in caloric intake. Between the 18th through the 25th day of chronic administration of buprenorphine, each subject received single test doses of placebo; morphine, 15 mg, and morphine, 30 mg, subcutaneously. To correct for the effects of buprenorphine, the response to morphine, 15 and 30 mg, was corrected by subtracting out the responses for placebo. Comparison of the placebo-drug differences for morphine, 15 and 30 mg, during chronic buprenorphine administration with effects of morphine, 15 and 30 mg, administered to the same subjects during the control period indicates that these effects were significantly decreased (Fig. 16). Subsequently, single doses of morphine to 120 mg were administered without any significant effects (Fig. 16). In an additional experiment, a placebo was substituted for the 8:30 a.m. buprenorphine injection under double blind conditions and a test dose of morphine, 30 mg, administered at 10 a.m. The morphine effects were blocked to the same degree as they were in the condition when buprenorphine had been administered 1 1/2 hours before morphine administration (Fig. 16) indicating that the blocking effects of buprenorphine persist undiminished for at least 25 to 30 hours after drug administration.

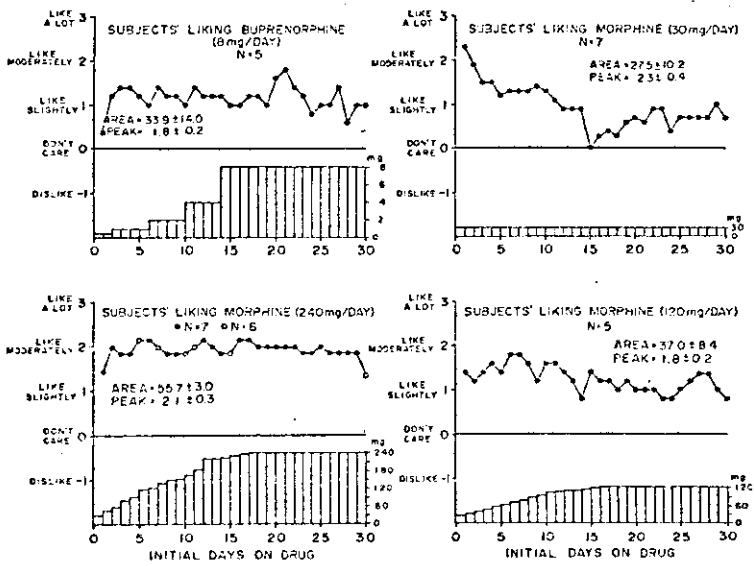


Figure 15. Mean liking scores during the period of chronic buprenorphine administration compared with liking scores obtained from 3 other groups of subjects during chronic morphine administration (unpublished).

Table 9. Mean and standard errors for 5 subjects over all observations during the pre-drug control period (14 days) and the period of chronic buprenorphine administration

	Pre-Drug Control	Chronic Buprenorphine	t	p
Pupils	3.9 ± 0.3	3.3 ± 0.1	3.25	<.05
Temperature	36.7 ± 0.1	36.9 ± 0.1	1.97	
Pulse rate	70.0 ± 1.6	73.1 ± 1.6	1.18	
Systolic BP	116.3 ± 4.6	114.3 ± 3.3	0.81	
Diastolic BP	72.7 ± 2.9	67.9 ± 1.5	2.95	<.05
Respiratory rate	17.1 ± 0.7	16.9 ± 0.4	0.23	
Body weight	78.3 ± 3.9	78.0 ± 3.6	0.60	
Caloric intake	1978 ± 154	1747 ± 67	1.30	

Two of the five subjects withdrew from the study prematurely. One subject withdrew after completing the tests of the blocking ability of buprenorphine (42 days of chronic administration). During these tests, he reported nervousness and irritability. His reasons for withdrawing were that the effects of the drug had become somewhat disturbing especially at night such that when in bed he would close his eyes and have episodes of seeing his thoughts. He would become frightened, short of breath, feel his heart beating rapidly, have tingling in his arms and legs, and feel the room closing in on him. These symptoms occurred only when he was alone and could be inhibited by talking to people. The second subject withdrew after completing three precipitation tests with naloxone. He had reported persistent nausea from the drug usually for 3 to 4 hours after drug administration. On the 47th day of drug administration he had an episode of nausea and vomiting occurring approximately 2 to 3 hours after drug administration. He requested to withdraw from the study because the nausea and vomiting were interfering with his job assignment.

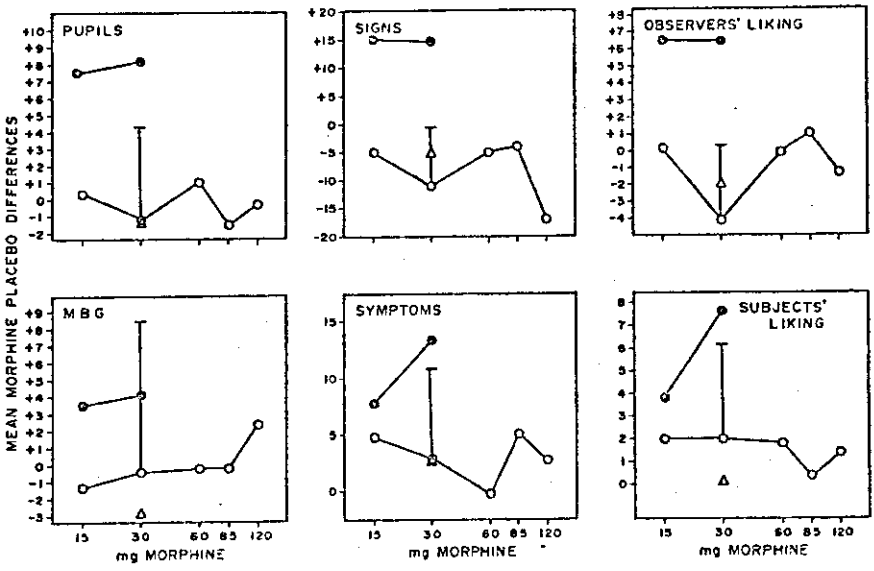


Figure 16. Responses to morphine 1) administered 1 1/2 hours after saline placebo (solid circles) during the pre-drug control period, 2) administered 1 1/2 hours after buprenorphine, 8 mg, (open circles), during chronic buprenorphine administration, and 3) 1 1/2 hours after saline (triangle) was substituted for the 8 mg dose of chronic buprenorphine.

Administration of naloxone to doses of 4 mg subcutaneously did not precipitate any discernible abstinence as measured by the abstinence score or by subjects' reports of withdrawal illness (Fig. 17). These same doses will precipitate abstinence in subjects dependent upon 30 mg of morphine daily (7.5 mg q.i.d.) and in subjects receiving chronic pentazocine or chronic butorphanol (Fig. 17). After completion of the precipitation tests, the 3 subjects who did not withdraw were stabilized on buprenorphine for 8 more days and then saline placebo was substituted under double blind conditions.

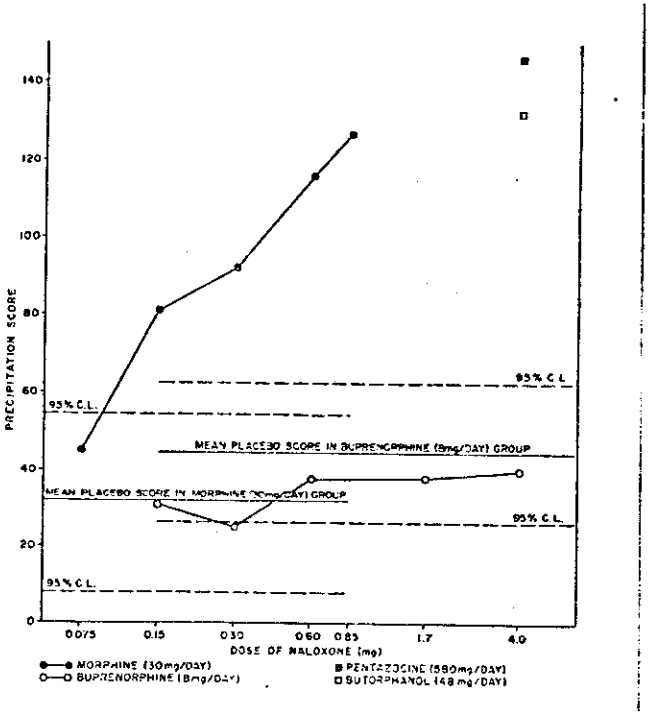


Figure 17. Abstinence scores following the administration of placebo and naloxone to subjects dependent upon morphine, 30 mg daily (7.5 mg q.i.d.), buprenorphine, 8 mg, butorphanol, 48 mg daily (12 mg q.i.d.), and pentazocine, 580 mg daily.

During the 2 days after discontinuing buprenorphine none of the 5 subjects reported any withdrawal symptoms. In those 3 subjects who underwent the withdrawal double blind, the substitution of placebo was not immediately discerned (Fig. 18). Beginning on the third day of withdrawal subjects began reporting intermittent episodes of hot flashes, chills and skin sensitivity. These were mild and subjects found them only mildly discomforting and did not seek relief from these symptoms with additional drug administration. They denied being sick (Fig. 18) or withdrawing. These symptoms persisted and did not increase markedly in intensity for the next 10 days.

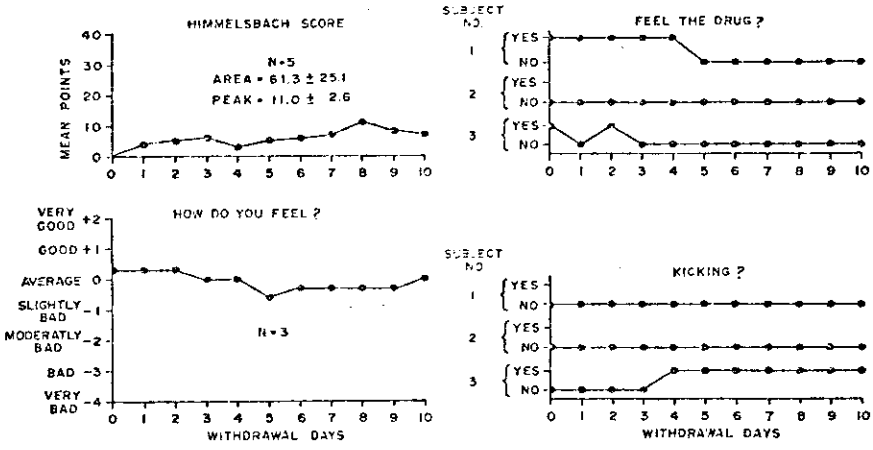


Figure 18. Mean daily Himmelsbach scores and responses on the chronic questionnaire in the 10 days following abrupt withdrawal of buprenorphine.

During the first 10 days of withdrawal Himmelsbach scores indicated the presence of mild abstinence (Fig. 18). The abstinence syndrome was below the level of clinical significance for morphine withdrawal. Comparison of the peak and total area scores for the first 10 days of withdrawal from buprenorphine is less than observed with other drugs which have produced mild abstinence syndromes in direct addiction tests (Table 10).

In the 2 subjects who withdrew, a test dose of 30 mg of morphine was administered on the 11th day of withdrawal and a placebo was administered on the 13th day of withdrawal to determine if buprenorphine was still present in significant amounts to block the effects of morphine. The lack of a clear abstinence syndrome suggested the possibility that buprenorphine was still present in large amounts. The responses to morphine were comparable to those obtained in the pre-drug control period. These 2 subjects reported increased withdrawal symptoms following these tests (14th - 17th day of withdrawal).

The other 3 subjects who were withdrawn double blind continued on observations and continued to show Himmelsbach scores in the range of approximately 10 points through the 13th day of withdrawal. On the 14th day of withdrawal, there was a marked increase in withdrawal signs and Himmelsbach scores increasing from a mean of 9 points on the 13th day to a mean of 23 points on the 14th day. Subjects reported feeling bad, were depressed and demanded relief of their symptoms with morphine. Nausea, vomiting, restlessness, insomnia and diarrhea were present for the first time indicating more severe withdrawal.

These and other studies indicate that buprenorphine 1) is a morphine-like agent in man which may be a partial agonist, 2) is relatively non-toxic in chronic administration, 3) has an extremely long duration of action, and 4) effectively blocks the effects of large doses of morphine during chronic administration.

These findings suggest that buprenorphine may have utility as a maintenance drug in the treatment of narcotic addicts. Buprenorphine has the duration of methadone, is an effective blocker of narcotics, has a lesser abuse potential than methadone, and is less toxic than methadone or d-propoxyphene.

Comparative Metabolism of *d*-Propoxyphene HCl and *d*-Propoxyphene Napsylate in Man

Five of eleven subjects participating in a double blind crossover experiment to evaluate the morphine-like effects of propoxyphene[1] agreed to participate simultaneously in this study to explore possible pharmacokinetic differences between propoxyphene HCl and propoxyphene napsylate.

Table 10. Comparison of peak and total area Himmelsbach scores for the first 10 days of withdrawal of buprenorphine and other agents.

Drug	Daily Dose	N	Potency	Morphine Equivalence	TAS	Peak Score	Reference
Morphine	240 mg	8	1	240 mg	198.1 ± 16.3	36.8 ± 2.7	6
Cyclazocine	13.2 mg	6	20	260 mg	103.6 ± 13.2	18.8 ± 2.9	4
Nalorphine	240 mg	7	1	240 mg	129.6 ± 10.6	18.2 ± 1.8	8
Nalbuphine	203 mg	5	5/4	243 mg	136.0 ± 6.4	24.4 ± 1.5	5
Pentazocine	580 mg	6	1/4	145 mg	106.0 ± 9.3	15.8 ± 1.8	7
Butorphanol	48 mg	6	5	240 mg	164.1 ± 15.2	26.3 ± 3.7	
Propiram	1786 mg	3	1/8	222 mg	129.5 ± 32.0	21.3 ± 3.4	17
Profadol	510 mg	4	1/2	255 mg	188.0 ± 21.3	33.7 ± 4.3	17
Buprenorphine	8 mg	5	30	240 mg	61.3 ± 4.2	11.0 ± 2.6	

In this 9 week crossover study each subject received 3 oral doses of *d*-propoxyphene HCl (210, 420 and 600 mg), 3 oral doses of *d*-propoxyphene napsylate (310, 620 and 700 mg), 2 subcutaneous doses of morphine, and a placebo in random order at weekly intervals. Blood samples of 5 or 10 ml were drawn by venipuncture into heparinized tubes 1/2 hour before drug administration and after drug at 1/2 hour, 1, 2, 3, 5, 12 and 24 hours. Plasma was immediately separated and frozen until analyzed. Plasma samples were also collected from one subject approximately every other day (at 2 hours post oral drug) during substitution of propoxyphene napsylate, 300 mg p.o. q.i.d., for morphine, 15 mg subcutaneously q.i.d. The substitution period was 21 days followed by 10 days of abrupt withdrawal (under blind conditions).

Samples were analyzed for plasma concentrations of propoxyphene, norpropoxyphene and cyclic dinorpropoxyphene by the gas chromatographic method of Nash *et al.*[18] who assisted in setting up the procedure.

Mean plasma propoxyphene concentrations are shown in Fig. 19. There was a significant positive correlation of these values (and also mean norpropoxyphene levels) with mean decrease in pupillary diameter, with correlation coefficient equal to 0.85. Propoxyphene HCl was somewhat more rapidly absorbed than propoxyphene napsylate, giving significantly greater propoxyphene concentrations in the first 2 hours after drug administration and showing peak mean levels at 2 hours compared to 3 hours for the napsylate. Peak mean plasma propoxyphene levels were slightly greater for the HCl than the napsylate in the low and middle pairs of doses, which were approximately equimoler in propoxyphene for the 2 preparations. However, in the high doses mean propoxyphene levels were approximately equal for the 2 salts, even though the napsylate dose was lower than the HCl dose in this pair. Propoxyphene napsylate showed a linear dose response relationship in peak mean propoxyphene levels. However, propoxyphene hydrochloride also showed a significant quadratic relationship with peak mean propoxyphene levels approximately the same for the middle and high doses. After 2 hours post-drug only a linear dose response relationship was seen in mean propoxyphene levels. This could indicate a dose-related difference in absorption of propoxyphene hydrochloride or, with a small n of 5, it could be a random statistical anomaly. Mean plasma propoxyphene values found after the largest propoxyphene doses of both salts were in the range of 400-500 ng/ml, which may represent near maximum non-toxic plasma levels in non-tolerant subjects.

Peak norpropoxyphene levels were 10 to 75% greater than propoxyphene levels and occurred 2 to 6 hours later. The dose response relationships were not as clearly defined as for the propoxyphene levels. Norpropoxyphene values in the order of 50 ng/ml were seen consistently 7 days after

the large single oral doses of both salts. Very small amounts of dinorpropoxyphene were found in a few samples.

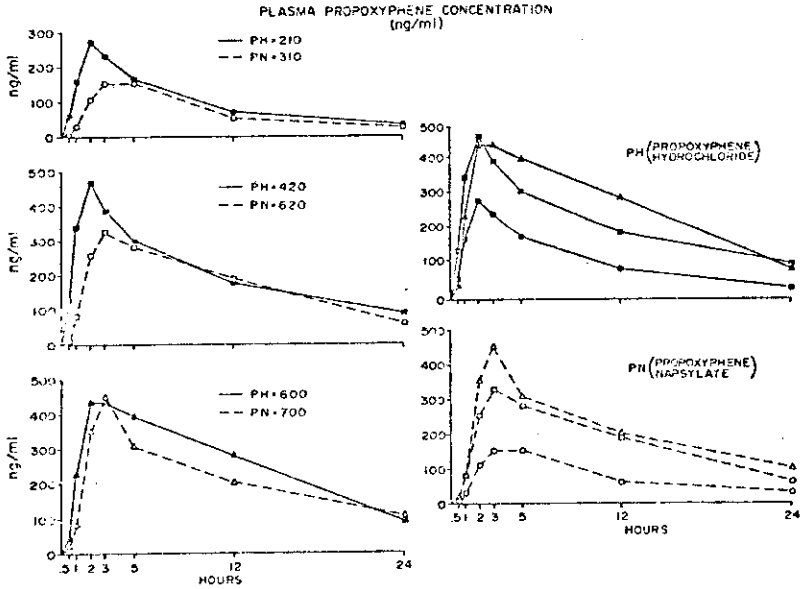


Figure 19. Plasma propoxyphene concentrations in 5 subjects following single oral doses of *d*-propoxyphene hydrochloride (PH) and *d*-propoxyphene napsylate (PN).

During substitution of oral propoxyphene napsylate in one morphine-dependent subject plasma propoxyphene levels reached approximately constant values of 800 to 1000 ng/ml 7 days after initiation of propoxyphene administration. Norpropoxyphene plasma levels increased rapidly to 3300 ng/ml by 14 days after beginning propoxyphene, and then increased to about 3500 ng/ml over the last 7 days of chronic administration. Dinorpropoxyphene plasma levels increased gradually and continuously during the entire

3 weeks of propoxyphene administration, reaching a peak value of 117 ng/ml. Following abrupt withdrawal, propoxyphene was detectable in the plasma for 8 days and nor- and dinorpropoxyphene were detected on the 10th day at levels of 87 and 19 ng/ml respectively.

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BEFORE THE MONOPOLY SUBCOMMITTEE OF THE SENATE SMALL BUSINESS COMMITTEE ON WEDNESDAY NOVEMBER 10, 1976 AT 10:00 A.M.

Senator Nelson, members of the subcommittee, it is a privilege to be here with you today to provide a summary of my findings resulting from clinical investigations of amphetamine and related drugs used as adjuncts in the treatment of obesity and my thoughts in regard to the applicability of these drugs in clinical medicine. It is a particular honor to discuss these matters with you, Senator Nelson, one of the truly distinguished citizens of my home state.

By way of introduction, Biometric Testing Inc. is an independent testing laboratory, engaged in clinical research performed for the food, drug, cosmetic and chemical industries on a contract basis. As a recognized clinical pharmacologist with over 20 years of experience in drug research and development, my technical function is to design appropriate studies on test products, closely monitor their progress, evaluate responses to the test products and provide a comprehensive interpretation of the data obtained. I should emphasize that I am a researcher and do not practice medicine.

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Our list of sponsors includes a wide spectrum of large, intermediate and small firms. Of particular interest is our work for the small drug manufacturers. It is probable that we have conducted more bioavailability comparisons with generic drugs than any other research group in the world. We are well known by both the industry and the Food and Drug Administration for our work in this field.

The amphetamine-like drugs fall into the general category of sympathomimetic agents. That is, they mimic a part or all of the responses seen from activation of the sympathetic nervous system, the so-called fight or flight mechanism of the body. These responses include: an increase in blood flow to the heart, lungs, skeletal muscle and brain; stimulation of the heart with an increase in cardiac output; dilatation of the bronchi and bronchioles of the lungs to allow more efficient oxygenation of the blood; and, central nervous system stimulation counteracting fatigue and increasing mental alertness.

Metabolic effects include elevation in blood glucose and fatty acids and an increase in metabolism mainly through breakdown of fatty acids.

It is important to recognize that there are numerous drugs in this category which produce sympathomimetic actions in various degrees. Therefore were amphetamine products, for example, to be removed from the market, other commercially available drugs could be substituted for them.

This question will be considered in our discussion as will the possibility of imposing further restrictions on the distribution of some or all of these products.

Of the series, methamphetamine and amphetamine are the most powerful central nervous system stimulants. The stimulant actions of one of these, amphetamine, were first described by Alles in 1933. In 1935 Prinzmetal and Bloomberg initiated clinical use of amphetamine for the treatment of narcolepsy, a disease characterized by inability to stay awake. Since that time, amphetamine products have been employed for a variety of conditions including chronic fatigue, parkinsonism, epilepsy, childhood hyperkinesis and poisoning by CNS depressants. Of course, the most popular use of amphetamine products today is in the treatment of obesity.

Of the various clinical applications, experts still consider amphetamine as valuable in the treatment of patients with narcolepsy and for children with hyperkinesis in selected cases. This condition is very prevalent - experts estimating that some 5% of our children are affected to some degree. One of my children, for example, exhibited sufficient hyperactivity, lack of attention span, and associated behavioral problems to require therapy. Similar symptoms were exhibited by some of my other children and drug therapy might have been useful. In retrospect, I probably also presented similar symptoms during childhood. Hyperkinesis in children

requires more intensive study and greater recognition. It is frequently associated with learning, speech and other perceptual deficits. My own son suffered severe emotional problems related to the disease which one psychologist felt represented a borderline psychosis. The mental and emotional scars that are unavoidable sequellae represent the most damaging hazards associated with this disorder. Fortunately, the symptoms usually moderate with age and are seldom apparent in young adults.

Obesity of course is the most prevalent disease in our society. Just from the cosmetic standpoint, the disease can represent a serious threat to well-being, and we all appreciate the importance of the quality of life as opposed to its duration. The contribution of obesity to the incidence and severity of other diseases; particularly those involving the lungs, heart and blood vessels are considered by most experts to be significant. However, epidemiological surveys suggest that remarkable influences on longevity are only seen with early onset obesity; dating back to the teen-ages, twenties and early thirties. Conversely, moderate obesity does not appear to significantly change morbidity and mortality associated with pulmonary and cardiovascular disease when weight gains start in later years (after 40). Of course, severe obesity at any age represents a serious disease state which can adversely effect the function of all organ systems.

There should be no question that amphetamine and related drugs are effective adjuncts in a therapeutic program for obesity. Their actions are clear-cut and reproduceable.

My evaluation of the research work accomplished with amphetamine-like drugs has been requested. With the disclaimer that specific projects cannot be evaluated with precision unless they are monitored and the data thoroughly reviewed, my general opinion is that the background of animal and clinical work on these drugs is both extensive and adequate to make a judgement of effectiveness under conditions of use. The actions of these drugs are clear-cut and even under relatively lax experimental conditions, should be reproduceable. Controlled studies to demonstrate effectiveness in comparison to placebos require hard work but no unusual skills. Study administrators may frequently be tempted to guess which patients are being treated with active drugs because of the side effects exhibited. This is a research problem common with the study of most pharmacologically active drugs. Experienced researchers discourage such speculation by the technical personnel.

Those who do engage in guessing games will often find out that they were wrong. The actions of a placebo will often match and sometimes exceed those of an active material. Conversely, a very potent drug may not elicit any remarkable signs or symptoms in some individuals. Regardless, when objective endpoints are available, such as actual weight loss, assessments are simplified and data are more concrete. Moreover, when results obtained from a number of research sites prove essentially equivalent, it can be concluded that the findings are valid. On this basis, the effectiveness of amphetamine-like products as adjuncts in the

treatment of obesity has been generally accepted by experts qualified by training and experience to make these judgements. Our data, confirmed by other investigators and resulting from separate investigations of amphetamine formulations and two related drugs can be summarized as follows:

1. Patients treated with amphetamines who complete the study requirements (weekly clinical visits, maintenance of the prescribed dosage intake, continued diligence during study periods ranging from 8 to 16 weeks) on the average will lose more weight than patients who are maintained on placebo medication during equivalent periods of time.

2. Weight loss in both placebo and treated groups are more notable when dietary plans are detailed and maximum caloric intakes are calculated for each patient on the basis of height and body build, in contrast to weight losses associated with less rigid programs involving non-specific dietary restrictions.

3. Fewer patients treated with placebo can maintain the personal motivation required to complete a weight reduction program, in comparison to patients treated with an amphetamine formulation or related product. There will be significantly more drop-outs in the placebo group prior to completion of the study requirements.

4. The most important aspect in a weight reduction program is personal motivation. Unless highly motivated an individual cannot stay on a diet and no program will be successful.

5. Patients do not appear to become resistant to the effects of amphetamine, rather they gradually lose motivation.

6. Very obese patients have great difficulty in reducing caloric intake and losing significant amounts of weight with or without an amphetamine crutch. Such individuals are often called compulsive eaters or food addicts.

7. The amount of attention paid to the trials and tribulations of obese subjects is directly proportional to the success attained. Reviewing progress, counseling, gentle persuasion and strong encouragement are important facets of a weight reduction program.

A rather dramatic illustration of the profound influence of the human psyche on eating habits is afforded by reviewing results of administration of sympathomimetic drugs to experimental animals. In the so-called lower forms these drugs are truly anorexigenic - appetite reducing - drugs. Most of us regard our canine friends as the most hedonistic of all creatures when it comes to food. Yet dogs given amphetamine will

frequently stop eating entirely and literally starve themselves to death. The effects in rats and monkeys are a little less extreme but still remarkable. None require diet programs, motivation, tender loving care or any of the other forms of psychological bolstering so important for humans.

Clearly, if we resembled our animal predecessors just a little more closely, amphetamines might be fine, reasonably safe drugs for treatment of obesity. True, they may produce numerous side effects such as anxiety, tenseness, restlessness, throbbing headaches, tremors, weakness, dizziness, and palpatations and, most important, difficulty in sleeping. But the side effects are usually controllable by dose reductions and tend to abate with continued use.

Surprisingly, the stress which amphetamines induce on the system does not appear to produce any appreciable harm with moderate doses during short periods, except possibly to individuals with advanced cardiovascular disease.

Rather the problem with the amphetamines as with many other drugs which affect the central nervous system relates to that intricate, mysterious, perverse tissue mass, the human brain; responsible for the indefinable human psyche. During a relatively short span of availability, amphetamines have emerged as major drugs of abuse.

In consideration of the number of very unpleasant side effects a reasonable question is why? Like most drugs subject to abuse, amphetamines produce desirable responses that for some individuals outweigh any associated discomfort or, in gross overdosage, physical distress.

Compulsive users of amphetamines fall into roughly two categories. Individuals who consume therapeutic doses or doses only slightly in excess of therapeutic doses routinely, but not necessarily daily, fall into the first category. Such individuals have learned to rely on the drug to help them cope with the demands of their social environment. Amphetamines produce an elevation in mood and increased alertness. They counteract fatigue and improve the ability to concentrate. Physical performance may be enhanced considerably at times. Perhaps the most insidious perceived benefit is an increase of initiative and self-confidence.

Even though, on occasions, paradoxical responses occur, it is easy to understand how the student, the athlete, truck drivers and other individuals who receive rewards for either intense or prolonged efforts can be hooked. Consider also the overworked or harassed executive who finds that amphetamines improve the quality and quantity of his work output, while increasing self-confidence and the housewife who may use the drug simply to counteract boredom.

Some of these mildly addicted individuals use the drug for years and don't present any remarkable social problem except occasional distressing loquaciousness. With moderation, amphetamine effects sound good and have a definite appeal. Unfortunately all is not as rosy as it sounds. Users have difficulty sleeping and tend to either become exhausted or to use sedatives starting the classical "upper-downer" cycle. Some find alcohol an effective antidote for the stimulant side effects. Alcohol and sedatives as a whole are really more pleasant drugs and can become a far greater problem than the amphetamines. Actually people don't become physically dependent on amphetamines. They can stop use without any terribly unpleasant responses. But they can and do become physically dependent on alcohol and some even to the sedative hypnotic drugs.

Other problems associated with chronic use are less well defined; however, mental depression and gastrointestinal diseases appear to be frequent concomitants of routine amphetamine intake. The most important side effect of weight reduction programs in which amphetamine is employed as an adjunct, is therefore chronic compulsive use of moderate doses.

Experts regard even this form as abuse as more often a result of experimentatio and subsequent reinforcement of a sensation of need for the drug in order to function, rather than as an iatrogenic problem. This pathway appears to be characteristic of all drugs of abuse. However, susceptibility to moderate abuse seems widespread and the risks involved even with adequately supervised short term use are undoubtedly real.

Self-administration of gross overdoses of amphetamine-like products either orally, by inhalation or by intravenous injection represent a second and extremely hazardous form of abuse. Such activities are restricted preponderantly to members of our "drug culture". Individuals who employ large doses of amphetamine, methamphetamine or similar drugs usually abuse other central nervous system drugs including alcohol, opiates, barbiturates and marihuana. It seems that any mechanism that can provide them with a means of escape from the expectations and impingements of society, their conscience and even consciousness, is subject to adaption by these individuals. Amphetamines are valued because of a "rush" sensation produced particularly when injected. The exhilaration experienced reportedly resembles a sexual release. Cardiovascular and CNS side effects are of course magnified and it is difficult to understand how any degree of pleasure can compensate for the associated unpleasantness. I've only seen the results of acute amphetamine abuse on one occasion during a day long visit at the home of a university professor, a psychologist by training. On arrival in the morning, his wife appeared to be floating on air. She remained that way until shortly before our departure in the evening, when she collapsed into a deep sleep. During the day she would not or could not maintain a given conversation or sit for any length of time. She was inordinately garralous and obviously edgy. This response was purportedly the result of sniffing a quantity of dextro-amphetamine.

Most of us have seen the results of chronic, gross amphetamine abuse on TV, or at least read descriptions in the lay press. The anorexic actions of the drugs are illustrated by the fact that chronic users generally appear emaciated. But signs of mental disturbances are also obvious during periods of prolonged and repeated use. Diminished intelligence level can be appreciated particularly in previously highly intelligent individuals. Delusions and frank hallucinations are common. Feelings of persecution, suicidal urges and even homocidal responses are characteristi of this category of amphetamine addiction. Deaths resulting from amphetamine overdosage can occur, but most often are a result of administration of companion drugs. Actually, it is amazing how resistant the cardiovascular system of the human being is to this form of grievous assault; particularly when one considers that the death rate from cardiovascular disease remains our leading killer.

Fortunately, when an amphetamine addict is "dried out" mental and physical pathology usually prove reversible. Nor do chronic, high dose, amphetamine abusers suffer withdrawal symptoms seen with addiction to depressant drugs; unless they happen to be addicted to any of these materials at the same time. Also, gross amphetamine abuse is usually episodic rather than continual as with classical opiate, sedative addiction. However, the property of tolerance to high doses is shared by this group. A dose of amphetamine which might prove fatal to a normal person may be employed

routinely by some. Finally, it should be emphasized that this form of addiction to amphetamine is regarded by many experts to present the greatest potential for social aberrancies of a hazardous nature among the whole group of drug abuse problems. These individuals can be mutilators of children as well as adults, rapists and cold blooded killers. One wonders for example, if the Manson Cult were amphetamine freaks.

The issue remains whether the risk to benefit ratio associated with the therapeutic use of amphetamine for obesity or any other disease, is sufficiently low to justify their continued commercial availability. At present straight amphetamine and methamphetamines are included in Schedule II of the Controlled Substances Act along with morphine, cocaine and other drugs of abuse. Should these two drugs in particular be relegated to Category I, thereby prohibiting any form of commercial distribution? Should their use be restricted to cases of narcolepsy or childhood hyperkinesis in which they may well represent drugs of choice?

Those who hold that an elevation to the Category I status would be overkill point out that initial results obtained through imposing the Category II restrictions have been moderately effective in diminishing the low-dose amphetamine abuse problem and that with improved surveillance this form of moderate abuse will be effectively retarded. Many have doubts that a Category I status would have any appreciable effect on

severe abuse incidence in spite of increased effectiveness of our enforcement officials. The street price of amphetamines which rumor tells us is presently about $3.00 per dose would certainly increase which may afford some deterrant action; but, more likely, such an increase would prove of greater efficacy in supporting the ventures of organized crime.

Speaking to the pro-Category I question, the therapeutic merit of amphetamine products are probably not sufficiently remarkable to dictate that they remain available even with further labeling restrictions.

It seems unlikely that clinicians on the whole would strenuously object if the amphetamine products were completely banned; particularly if they could be assured that deletion of thess occasionally very useful drugs would not be an exercise in futility.

An investigative reporter, with whom I've become friendly recently disclosed to me that reliable information exists suggesting that other sympathomimetic drugs are presently achieving the wide-spread abuse category. He specifically designated the drug, phenteramine as a popular amphetamine substitute. This drug is presently listed among the drugs with low abuse potential in Category IV. Our work at Biometric Testing Inc. indicates that at effective therapeutic doses some of the sympathomimetic side effects may occur (dry mouth, palpitations, nervousness) but that the mood-elevating, anti-fatigue actions associated with amphetamine and methamphetamine are minimal.

Although not as extensively studied as amphetamine, phenteramine and other drugs with similar activity have been well characterized pharmacologically. Jerome Jaffe in the standard test, Goodman and Gilman cites the work of Martin and his associates (Clin. Pharmacol. Ther. 12:245, 1971) which suggest that some representatives of the series can produce central nervous system stimulation in experimental animals comparable to that of amphetamine depending upon the dose administered. Since human investigations have been restricted to recommended doses, the relevancy of these data in humans cannot be defined. However, as a response to the invitation to discuss this problem with you I have explored this possibility further. A former classmate and expert in the pharmacology of drug addiction, Dr. Gerald Deneau, provided me with data showing that primates under given conditions will self-administer some of these presumably less stimulant sympathomimetics. These data support the work of Martin et al and suggest that the appreciated amphetamine responses might be obtainable with elevated doses.

Most investigators would discount a significant abuse potential for phenteramine and similar drugs on the basis of the data available in the literature. The drugs have just not proven to elicit sufficiently rewarding responses in comparison to associated discomfort. Yet, we cannot sell the human animal short. A lesser crutch will frequently be acceptable if the parent is not available, even though it is reasonable to assume that unwanted side-effects will be proportionately amplified with higher doses.

Any evidence suggesting a significant abuse potential requires critical evaluation before conclusions are warranted.

To achieve a conclusion that a given amphetamine-related product possesses abuse potential of an order to dictate added sanctions, it should be possible to document an increasing incidence of abuse. In contradiction to my reporter friend, another close observer has failed to note any remarkable or alarming upsurge in recreational, non-medical use of the amphetamine-related drugs. He states that fenfluramine, a newer introduction more likely to produce drowsiness than stimulation, appears to present as many problems as some of the older products. Yet, on the basis of limited data, it seems that baboons, at least, do not enjoy fenfluramine and will not self-administer the drug abnormally. Perhaps baboons are more discriminating than humans.

Undoubtedly our DEA, regulatory officials will be able to provide us with more definitive information in regard to the current incidence of cases of confirmed abuse of amphetamine-related drugs; particularly the incidence associated with the inhalation and intravenous routes of administration.

If indeed the related drugs prove to possess an abuse potential approaching that of amphetamine, then clearly they should be placed in Category II.

If new findings illustrate that a drug is favored by the "drug culture" as an agent of gross abuse, it may well merit Category I status. Under any circumstances, we should remain diligent in defining degrees and hazards of abuse associated with those drugs retained on the market, and any potential substitutes should they be withdrawn.

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STATEMENT BY
EDWARD A. KING JR., A.C.S.W., DEPUTY DIRECTOR
TOWN OF HUNTINGTON YOUTH BUREAU
1328 NEW YORK AVENUE, HUNTINGTON STATION, NEW YORK 11746

BEFORE THE SUBCOMMITTEE ON MONOPOLY
SENATE SMALL BUSINESS COMMITTEE

NOVEMBER 11, 1976

MR. CHAIRMAN, MEMBERS OF THE COMMITTEE, MY NAME IS ED KING. I AM DEPUTY DIRECTOR OF THE TOWN OF HUNTINGTON YOUTH BUREAU, AND PROGRAM DIRECTOR OF THE TOWN'S COMMUNITY-BASED DRUG PROGRAM.

MY TESTIMONY TODAY IS BASED ON OVER SEVEN YEARS OF EXPERIENCE IN MY PRESENT POSITION WITH HUNTINGTON TOWNSHIP, WHICH IS A LARGE LONG ISLAND SUBURB OF NEW YORK CITY, WITH A POPULATION OF 220,000 PEOPLE.

IN 1968, THE TOWN OF HUNTINGTON ESTABLISHED THE FIRST TOWN-LEVEL YOUTH BUREAU IN NEW YORK STATE FUNDED BY THE NEW YORK STATE DIVISION FOR YOUTH, AND OUR YOUTH BUREAU WAS AMONG THE VERY FIRST AGENCIES TO RECEIVE STATE FUNDS TO OPERATE A COMMUNITY-BASED PROGRAM FOR THE PREVENTION AND CONTROL OF YOUTHFUL DRUG ABUSE IN 1970. IN 1971, THE TOWN OF HUNTINGTON INSTITUTED THE FIRST VOLUNTARY AMPHETAMINE BAN IN THE UNITED STATES.

THE TOWN'S COMPREHENSIVE YOUTH PLAN INCLUDES EIGHT PRIVATE, NON-PROFIT CORPORATIONS KNOWN AS YOUTH DEVELOPMENT ASSOCIATIONS SERVING LOCAL NEIGHBORHOODS WITHIN THE TOWNSHIP, AND SEVERAL SUPPORT PROGRAMS IN THE AREAS OF JOB DEVELOPMENT, SUMMER CAMPS, RUNAWAY PLACEMENTS, FAMILY ADVOCACY, AND COURT DIVERSION, AS WELL AS THE DRUG PROGRAM WHICH CONSISTS OF A HOTLINE, COUNSELLING CENTER, AND OUTREACH WORKERS ASSIGNED TO THE LOCAL YOUTH DEVELOPMENT ASSOCIATIONS.

WE FEEL THAT OUR EIGHT YOUTH DEVELOPMENT ASSOCIATIONS ON CONTRACT WITH THE YOUTH BUREAU PROVIDE THE KEY TO THE DEVELOPMENT OF PROGRAM STRATEGIES SPECIFIC TO REDUCING DRUG ABUSE. THEY ARE OPERATED BY LOCAL BOARDS OF COMMUNITY CITIZENS (ADULTS AND YOUTHS), AND ARE IN THE BEST POSITION TO RECOGNIZE LOCAL PROBLEMS AND THEIR

SOLUTIONS IN COOPERATION AND COORDINATION WITH OUR YOUTH BUREAU PROFESSIONAL STAFF. THIS ELABORATE SYSTEM OF CITIZEN INVOLVEMENT IN LOCAL GOVERNMENT INCLUDES, (IN ADDITION TO LOCAL NEIGHBORHOOD BOARDS), CENTER COUNCILS, TASK FORCES, SPECIAL COMMITTEES AND PROGRAM VOLUNTEERS, WORKING WITH THE UNDERSTANDING AND SUPPORT OF THE APPOINTED MEMBERS OF THE YOUTH BOARD AND THE ELECTED OFFICIALS OF THE TOWN COUNCIL.

WE DESCRIBE THIS GRASS-ROOTS VOLUNTEER EFFORT WITH OBVIOUS PRIDE, MR. CHAIRMAN, TO ILLUSTRATE THE IMPORTANCE OF THE WORK OF THIS COMMITTEE. WITH ALL OF THIS LOCAL COMMUNITY CONCERN AND EFFORT TRANSLATED INTO QUALITY PROGRAMS AND PROFESSIONAL SERVICES, WE WILL ULTIMATELY FAIL TO FREE OURSELVES OF DRUG ABUSE UNLESS INSTITUTIONALIZED FORMS OF DRUG ABUSE ARE ADDRESSED AT THE FEDERAL LEVEL.

I WOULD LIKE TO OFFER A VERY SPECIFIC ILLUSTRATION AT THIS TIME. IN FEBRUARY OF 1972, THE TOWN OF HUNTINGTON PROVIDED EXPERT TESTIMONY IN THE PERSON OF EDWARD M. GUROWITZ, PH. D., THEN DIRECTOR OF CLINICAL SERVICES OF THE TOWN'S NARCOTIC GUIDANCE COUNCIL, BEFORE A SENATE SUBCOMMITTEE CHAIRED BY THE HONORABLE PAUL G. ROGERS, DEALING WITH THE VERY SAME CONCERNS OVER AMPHETAMINE ABUSE WHICH WE ARE ADDRESSING HERE TODAY.

IN THAT TESTIMONY, DR. GUROWITZ REFERRED TO A DOCTOR WITH A "DIET PRACTICE" WITH OFFICES IN THE SAME BUILDING AS OUR TOWN'S COUNSELLING CENTER, AND ALSO HOUSING THE SUFFOLK COUNTY METHADONE MAINTENANCE CLINIC. HE SPOKE OF HIS DIFFICULTY IN EXPLAINING THIS

TO YOUNG CLIENTS WHO SAW LONG LINES OF PEOPLE, MANY OF THEM YOUNG, FEW OF THEM OBESE, WAITING TO OBTAIN DRUGS FOR WEIGHT CONTROL. THE SITUATION WAS AGGRAVATED BY THE FACT THAT MANY OF THESE CLIENTS WERE COURT REMANDED FOR TREATMENT AFTER ARREST AND CONVICTION FOR THEIR ILLICIT DRUG ABUSE, AND HAD REAL FEELINGS ABOUT THE DAILY PARADE OF "LEGITIMIZED" DRUG TRAFFIC WHICH THEY WERE WITNESS TO.

THE FOLLOWING STEPS WERE TAKEN ON THE LOCAL LEVEL: THE SUFFOLK COUNTY DISTRICT ATTORNEY'S OFFICE WAS ALERTED TO THE SITUATION; THE SUFFOLK COUNTY MEDICAL SOCIETY WAS INFORMED (BUT THE DOCTOR WAS NOT A MEMBER, AND THEY COULD IMPOSE NO EFFECTIVE SANCTION); THE TOWN'S COUNSELLING CENTER WAS MOVED TO A NEW LOCATION; AND, SOON AFTER, THE COUNTY'S METHADONE CLINIC MOVED AWAY ALSO. AS OF THIS WRITING, THIS SAME DOCTOR REMAINS UNDER INVESTIGATION OF THE DRUG ENFORCEMENT ADMINISTRATION, AND IN ACTIVE PRACTICE IN THE SAME LOCATION WITH AN ESTIMATED WEEKLY CASELOAD OF OVER 800 PATIENTS.

IN JANUARY OF THIS YEAR, ONE OF THOSE PATIENTS, A TWENTY YEAR OLD FEMALE, CAME TO OUR COUNSELLING CENTER WITH THE HOPE OF BREAKING A ONE YEAR ADDICTION TO AMPHETAMINES. THE PILLS WERE GIVEN TO THIS CLIENT ON A REGULAR AND UNREGULATED BASIS. SHE STATED THAT SHE WAS GIVEN THE PILLS DIRECTLY BY THE DOCTOR, AND THAT SHE WAS ABLE TO GET MORE THAN THE USUAL WEEKLY ALLOTMENT OF TWENTY-ONE PILLS WITH EASE. SHE FURTHER STATED THAT, AFTER THE FIRST VISIT, NO SIGNIFICANT EXAMINATION WAS MADE OF HER PHYSICAL OR EMOTIONAL CONDITION.

DURING THAT YEAR, BEFORE SHE CAME TO US, SHE WAS OFTEN DEEPLY DEPRESSED, HAD VISUAL HALLUCINATIONS, WAS DELUSIONAL IN HER THINKING, AND ATTEMPTED SUICIDE ON THREE SEPARATE OCCASIONS. SHE WAS HOSPITALIZED EACH TIME.

ON FEBRUARY 2ND OF THIS YEAR, WE REFERRED HER TO A LOCAL DETOX UNIT, AND THEY REFERRED HER TO A LOCAL RESIDENTIAL TREATMENT PROGRAM. SHE WITHDREW AFTER TWO DAYS, BUT OUR FOLLOW-UP DETERMINED THAT SHE REMAINED DETOXIFIED FOR TWO MONTHS BEFORE SHE RETURNED TO THE DOCTOR'S OFFICE FOR MORE PILLS WHICH SHE RECEIVED.

ON MAY 4TH, IN THE PRESENCE OF ONE OF OUR WORKERS, SHE WROTE A LETTER TO THE DOCTOR, AND TOLD HIM OF HER ADDICTIVE HISTORY WITH THE PILLS HE HAD BEEN GIVING HER, AND PLEADED WITH HIM TO NEVER GIVE HER PILLS AGAIN, EVEN IF SHE BEGGED HIM.

I WISH THAT I COULD SAY THAT THIS IS AN ATYPICAL AND OVERLY DRAMATIC CASE, MR. CHAIRMAN, BUT THIS SAD STORY IS UNUSUAL ONLY IN THE SENSE THAT THIS YOUNG WOMAN CAME FOR HELP. WHEN AMPHETAMINES ARE INVOLVED IN AN ESTABLISHED PATTERN OF DRUG ABUSE, DEEP DEPRESSIONS, AGGRESSIVE ACTING OUT, PARANOIA, SUICIDAL TENDENCIES AND RESISTIVENESS TO CHANGE ARE THE COMMON TRAITS.

JUST AS THESE HEARINGS ON ANTI-OBESITY DRUGS ARE PART OF A LARGER STUDY OF THE DEVELOPMENT, MARKETING, AND DISTRIBUTION OF PRESCRIPTION DRUGS IN GENERAL, THE ABUSE OF AMPHETAMINES IS USUALLY COMBINED WITH THE ABUSE OF TRANQUILIZERS, SEDATIVES, AND BARBITUATES OBTAINED, FAR TOO OFTEN, FROM OTHER DOCTORS.

MANY ADULTS IN TOWN, AS WELL AS YOUNG PEOPLE, FIND THEMSELVES ON A CHEMICAL ROLLER-COASTER OF "UPS" AND "DOWNS." THE SUBURBAN HOUSEWIFE SEEMS TO BE A PARTICULARLY HIGH-RISK POPULATION FOR THIS KIND OF DRUG ABUSE. SOME START WITH DEPRESSANT DRUGS, DEVELOP TOLERANCES, AND THEN GO TO A "WEIGHT DOCTOR" FOR AMPHETAMINES TO HELP THEM GET UP IN THE MORNING. OTHERS GET "STRUNG OUT" ON THEIR

INCREASED TOLERANCE FOR AMPHETAMINES AND GO TO ANOTHER DOCTOR WHERE THEY PRESENT THE SYMPTOMS OF EXTREME FATIGUE, ANXIETY, AND TENSION, AND TRANQUILIZERS OR SEDATIVES ARE PRESCRIBED.

WE HAVE FOUND VERY FEW AMPHETAMINE ABUSERS IN OUR TOWNSHIP WHO HAVE OBTAINED THEIR DRUGS FROM THE STREET IN RECENT YEARS. THIS IS NOT THE CASE WITH TRANQUILIZERS, SEDATIVES AND BARBITUATES, WHICH ARE MORE COMMON IN GENERAL AND MORE AVAILABLE IN THE ILLICIT DRUG TRAFFIC.

IF WE COULD SOMEHOW CONTROL THE PRODUCTION OF TRANQUILIZERS, SEDATIVES, AND BARBITUATES SO THAT TOMORROW THEY WOULD BE AVAILABLE FOR ONLY THE APPROPRIATE MEDICAL USES, I WOULD THINK TWICE BEFORE DOING IT. I CERTAINLY WOULD NOT WANT TO DRIVE IN HEAVY TRAFFIC THE NEXT DAY!

THE KIND OF HUMAN SERVICES NECESSARY TO ENABLE LESS FORTUNATE MEMBERS OF OUR SOCIETY TO COPE IN A HEALTHY AND RESPONSIBLE WAY WITH THE STRESSES AND ANXIETIES OF MODERN DAY LIFE ARE SIMPLY NOT IN PLACE. THIS IS NOT TO SAY THAT DEPRESSANT DRUGS ARE NOT GROSSLY OVER-PRODUCED AND OVER-PRESCRIBED. THEY MOST CERTAINLY ARE, AND FEDERAL CONTROLS ARE URGENTLY NEEDED. HOWEVER, THESE CONTROLS SHOULD BE DEVELOPED CAREFULLY AND INSTITUTED WITH CAUTION. A PHASE-IN PERIOD OF SEVERAL YEARS IN WHICH PRODUCTION LIMITS WOULD TIGHTEN IN SET STEPS WOULD ALLOW FOR THE NECESSARY ON-GOING EVALUATION WHICH THIS EFFORT WOULD REQUIRE.

AMPHETAMINES ARE A DIFFERENT STORY. THE TESTIMONY OF DR. GUROWITZ FIVE YEARS AGO CAREFULLY ESTABLISHED 1,200 KILOS AS A REASONABLE NATIONAL PRODUCTION LIMIT FOR AMPHETAMINES. THIS WOULD PROVIDE AN ADEQUATE SUPPLY TO SUPPLEMENT THE NON-AMPHETAMINE DRUG OF CHOICE (RITALIN) FOR THE TREATMENT OF THE RARE CONDITIONS OF NARCOLEPSY AND HYPERKINESIS. THE LATTER CONDITION IS PRESENTLY THOUGHT BY MANY TO BE CAUSED BY ALLERGIC REACTIONS TO DYES AND PRESERVATIVES IN FOODS; YET ANOTHER FORM OF INSTITUTIONALIZED SUBSTANCE ABUSE.

IT SEEMS TO ME, MR. CHAIRMAN, THAT AMPHETAMINES ARE THE PLACE TO START WITH STRICT CONTROLS ON PRODUCTION. WHILE THE ABUSERS OF DEPRESSANT DRUGS ARE OFTEN SELF-MEDICATING TO CONTROL THE SYMPTOMS OF UNDERLYING EMOTIONAL TURMOIL, AMPHETAMINES ONLY AGGRAVATE AND INTENSIFY THOSE VERY SAME SYMPTOMS. THE PERSON WITH UNDERLYING HOSTILITY BECOMES MORE HOSTILE. THE PERSON WITH UNDERLYING DEPRESSION BECOMES MORE DEPRESSED. THE PERSON WITH UNDERLYING PSYCHOSIS BREAKS MORE COMPLETELY WITH THE REALITIES AROUND HIM.

THE OVERALL IMPACT OF THIS AGGRAVATED AND INTENSIFIED CONFLICT ON FAMILY LIFE IS BEYOND CALCULATION, BUT MOST CERTAINLY WIDE SPREAD AND TRAGIC IN ITS EFFECT.

WE, IN THE TOWN OF HUNTINGTON, ARE PLEASED AND GRATEFUL THAT THIS COMMITTEE IS ONCE AGAIN FOCUSING ATTENTION ON THE CRITICAL NEED TO CURTAIL THE OVER-PRODUCTION OF COMMONLY ABUSED PRESCRIPTION DRUGS BY BIG INDUSTRIES THROUGHOUT OUR NATION. BY BROADENING THE FOCUS OF OUR PUBLIC CONCERN OVER DRUG ABUSE IN THIS WAY, WE CAN

TAKE REAL STEPS TO DEMONSTRATE INTEGRITY IN OUR NATIONAL EFFORT.

YOUNG PEOPLE ABUSING DRUGS OBTAINED ON THE STREET HAVE BEEN SCAPEGOATED FOR TOO LONG IN OUR SO-CALLED "WAR ON DRUG ABUSE." YOUNG PEOPLE IN GENERAL ARE EXTREMELY SENSITIVE TO HYPROCRACY, AND WOULD BE QUICK TO RECOGNIZE ANY REAL STEPS TO DEAL FAIRLY AND SQUARELY WITH INSTITUTIONALIZED DRUG ABUSE AS ALSO BEING STEPS TO REDUCE SIGNIFICANTLY THE ALIENATION YOUNG PEOPLE FEEL FROM THIS NATIONAL EFFORT AT THE PRESENT TIME.

YOUR LEADERSHIP WILL GO A LONG WAY TOWARD UNITING YOUNG AND OLD ALIKE IN A NATIONAL EFFORT TO FIND HEALTHY AND RESPONSIBLE WAYS TO LIMIT AND CONTROL DRUG ABUSE AND THE CLOSELY RELATED HUMAN ABUSES OF ALL KINDS.

WE THANK YOU FOR THE OPPORTUNITY TO BE A PART OF THAT PROCESS, AND STAND READY TO ASSIST IN ANY WAY POSSIBLE.

THANK YOU.

Statement of Isaac R. McGraw, President
Pharmaceutical Division of Pennwalt Corporation
Submitted to Senate Monopoly Subcommittee

November 19, 1976

INDEX

At the request of your Committee, I am appearing on behalf of Pennwalt Corporation's Pharmaceutical Division in order to provide the Committee with our comments on the subject of anti-obesity drugs.

Introduction

In my appearance today on behalf of Pennwalt and its Pharmaceutical Division, I will review those major considerations which we believe to be responsive to this Committee's invitation.

In order that you may readily comprehend our views, I should like to summarize them at the outset and then deal with them more fully by major category.

As part of Pennwalt Corporation, a 126-year old firm founded and still headquartered in Philadelphia, Pennsylvania, with annual sales of approximately $750 million, we share its pride in our collective integrity. (I should note that our division represents less than ten percent of the Company's total sales, and that our anti-obesity products represent less than three percent of total sales, with less than one percent in anorectic amphetamine products.)

Anti-obesity prescription medicine is the only federally recognized effective medicinal aid available in a course of medically supervised anti-obesity treatment available to the 30 to 40 million Americans who are obese, namely, those who are at least 20 percent overweight.

Obesity is a recognized illness, in medical terms, as well as an emotional burden. It also complicates other quite serious medical problems.

Our Pharmaceutical Division clearly recognizes that its anorectic products should not be used unless prescribed by a physician. We firmly believe that our marketing program fully reflects this recognition and contains no suggestion that we seek to sell the patient <u>any</u> use of our anorectic products.

As this Committee is aware, the Food and Drug Administration has found our anorectic products to be safe and effective and, in our judgment, we have continued to achieve very satisfactory compliance with the regulatory standards and programs which are the responsibility of the Drug Enforcement Administration.

We believe that you should find the factual evidence on the prescription dosage units of our products, per patient, to be consistent with their use as a short-term aid to the medically supervised obese patient.

We do not believe there is any probative evidence that our anti-obesity products show any meaningful statistical or other factual evidence of abuse.

We recognize that in a population of 215 million Americans there is a very small but highly visible segment who are troubled and who may be determined to misuse or abuse legitimate products.

We believe, however, that the safety, effectiveness and judicious prescription of anti-obesity products cannot reasonably be condemned by the very limited factual evidence of their statistically quite infrequent misuse.

The Congress and 42 state legislatures have created, and the FDA, DEA and State agencies administer, monitor and enforce sophisticated and effective programs designed to ensure proper medically supervised use of anorectic products.

We fully support these programs and cooperate readily with these agencies.

We believe that a scientific, technical or legal analysis fully and fairly considered, on the basis of factual rather than hearsay evidence,

will continue to require the conclusion that our anorectic products serve a very worthwhile medical and human need--assistance to the physician who finds that his patient requires this medication.

I shall now turn to a more detailed review of the bases for the views I have just summarized.

Corporate History

Pennwalt Corporation was founded in 1850, in Philadelphia where it continues to maintain its corporate headquarters. Pennwalt has more than 14,000 employees who are engaged in manufacture, sale and distribution of its products in the United States, Europe and elsewhere in the free world. Pennwalt's total annual sales are expected to exceed $750 million in 1976, derived from its operations in Chemicals (approximately 50%), Specialized Equipment (approximately 25%), and Health--including both Dental and Pharmaceutical operations (approximately 25%). The Pharmaceutical Division has annual sales of approximately $70 million and employs approximately 1,100 people.

Pennwalt's Pharmaceutical Division

The Pharmaceutical Division manufactures and makes available to the medical profession a variety of therapeutic agents including anti-hypertensives, diuretics, anti-anxiety drugs, local anesthetics, antifungals, antispasmodics, antitussives and antihistaminics as well as anorectics.

The total sales of Pennwalt's only amphetamine product, Biphetamine, are less than one percent of Pennwalt's annual sales, and the total sales of both Biphetamine and Pennwalt's non-amphetamine anorectic, Ionamin, are less than three percent of Pennwalt's annual sales.

Our Pharmaceutical Division is headquartered in Rochester, New York, where it maintains its production, research and marketing organizations. Our business was founded by the Strasenburgh family in Rochester, and was privately owned until 1960, at which time it was acquired by Wallace & Tiernan, Inc., headquartered in East Orange, New Jersey with plants located in several areas of the United States and abroad. On March 31, 1969, we became part of the Pennwalt Corporation, by virtue of its acquisition of Wallace & Tiernan on that date.

Biphetamine is scheduled by the Drug Enforcement Administration ("DEA") as a controlled substance under Schedule II. As such, the manufacture of this product is specifically limited in terms of quantity and is strictly regulated at every stage in its chain of distribution by the DEA, as I will discuss more fully later. Ionamin is scheduled by the DEA as a Schedule IV substance. It, too, is strictly controlled and regulated at each level of distribution. Both products have been approved by the Food and Drug Administration ("FDA") as safe and effective, as recently as 1974.

In our pharmaceutical operations at Rochester, we maintain a research and development facility, manned with qualified professionals including 4 doctors of medicine, 23 doctors of pharmacology and doctors of chemistry, and other related disciplines. This staff and our administrative staff (quality control, governmental compliance, finance, personnel, etc.) perform the various functions which these titles suggest.

The Problem of Obesity and the Use of Anorectics

Internationally known medical and nutritional experts in the United States are generally agreed that there are approximately 30 to 40 million Americans between the ages of 21 and 65 who are at least 20 percent overweight.

To be 20 percent overweight is to be "obese", a condition that seriously affects the individual's well-being and life expectancy. Obesity also compounds other diseases. Medically, obesity is correlated with considerable increase in cardio-vascular diseases, diabetes, liver and kidney diseases and even accidents.

Indeed, to be obese is to be ill. The problem was defined by one reputable physician, Dr. Halberstam as follows: 1/

> "Fatness may be the single most important illness in America. It is certainly the most important form of malnutrition. Fat people have higher incidence of stroke, of high blood pressure, and, to a less marked degree, heart attacks. On all life insurance tables fat people live shorter lives than normals." (Emphasis supplied)

In addition to physical disability, the obese frequently carry an additional emotional burden, which Dr. Halberstam has described in these terms:

> "Worse, the fat middle-class person lives not only with a physical burden, but with a psychologic stigma. The sociologist, David Riesman, has said that America is a "physionomic democracy." That is, we increasingly will accept into our social circles and business lives people of any race, creed, or color--so long as they are attractive. The other side of this is that we shun the ugly, the crippled, the fat. The next time you are at a gathering of strangers or getting on a bus or sitting down at a lunch counter, check your own reluctance to sit down alongside a fat person.

1/ Dr. Michael Halberstam, The Pills in Your Life, Ace Books, 1972, pp. 141-142.

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> "Fatness has become a stigma--we associate it with poverty, ignorance, bad smell., sour lives. To a large extent this is correct--and the fat person knows it."

In discussing the proper role of anorectics in the treatment of obesity, we are confident that while this Committee will consider the testimony of the experts, the layman, and others who have their respective and differing views, the Committee will continue to be most interested in that which can be established factually.

We are equally confident this Committee will examine the question of antiobesity medication in the context in which it arises--a population containing 30 to 40 million obese citizens who are entitled to medical and other therapeutic assistance in obtaining relief from their physical and emotional disabilities.

These disabilities cannot be dismissed with the notion that "will-power" or "self-discipline" or "counseling" are all that are needed. We can tell the sinners, the alcoholics, the chain-smokers or the obese how to behave and turn our backs on them if they do not. But quite clearly preachment is not the cure for any serious disability.

We think it noteworthy that despite great medical progress in this country, the treatment of obesity is one of the few areas of preventive medicine being practiced today. Most other medical practice today remains remedial or post-traumatic. Medical attention is available to help the obese patient in his efforts to attain a more satisfactory level of physical condition by supervised weight loss.

Indeed, there seems to be general agreement in the technical as well as popular literature that the obese should seek a doctor's advice before undertaking any serious program of individual dieting.

If we have approximately 30 to 40 million obese individuals in the United States, and if we and they recognize that wishing "won't make it so", what remedies are appropriate?

Our Pharmaceutical Division believes that the obese individual has a medical problem which is best treated by a physician and aided by counseling and supportive techniques which will motivate the patient to attain his goals.

Pennwalt has acted on this belief in educational programs directed to both physician and patient. We believe that prescription of anorectic medication--ours or that supplied by other reputable pharmaceutical companies--is entirely the prerogative of the physician.

For more than fifteen years, we have provided the patient, through his doctor, with literature intended to educate the patient--not sell him our products. Indeed, our products are not mentioned in this literature.

More than 10 million copies of our long-established and free booklet, "Are You Really Serious About Losing Weight?", have been distributed. It contains over 70 pages of highly useful information for the patient and no reference to Pennwalt products.

The educational value of our booklet was described by the internationally renowned Dr. Jean Mayer of the Harvard University School of Public Health, who said: 2/

> "There have been so many popular books and articles on obesity which make the most unreasonable promises to patients that it is

2/ See Preface to "Are You Really Serious About Losing Weight?", copies of which have been supplied to the Committee.

pleasant to see a booklet taking the reasonable and truthful position that weight reduction is dependent on maintaining a negative energy balance--preferably based both on decreasing food intake and increasing energy expenditure.

"It is even more gratifying to see that the booklet is sponsored by an enlightened pharmaceutical company which realizes that while anorexigenic drugs can, in the hands of competent and well-informed physicians, make an important contribution to treatment during the initial period of weight reduction, they cannot substitute for reeducation of the patient as regards eating and living habits. They can gain time and make it easier for the obese individual to become used to smaller food portions. But a great deal of information and motivation also need to be given to the patient.

"Because the doctor's time is not unlimited, he needs teaching material, which this booklet quite adequately conveys. Reading the booklet should give the patient the chance for a more informed dialogue with his doctor."

In this same booklet, the patient is advised to "Count your facts before you count your calories" and then asked to take a True-False quiz on basic propositions alleged to relate to dieting, with 28 questions and answers.

I call your attention specifically to question No. 26 and our answer to it (at pages 3 and 5 of the booklet):

Proposition: 26. A diet "pill" is an easier way of losing weight than dieting.

Answer: 26. False. No pill can take the place of dieting. A diet pill is only a "training" aid to help cut down appetite for food while learning to adjust to eating less. It takes time to correct faulty eating habits--the <u>real</u> cause of overweight. Do not use any dieting drug unless it is prescribed by your physician for you."

In summary, our educational program is specifically addressed to a four-part theme: (1) dietary counselling by the physician; (2) individualized dietary control addressed to the specific patient; (3) prescribed exercise; and (4) if necessary, anti-obesity prescription.

The Regulatory System

As this committee is fully aware, amphetamines and non-amphetamine anorectics are scheduled drugs which are regulated and controlled by the Food and Drug Administration, the Drug Enforcement Administration, and state authorities.

In 1970, the Congress passed the Drug Abuse Prevention and Control Act ("Controlled Substances Act") at which time the Food and Drug Administration Bureau of Drug Abuse Control and the Department of Narcotics within the United States 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 Biphetamine 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 safe-keeping 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, Biphetamine, 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 three 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 year-end at our current usage rate.
    (3) A resultant computation of the additional allocation we require.
    (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 (IMS) audits of drug store purchases and prescription utilization.
        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 ensure 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 (i.e. Pennwalt's Ionamin) has been marketed in the United States since approximately 1959. During the sixteen (now seventeen) years since then, approximately five hundred million (500,000,000) 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 sixteen 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 Biphetamine, 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, follow-up 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, forty-two 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 in 1970, there has been a marked change in the prescription experience for anorectic products. These changes may be summarized as follows: 3/

		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 second or subsequent prescriptions	7,707,000	7,213,000
	Total anorectic prescriptions:	26,080,000	19,626,000
3.	Total anorectic prescriptions		
	(1) Amphetamines: (Initial prescriptions)	16,232,000 (13,201,000)	5,504,000 (2,745,000)
	(2) Non-amphetamines: (Subsequent prescriptions)	9,848,000 (5,172,000)	14,122,000 (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

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

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 intra-plant and to customers, its size and the identity of the customer.

At the present time, Pennwalt sells its prescription products, including Biphetamine and Ionamin, only to non-profit 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 addition 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 Biphetamine and Ionamin to physicians have decreased. By 1975, approximately seven percent of Pennwalt's sales of Biphetamine, and approximately four 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 Biphetamine since 1971. Since that date, we have not detailed or sampled Biphetamine 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.

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.

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 anti-obesity drug sales. (As noted, we have no promotional expenditures for Biphetamine.)

These figures may be compared to the promotional expenditures for the most popular over-the-counter anti-obesity 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. 4/

Purchases By Retail Pharmacies: 1971 Compared to 1975

		1971	1975
1.	Total pharmacy purchases:	$78,636,000	$83,247,000
2.	Total pharmacy purchases		
	Amphetamine anorectics:	46,670,000 (59%)	23,237,000 (27%)
	(Pennwalt sales)	(8,394,000 (19%)	(6,761,000 (29%)
	Non-amphetamine anorectics:	31,966,000 (41%)	60,010,000 (73%)
	(Pennwalt sales)	(3,244,000 (10%)	(11,920,000 (20%)
3.	Total Pennwalt anorectic sales:	$11,638,000 (14.8%)	$18,681,000 (22.4%)
4.	Total anorectic sales of:		
	(1) Other two 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

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.

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

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	
Ionamin	31.1 Capsules
Biphetamine	33.5 Capsules

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 anti-obesity 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, except for Canada. 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.)

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 Cpuncil ("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 re-determination. Pennwalt therefore discontinued further manufacture of the product and recalled all stocks from the distribution chain, at a cost of approximately one million dollars.

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 anti-obesity 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.

Pennwalt is aware that the notoriety of amphetamine commenced in the 1960's, when some troubled individuals received, or administered to themselves, either injections or inhalations of methamphetamine, known commonly as "Speed".

Pennwalt is also aware of the fact that the aberrant will seek bizarre experiences by a variety of means. We deeply regret those instances of actual tragedy which befall those unfortunate people. We do not conclude, however, that these alleged cases narrated by those who appear in public to report their reformation, or their counselling association with alleged abusers, amounts to the kind of factual evidence which would permit a meaningful conclusion with respect to the actuality of those alleged experiences or the lessons that should be drawn therefrom.

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 anti-obesity products, and those of other responsible manufacturers, remain recognized as the only effective prescription medicinal aid available in a

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course of anti-obesity 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.

(STATEMENT BY
(DR. JAMES J. NORA, PROFESSOR OF PEDIATRICS,
DIRECTOR OF PEDIATRIC CARDIOLOGY, UNIVERSITY
OF COLORADO MEDICAL CENTER, DENVER
(BEFORE SUBCOMMITTEE ON ANTI-OBESITY DRUGS
(SENATE SMALL BUSINESS COMMITTEE
(NOVEMBER 9, 1976

Certain Central Nervous System Stimulants and Birth Defects

My charge, as I understand it, is to speak to the possible role that amphetamines and related drugs may play in the production of birth defects, if there is exposure at a vulnerable period of embryonic or fetal development, and if there are both a genetic predisposition to react adversely to these drugs and a genetic predisposition to some form of maldevelopment. All of the qualifications of the previous sentence must be applied to amphetamines and to most potential teratogens. Fortunately there are few agents in our environment that possess the disastrous teratogenic potential of thalidomide or rubella virus. And, conversely, under the right combination of genetic predisposition and exposure at a vulnerable period of development, one could project that almost any agent that has pharmacologic activity could be teratogenic. Between these extremes, I believe there exists a number of agents causing birth defects in enough susceptible individuals to constitute a significant health hazard. It is in this latter category that I believe dextroamphetamine may belong.

Some of my co-workers and I have devoted a not inconsequential portion of our research activity to investigating such teratogens, which are difficult to identify in the epidemiologic sense. To give an example: Thalidomide causes malformations, including a rare sentinel anomaly, phocomelia, in 50-80% of infants who have had a maternal exposure during the vulnerable period of embryogenesis. With these factors in favor of

prompt detection of the teratogen, thalidomide was on the market for over two years before the first suspicions about its safety were voiced. How much more difficult is it to implicate a "low risk agent" that causes maldevelopment in only 1% of exposures? Yet. if the exposures are frequent, say, in 10% of pregnancies then 3000 malformed infants would be delivered in the United States each year as a result of taking such a "low risk agent."

The pitfalls in conducting epidemiologic studies that will yield a confident answer as to whether or not an agent is teratogenic are many. In brief, precise verification is essential in both retrospective and prospective studies. But, even with careful verification, the possibilities for systematic bias and the limitation in the type of data obtained (no population frequency rates) make retrospective studies less conclusive than prospective ones. The published studies of the potential teratogenicity of amphetamines are retrospective. Prospective studies, in which one could be more confident, have not been done. The reason is simply this: prospective studies require many more patients and no one to date has accumulated a large enough series to address this question prospectively.

We have considered that amphetamine provides a good model to illustrate the obstacles in the way of reaching confident conclusions about the presence or absence of teratogenic effect of a given agent.[1] Our own experience with this drug may be summarized briefly. In 1962, the mother of an infant born with transposition of the great vessels (a complex and frequently fatal congenital malformation of the heart) expressed more than the usual concern about the cause of the heart defect in her infant son.

She volunteered that she had taken amphetamine diet pills during her pregnancy and asked directly if the amphetamine could have caused the problem. We were unable to find any evidence in the literature of such an association and so reassured the mother. But within two weeks we encountered two more such cases of transposotion and first trimester exposure to amphetamines. These three cases represented a very provocative epidemiologic cluster. At this point we began three studies:

1. a retrospective study to compare histories of maternal exposures to amphetamines in congenital heart patients and in normal children;
2. an animal homology study to see if we could produce transposition of the great vessels giving amphetamines to mice and chicks; and
3. a prospective study, starting with mothers prior to delivery who had documented amphetamine exposure in the first trimester and were awaiting the outcome of their pregnancies.

We reported the results of the animal studies in mouse first,[2] and in mouse, chick and drosophila later.[3] Amphetamine produced malformations in all three models. But this doesn't mean it produces malformations in humans. The fact that three phyla were affected, and that two strains of one species were also affected was suggestive of the teratogenic potential of the drug. An unexpected finding that greatly influenced our thinking about the etiology of congenital heart diseases in general was that in one species of mouse we caused ventricular septal defect and in another species we caused atrial septal defect.[4] We were unable to produce transposition. It appeared that amphetamines brought out the malformation to which the strain was predisposed. And it was this observation that led us

to the belief that there must be a predisposition to a given malformation together with a predisposition to react adversely to an agent given at the vulnerable period of development as the three essentials of teratogenesis.

The first retrospective study of congenital heart patients was inconclusive.[5] We did not find a statistical difference at the .05 level. After publishing these findings we redesigned our protocol, admitted younger patients into the study (to reduce maternal memory bias) and tightened our verification procedures. After two more years we analyzed our new data, found a statistically significant difference between the congenital heart and control groups, and were forced to retract our previous report that there was no significant amphetamine influence in congenital heart disease.[6] Thus two studies by the same investigators led to opposite conclusions. We believe the second study to be the more reliable one.

It has already been pointed out that retrospective studies are less conclusive than prospective ones, so we put our eggs in the basket of a large obstetrical practice that used amphetamines liberally. I carefully avoided telling the obstetricians which of the many drugs on our questionnaire we were most interested in, but a medical student working with me spilled the beans and the obstetricians immediately stopped using amphetamines--and lost interest in our project. That was at a time when malpractice insurance was $60 per year. You can imagine what a threat such studies are now. We did publish a small prospective study of 240 patients, eight of whom delivered infants with malformations, three of which were associated with maternal exposure to amphetamines.[7] The loss of a prospective study of sufficient size was probably of positive benefit to the patients, but it has obviated our reaching the confident conclusions we desired.

Since I have brought up the subject of malpractice suits, I would like to call attention to a trend which I consider to be indefensible. From the number of communications I receive from legal firms all over the country regarding the role of maternal drug exposure in birth defects, it appears that some of our legal colleagues believe that the way to demonstrate that a drug is a teratogen is through passionate litigation rather than through dispassionate investigation. The idea has been fostered that one need only to demonstrate the possibility that a given agent could have caused a malformation in an individual. But as I have said (and I believe that most teratologists would agree) under the the right conditions almost any drug can be teratogenic.

However, the question we are addressing here is whether or not amphetamines cause birth defects to the extent that they represent a significant health hazard. From our retrospective data and the peripheral evidence from experimental studies of mechanisms of action in animal models, I would give a qualified yes to the question.

There have been a number of retrospective studies published by other investigators of teratogenic affects attributed to amphetamines and related sympathomimetic drugs, such as phenmetrazine. Levin[8] found a significant increase in biliary atresia following maternal exposure to amphetamines, and we have some confirmation of this in our study. Matera and co-workers[9] reported an infant with exencephaly, which is one of the prominent malformations we found in our mouse studies. Nelson and Forfar[10] in a retrospective study of 1369 patients found an excess of infants with maternal exposure to appetite suppressants among those with abnormalities. Lenz[11] found a case of diaphragmatic hernia and Powell and Johnston,[12] two cases, following maternal phenmetrazine administration. Moss[13] found limb anomalies in the

the infant of a mother who had taken phenmetrazine.

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

If appetite suppressants (which is just a polite term for "uppers") had a useful function in the medical armamentarium, one could not accept the present retrospective data as sufficient evidence to abrogate the use of these drugs. We are currently trying to resolve the problem of conflicting retrospective data regarding birth defects and the "Pill" and various progestogens and estrogens through a prospective study. The point is: the world needs the "Pill" or some agent that can perform its function equally well. I am unable to identify a similar need for amphetamines and related drugs.

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STATEMENT

BY

THADDEUS E. PROUT, M.D.

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GREATER BALTIMORE MEDICAL CENTER

BEFORE THE

SUB-COMMITTEE ON MONOPOLY

SENATE SMALL BUSINESS COMMITTEE

NOVEMBER 9, 1976

Mr. Chairman, Members of the Committee:

I have been asked to come before you today to discuss the use of amphetamines and related compounds in the treatment of obesity. I have had the privilege of appearing before this Committee on previous occasions and realize only too well the seriousness of this Committee's work.

In my remarks today, I would like to discuss first the trivial effect of these drugs on the lifetime condition of obesity and to draw conclusions based on the present knowledge of the use of these agents and the attitude of the pharmaceutical companies in their promotion.

You will recall that as chairman of a board of evaluation of prescription drugs proposed for the purpose of weight reduction, the following conclusions and recommendations were sent to the Commissioner of the Food and Drug Administration after careful study of available information:

CONCLUSIONS

1. Adult obese subjects instructed in dietary management and treated with "anorectic" drugs on the average tend to lose more weight than those treated with placebo and diet in relatively short-term trials.

2. The amount of weight loss associated with the use of an "anorectic" drug varies from trial to trial. The possible origins of the increased weight loss due to the various drug effects are not established. The increased weight loss appears to be related to variables other than the drug prescribed, such

as the physician investigator, the population treated, and the diet prescribed. Studies do not permit conclusions as to the relative importance of the drug and non-drug factors on weight loss.

3. The magnitude of increased weight loss of drug treated patients over placebo treated patients was only a fraction of a pound a week. The rate of weight loss was greatest in the first weeks of therapy for both drug and placebo subjects and tended to decrease in succeeding weeks.

4. 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 than of diet alone must be considered clinically trivial. The limited usefulness of these agents must be measured against any possible risk factors inherent in their use.

5. The amphetamines including methamphetamine have been widely abused in numerous populations. It is thus in the best interests of the public health to limit the use of amphetamines as far as is compatible with adequate therapy. This is both to minimize the risk of dependence in susceptible patients being treated and to decrease the amount of drugs being distributed, since widespread prescription of a dependence-producing drug inevitably increases the possibility for diversion to non-medical use and abuse.

6. Evidence presented for newer "anorectic" congeners of the amphetamine family and non-amphetamine drugs do not set them apart as having higher benefit or lower risks than older available drugs. The risk potential of Fenfluramine may be an exception to this general statement.

7. There was no evidence in the data reviewed which showed that combination of an "anorectic" agent with other drugs increase the benefits or reduce the risk of the "anorectic" agent.

8. There are no clinical data which support the parenteral use of these drugs in the treatment of obesity. Obesity is not an indication for the parenteral use of these agents.

RECOMMENDATIONS

On the basis of the data reviewed and from all evidence at hand, the following actions are therefore recommended:

1. That all "anorectics" reviewed (dl-amphetamine, d-amphetamine, methamphetamine, benzphetamine, phentermine, chlorphentermine, clortermine, phenmetrazine, phendimetrazine, fenfluramine, mazindol, and diethylpropion) with the exception of fenfluramine, be placed on Schedule 2 on the basis of abuse potential.

2. That combinations of "anorectics" with other drugs be evaluated in accordance with the policy of the FDA on combination drugs, that each constituent of the drug combination contribute to the total effect claimed for the combined drugs, and that the present available and proposed drug combinations be handled in this manner in view of the lack of demonstrated efficacy for each of the constituents of the drug combinations reviewed.

3. That amphetamines prepared for or in a form suitable for parenteral use not be approved for use in the treatment of obesity.

4. That single-entity oral "anorectic" preparations including the amphetamines be permitted to be labeled for restricted use in obesity provided that they are used in association with a specific weight reduction program and that the clinically trivial contribution of these drugs to the overall weight reduction is properly emphasized. To carry out the latter recommendation, a statement such as that made in the conclusions drawn from this review must be included in all labeling and promotional products. This statement should include the following points:

Studies of the effect of "anorectic" drugs in the treatment of obesity when compared with the effects on patients treated in a similar manner without the use of the drugs demonstrate that the magnitude of weight loss of drug treated patients over non-drug treated patients was only a fraction of a pound a week. The rate of weight loss was greatest in the first weeks of study for both the drug and the non-drug treated subjects and tended to decrease in succeeding weeks. The natural history of obesity is measured in years whereas the studies offered for review are restricted to a few weeks duration. Thus, the total impact of "drug induced" weight loss over that of diet alone must be considered clinically trivial. The limited usefulness of these agents must be measured against any possible risk factors such as nervousness, insomnia and drug habituation that might be inherent in their use. Moreover, these agents can only be recommended for use

in the treatment of obesity in a carefully monitored and specified weight reduction program under the care of a physician.

5. That future approval of all "anorectic" drugs prepared for future use be based on demonstration of efficacy as measured by statistical superiority of the drug over placebo in trial using FDA recommended protocols. These protocols should include provisions, among others, for the testing of a specific target population, specification of a minimum duration trial to assure clinical relevance of the study and give consideration to the handling of patient drop-out.

6. Further, that appropriate summary data derived from efficacy studies be presented in labeling and in all promotional material to indicate the degree of weight loss that was found. For this purpose the guidelines noted in (4) above should be supplemented by the addition of the specific facts found for the specific drug under consideration.

Only part of these recommendations have been put into effect. The amphetamines and some, but not all, of the related drugs reviewed were placed in Schedule 2. For those in Schedule 2, quotas for production were established as required by law. The remaining drugs were placed on Schedule 3 or 4 without production quotas. As predicted, there was a shift from the Schedule 2 to the drugs in Schedule 3 and 4 which require very little change in the prescribing habits of the physician. Extraordinary production and sales have been realized by certain companies to meet this increased usage. Pennwalt, producers of Ionamin, a resinated preparation of phentermine, has been cited as one of those companies with unusual sales. We must express serious concern that the

pharmaceutical companies continue to produce amounts of these chemicals that appear to be far in excess of any potential medical need. If this be the case, it clearly demonstrates the wisdom of the prior recommendation, it exceeds the tolerance of society to allow them to continue, it certainly belies the statement made in an open meeting of the then Medical Director of the Pharmaceutical Division of Pennwalt Company who said, "I assure you that the drug manufacturer wants his drug to be used as well and as accurately as it can possibly be", and it begs for curtailment of the rapacious attitude of some pharmaceutical companies toward society.

In 1972 the Canadian government, led by the medical profession of Canada, withdrew the acceptance of amphetamine and related compounds for the treatment of obesity. I know of no information which suggests that this has caused any hardship or that Canadians today are fatter than they were four years ago. A similar move in the country would save our citizens something over $85 million per year in prescription sales alone for these agents.

Experience in Sweden and Japan, to cite two of the countries on which we have some information as well as in the United States, suggests that the use of amphetamines in the street represents on the one hand the interface between legitimate and illegitimate drug usage and, on the other hand, the start of the trail that leads deeper and deeper into the wilderness of the drug cult. For these reasons we must recognize that production of these agents which is clearly in excess of present

medical usage is unquestionably finding its way into non-medical and, hence, non-legitimate usage. It also reminds us that we are a principal proveyer and consumer of drugs in the world today, and if Sweden's attempt to limit drug traffic through legislation has been somewhat less successful than they and the world had wished for, it may well be that we and other nations as members of the world society must all tackle this problem simultaneously.

Today, however, we must get our own house in order, and it is therefore my recommendation that the recommendations of the Committee that I have just laid before you be activated and extended as follows:

1. It has been demonstrated that the amphetamines and related compounds have trivial indications for therapeutic use in obesity, yet this remains the major medical excuse for the large quotas of these pharmaceuticals now being manufactured. From the point of view of society, the risk of overproduction far exceeds the benefit that might be cited through anecdote of a few patients who, in association with rigid dieting, have believed that the so-called anorectics were the causative agent in their particular weight reduction. I would, therefore, recommend that obesity be withdrawn as an indication for the therapeutic use of these drugs.

2. The increasing traffic in the amphetamine related medications indicates that the previous recommendations to place in Schedule 2 all drugs with abuse potential should be followed. This measure has been effective in limiting the use of those placed in Schedule 2 three years ago.

3. It is also recommended that quotas of production be sharply curtailed to at least less than 10 percent of present production for those pharmaceuticals that are recommended for use in some condition other than obesity. Drugs marketed only for use in obesity that have abuse potential may well be forced to withdraw from the market.

4. Eliminate the manufacture of combinations of pharmaceuticals involving this class of drug and of all intravenous preparations.

5. Enforce the efficacy and safety regulations for drugs and require that all agents proposed for the treatment of obesity in the future pass the test of efficacy and safety before acceptance by the FDA based on an FDA regulated protocol designed to eliminate trivial products.

6. Eliminate the over-the-counter pharmaceuticals since they have been found to be entirely worthless in the treatment of obesity. It is much too costly for the government to tackle these one by one under trade name when the company need only change its name and the name of the product and be out from under the law again. All such preparations should be eliminated as worthless unless they can pass the standards set by FDA for new products.

Although this would, in effect, impliment the concerns of the Committee in relation to its single-minded pursuit of the relation of these compounds to the treatment of obesity, it would not take care of other very real problems. The bigger question that needs to be reviewed is the rapacious attitude of

some of the pharmaceutical companies. To do this, legislation should establish other requirements:

1. Review the practice of bulk shipment of drugs to individuals and to clinics for direct dispensing and, if necessary, eliminate it. Shipments in bulk to facilities of 100,000 dose units can no longer be justified, even if obesity continues to be an indication for these medicines and will certainly not be justifiable if obesity is withdrawn as an indication. The pharmaceutical houses are aware of this, but they are unfortunately in business to sell drugs and not to serve society.

2. Require the pharmaceutical houses to show the cash flow to physicians and medical institutions for support of "research", "consultation", "teaching", "goodwill" or any other word that might be used for the favor that they curry with their largess. We will speak to the problem of physician education in a later section.

3. Expose the ownership of the "throwaway journals" that bombard physicians daily and limit the use of funds for this and other types of promotion by pharmaceutical houses so that the savings on drug cost can be passed back to the consumer. These institutions should be singled out and made to pay the true cost of distribution of this literature and not be virtually subsidized by the taxpayer by having this material transported at less than cost by the overtaxed facilities of the U.S. mail.

In addition, we need to strengthen the process by which drugs are reviewed for use by the general public and are accepted for purchase by the medical installations of the U.S. government.

Whether this is done by the FDA under the present structure or by some other system will require study. A suggestion that was made in 1972 before this Committee bears repetition. Congress should establish a committee of "blue-ribbon untouchables" similar to the Council on Pharmacy and Chemistry previously active in the American Medical Association. This possibility deserves further thought and discussion, especially since it drew the fire of no less a spokesman than the later Morris Fishbein. Such a committee, in association with the FDA, could:

1. Become the responsible authorizing agent for drug procurement by all agents of the U.S. government. Billions of dollars are spent on worthless products by medical facilities of the U.S. government at this very time. This must be eliminated if the taxpayer is to look to the federal government for help in medical expense.

2. Begin a more thorough study of the ways in which new drugs can reach the market. This could perhaps implement and speed up the process of review as well as work out the very difficult problem of requiring so-called Phase 4 studies. These studies would require that surveillance of drug products be continued after they are placed on the open market in order to retrieve long-term answers to the question of efficacy and safety.

3. Make available to the consumer relevant information about drugs and drug usage and work out details for the production of a consumer package insert. The task of this committee would be to design a drug description understandable by patients and available to them if not contraindicated by

their condition. In December 1972 I asked that this committee become seriously committed to the problem of consumer education. The people expect and need it, and it is not difficult to provide. It should not wait for other more far reaching legislation in the health insurance field.

Finally, Mr. Chairman, but not least, we must think of the educational process of the physician himself. It is a disgrace to our country that most of the postgraduate education of physicians takes place in their offices by the representatives of the pharmaceutical companies. Continuing medical education must not be neglected in the future, and any plan to deliver health care to the American public must recognize and formulate a plan for dealing with this problem. The pharmaceutical houses have stepped into a void that is not being completely met by the society primarily because they do not always perceive the dangers of accepting the benefits of pharmaceutical gifts. A large proportion of the physician courses are subsidized by industry and are designed to downgrade scientific work that is not promotional and upgrade that which is. Attitudes toward the oral hypoglycemic agents in contrast to those on the hypotensive agents are excellent examples of this process. In the former, only physicians known to be complimentary to the pharmaceutical industries are accepted on programs of continuing medical education to discuss the oral hypoglycemic agents. Every effort is made to downgrade and to cast suspicion on scientific work that threatens an industry worth at least $100 million a year in gross sales and twice that amount in retail sales. In contrast to this, the hypotensive agents found on the basis of one study to be highly efficacious even at

levels of pressure not ordinarily treated by the practicing physician is being given wide exposure and support by the companies who make these products. If we do not rescue postgraduate and continuing medical education of our physicians from the pharmaceutical houses, our citizens will be even more medicated and undertreated than is true today. The method by which this should be done needs further study. The creation of traineeships in clinical pharmacology in programs involving medical schools and community hospitals has many virtues.

In brief summary then, Mr. Chairman, I would recommend:

1. That the former recommendations of the committee be implemented.

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

3. Eliminate over-the-counter nostrums advertised for the purpose of reducing obesity.

4. Curtail the activities of the pharmaceutical industries and in particular make certain that they pay their way from their swollen profits for all of their promotional efforts.

5. Establish an authority or strengthen the existing authority to study a) the problem of drug selection for the medical agents of the U.S. government, b) plan Phase 4 studies ofof new drugs, and c) address the probme of consumer education.

6. Review the question of continuing medical education of the medical profession and replace the pharmaceutical manufacturers as the principal proveyer of postgraduate training through the evolution of a federal plan for this purpose.

Statement by-

Frank M. Reynolds, National Teen Challenge Representative, before Monopoly Subcommittee of Senate Small Business Committee, November 18, 1976.

Teen Challenge is a ministry to street people. It began in 1958 as a ministry to street gangs by David Wilkerson. As the work progressed we began to encounter drug addicts. Many heard the message of hope in Jesus Christ and began to respond in a positive manner.

From this beginning has grown a ministry that now is in 24 states, the District of Columbia, and Puerto Rico, with ministries in 62 cities. Through coffee houses, and street workers, Teen Challenge made contact with over 380,000 people in 1975. In our various residential facilites we have 1000 people any day. I say this to let you know that we have a broad contact with a lot of young people at the street level where the action is.

Our experience has been primarily at the street level, although the past few years we have received more and more people referred by other agencies, both public and private.

Our primary thrust has been to what we have called "troubled youth". This has resulted in our also working in a preventive type ministry with drug education programs in schools and community youth groups.

Through these presentations we had many opportunities to deal with young people in a confidential manner about their own drug involvement. We were able to get a good reading of what was happening in the drug scene.

In the early 1960's we primarily reached the inner city heroin addicts. With the "drug explosion" of the mid and late sixties we bagan to reach people with various dependencies on many different drugs: tranquilizers, barbiturates, amphetamines, hallucinogens, as well as alcohol and the opiates.

Today, most of the drug dependent persons we work with are so-called poly-drug users. By that we mean they use many different types of drugs and mix them with alcohol.

I know this hearing is primarily concerned with the use and abuse of amphetamines. But, I think, we are going to be remiss if we do not realize that this is part of an overall problem and, perhaps, a philosophy of the medical and pharmaceutical business.

That philosophy is; that there is a solution to every problem in a pill and its wrong to suffer any discomfort, physical or emotional. Perhaps, it is a problem of our "cradle to the grave security society".

This is promoted in the advertising, on television and other media. Since I am concerned primarily with our youth 14-25, what are we teaching them? I have an important meeting, I must be up for it, so I eat or drink something to pick me up so I can put my best foot forward. Then we get pushed out of shape when our teenagers do the same thing for their earth shattering date, party, or whatever. "That is different, this is a $500,000. deal," we argue. "But," the young person says, "This is the chance of a lifetime to really impress someone that will change my whole future."

What have we done? Instead of preparing ourselves spiritually, physically, and emotionally we try to substitute an artificial booster

or tranquilizer. We do not deal with the real problem.

Let me illustrate. Four weeks ago a young man was released from a certain penal institution. While he was there he got under a lot of tension. So the doctor gave him some Valium. As the tension built so did his intake of Valium, legally. He was released, having completed his sentence, with a legal prescription and is using 40-50 mg. of Valium per day. He is "free" from jail, but he cannot function in the "straight" 8-5 society. The 40-50 mg. of Valium does not handle the additional tension so he has added a little alcohol to help out. Now he is in danger of violating the conditions of his release.

What is the problem? Is it tension? Or do we need to dig a little deeper? Then give the individual the coping mechanism to deal with the problem. I have had only 20 minutes with this individual and discovered his tension started when his wife divoriced him while in prison. Maybe there was no way to save the marriage, but there is a better way of handling the succeeding emotional problems than a chemical cop out.

I am not sure this legislative body can solve the problem, but I believe unless we are willing to see why we get pushed into using chemical substitutes we will continue to seek chemical solutions to emotional and spiritual problems

Dr. Blum stated in an article in Look magazine, several years ago, in a discussion of various solutions to the drug abuse problem, "If we are looking for a drug to solve the drug problem we will fail. We will never solve the drug problem until we make up our minds what our minds are for."

Now to speak specifically to our experience with the amphet-

amine group.

We first began to see people coming in with this problem in 1967 and 1968. Not large quanities, but when a person had been involved with heroin and other depressant drugs he would buy "Bennies" to give him a lift to get out and do his "thing" to get the money for the heroin.

When the fad of taking drugs hit our high school and college groups, they would have what some called "cocktail parties". Each would bring the medications from their private drug store, i.e. the home medicine cabinet. All the pills would be put in the bowl. Different parties were run different ways. Some would portion a quanity to each one with no regard to what they took. Others would divide them by color or shape and compare notes.

What was the main problem? Availability—they discovered that with Mom's diet pills they could dance and go and go without stopping. Hey man, that's terrific.

Someone thought we could solve the fat problem without discipline and without pain by taking dexedrine.

The college crew is no different than when I was in school. We did not get our work done until it was due. We did not study until the night before exam. But in the early forties we had to depend upon the coffee pot and cold water in the face to stay awake.

Now, thanks to "better living through chemistry" we can swallow a couple of pills, obtainable legally for the diet, the tired feeling, the depressed state or whatever other excuse (fancy word for lie) I can convince the doctor of.

Then suddenly you have people living on this stuff. Then comes

controls in the early seventies.

By this time we have coming into the program the Speed Freaks and the spacies. They have in their own words "fried their brains". Where did they get the stuff? One student in the program from an Ohio college, who came into the program in 1970, floated a loan, flew to Mexico and brought back amphetamines of various kinds, manufactured in the U.S.A., and netted $7000. for the weekend risk and trouble.

The problem arose for him when he became his own best customer. Messed up his mind; could not study, dropped out of school with 1½ semesters to go for graduation.

I am amazed that some, as late as last year, discovered an over production with shipment out of the country to be brought back in illegally. This was common knowledge to us working the streets. We assumed if we knew it, certainly, the professional agencies knew it.

Some have told of stealing them off the loading docks by the barrel full.

I do not need to restate the statistics, you have them, undoubtedly, on file.

The last three years I have been in an administrative position and only working as a volunteer with troubled people. It is disturbing and frustrating to me to start dealing with people and discover the amount of mood altering medications prescribed to cover up the problem. Yet, no one stops to try to solve the problem or provide a way of handling and dealing with the difficulties.

At Teen Challenge our approach to the drug abuser has been

that your drug taking is not the problem. It is a symptom. We were saying this when others said we were foolish to talk like that.

The problem is inside of you. Invariably when we begin to relate to the needy they would speak of the emptiness inside. Nobody wants the blahs. And when someone offers a chemical, easy solution, you have a good candidate.

Our approach is first acceptance of them as a person, regardless of their physical appearance.

The speed freak usually comes in skinny and starry eyed, extremely nervous and suspicious. Not trusting anyone. They have been ripped off emotionally.

Then we share the love of God we have found and the inner peace we have. The next logical step is, "You can have it too. God so loved you that he gave His best for you."

Now, here is where we had to regroup our forces. The heroin addict was quite predictable. After he would withdraw, his head was normal.

Not so with the amphetamine user. His attention span is short. He is depressed very easily and is just liable to space out on you.

Another complication we ran into was that the amphetamine user quite often has used L.S.D., mescaline, and other hallucinogens.

I am not a technical man. So how much of our problems can be attributed to which chemical, is difficult to assess. As I said before, at the street level you do not get someone that does

just one drug.

After speeding he knows he is going to crash. When he crashes he knows he is not going to be able to sleep, so he will seek downers—barbiturates.

Most can walk into a doctor and give a good con story and get some sleeping pills. If all else fails, he can put on a scene and get rushed to the emergency ward and compassionate people will give him what he wants. Remember these people know what symptoms to describe in order to get the doctor to give the "right" prescription, and they do.

It takes long patience. About the time you think you are making progress, he flips out.

Where with the heroin addict we could put pressure on him and get pretty hard nosed, we find we would have to back off from the amphetamine user. Cut down the pressure until he could settle down. I believe it takes the power of God to help and heal some of the scrambled heads we have worked with.

We have not won on all of them, but we have as good a record as any.

Gentlemen, let me recap.

What is the problem?

1. We are too prone to look for easy, painless solutions to life's problems.

2. Chemicals that can alter the mood are available legally and illegally from "legitimate" manufactures.

3. The knowledge that it is available is well advertised.

4. The whole health-care field has got to shoulder their responsibility in causing the spread of the drug abuse problem.

5. We can no longer bypass the fact that men have spiritual needs, as well as physical and social needs.

Some hopeful signs.

1. Many of us are redoubling our efforts.

2. Medical schools are now requiring medical doctors to take courses in interpersonal relations.

3. Many professionals are acknowledging that there are spiritual needs that can be met. More cooperation between these two areas.

4. This hearing is being held and we have been able to share from the street level, where the action is.

For an idea of the effectiveness of the Teen Challenge program you may refer to a study done under grant # 1 H81 DA 01505-01

STATEMENT

OF

Frederick A. Rody, Jr.
Acting Deputy Administrator
Drug Enforcement Administration
U.S. Department of Justice

before

the

Subcommittee on Monopoly
(Gaylord Nelson, Chairman)
Senate Committee on Small Business

November 19, 1976

Mr. Chairman and distinguished Members of the Subcommittee:

My name is Frederick A. Rody, Jr. and I am the Acting Deputy Administrator of the Drug Enforcement Administration within the Department of Justice. Today, I am appearing before you on behalf of Mr. Peter B. Bensinger, our Administrator, who is presently out of the country on official travel. Appearing with me are Mr. Robert J. Rosthal, Deputy Chief Counsel; Mr. Kenneth A. Durrin, Acting Director of our Office of Compliance and Regulatory Affairs; and Mr. Ernest A. Carabillo, Jr., Chief of our Regulatory Support Division.

The Controlled Substances Act creates a partnership between the Attorney General and the Secretary of Health, Education, and Welfare. The Attorney General is empowered to place a drug under control of the Act, to remove a drug from control or to move a drug from one schedule to another schedule.

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To exercise this power, however, the Attorney General must have the concurrence of the Secretary that the contemplated action is medically and scientifically correct. The law states that the recommendations of the Secretary on medical and scientific matters are "binding" on the Attorney General and if the Secretary recommends that a drug not be controlled the Attorney General cannot control it.

As the subcommittee has requested, I will briefly outline how that partnership has worked in the area of stimulant drugs.

The Controlled Substances Act, as it related to the stimulants, represented a Congressional compromise under which Congress originally placed liquid injectable methamphetamine ("speed") in Schedule II and the amphetamines and methamphetamine in Schedule III. However, it was clearly understood by the managers of the legislation for the House and the Senate that "proceedings will be initiated (by the Attorney General) involving a number of drugs containing amphetamines after the legislation has become law."

DEA's predecessor agency began a study of the abuse potential and actual abuse of the amphetamines and methamphetamine then in Schedule III and in February of 1971 forwarded the results of its study to HEW. In April, HEW agreed that the amphetamines and methamphetamine belonged in Schedule II and on May 25, 1971 we proposed in the Federal Register that the rescheduling take place. Thirty days were given for objections by interested parties.

Three major manufacturers filed objections:

1. Smith, Kline & French Laboratories requested a hearing on the transfer of its product, Eskatrol.

2. Mission Pharmacal Company requested a hearing on the transfer of its product, Fetamin.

3. Pennwalt Corporation requested a hearing on the transfer of its product, Biphetamine.

On July 7, 1971, all amphetamines and methamphetamine, with the exception of the three drugs for which hearings had been requested, were ordered transferred from Schedule III to Schedule II. As to these three, application of the order was reserved pending a review of each drug and subsequent administrative hearings. Our review began with service of

a subpoena on Smith, Kline & French which in effect called for every piece of relevant information the company possessed on Eskatrol. Subsequent to that service, SKF, Mission, and Pennwalt withdrew their objections and requests for hearings and by Federal Register notice of August 19, 1971, their drugs joined the other amphetamines in Schedule II.

Mr. Chairman, let me digress for a moment to note a fact important to the purposes of this subcommittee. In our efforts at that time to place the most rigorous controls on the amphetamines we received the support of the American Medical Association. Through its House of Delegates, the AMA expressed approval of the rescheduling and urged "all physicians to limit their use of amphetamines and other stimulant drugs to specific, well-recognized medical indications."

It was early recognized that if our efforts to place the amphetamines in Schedule II succeeded, a new danger to the public might arise. Two drugs - phenmetrazine (Preludin) and methylphenidate (Ritalin) - had been placed in Schedule III by the Congress.

These drugs, while not true amphetamines, have been described as "amphetamine-like". It was considered highly possible that should amphetamines be moved to Schedule II with its stringent controls, there could be a movement by drug abusers from the amphetamines to Ritalin and Preludin. Accordingly in April, 1971 we sought the position of HEW on whether we could properly place these drugs in Schedule II.

On July 29, 1971, HEW approved that re-scheduling and negotiations began with representatives of the Ciba-Geigy Corporation, then manufacturer of both products, and Boehringer-Ingelheim Limited, owner of the United States patent on Preludin. It was the purpose of these negotiations to reach an agreement on placement of Ritalin and Preludin in Schedule II without the need for lengthy hearings. The companies ultimately agreed and, on October 28, 1971, Ritalin and Preludin were placed in Schedule II.

Turning now to the non-amphetamine anorectics - on February 15, 1973, HEW recommended that seven of these drugs be placed in Schedule III of the Controlled Substances Act and one, fenfluramine, be

placed in Schedule IV. In Federal Register notices on May 9 and May 10, 1973, we proposed the precise scheduling recommended by HEW.

No objections were received from such major manufacturers of the anorectics proposed for Schedule III as the Upjohn Company (Didrex), Warner/ Chilcott (Pre-Sate), USV Pharmaceutical (Voranil), Sandoz Pharmaceuticals (Sanorex), or Ayerst Laboratories (Plegine). No objection to the proposed scheduling of fenfluramine (Pondimin) in Schedule IV was received from the A. H. Robins Company.

Two major manufacturers filed objections:

1. Merrell-National Laboratories requested a hearing on the scheduling of its product, Tenuate, in Schedule III.

2. Pennwalt Corporation, on the scheduling of its product, Ionamin, in Schedule III.

The Merrell and Pennwalt hearing requests presented a grave policy issue involving fundamental fairness. All but these two companies had agreed to the HEW-DEA scheduling proposals. If the products

of the cooperating companies were scheduled by DEA while the Merrell and Pennwalt products remained uncontrolled during lengthy hearings, the economic inequity to the cooperating manufacturers and the danger that Tenuate and Ionamin would become abuse drugs of choice was obvious. Further, three of the anorectics, Voranil, Sanorex, and Pondimin, had never been on the U.S. market and had no domestic history of efficacy or abuse upon which scheduling comparisons with the Merrell or Pennwalt products could be made.

Merrell and Pennwalt finally agreed to placement of Tenuate and Ionamin in Schedule IV pending the outcome of their hearings. This enabled us, on June 10, 1973, to place five of the anorectics in Schedule III and fenfluramine in Schedule IV as originally recommended by HEW. On July 6, 1973 Tenuate and Ionamin were added to Schedule IV.

Clearly the resolution of the immediate problem did not resolve the permanent problem. We needed to know more about <u>all</u> the non-amphetamine anorectics and recognized we could find less than satisfactory answers in isolated, fragmented hearings concerned with Tenuate and Ionamin. It was decided, therefore, to monitor the manufacture, distribution, and use in the United States of all anorectics

controlled in June and July, 1973, paying special attention to indications of diversion and to chemical research on the abusability and dependence forming characteristics of these substances. It was further decided that eighteen months under control should provide sufficient information upon which our review could then be based.

DEA, after discussions with the National Institute on Drug Abuse and the Food and Drug Administration, began its review as scheduled.

In addition to employing our own resources on the monitoring program, DEA contracted in March 1975 with the Stanford Research Institute to assist in the development of a method to schedule drugs objectively. That study concentrated on the anorectics as models. We received the results of the Stanford study in April of this year. We have also received, under contract with the Research Planning Corporation, the results of a study devoted in major part to identifying and quantitating abuse levels of the drugs in question.

On May 13, 1975, DEA forwarded a letter to each major manufacturer of a non-amphetamine anorectic

drug asking information concerning the abuse potential of its particular product. On December 9, 1975 another letter to these companies requested manufacturing and distribution data. This massive amount of information has been received and is under review.

Thus, the hearings of this subcommittee have come at a fortuitous time. The testimony given by the witnesses who have appeared here and the conclusions the subcommittee draws from that testimony, together with the information we have been reviewing, will be closely considered by DEA in reaching our judgments on the drugs in question. Then, as contemplated by the Controlled Substances Act, those judgments and the supporting data will be forwarded to HEW through the Food and Drug Administration for the definitive medical and scientific evaluation. Mr. Chairman, it should be said at this point that HEW and FDA have always cooperated fully with DEA in those areas in which our responsibilities are joined. We could not ask for better partners.

This subcommittee has requested information on the current patterns of abuse and diversion of

anti-obesity drugs. Three sources have been employed to gather the information I will summarize:

1. The Drug Abuse Warning Network (DAWN), jointly sponsored by DEA and the National Institute on Drug Abuse, receives all drug mentions from selected emergency rooms, crisis centers, and medical examiners throughout the nation and publishes this information on a monthly basis.

2. The System to Retrieve Information from Drug Evidence (STRIDE) constitutes a compilation of reports on all drugs received for examination by all DEA domestic and foreign laboratories.

3. A recent telephone survey of DEA's domestic regions.

Mr. Chairman, there has been a 28% increase in DAWN mentions of amphetamines in the last twelve months. The increase of chronic effects as the reason for seeking emergency help strongly suggests that ever greater numbers of abusers have access to a continuing supply of amphetamines. At the same time, our laboratories report the appearance of less illicitly manufactured amphetamines and there are

fewer reports of amphetamines being diverted from legal distribution systems. Accordingly, it must be concluded that increasing amounts of abused amphetamines come from home supplies and that these supplies are created largely by prescriptions and direct dispensing by physicians. The suggestion is implicit that significant numbers of physicians are prescribing and dispensing well over their patients' actual medical needs.

Phenmetrazine (Preludin) has become a serious problem as a street drug in areas of the United States ranging from Pennsylvania in the east to Nebraska in the west. Pockets of heavy abuse appear in Texas. The District of Columbia and surrounding states have been particularly hard hit. In the District, for example, we find Preludin trafficked under the street name "Bam" at $10.00 for a single 75 mg. dosage unit. Since Preludin is water-soluable it is frequently injected intravenously and used in conjunction with heroin.

The United States Attorney for the District of Columbia has focused public attention on the

Preludin problem here by highly successful criminal and civil cases involving physicians and pharmacies. Continuing investigations by DEA indicate the existence of sophisticated criminal enterprises employing prescriptions obtained from doctors and forged prescriptions to build street supplies. Thefts from pharmacies also play a part in supplying the illicit traffic in Preludin.

In 1975 Western Fehr Laboratories, manufacturers of the basic ingredient in Preludin, Ciba-Geigy Corporation, the sole manufacturer of Preludin in dosage form, and Boehringer-Ingelheim Limited, the sole distributors of Preludin to wholesalers, petitioned DEA for an increase in the 1975 manufacturing and procurement quotas for Preludin previously set by DEA. That petition was rejected by DEA and it was again rejected by an Administrative Law Judge following a lengthy hearing demanded by the companies. This resulted in an appeal by the companies to the United States Court of Appeals for the First Circuit which, on January 28, 1976,

issued the final rejection. In a unanimous opinion the court found in part that, "DEA had the obligation when it found substantial evidence of broad scale diversion to achieve a more Spartan pipeline, even though this might cause inconveniences to manufacturer and distributor."

Mr. Chairman, just three weeks ago, on October 29, 1976, attorneys for Western Fehr Laboratories and Boehringer-Ingelheim Limited filed with Administrator Bensinger objections to DEA's proposed 1977 production quota for Preludin. Once again an administrative hearing has been demanded by the companies.

Methylphenidate (Ritalin) differs from the other substances under consideration here today. It is not indicated as an anti-obesity drug. Ritalin is described as "effective" in the treatment of minimal brain dysfunction in children and in the treatment of narcolepsy (a form of sleeping sickness). It is considered "possibly effective" for mild depression. It is ironic that under the heading "Adverse Reactions" in the Physicians' Desk Reference

the manufacturer of Ritalin warns against loss of appetite in children leading to "weight loss during prolonged therapy."

Between July 1, 1973, and July 31, 1976, there were more Ritalin related abuse episodes reported in DAWN than any one of the ten brand name amphetamines or non-amphetamine anti-obesity products surveyed. The profile of Ritalin abuse is unlike the others. The great majority of the amphetamine and non-amphetamine anorectic reports come from crisis centers, the usual haven for street abusers in various phases of illness. Two thirds of the Ritalin episodes were reported from hospital emergency rooms to which the more seriously ill are most often taken. Illicit sources such as street buys, forged prescriptions, stolen dosage units or gifts were listed in over half the episodes.

Mr. Chairman, before summarizing the information on the non-amphetamine anorectics let me say that one of them, fenfluramine (Pondimin), may possibly be improperly described as a stimulant. Since coming on the market in 1973 fenfluramine has been reported as showing the indicia of a depressant causing some of the responses of an hallucinogen such as PCP.

The non-amphetamine, anti-obesity products have received far fewer mentions in DAWN than the amphetamines, Ritalin, or Preludin. The anorectics are reported primarily from crisis centers as opposed to emergency rooms or medical examiners. Over 75% of the incidents involve legal prescriptions as the source. As with the amphetamines, the suggestion is implicit that significant numbers of physicians are prescribing and dispensing well over their patients' actual medical needs.

Mr. Chairman, Benjamin Gordon of the sub-committee staff has asked DEA for a more detailed report on one non-amphetamine anorectic, Ionamin. I have been told that Mr. Gordon's concern with this substance is not based on any known significant differences between Ionamin and most of the other non-amphetamine anorectics. Rather Mr. Gordon's concern is predicated on the past history of the Pennwalt Corporation, manufacturer and distributor of Ionamin.

In May 1971, as earlier noted, Pennwalt requested a hearing on the proposed transfer of its amphetamine product, Biphetamine, from Schedule III

to Schedule II. That request was subsequently withdrawn and in August 19, 1971, the drug became subject to the Attorney General's power to limit manufacture by setting production quotas.

Mr. Chairman, the dates in this matter are most important. Until some time in June, 1971, Pennwalt exported to Mexico City large quantities of the resin complex from which Biphetamine is manufactured. In Mexico City at a Pennwalt subsidiary, the resin complex was encapsulated and sold under the Mexican trade name Bifetamina.

Within months, Bifetamina appeared on the illicit market in the United States. A special task force working under the code name "Operation Blackjack" established that the southeastern and southwestern states were being flooded with Bifetamina and that the drug was being smuggled into the United States at six principal points along the Texas-Mexico border.

Pennwalt was ordered to show cause why its registration to export amphetamine products should not be revoked. The company chose not to contest the order and is now barred from exporting its amphetamine products to any part of the world.

Mr. Chairman, the Order to Show Cause in that case said in part, "the illicit importation of Bifetamina from Mexico and the subsequent illegal sale of Bifetamina in the United States substantially subverts the purpose of placing all amphetamines in Schedule II."

The history of Pennwalt and Ionamin has a similar beginning. In May, 1973, as earlier noted, Pennwalt requested a hearing on the proposed placement of its anorectic product, Ionamin, in Schedule III. Whether that hearing takes place will depend in large part on the results of DEA's comprehensive review of all the anorectics which will include the report of this subcommittee. Meanwhile, Ionamin remains in Schedule IV.

In 1975, Pennwalt exported to Mexico City 300 kilograms of the bulk powder from which Ionamin is manufactured. Thus far in 1976, another 300 kilograms of that same bulk powder has been exported to Mexico City. In Mexico City, at the same Pennwalt subsidiary where Bifetamina was once produced the bulk powder is encapsulated and sold under the Mexican trade name, Ionamina.

Mr. Chairman, a report on the most recent survey of illicit sales of Ionamin and Ionamina will

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be forwarded to the subcommittee. For the purposes of today's hearing, I will say that Ionamin is a relatively minor problem in most of the United States. However, in Texas we find heavy trafficking and abuse of Ionamina in all areas of the state adjacent to the Mexican border. Since July 1973 through April 1976, some 25 cases have been made involving Ionamina, with seizures and purchases totaling over 104,000 dosage units.

STATEMENT BY
BARRETT SCOVILLE, M.D.
BEFORE SUBCOMMITTEE ON MONOPOLY
SENATE SMALL BUSINESS COMMITTEE
NOVEMBER 10, 1976

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

I have testified before this Committee in the past about the FDA review of drugs used in treating obesity. To recapitulate, in 1971 and 1972, the Food and Drug Administration was confronted with decisions on the efficacy and safety of old and new anorectic drugs, some 11 chemical entities in all, over 130 drug products. The questions about efficacy included questions on the amount of weight loss, if any, associated with the use of anorectic drugs by obese patients, the duration of administration of the drugs, and possible differences in efficacy among the different chemical entities evaluated.

The safety questions involved chiefly the public health hazards of a special toxicity, that of the potential of these drugs for producing dependence and for being abused. Data bearing on the efficacy questions included over 200 controlled trial involving almost 10,000 patients,

trials carried out by drug manufacturers and submitted to FDA as part of various applications. The data on safety were a more heterogeneous assemblage of different sorts of evidence - chemical, animal and human - which might have some bearing on abuse potential and other safety questions. The efficacy review involved an unprecedented re-examination of all individual patient data sheets, representing 70,000 patient visits, computerization of the data, and FDA re-analysis of the data, using its own computers and statisticians - who deserve much credit for the massive job.

In making the final decisions on the drugs, the FDA was advised by a consultant panel headed by Dr. Thaddeus Prout. The former Council on Drugs of the American Medical Association, headed by Dr. Harry Shirkey, also gave us its opinion on the proposed actions. The institutional FDA decisions were embodied in a comprehensive memorandum proposing various alternatives with the pros and cons of each, the final decisions being initialed by the Commissioner of Food and Drugs. In carrying out the decisions, the FDA itself implemented decisions with respect to marketing approval and relabeling. Decisions on controls to be imposed because of abuse potential were and are the primary responsibility of the Bureau of

Narcotics and Dangerous Drugs, now the Drug Enforcement Administration, although the FDA does have major statutory responsibilities in this area, too. Recommendations were forward to the BNDD and controls were imposed by that agency.

The results of our review, which ended in the latter half of 1972 with implementation of the decisions in early 1973, were as follows. First, a consistent policy and set of regulatory actions for all anorectics, based on a better characterization of their limited but unequivocal superiority to nondrug therapy and including recommendations that they be used only for short-term use as adjuncts to diet. Second, the elimination of a large number of combination drug products. Only two major combination products remain on the market, with litigation ongoing. The position of the manufacturer of these drugs, Smith, Kline and French, appears ethically and legally weakened by their failure to report important adverse information on the abuse potential of one of their products. Third, controls bearing on abuse potential were imposed on eight of these drugs for the first time, in a precedent setting class action. Fourth, all injectable anorectics were eliminated from the market.

You may wish to know what I think of these decisions

with the benefit of hindsight, over three years after the fact. I believe that the basic efficacy decision remains a good one. Obesity remains a chronic disease, extremely difficult to treat, and even the limited efficacy of anorectic drugs is better than nothing. The safety decisions appear in need of revision. It is my understanding that you will hear Government data suggesting or showing that amphetamines remain the leading stimulant drug of abuse - with the possible exception of cocaine - in spite of the most restricted measures. If so, it would seem reasonable to withdraw approval of amphetamines for use in obesity, for which safer drugs are available. In a parallel fashion, the use of any other Schedule II drugs in obesity should be examined to see if there may be a similar abuse problem.

The other anorectics were quite difficult to evaluate for abuse or abuse potential in 1972. Data were scanty, and none had been subject to epidemic abuse. We nonetheless recommended control on grounds of abuse potential. It is my understanding that in the interval, some of these drugs have been better tested, with confirmation of their abuse potential, and that observers of patterns of abuse have seen abuse potential turn into actual abuse in the street for some of these drugs. You

have or will have obtained testimony on this problem from more expert witnesses than me. If the data are as I suggest, they will support greater controls for some of the drugs currently in Schedules III and IV.

BS:ck

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Reprinted from *Pediatrics*, Vol. 51, No. 2
February, 1973

USE OF d-AMPHETAMINE AND RELATED CENTRAL NERVOUS SYSTEM STIMULANTS IN CHILDREN

THE abuse of amphetamines has become a problem of international significance. Japan was the first country to recognize this problem, and by 1954 there were an estimated 500,000 to 600,000 abusers in Japan. More than ten years ago Japan banned the use of amphetamines. The United Kingdom restricted distribution of amphetamines to hospital pharmacies in 1968. Sweden categorized amphetamine as a narcotic in 1944 because of abuse; and in 1965 phenmetrazine (Preludin) and in 1968 methylphenidate (Ritalin) were removed from the market. Patients now requiring amphetamines are registered with the government. Sweden has about 10,000 drug addicts (almost all between 15 and 30 years of age) using central stimulants intravenously; this is about the same percentage of their population as the estimated percentage of heroin addicts in New York City.[1] In contrast, the number of heroin and opiate addicts in Sweden is estimated to be less than 500.

In 1970, the Food and Drug Administration (FDA) responded to the problem of amphetamine abuse in the United States by limiting the package insert labeling for amphetamines to three indications: narcolepsy, hyperkinesis in children, and the short-term treatment of obesity. Currently, the latter indication is being reviewed and may no longer be valid.

Among the related agents there is some specificity in labeling, e.g., methylphenidate is approved for use in adults with mild depression, narcolepsy at any age, and children with minimal brain dysfunction but not obesity; phenmetrazine for use only in obesity, etc. However, in the broad view there is a similarity in the pharmacologic properties, side effects, and abuse liability of dextro-amphetamine, methamphetamine, methylphenidate, and phenmetrazine. Since the latter two drugs are available only through a single company as a trademarked product, control has been strict and large scale diversion to illicit channels has not been a problem in the United States.

The FDA also has limited the amount of amphetamine which can be manufactured. In 1972 procurement of methylphenidate was cut in half (from 2,854 kg produced in 1971), and that of phenmetrazine was reduced from 4,638 kg to 2,672 kg.

In addition, amphetamine, phenmetrazine, methamphetamine, and methylphenidate were elevated to Schedule II substances, the same category as opium, codeine, and morphine. Schedule II drugs are those considered to have a high potential for abuse, and such abuse may lead to severe psychologic or physical dependence. The Health Protection Branch of the Department of National Health and Welfare of Canada, with the endorsement of the Canadian Medical Association and l'Association des médecins de langue française du Canada, has moved to prohibit the use of amphetamines and related compounds for weight reduction purposes as of September 1, 1972.

The actions by governmental agencies prompted this review of the medical indications for the use of amphetamine in the pediatric age group. The Committee will also consider ways in which these agents become diverted to illegal usage.

At present there are only two valid indications for the use of amphetamines in childhood: (1) the hyperkinetic syndrome,

The statements presented herein do not preclude alternatives which may be more appropriate, taking into account local situations and all other relevant facts.

Executive Board, AAP

and (2) the rare condition of narcolepsy. Although adequate studies are not available, the usefulness of amphetamines for the treatment of obesity appears to have short-term value without a lasting effect on weight gain attained during adulthood. The use of amphetamines for cramming for examinations and improving athletic performance cannot be condoned.

The hyperkinetic syndrome is characterized by motor restlessness, short attention span, poor impulse control, learning difficulties, and emotional lability.[2] It affects an estimated 3% of grade school children,[3] and apparently resolves spontaneously in most instances by puberty. Carefully selected patients respond favorably to long-term medication with d-amphetamine or methylphenidate in about 65% of patients.[2-4] The mechanism of drug action is unknown, although certain inhibitory centers in the brain may be activated. Children responding to medication promptly and unequivocally exhibit increased attention span and control over spontaneous motor activity. Omission of a single dose may result in return of the hyperactivity. Also, academic and behavioral performance may become more productive because treatment may break the vicious cycle caused by the effects of the disturbing restless, impulsive behavior on the family and on the school situation.

In a 12-year follow-up study of 340 hyperkinetic patients,[5] no major problems resulting from drug toxicity were found. Similarly, follow-up studies on patients treated during childhood give no indication of increased use of amphetamines or other drugs in later years.[2] In fact, there has been a lack of willful increase in dosage, presumably resulting from the lack of euphoric effect from amphetamine in these patients. A recent paper[6] documents lesser weight gains in nine children on medication (d-amphetamine, 10 to 15 mg, or methylphenidate, 30 to 40 mg/day) for two years. Although there was a correlation between depression of weight gain with linear growth, further studies will be needed to ascertain if adult height is compromised by long-term therapy.

Narcolepsy is a lifelong disorder characterized by excessive daytime sleep patterns (narcolepsy proper); in some patients it is accompanied by emotion-induced muscular weakness (cataplexy, 66%), sleep paralysis (20%), and presleep-hypnagogic hallucinations (30%). The exact incidence of this disease in the pediatric-aged population is unknown, although it is a rare condition. In a report from the Mayo Clinic,[7] 400 narcoleptic patients were seen in a seven-year period. Sixty percent had onset of symptoms before the age of 15, although only 16 of the 400 requiring treatment were under age 15. d-Amphetamine and similar agents provide symptomatic relief of narcolepsy proper and a 50% reduction in cataplexy. The dosage required is in the low range (5 to 10 mg, two or three times a day), similar to that used for the hyperkinetic child. Caffeine is also effective, and the dose of d-amphetamine can be tapered if caffeine is coadministered; caffeine can be given in tablet form, as coffee, or as a cola beverage.

Amphetamines are popularly promoted for the treatment of obesity without proof of lasting benefit; therefore, their use in weight reduction programs cannot be endorsed. Regardless of initiating cause or causes, obesity results from caloric intake exceeding metabolic expenditure. The problem of obesity in childhood is important because 80% of these children become even more obese during childhood.[8] The relatively few double-blind control studies in adolescents treated with various amphetamines and amphetamine-type drugs have shown that any beneficial effect on weight loss is generally evanescent, lasting four to eight weeks.[9] Studies purporting to show beneficial effects are almost all of short duration. A familiar pattern is that weight loss occurs during the first few weeks of the trial; the patient then becomes refractory, an increase in dosage is necessary, and this increase causes side effects. No well con-

trolled study has demonstrated a long-term beneficial effect on body weight of obese adolescents. Reports in the literature concerning adults who abuse drugs frequently indicate that their first exposure to stimulant drugs was through a physician prescribing amphetamines for weight reduction. Moreover, a fair percentage of adolescents are over-weight and this age group is particularly vulnerable to becoming abusers, in contrast to the young child who receives medication for hyperkinesis.

The availability and use of amphetamines is commonplace among teenagers. In a study[10] of 1,300 students in five San Francisco area colleges, only 8% reported having any difficulty in obtaining a supply of amphetamines. In the 1971 *Playboy* survey of 3,000 college students, use of amphetamines while in college was registered at 30% and was exceeded only by use of alcohol and marijuana. Over 60% of those who used amphetamines denied chronic use; most used them when "cramming" for examinations, attempting to lose weight, or hoping to excel in athletic competition. These patterns of abuse probably should be considered as distinct from the abuse by intravenous administration of high doses in a chronic manner. A physician prescribing the drug is frequently the initial source of supply; its use can then be continued by its easy availability from peers. The abuse of stimulants is frequently concurrent with sequential abuse of depressive drugs, particularly barbiturates and alcohol. Thus, the signs and symptoms of abuse may range from undetectable to those of paranoid delusions and wildly destructive behavior associated with heavy use of intravenous methamphetamine in so-called runs, i.e., the administration every few hours for as long as several days.

The misuse of these agents frequently can be traced to mistaken ideas about their usefulness as therapeutic agents. Pediatricians have had unduly optimistic expectations of therapeutic responses for the child with poor school performance, the overweight child, or the teen-ager with mild depression. School and team physicians have allowed or overlooked the use of amphetamines and similar agents in athletic contests. Pediatricians are also under pressure from educators and parents who are concerned regarding children who act out in school or are difficult to manage.

Agents such as methylphenidate (Ritalin), phenmetrazine (Preludin), methamphetamine (Desoxyn), and chlorphentermine (Pre-Sate) have properties similar to d-amphetamine. When tested in a randomized, double-blind fashion under carefully controlled conditions, experienced abusers did not distinguish among intravenous amphetamine, methamphetamine, phenmetrazine, and methylphenidate.[11]

An estimated 8 billion amphetamine-containing tablets are manufactured annually in the United States; this is enough to give every man, woman, and child in the nation 35 substantial doses. This indicates a widespread misuse of an agent having extremely limited therapeutic value. Pediatricians must reflect on their role in introducing patients to these agents; they must not unwittingly contribute to the current problem of overuse, misuse, and abuse. Moreover, physicians must be aware of the widespread use of these agents by some of their patients so they can accurately diagnose illnesses ranging from mild problems of insomnia, nervousness, and depression[12] to such severe conditions as hepatitis, septicemia, and psychotic reactions which may result from intravenous abuse.

The Committee on Drugs recommends that:

1. the use of d-amphetamine and similar agents be limited to children with a clearly defined hyperkinetic syndrome or narcolepsy;

2. d-amphetamine and related agents should not be used in the treatment of obesity;

3. pediatricians become familiar with the wide variety of signs and symptoms that may result from use and abuse of amphetamine-like drugs;

4. the use of central nervous system stimulants in athletics be condemned.

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STATEMENTS PRESENTED BY REVEREND REGINALD YAKE, EXECUTIVE DIRECTOR, TEEN CHALLENGE TRAINING CENTER, REHRERSBURG, PA.

The doctor's office, at all times, would be packed with young people ranging in age from 18 to 35 or 40. From their conversations I could tell what their motive was for seeing the doctor. All of them were after prescriptions for speed, of which this one was phendimetrizine. The people there were from different cities, Boston, Fall River, Brockton, etc. They traveled from all over to this doctor. How did they find out about this particular doctor? News in the street travels fast.

The other doctor who gave out Biphetamines also had an office packed with patients, but he also had some older folk that were there for reasons other then to obtain speed. The people there for prescriptions for speed greatly out-numbered the older patients. I learned from being in this con game with doctors that there were various other ways to get other prescription drugs from doctors. For example, in order to get a certain drug, you would have to have a certain story for the doctor to believe, but not everybody knew these stories. I am talking about Barbituates and Delada now. These stories would cost money along with certain doctor's names. I am just trying to show how easily it is for someone that is a good con to be able to get what he wants from certain lenient doctors. Also all of these doctors kept records of these visits for the government or the Medical Association to inspect if ever necessary, so I see that it isn't only the doctors that are lenient but the people that are over them also.

Most people using speed in the street don't see themselves as drug users because they are usually house mothers, college students studying for exams or just the good people in society that are very social. This speed, which they don't call it, is just something to pick them up; it doesn't make them silly or incapable of doing work but in fact helps them. They don't realize it's potency and effect on their lives until it is too late. Then they find they can't function without it and when they are deathly sick because of the lack of nutrition that they deprive their bodies of when they take these so called diet pills, and then they find out they are a nervous wreck because of the abnormal effect of the drug, such as being able to stay awake for maybe 24 hours, 48 hours or even 72 hours at a time. Diet pills are being used for everything but dieting. Oh yeah, it is popular around heavy drinkers; speed allows the drinker to drink in excess without falling all over the place.

I have nothing against the medical profession or the laws of this country, but there is always one bad apple in every bunch, and the odor of this rotten apple i s smelled by everyone and takes away the sweet fresh fragrance of the other good apples.

November 10, 1976

"On or about the early part of 1970 myself and several friends were involved in the purchase of Methodone in the southwestern part of Washington D. C. We were able to purchase as much Methadone, (which on some days ranged up to the hundreds of dollars' worth.)"--as we were able to pay for.

"The doctor was completely aware of what was going on, and made no effort to hide it. Not too far from this same location was another doctor who was doing the same exact thing. The drugs which were purchased were taken to Baltimore where they were sold on the streets for higher prices.

From about the middle of 1973, up till the later part of 1975 I was involved in the buying of pills through doctors in the Baltimore area. This was set up so that I had medical assistance, and could go to various doctors during the day. I was able to purchase various types of drugs, including valium, parest, nebutal, seconal, tuinals, placidyalls, and many others, including class A narcotics.

These doctors were aware that I was on a drug program, and still would prescribe drugs. The doctors, (some, not all) were careful of how they dispensed the drugs. They would prescribe only enough for one month's supply, but would prescribe several different types of medication.

Other doctors would insist that several different people would come so they could prescribe to (them), but I would receive the drug after we left (the office.) Some, though, would prescribe a large amount and tell you not to come back. On one occasion I can recall, I told a doctor I was strung out on valium, and needed to be detoxed off of them, I was told I could handle it myself if he could prescribe a large amount. He did so willingly. This I did on several different occasions, to the same doctor.

On another occasion in the Baltimore area, my girl-friend was approached while in a doctor's office and asked if she would exchange sex for an assorted amount of drugs.

There are many, many instances I could give you of how doctors have sold drugs to myself and many of my friends, knowing they were being used illegally."

November 10, 1976

I am here to inform you that I had the distasteful confrontation in meeting and dealing with the so-called doctors of this day and time. I am not referring to all doctors, but specifically some who should have their license terminated for a period of time. These particular doctors offer you any kind of drugs for a price, knowing that they are very dangerous to withdraw from; they offer you barbituates in quantities, for cash money. I believe they should be under strict control in terms of dispensing these drugs. I was getting it from five different doctors while under the influence of alcohol and Methadone, this mixture will kill any creature on earth.

Today there are many young people that are turning to drugs because they are very simple to get their hands on.

I pray to God that there would be something done about this. We are dealing with precious lives. God bless you.

MATERIAL SUPPLIED FOR THE RECORD BY
SENATOR GAYLORD NELSON

ACTIONS BY THE FOOD AND DRUG ADMINISTRATION AND DRUG ENFORCEMENT AGENCY SINCE TERMINATION OF HEARINGS

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852 20857

Honorable Gaylord Nelson
Chairman, Subcommittee on Monopoly
Select Committee on Small Business
United States Senate
Washington, D.C. 20510

FEB 16 1977

Dear Senator Nelson:

In response to a request from Mr. Benjamin Gordon of your staff, I am writing to outline our current thinking in regard to amphetamines.

We presented the issue of the need for amphetamines in the treatment of narcolepsy and minimal brain dysfunction to our Neurologic Drugs Advisory Committee on February 3, 1977. It was the view of this group that there are alternate safe and effective, but not fully equivalent, treatments for minimal brain dysfunction. Therefore, the withdrawal of amphetamines from the market would have a deleterious effect on the treatment of patients with minimal brain dysfunction. They further stated that there are alternatives to the amphetamines for the therapy of narcolepsy, but these are not equivalent, let alone superior to the amphetamines. Thus, the Committee concluded that the withdrawal of amphetamines from the market would have a deleterious effect on patients with narcolepsy. Additionally, the Committee considered that, although there may be safe and effective alternatives to the use of amphetamines in certain forms of epilepsy and in alleviating the sedative effects of anticonvulsants, withdrawal of the amphetamines from the market would have a deleterious effect on the treatment of some patients with seizure disorders.

Given the above advice from our Neurologic Drugs Advisory Committee, it seems unlikely that total removal of the amphetamines from the market would be in the interest of good medical care for patients with these serious conditions.

Our current plan is to present our overall approach for relabeling amphetamines and promoting their proper use in medical care at a public meeting in April or May. At that meeting, we would present the final data received from the Drug Enforcement Administration (DEA) and the National Institute on Drug Abuse (NIDA) and solicit testimony by experts in the field of drug abuse. We would also invite members of medical professional associations, State Boards of Medicine, and the interested public. Regulatory action on our part would then be based on the data submitted as well as expert advice related to those data. We will, of course, include in our deliberations the testimony of the expert witnesses who appeared at your Subcommittee meetings last November.

While I cannot be certain at this time, I suspect that our overall approach will include a proposal to withdraw the obesity indication for amphetamines and to include a patient package insert in all amphetamines emphasizing that their proper use is only in patients with minimal brain dysfunction, narcolepsy, or certain types of convulsive disorders. In addition, we may be in a position by then to recommend scheduling changes for other anorectic drugs should the data being gathered by DEA support such a position. We would also hope to have gathered the formal support of a number of medical organizations by that time so that any regulatory action on our part has broad support from the medical profession. It has become clear to us that combined Government-professional action is likely to produce the best result in limiting the use of amphetamines to their proper indications. While it will take longer than we originally predicted to develop such a combined program, we believe this will be time well spent in the long run.

In addition, we would expect that State level legislation (as in Maryland), vigorous activities of such groups as the Federal-State "Diversion Investigation Units" (supported by the Law Enforcement Assistance Administration (LEAA) and administered through DEA) and articles in the FDA Drug Bulletin and professional journals will be influential in keeping inappropriate prescribing of these drugs to a minimum.

We will keep you informed as to the outcome of our data review and the upcoming public meeting on this important issue.

Sincerely yours,

J. Richard Crout, M.D.

J. Richard Crout, M.D.
Director, Bureau of Drugs

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

January 28, 1977

Mr. Benjamin Gordon
Staff Economist
Senate Small Business Committee
Room 424
Old Senate Office Building
Washington, D.C. 20510

Dear Ben:

As per our telephone conversation, I would like to keep you abreast of the latest activities in our review of the anorectic drugs. As per Mr. Rody's testimony, the Drug Enforcement Administration transmitted their findings on the current abuse of amphetamines to us on December 20, 1976. The findings include field data on amphetamine diversion, audit reports, and field intelligence as well as DAWN data and recent production figures. I understand from DEA that they have already forwarded you a copy of their report.

Following FDA staff review of that material, on January 14, 1977, Mr. Peter Bensinger, Administrator of DEA, Dr. DuPont, Director, NIDA, and I met together with our respective staffs to discuss the preliminary DEA data and to discuss FDA data needs. We stated those questions which we felt must be answered prior to our initiating any regulatory procedures. We shared our present understanding of the current level of anorectic drug abuse and the various data systems that are available to our respective agencies to further expand our knowledge. The data which DEA has transmitted to FDA mostly pertains to the Schedule II anorectics and particularly to the amphetamines. At our meeting, we agreed that action might appropriately be taken on any member of the entire class of anorectic drugs, should the data developed reveal that the most significant drug abuse problem was with that particular drug or group of drugs. We need not be constrained by schedule or chemistry of these drugs.

I pointed out to the group that for us to take action on any of the drug products, we would need to be able to show that those specific anorectic drugs present a significantly greater drug abuse problem than the others, and that those specific products causing this problem are legitimately produced. The respective agencies understood our position and generously offered their staff assistance to work with FDA personnel on the collection and analysis of further data. An inter-agency working group was identified and, I am pleased to say, had its first meeting this past Friday, January 21.

Page 2 - Mr. Benjamin Gordon

I also informed Dr. DuPont and Mr. Bensinger that FDA plans to discuss appropriate treatment of hyperkinesis and narcolepsy with our Neurology Advisory Committee on February 3, 1977. That committee will provide us with expert advice on the current state-of-the-art in this area.

I also explained our proposed administrative approach to any regulatory action. In short, for those drugs which are associated with the greatest drug abuse, we will develop a Notice of Opportunity for a Hearing that will be published in the Federal Register. Our current target date for such a Notice is March 1977. We anticipate a hearing would be requested and, if so, this would prolong any final action by a number of months.

We also discussed the possibility of rescheduling the anorectics should the data suggest that this is appropriate. DEA has been developing information on the level of abuse of phenmetrazine as well as the Schedule III and IV anorectics for some time and expects to report their findings to us within several months.

I am pleased with progress to date and consider the work by our respective staffs to be on schedule.

Best wishes for the New Year.

Sincerely yours,

J. Richard Crout, M.D.

J. Richard Crout, M.D.
Director
Bureau of Drugs

DEC 20 1976

Mr. Sherwin Gardner
Acting Commissioner of Food
and Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Dear Mr. Gardner:

In accordance with the commitment undertaken during the recently concluded hearings on safety and efficacy of the anti-obesity drugs before the Monopoly Subcommittee of the Senate Small Business Committee, Senator Gaylord Nelson, Chairman, I am forwarding this agency's findings reflective of the current abuse of amphetamines. These findings include field data i.e., amphetamine diversion, audit reports and field intelligence as well as DAWN data and recent production figures.

Collectively, these findings are indicative of an unacceptable level of abuse despite recently imposed Schedule II restrictions. The issue remains whether the risk to benefit ratio associated with the therapeutic use of amphetamines for obesity or any other disease is sufficiently low to justify their continued commercial availability.

Additional updating of field surveys and analysis of the level of abuse of phenmetrazine and the Schedule III and IV anorectics is underway. This task will require an additional two to three months and will be forwarded when completed.

Sincerely,

/s/ Donald J. Miller

Peter B. Bensinger
Administrator

AMPHETAMINE DIVERSION

Background

In the White Paper on Drug Abuse published during September, 1975, the Domestic Counsel Drug Abuse Task Force reported that the use of various dangerous drugs (including barbiturates, tranquilizers, and amphetamines) has increased rapidly in the United States during the last decade. This report further states that, "These drugs are being prescribed more frequently and used more often in the general population... Most of this use is under medical direction and controlled by prescription. But uncontrolled non-medical use of these drugs has grown sharply during this period of increasing usage..."

Abused amphetamine can be categorized in two broad classes - those originating from legitimate sources (manufacturers, wholesalers, physicians, pharmacies, etc.) and those of clandestine origin. This paper will attempt to put into perspective the extent of abuse of amphetamine originating from legitimate sources.

Amphetamines For Human Use

On February 12, 1975, the Food and Drug Administration of the Department of Health, Education and Welfare published in the Federal Register, Volume 38, No. 4249-50, a statement relative to "Amphetamines for Human Use." A copy of this notice is

attached as Attachment A to this report. This notice served to approve the following indications for the use of amphetamine:

(1) Narcolepsy (a condition marked by an uncontrollable desire for sleep or by sudden attacks of sleep occurring at intervals).

(2) Minimal brain dysfunction in children (hyperkinetic behavior disorders) as an aid to general management.

(3) Management of exogenous obesity as short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction for patients in whom obesity is refractory to other measures.

Analysis of Amphetamine Abuse Trends

DEA's Special Programs Division conducted an analysis of amphetamine abuse trends and piecing together data obtained from DAWN, STRIDE, and theft reports concluding the following:

(1) We are experiencing a trend of increasing amphetamine abuse. The increase of chronic effects as the reason for seeking emergency

help suggests that increasing numbers of abusers have access to a continuing supply of amphetamines.

(2) The decreasing amount of presumed illicitly manufactured amphetamine appearing in STRIDE reports suggests that increasing amounts of legally manufactured amphetamines are contributing to the increase in amphetamine abuse. However, the decreasing amount of stolen amphetamine suggests that the diversion from legal distribution systems is becoming less important as a source of abuse of amphetamine.

(3) The above suggests that increasing amounts of abused amphetamine come from home supply. This supply provides not only the increasing "legal prescription" source, but also much of the increasing "street buys" source reported by DAWN.

(4) This availability of amphetamines beyond what is needed for immediate medical needs in family medicine chests, to the extent that abusers have sufficient supply to

> accrue chronic effects from the drug, suggests that significant numbers of physicians may be prescribing well over their patients' actual medical needs.

A complete copy of the report leading to the above conclusions can be found as Attachment B to this report.

Theft Reports (as provided by DEA)

In addition to the theft data reviewed as part of analysis of amphetamine abuse trends, the following figures are noteworthy:

A. Drug Thefts By Volume:

	FY'73 Dosage Units	FY'74 Dosage Units	FY'75 Dosage Units	FY'76 Dosage Units
Amphetamines	15,398,776	7,331,454	8,644,550	5,528,247

B. Volume of Thefts from Pharmacies:

FY'73	FY'74 Dosage Units	FY'75 Dosage Units	FY'76 Dosage Units
Figures Not Available	6,626,095	6,380,696	4,495,313

Documented Diversion

Each of DEA's domestic Regions have provided an analysis of the diversion problem of legitimately manufactured amphetamines

in their respective Regions. The following summarizes the degree of each Region's amphetamine abuse problem.

Region 1 - BOSTON

Legitimately manufactured amphetamine products are readily available on the illicit market in Region One (1). Source of supply for these amphetamines can be broken down into two (2) main areas; (a) Drug Store break-ins/armed robberies, (b) diversion from the retail level (practitioners, pharmacies etc).

Information received from cooperating individuals indicates that amphetamines can be obtained in lots of 100's to 1,000's with the price varying according to the strength of the dosage units and the quantity purchased.

Since January 1, 1974, Region One (1) has participated in or initiated more than thirty (30) investigations of practitioners involved in the diversion of amphetamines into the illicit market. The majority of these cases were concerned with the indiscriminate prescribing and dispensing of amphetamines by physicians. In one case, a New Hampshire physician was responsible for the dispensing of approximately one half of the total amphetamines purchased by all of the registrants in that state. The same physician was also responsible for the dispensing of two thirds of the total methamphetamine purchased by all of the registrants in that state.

In all of the above mentioned cases, each defendant was responsible for the diversion of at least 100,000 dosage units of amphetamines into the illicit market during a period of one (1) year. It should be noted that these violative practitioners are responsible for the purchase of 60% of the amphetamines marketed in Region One (1).

A conservative estimate as to the percentage of legitimate amphetamine dosage units encountered on the street in the Region, would be approximately 70%. It is impossible to compile exact figures as to the abuse of legitimate manufactured amphetamines, since none of the states in this Region have the capability of distinguishing or identifying the sources as licit or illicit. One state, however, Rhode Island did advise this office that in excess of 90% of the amphetamines encountered on the street were of legitimate origins.

Investigators from the Boston Regional Office and Hartford District Office surveyed the records of two (2) dispensing practitioners, two (2) prescribing practitioners and two (2) retail pharmacies which specialize in filling "weight control" amphetamine prescriptions. Based upon these studies, it can be safely stated that none of these practitioners or pharmacies are adhering to the indications established by the FDA for the use of amphetamine for short term weight control.

One of the pharmacies surveyed purchased in excess of 1,100,000 dosage units of amphetamines (mostly Dexedrine and generic Dextro Amphetamine Sulfate) since January 1, 1974. The amphetamine prescriptions on file in that same pharmacy account for approximately 98% of its total Schedule II prescription business.

In general, all practitioners throughout Region One (1) who have practices limited to weight control, disregard the FDA and PDR guidelines concerning short term use of amphetamines.

Region 2 - New York

The diversion of legitimately produced amphetamines appears to occur at the practitioner level in the Region 2 area. Based upon a review of records maintained by practitioners and several on-going investigations, it appears that amphetamine products are generally dispensed in violation of current Food and Drug Administration standards for obesity treatment.

Amphetamines are readily available to the abuser population through the utilization of fraudulent prescriptions as well as from the sale, by patients, who obstensibly obtained the amphetamine products for weight control.

A few individuals, in the legitimate drug industry, who would not agree to be quoted, were of the opinion that availability of amphetamines is attributable, to some degree, to the aggressive sales policies pursued by several manufacturers and distributors. These individuals further stated that the policies mentioned are in complete disregard of the current accepted medical needs of the country. Therefore, although volume sales by some manufacturers to practitioners may not be classified as outright diversion, such sales contribute significantly to the attitudes professed at the practitioner level relative to amphetamine products.

Most of the information supplied by informants relates to illicit laboratory operations. Information relating to the diversion of legitimate amphetamines is not commonly encountered.

SIGNIFICANT CASES

A New York physician was arrested twice by state and local authorities for illegal sales and dispensing of amphetamine capsules (Biphetamine and Delcobese). As a result of these arrests, this practitioner's license to practice medicine in New York State was revoked. This doctor then moved to the state of Florida. This doctor ordered over 330,000 dosage units of Delcobese in the month and and a half before he moved to Florida (prior to his license revocation). Attempts are being made to locate this doctor and effect the seizure of the Delcobese.

Undercover purchases of 12,703 dosage units of amphetamine (Delcobese) and 6,235 dosage units of other anorectics were made from a pharmacist in Queens, New York. The pharmacist's source of supply was identified and an additional undercover purchase of 5,000 dosage units of amphetamines (Delcobese) was made from this source. It was further ascertained that this source of supply was operating in the capacity of a physician in practitioners office, although he was not

licensed as a physician and had been twice arrested on charges relating to the unlawful practice of medicine. Investigations at physicians offices have revealed evidence of illegal sales of controlled drugs (Delcobese), diversion by other employees, maintenance of fraudulent records and failure to maintain required records. Evidence has been presented to a Federal grand jury. Three (3) significant burglaries have occurred at this practitioner's offices since February, 1976, in which over 50,000 dosage units (35,000 recovered) were stolen. The doctor is currently ordering over 2,500,000 dosage units of Delcobese per year as well as substantial amounts of Schedule III and IV anorectics.

Another physician, who is currently ordering at the rate of approximately 3,000,000 dosage units of amphetamine (Delcobese) per year has been the subject of two (2) investigations by state authorities. These investigations have disclosed that (a) the doctor caused to be dispensed large amounts of Delcobese by non-medical personnel when he was not present in the office, (b) large shortages of Delcobese, and (c) failure to maintain required records. The doctor is currently the subject of a state investigation relative to the fraudulent dispensing of controlled drugs

(use of a fictitious name for a patient). In addition, several undercover purchases of amphetamines were made from this doctor by the New York City Police Department, Diversion Investigation Unit. No prosecution resulted from these undercover purchases.

A New York practitioner is currently the subject of a joint DEA/Bronx District Attorney's Drug Squad Investigation. Four (4) undercover purchases of amphetamine (Delcobese) have already been made. This doctor is currently ordering at the rate of approximately 3,000,000 dosage units of Delcobese per year. Videotapes of the doctor's office have revealed an inordinate amount of patient traffic.

Another physician was arrested after a series of undercover purchases and an audit identified him as a major source of illicit amphetamine (Delcobese). This doctor was classified as a Class I violator based on a diversion of an estimated 130,000 dosage units of Delcobese.

An investigation by the New York State Police resulted in the arrest of a doctor's son and the seizure of a large quantity of anorectic controlled drugs. A follow-up accountability by the Drug Enforcement Administration and state authorities disclosed a shortage of over 58,226 dosage units of amphetamine

(Delcobese and various generic products) as well as a shortage of 277,000 dosage units of Schedules III and IV anorectics. Investigation continues.

Region 2 is currently conducting active investigations of several large manufacturers and distributors of amphetamine products.. Specific details relative to these cases cannot be revealed at this time as it is felt that the release of even general information could jeopardize these ongoing cases.

INFORMATION FROM LOCAL LAW ENFORCEMENT AND REGULATORY AUTHORITIES

The New Jersey Diversion Investigation Unit reports that physicians continue to present a major problem by issuing illegal prescriptions for amphetamines. The prescriptions are generally for 30 to 60 D.U.'s each. In itself, this is not a significant amount of drugs, however, when multiplied by the hundreds of prescriptions written, it emerges as a significant diversion of licit drugs.

The New Jersey State Department of Health, Drug Control Program estimates that 30% of the legitimately prescribed amphetamine products eventually find their way into the illicit market.

The New York State Department of Health, Bureau of Narcotic Control, advises that practially all amphetamines encountered illegally have originated from "legal" sources, i.e. doctors specializing in the treatment of obesity.

REVIEW OF RECORDS OF DISPENSING PRACTITIONERS

A. As an integral part of this current survey, a sample number of dispensing practitioners were visited in an attempt to verify their adherence to the indications established by the Food and Drug Administration for the use of amphetamines in cases of obesity (short term use).

The results of these visits are as follows:

A Brooklyn, New York practitioner has a large practice as a Bariatric Specialist. This doctor dispenses 42 dosage units of Delcobese bi-weekly to patients at each visit. The strengths of the medication vary with each patient.

Of the selected group of 40 patients records reviewed, the following was revealed: At least 25 patients received amphetamine products for a period of more than 21 days and some for a period of up to one year. Another group received medication intermittently for a period of several weeks to more than two or three months.

Weight loss was achieved in most of the patients whose records were reviewed. The doctor stated that amphetamines were in many instances used as a maintenance drug in an attempt to keep weight from fluctuating.

A New Jersey practitioner has a large practice primarily limited to family medicine. He indicated that 50 to 75 patients were treated by him for obesity. Patients are seen approximately every two (2) weeks and are given 42 dosage units of Delcobese of various strengths.

The records reviewed at this physician's office indicate that most patients were treated for more than several months, some for more than a year. Some patients were treated for several months, left and returned for additional months of treatment.

A Brooklyn, New York general practitioner treats approximately 175 patients for weight control. He dispenses either amphetamines (Delcobese) or other anorectic drugs. Over a period of time, various combinations of drugs are dispensed. Patients are seen either weekly or bi-weekly depending upon the individual. Eleven (11) patients' records were reviewed at this physician's office which showed them to be treated for a period of time in excess of 21 days. Some patients were treated for periods in excess of two (2) years.

A Bronx, New York physician maintaining a general practice stated that approximately four years ago when his brother, also a physician, passed away, he took over his weight control practice. In addition to his surgical practice, this doctor treats several hundred patients for weight control. He dispenses only Delcobese.

A review of 31 patients records at this physician's office indicated that most of his patients were treated for a period of more than 21 days, many for more than a year or two. For the most part, weight loss was quite questionable and gain in weight quite often resulted. The doctor stated that weight loss in many of his patients was difficult to achieve and amphetamine products were used in these instances to maintain weight once a loss was achieved.

A Flushing, New York physician stated that his average daily patient total is 150 persons and he dispenses amphetamines (Oby-Rex 5 mg., 10 mg., 15 mg., 20 mg. double-scored tablets) usually for a four (4) week period. This doctor further said that a patient may be taking amphetamines for a period of six months or even as long as a year on a continuous basis. Dispensing records for the month of December, 1975 were reviewed, during which time he dispensed 193,642 Oby-Rex tablets of various strength to patients during 3,197 separate visits.

Region 3 - Philadelphia

The Region 3 Intelligence Unit has nothing to indicate legitimately produced amphetamines are available in the illicit traffic. Cooperating individuals have not furnished any worthwhile information indicating any availability of amphetamines from legitimate channels. There is readily available throughout the Region clandestinely manufactured amphetamines and methamphetamines in bulk form.

A major Pennsylvania amphetamine manufacturer was the subject of an employee theft in April, 1974. It was determined that he had taken a minimum of 120,000 dosage units.

State and local law enforcement laboratories were contacted regarding the availability of amphetamines. Seven laboratories were contacted which showed that a total of 333 amphetamine exhibits were analyzed between January 1, 1976, and October 8, 1976. Of the total, 223 (or 66.9%) were considered to be from legitimate sources. The attached chart sets forth additional information concerning these exhibits.

Six dispensing physicians were inspected in order to determine their adherence to the indications of short term use of amphetamines not to exceed 21 days, as established by FDA, for the treatment of obesity. The following chart provides a composite obtained from the six physicians.

Time	Total Patients	Amount Dispensed
0 - 21 days	34	1,660 d.u.
22 - 90 days	101	19,754 d.u.
91 - 180 days	160	84,315 d.u.
180 - days	316	279,991 d.u.
TOTAL:	756	TOTAL: 385,700 d.u.

The procedure used to select the patient cards from which the above information was gathered was to take, when possible, every tenth card from the files. This procedure was followed with the exception that some patient cards pertained to other than obesity medical problems in which another card was selected. In addition, it was not possible to read some cards and one physician did not have any patient cards and only had a drug log book showing the patient's name, date, type, and amount of drug dispensed.

These six physicians have approximately 6,600 active patients whom they treat for obesity. Since January 1, 1976, they have purchased 1,104,875 dosage units of various strengths of amphetamines.

Each physician inspected as mentioned above was asked to comment on FDA's rule that amphetamines should be used only for short-term treatment of obesity. Two physicians stated that they did not accept FDA's guidelines and that they considered amphetamines effective in the treatment of obesity. Three physicians stated they had never heard about FDA's guidelines, and another stated that amphetamines, when used properly, have a value as a "pep" pill and can be used in place of Ritalin. He also felt that 21 days was not long enough to allow for a "maintenance" period. He stated

that since all patients are required to spend $50.00 for a complete blood test, it would be unreasonable, therefore, to limit treatment to three (3) weeks.

Region 4 - Baltimore

Legitimately manufactured amphetamines are infrequently encountered on the illicit drug market in Region 4. Questioning of Cooperating Individuals disclosed no information concerning amphetamine trafficking during this reporting period:

A review of significant cases involving amphetamines originating from legitimate sources encountered since January 1, 1974 is as follows:

A West Virginia physician received three (3) years probation and voluntarily surrendered his medical license after undercover purchases were made of prescriptions for amphetamines and methamphetamines. A prescription review in Wheeling, West Virginia, revealed that this physician had written 2,407 prescriptions for these controlled substances during a one year period.

A sales representative for North Carolina pharmaceutical distributor received a five year suspended sentence and a $2,000 fine for illicit sale of Eskatrol.

The following information was obtained from state and local law enforcement police laboratories and regulatory authorities concerning the availability of legitimately manufactured amphetamines through illegal channels.

Maryland - Small quantities of amphetamines are available on a sporadic basis throughout Baltimore and the rest of the state. Local Police Laboratories indicate that of the small quantities of amphetamines encountered, 40% are from legitimate sources.

Virginia - Very few legitimate amphetamines are encountered in the illicit drug traffic in Virginia. Amphetamines are not considered a significant problem in this state. Police Laboratories report that a very small percentage of drug submissions are legitimate amphetamines.

Washington, D.C. - Very little abuse of amphetamines in the District of Columbia. Large quantities of Preludin (a brand of phenmetrazine) are being abused.

West Virginia - There is little abuse of amphetamines in West Virginia and is not considered the drug of choice. Police Laboratories report that of the small quantities of amphetamines encountered, approximately 50% are from legitimate sources.

North Carolina - There is sporadic abuse of small quantities of amphetamines in North Carolina. Police Laboratories estimate approximately 25% of the amphetamines indicate diversion from legitimate sources.

A review of the records of ten drug stores and four dispensing physicians in the Maryland, District of Columbia and North Carolina areas disclosed that most physicians are not adhering to the indications established by FDA for short term use of amphetamines in obesity cases.

From information received from police departments and informants, it appears that legitimately produced amphetamines are not a significant problem in the illicit drug traffic in Region 4.

Region 5 - MIAMI

Amphetamines have been generally available throughout Region 5 over the past three (3) years. Drug store burglaries, pilferage at all levels, thefts from UPS drug shipments, and forged prescriptions are the major sources of amphetamines for drug traffickers. Multi-thousand quantities have also been brought into Region 5 from California and Mexico. The major areas of amphetamine abuse have been among young adults in the Northern Florida, Georgia and South Carolina College campuses and military bases, although high school students throughout the Region are also amphetamine abusers.

A 1976 investigation began as the result of an arrest of a drug pusher by the Hialeah Police Department. The original source of supply for the pusher was ultimately traced to a pharmacist who owned two drugstores in Miami. Subsequent investigation has resulted in the arrest of the pharmacist and one (1) other defendant and the identification and possible future indictment of sixteen (16) individuals in a chain of distribution covering the Miami metropolitan area. An audit of the two (2) firms owned by the pharmacist revealed the possible diversion over a two (2) year period of over 120,000 dosage units of amphetamine based drugs as well as 480,000 dosage units of other Schedule II drugs.

Law enforcement officers in the Florida area advise that amphetamines are very available in the illicit market. The source of most amphetamines are from pharmacy thefts, forged prescriptions and legal and illegal dispensing by dispensing physicians.

Region 6 - DETROIT

INTELLIGENCE OVERVIEW

Based on criminal intelligence received by the Regional Intelligence Unit, ethically produced amphetamines, and generally all ethical preparations, have become more available to users than previously. Their availability has increased at a greater rate than other controlled substances excluding marihuana. In the States of Ohio and Michigan, approximately 65% of arrests made for controlled substance violations, excluding marihuana, involved dangerous drugs. Of those arrests, 10% were for amphetamine violations. According to authorities in both states, the vast majority of those amphetamines seized were legitimately produced.

A second observation to be made is that the majority of those subjects arrested were users and that amphetamine and dangerous drug abuse is much more widespread than are heroin, or other totally illicit drugs. Amphetamines are readily available in small quantities throughout the Region.

Availability of legitimately produced amphetamines in the illicit market is primarily through the excessive prescribing habits of physicians. Abuse of amphetamines is primarily through "fat clinics" run by physicians. The most commonly prescribed amphetamines are equally divided between such products as dexamyl, dexedrine, biphetamine, eskatrol, etc.

A survey of the DIU files indicated that approximately 35% of the complaints received and investigated by the DIU are amphetamine related complaints.

Significant Case

The Compliance Group of the Cleveland District Office, monitored purchasing of amphetamines of an Ohio physician, beginning with the latter half of 1972 until November, 1975. The records show that doctor received 3,886,634 dosage units of controlled substances during that period, of which over 3,000,000 were amphetamine products. Numerous complaints throughout the area regarding the physician's activities, as well as the physician's daughter's activities had been received. The Summit County Sheriff's Office had reported the arrest of a former employee of the physician for possession of amphetamines. The Wadsworth, Ohio, Police Department reported that the doctor had numerous drug thefts involving large quantities of amphetamines; however, no DEA theft reports were on file. A DEA informant indicated that he/she had gotten dexedrine from the doctor several times without a physical examination. A Civil Complaint against the doctor was filed by the U.S. Attorney requesting a Declaratory Judgement by the court as to what constitutes a legal medical practice and also a permanent injunction to prevent the doctor from dispensing controlled substances. This action was based upon the contention that the doctor was not conducting a lawful medical practice, a violation of 21 USC 828(c). The

U.S. Attorney averred that the doctor purchased such a great quantity of controlled substances that this great amount could not possibly be used in the ordinary course of an ethical practice, and the number of patients the doctor sees precludes medically accepted diagnostic treatment. On April 27, 1976, a Consent Decree for Declaratory Judgement was filed; and the court stated that there are no standards for treatment of obesity and that each patient must be treated on an individual basis. The court further declared that ethical treatment for obesity is not met where dispensing and prescribing anorectic drugs to a large number of patients as standard treatment, nor are they met by only taking pulse, blood pressure, weight, stethoscopic examination of the patient, a five-minute personal interview with the physician, the delivery of a recommended diet, or a casual concern as to possible dependency or addiction of the patient to anorectic drugs. It further declared that it is improper for a single approach to be used in the treatment of obesity and that the dispensing of anorectic drugs be included as a routine part of the treatment of obesity. The court cited certain references as other modalities for treatment for obesity. The court also cited the CFR, Section 310.504, as being well taken and included as part of the Consent Decree. This is the FDA section of the CFR referred to in this survey for recommended use of amphetamines. No further action to this date has been taken regarding this practitioner; however, the Ohio Medical Board anticipates a citation of this physician.

PRACTITIONERS RECORD REVIEW

An Akron, Ohio, a dispensing physician, ordered over 500,000 dosage units of amphetamine products during a two-year period commencing October 1, 1974. This doctor's practice is 100% weight control. He has approximately 15-20% of his patients using amphetamines continuously from ten (10) weeks to a maximum of one (1) year. The doctor advised that he does not believe that amphetamine use is only effective for 21 days.

Another Akron, Ohio, dispensing physician, ordered over 350,000 dosage units of amphetamine products during a two-year period commencing in October, 1974. His practice is approximately 25% weight control, of which 80% are being treated with amphetamine products. His patients are maintained continuously on amphetamines from one (1) month to a maximum of four (4) months. This physician believes that FDA guidelines for 21-day use are too strict and that amphetamine use as an appetite suppressant is effective for a large period of time.

A Tallmadge, Ohio, dispensing and prescribing physician ordered over 300,000 dosage units of amphetamine products during a two-year period commencing in October, 1974. This physician's practice is approximately 15 to 20% weight control, of which about 50% are being treated with amphetamine products. His patients are maintained continuously on amphetamines for a maximum of three (3) months; however, his average overall maintenance is about six (6) months. This doctor believes that the FDA guidelines for amphetamine use should be six (6) weeks instead of 21 days.

A Kent, Ohio, despensing and prescribing physician, ordered over 200,000 dosage units of amphetamine products during a two-year period commencing in October, 1974. This practitioner's practice is approximately 20% weight control, of which about 20% are being treated with amphetamine products. His patients are maintained on amphetamines from two (2) to four (4) months and he believes that FDA's short term guidelines are too strict.

A Cleveland, Ohio, prescribing physician, prescribed over 90,000 dosage units of amphetamine products for a 15-month period commencing May 1, 1975, to August, 1976. This physician's practice is approximately 90% weight control. Prescriptions screened at a local pharmacy show that the doctor was maintaining patients on amphetamine products for the entire 15-month period. The doctor contends that the amphetamine products that he uses, Delcobese 5-20 mg., are not habit-forming; and, therefore, he is not concerned with FDA guidelines.

Region 7 - CHICAGO

The Regional Intelligence Unit advises that with the exception of the Milwaukee, Wisconsin, areas, there is no significant quantity of legitimately manufactured amphetamine products currently available on the illicit drug market. Two (2) confidential informants of the Milwaukee District Office have advised that approximately fifteen (15) to twenty (20) physicians in the Milwaukee, Wisconsin, area are involved in the illegal prescribing or dispensing of Biphetamine, generally in thirty (30) dosage unit quantities per prescription. A canvas of other active informants working in the dangerous drug area has failed to reveal any additional information indicating a significant diversion of legitimate amphetamine products.

The Milwaukee District Office has initiated four (4) criminal cases since January 1, 1974 involving physicians illegally prescribing Biphetamine.

A review of the case logs have failed to reveal any additional criminal compliance cases involving primarily legitimate amphetamine products since January 1, 1976.

The Regional Compliance Division has made contact with the Illinois State Crime Laboratory System (which analyzes all drug evidence submitted by state and local police agencies in the State of Illinois), the Wisconsin Crime Laboratory and the Milwaukee Regional Crime Laboratory (which together

analyze all drug evidence submitted by state and local police agencies in the State of Wisconsin), the Indiana State Police Laboratory, the Indianapolis (Indiana) Police Laboratory and the Fort Wayne (Indiana) Police Laboratory. These sources revealed that the availability of amphetamine products has dropped sharply since January 1, 1974. The sources further indicated that approximately one (1) percent to ten (10) percent of the amphetamine evidence analyzed comes from legitimate channels. The only exception to this was the Milwaukee Regional Crime Laboratory, which encompassed eight (8) counties surrounding Milwaukee, Wisconsin, whose director states that approximately eighty (80) percent of his amphetamine evidence originates from legitimate channels, much of which is Biphetamine - the most frequently abused amphetamine in Wisconsin.

Doctors in Region 7 who formerly dispensed large quantities of amphetamines in weight control practice no longer do this and have now converted to other drugs such as Phenmetrazine, Phendimetrazine or Preludin, with which they feel can achieve the same results. This is especially true in Illinois where the majority of the drugs used for this purpose are Schedule III and do not require either a Federal order form or a triplicate prescription at the state level.

Information obtained from the Illinois Department of Registration and Education; regarding the triplicate prescription system currently in effect in Illinois reveals that since January 1, 1974, prescriptions written for amphetamine have increased slightly. The system tends to

show that amphetamines currently are not widely prescribed or abused in Illinois. Statistics obtained from the Illinois Bureau of Investigation and Diversion Investigation Unit tend to substantiate this, as they have had no significant cases involving large-scale abuse of amphetamines. The prescribing in this area has been substituted significantly by prescriptions written for Preludin and Ritalin, two drugs that currently do not require the issuance of a state triplicate prescription, and produce essentially the same results. The States of Indiana and Wisconsin currently have no triplicate prescription system.

Region 8 - NEW ORLEANS

Intelligence indicates that the vase majority of amphetamines being abused are being diverted by registrants through the sale of prescriptions, although two (2) organizations, one in Mississippi and one in Alabama, were responsible for diverting in excess of 1 1/2 million amphetamines within the past five (5) years into Mississippi, Alabama, and Georgia.

Source information and investigations conducted by the Criminal Compliance Group, DEA, indicate that registrants are diverting in excess of a million amphetamines per month within Region 8.

A Mississippi physician sold nine (9) prescriptions over a period of two (2) months to DEA agents. This doctor was selling prescriptions to groups of people at a time and also stated that his only business was selling prescriptions for Schedule II drugs. Intelligence indicates that this doctor was responsible for diverting approximately 75,000 dosage units of amphetamines per month.

Another Mississippi physician is considered responsible for dispensing in excess of 50,000 dosage units of Schedule II drugs per month. Several prescriptions were purchased by DEA agents, the majority of diverted dosage units are amphetamines.

Still another Mississippi physician is considered responsible for diverting approximately 200,000 dosage units of controlled drugs each month, both Schedule II and Schedule IV drugs. A total of 18 exhibits (prescriptions) were purchased during this investigations by DEA undercover agents. It is estimated this physician diverts in excess of 100,000 dosage units of amphetamines each month.

A Louisiana practitioner was indicted on sixteen (16) counts of selling prescriptions to undercover agents. This doctor stated to agents that he was selling prescriptions to between 50 and 100 patients a week. This would indicate that approximately 75,000 dosage units per month of both Schedule II and Schedule IV drugs were being diverted of which the majority were amphetamines.

Another Louisiana physician sold a total of 77 prescriptions for Schedule II drugs to an undercover agent in a period of approximately 1 1/2 months. Based on the total number of patients observed in this doctor's office receiving prescriptions by DEA agents and the numerous telephone calls received from pharmacists in Louisiana and Mississippi concerning the number of people attempting to fill prescriptions written by him, it is estimated that he was diverting over 300,000 dosage

units of Schedule II drugs per month, of which approximately 200,000 dosage units were estimated to be amphetamines.

Another Louisiana physician sold a total of 875 dosage units of amphetamines and depressants to DEA undercover agents between April and June, 1974. Investigation revealed that a great number of pharmacies in the New Orleans area were refusing to honor this doctor's prescriptions because of the great number of prescriptions being issued by him. It is estimated that this doctor is diverting approximately 150,000 dosage units of amphetamines per month.

Information obtained throughout Region 8 from local law enforcement agencies indicates that an average of 80% of legitimate amphetamines in the illegal market are from prescribing and/or dispensing physicians. The remaining 20% are from retail/wholesale thefts and forged prescriptions. It is the consensus of state and local police laboratories throughout Region 8 that the majority (approximately 85%) of all amphetamines analyzed are legitimately manufactured. The remaining 15% would be clandestinely manufactured.

Tightening controls over amphetamines also encouraged many abusers to settle for lower scheduled anorectics. The advent of methamphetamine and phenmetrazine (Preludin) also encouraged

doctors to prescribe or abusers to seek these drugs, when unable to obtain amphetamine. Although a serious amphetamine problem still exists in this Region, the growing abuse of other Schedule II drugs, such as Preludin and Desoxyn and Schedules III and IV anorectics, such as Fenfluramine, Phentermine and Phendimetrazine has rapidly outplaced the older established amphetamines.

Region 10 - KANSAS CITY

A review of Region 10 intelligence files and cooperating individual debriefings relative to amphetamine diversion for the period 1 January, 1974, to the present indicates sporadic availability of legitimately produced amphetamines.

Beginning at the end of 1974, and continuing through the early part of 1975, there was a significant decline in the availability of clandestinely manufactured amphetamines with a corresponding increase in the availability of counterfeit products. As the availability of clandestinely manufactured amphetamines continued to decline, the availability from the alternate sources continued to increase. During June 1975, the availability of amphetamines from legitimate sources significantly increased and then decreased slightly. During July and August of 1975, the availability of diverted drugs continued to increase while availability of both clandestinely manufactured and counterfeit products showed a marked decrease. For the remainder of 1975, and into March of 1976 the availabilities from all three source areas remained at farily constant levels and proportions. In April, May and June of 1976 the availability of diverted amphetamines from legitimate sources showed a significant rise while amphetamines from clandestinely manufactured sources showed a slight decrease on availability. From July of 1976 to the present the availability

of amphetamines diverted from legitimate sources remains at a constant level with periodic reports of one thousand lots being available for rather short periods of time.

Generally throughout the Kansas City Region the percentage of amphetamines obtained from legitimate sources is relatively low when compared with the availability of clandestinely manufactured and counterfeit amphetamine products. The most common method of diversion utilized in the Kansas City Region is through the use of prescriptions, either forged or provided by a doctor. In the majority of these cases, the individual who obtains these prescriptions is also the ultimate consumer and does not intend to resell the amphetamines. If he does resell the amphetamines, the number involved is usually only a small percentage of that which was obtained. The other method of diverting drugs is through theft and diversion at the wholesale level. Amphetamines obtained through these methods are usually resold "on the street" to the ultimate consumer or a few levels from the ultimate consumer. Most thefts that do occur are from establishments that maintain small stocks of amphetamines, i.e. several thousand lots.

Throughout Region 10, the majority of case investigations involving amphetamines originating from legitimate sources are at the G-DEP level III or IV violators. These investiga-

tions generally involve diversion by doctors through the use of prescriptions. In order to provide significant amounts of diverted amphetamines, it would necessitate a doctor or a group of doctors writing a large volume of prescriptions, since a single prescription would average between 20 and 30 D.U. The majority of the doctors encountered who do divert amphetamines either do not have a large patient volume to mask significant diversion or else the doctors are reluctant to become so heavily involved in criminal activity due to strict regulatory requirements.

Since January 1974, the Missouri State BNDD has suspended or revoked the CSA prilileges of thirteen (13) practitioners due to amphetamine diversion or abuse. The State of Kansas has placed five (5) practitioners on probation since January 1976 for the same reason. The States of Nebraska, Iowa, South Dakota and Minnesota have had no state investigations involving the diversion of amphetamine by practitioners. The State of North Dakota has had one doctor under investigation for amphetamine diversion which is presently pending in state court.

A survey of state and local law enforcement and regulatory authorities indicate that from 0% to 5% of all drug investigations involve legitimately manufactured amphetamines available through illegal channels.

Of the amphetamine samples analyzed by state and local laboratories, the survey indicates that the percentage of amphetamine dosage units originating from legitimate sources ranges from 0% to 95%. Most state and local laboratories usually report the range between 3% and 5%. The agency reporting the 95% is the St. Louis Missouri Police Department Chemist.

The States of Minnesota, South Dakota and Nebraska indicate that diversion of legitimately manufactured amphetamines either is not a problem or a very minimal one. The Iowa Board of Pharmacy Examiners indicates that the present low availability of legitimate source amphetamines will continue to decline due to the fact that many practitioners are moving away from the prescribing of amphetamines and are using alternate drugs.

The North Dakota State Laboratories Department has received five (5) submissions of legitimately manufactured amphetamines since January 1976. This number constitutes less than 1% of the total amphetamine samples received. The Kansas Bureau of Investigation Laboratory advised that since January 1974, they had analyzed 2,800 drug samples of which 2 to 3% involved amphetamines from legitimate sources. The laboratory also stated that the 2 to 3% figure included such non-amphetamines as preludin and phendimetrazine.

Region 11 - DALLAS

Region 11 reports the following:

1. Amphetamines are readily available from prescribing and dispensing doctors.

2. Records indicate almost all weight control programs dispense more than a 21 day supply, and approximately 30% to 50% of the patients are given medication for two months or longer.

3. It appears that from 3% to 10% of all amphetamines purchased or seized in Texas and Oklahoma are from legitimately manufactured sources.

4. It also appears that approximately 99% of the legitimate amphetamines purchased or seized by DEA agents in Texas in 1975 and through September 1976 were of Mexican origin.

5. Accountability investigations during 1974, 1975, and 1976 to date reveal wholesalers with only minor deviations in accountability regarding amphetamine products. Two Type A registrants a pharmacy and a doctor, and one manufacturing representative had significant deviations.

6. Texas Diversion Investigation Unit has made cases against doctors prescribing or dispensing amphetamines.

Investigators of the Dallas Regional Office visited six (6) pharmacies in the Dallas/Forth Worth area. Seventy-five (75) patient records were reviewed. These records reflected that 50 patients had been prescribed amphetamines in excess of 21 days at a time, and 33 of these 50 patients had amphetamines prescribed more than twice in a six (6) month period.

Investigators also visited seven (7) dispensing doctors, five (5) in the Dallas/Forth Worth area and one each in Austin and Lubbock, Texas. Two (2) of these doctors did not dispense amphetamines but dispensed Phendimetrazine. Records reflected that all 302 patients' records reviewed showed the patients had been prescribed amphetamines in excess of 21 days, and 91 of these patients were given amphetamines in excess of two (2) months.

Investigators also reviewed records in Oklahoma of four (4) pharmacies, five (5) dispensing doctors, and two (2) prescription writing doctors whose prescribing patterns were obtained from the pharmacies. A total of approximately 330 patient records were reviewed, which revealed that 106 of these patients received amphetamines in excess of 21 days and the other 184 patients received 50 or more dosage units of amphetamines. This is broken down as follows: 30 patients receiving 300 or more dosage units of amphetamines (a high of 2,060 dosage

units over a span of 1,007 days); 30 patients receiving 200 or more dosage units of amphetamines; 85 patients receiving 100 or more dosage units of amphetamines; 36 patients receiving 50 or more dosage units of amphetamines; 3 patients receiving injectable amphetamines in excess of 21 days.