APPENDIX

ANNUAL PROGRESS REPORT

By

#84

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It is almost impossible to summarize the work of the NIMH Addiction Research Center for a year in a short presentation, and this is becoming steadily more difficult as our activities increase in size and scope. The program now encompasses work in clinical pharmacology of analgesics, clinical studies on psychosomimetics, clinical psychopharmacological investigations, biochemical experiments ranging from clinical endocrinology to drug metabolism, complex neuropharmacological and neurophysiological investigations, and psychopharmacological studies in animals. In each of these areas a great amount of work has been completed during the year, so obviously I can do no more than touch very sketchily on a few of the highlights of work with which I have been directly involved and which, I hope, will be of interest to this group.

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New Methods for Determining Addictiveness of Analgesics.

As you know, Dr. Fraser has found that substitution of new analgesics for morphine in addicted patients for a period of 24 hours is a sensitive and useful test of the ability of a drug to suppress abstinence from morphine. Substitution for 24 hours has several advantages: Only minimal amounts of new analgesics, the toxicity of which is frequently unknown in man, are required. Very little tolerance and dependence are lost because of the short period of substitution. Patients do not become too uncomfortable during the test period, so that experiments can be repeated weekly. 24-Hour substitution has reflected relatively well the results with the classic 10-day substitution method. The 24-hour procedure does not, of course, reflect the intensity of abstinence following withdrawal of the test drug after substitution for morphine.

Because of our interest in studying dissociation in drug effects (e.g., "euphoric" potency as contrasted with potency in suppressing abstinence, or intensity of abstinence on withdrawal), we are attempting to develop more quantitative ways of studying these phenomena.

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During the year, Dr. Fraser has collected hourly point scores obtained during substitution of 100, 50, 20, 10 and 0 per cent of the patients' accustomed dose of morphine in a 24 hour period. The procedure used was as follows: Patients were stabilized on 60 mg. of morphine four times daily; at 4 p.m. on day prior to the test, the last regular dose of morphine was given; at 10 p.m. of the same night, 6 a.m. and 10 a.m. of the following morning patient received a subcutaneous dose of an "unknown" medication (actually morphine in doses of 60, 30, 12, 6 mg. or a placebo). Usual observations for intensity of abstinence were made from 6 a.m. to 4 p.m. on the test day (14th to the 24th hour of abstinence), and the hourly point scores calculated according to the Himmelsbach system (1). Area under the curves was calculated by the method of Winter and Flataker (2), thus converting all the data on a particular patient for a particular day to one figure, called "point-hours." In all, we have collected data on 39 patients after substitution of placebo, on 24 after substitution of the regular dose of morphine, and on 9 after substitution of 10, 20, and 50 per cent of the accustomed dose of morphine. Results are shown in Figure 1. The brackets at each point indicate two standard errors above and below the mean for that particular point. Obviously the data form a very promising but incomplete dose-effect curve.

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It is our hope that this curve can be defined so well by adding other patients at the points already studied, by studying other doses, and determining limits of variations for different groups of men, that we can make reasonably accurate estimations of the dose of new analgesics which would be equivalent to a standard amount of morphine in suppressing abstinence. We will have to study the suppressive potency of two or more dose levels of new analgesics and compare the dose-effect curves so obtained with the new drug with that of the standard morphine curve. Since we can use a patient only once a week and for a limited number of trials, this is obviously going to be a long-range project. We do not expect to use it with all compounds submitted to us. Only those drugs of some theoretical interest will be studied in this way.

We also hope to develop a quantitative system for evaluating "euphorogenic" potency. The initial effort in this line is being carried out by determining the percentage of patients who make positive identifications that the subjective effects of "unknown" drugs -- in reality, various doses of morphine -- resemble those of opiates or some other drug which addicts regard as pleasant. This is an all-or-none endpoint and the results will be subjected to probit analysis. As yet a sufficient number of patients has not been studied to determine the potential value of the procedure.

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Finally, we are studying the efficacy of a short "direct addiction" procedure in determining the intensity of abstinence after direct withdrawal. Patients will receive the new drug for a period of 19-20 days with the dose being elevated as rapidly as tolerance permits and observations for intensity of abstinence carried out for 10 days after abrupt discontinuation of the medication. Calculations for intensity of abstinence will be converted to area figures ("point-days" in this case) and compared with the intensity after morphine or codeine. Currently seven drugs, including NIH-7519 and NIH-7525, are being studied by this method.

At the time this report was written studies on all the new analgesics submitted to us since March 1950 are still incomplete so that no final evaluation of any of these drugs is possible. However, some of the results are of considerable interest so the following preliminary reports are being made.

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Ethyl 4-phenyl-1[3-(phenylamino)-propyl]-4-piperidine carboxylate ethane sulfonate (WIN 16,098, NIH-7590).

This compound is a congener of meperidine, or demerol, and possesses a morphine-like spectrum of pharmacological activity. NIH-7590 is approximately twice as active as morphine as an "analgesic" in mice. It is about 10 times as potent as morphine in suppressing abstinence in the monkey. The drug is an effective analgesic in man, and is probably as potent as morphine in this respect.

15 to 20 mg. of NIH-7590 induced subjective effects in 10 nontolerant former addicts which were identified as resembling those of heroin or morphine by the majority of the subjects.

Four patients who were actively addicted to and stabilized on 240 mg. of morphine sulfate daily received NIH-7590 in three 24-hour tests for suppression of abstinence. In the first test 12 mg. of the drug were given every six hours (total of 36 mg.); in the second, 10 mg. were given every three hours (total of 30 mg.); and in the third, 15 mg. every three hours (total of 75 mg.). The results are shown in Figure 2. The average score with 12 mg. every six hours was 139 "point-hours" which corresponds approximately to the level of abstinence seen when 20 per cent of the dose of morphine is substituted (36 mg. of

morphine in three doses); the average score with 10 mg. every three hours was 79 "point-hours;" the average score with 15 mg. of NIH-7590 every three hours was 58 "point-hours," which corresponds to a point on the morphine curve below the level seen after substitution of 50 per cent of the accustomed dose of morphine.

Because of the small number of subjects, we have not made the statistical calculations for scope, parallelism, and comparative potencies on these curves. This will be done when more data have been accumulated. As you see in Figure 2, we have drawn the curve for NIH-7590 through the two points obtained with 10 and 15 mg. every three hours and have disregarded the point obtained after 12 mg. every six hours. The reason is that in the first test (12 mg. every six hours) it was evident from inspection of the data that NIH-7590 was suppressing abstinence for only three hours, or, in the words of the addicts, was a "quick-burning" drug of short length of action. The six-hour schedule, therefore, gives an impression of suppressive potency which is somewhat too low. By interpolation from the curves as drawn, 8.5 mg. of NIH-7590 is estimated to be equal to 1 mg. of morphine. This is only an estimate which may be revised as more data become available and statistical calculations made. It is, however, evident that NIH-7590 is very effective in suppressing abstinence and is at least as potent as morphine in this respect. It is, of course, not nearly as potent in man as in the monkey.

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I-3-Hydroxy-N-phenacylmorphinan methane sulfonate (NIH-7525, Ro 4-0266/1).

This compound is of considerable interest because, although it is approximately 30 times as potent as morphine in analgesic tests in mice, it is only one-fifth as potent as morphine in suppressing abstinence in the monkey. It, therefore, seemed possible that a considerable dissociation between analgesic effect and ability to suppress abstinence might have been achieved in this drug.

In 7 nontolerant former addicts, doses of 2 or 3 mg. of NIH-7525 subcutaneously induced subjective effects resembling those of morphine in 13 of 16 trials. NIH-7525 is probably 5-10 times as potent as morphine as an euphoriant.

Three patients who were addicted to and stabilized on 240 mg. of morphine sulfate daily received 3 mg. (one patient, total dose 9 mg.) or 5 mg. (2 patients, total dose 15 mg.) of NIH-7525 subcutaneously every six hours during a 24-hour substitution test. The "point-hour" scores on the 3 patients were 73 (9 mg. total dose), 98 (15 mg.) and 99 (15 mg.). These scores are equivalent to average suppression by 84, 112 and 112 mg. of morphine during the same period of time. Thus, as

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a rough preliminary estimate, NIH-7525 seems to be 7-8 times as effective as morphine in suppressing abstinence in man. Further tests are currently underway in order to determine suppressive potency more exactly.

One short direct addiction test has been completed. One nontolerant former morphine addict received NIH-7525 in doses increasing from 1 mg. to 7 mg. subcutaneously over the course of 19 days. Marked morphine-like behavioral and subjective changes were observed, including pupillary constriction, depression of respiratory rate, nausea, and vomiting. The patient had toxic effects with doses of 5 mg. four times daily. On the 17th day of addiction, 5 mg. of nalorphine subcutaneously precipitated mild but definite symptoms of abstinence. Following abrupt withdrawal of NIH-7525, mild but definite abstinence appeared on the third day and persisted through the seventh day.

The results are sufficient for a tentative statement that NIH-7525 has addictive properties. Assessment of the degree of addictiveness must await completion of additional experiments.

d1-2'-Hydroxy-2,9-dimethyl-5-phenethyl benzmorphan (NIH-7519, SF-6574).

This compound is one of a new series prepared by Dr. Everett May at NIH and studied by Dr. Nathan B. Eddy. It is nearly 10 times as effective as morphine as an analgesic in mice. Despite this, it is much less effective than morphine in suppressing abstinence in monkeys (Dose equivalent to 3 mg. of morphine is approximately 17 mg.). Preliminary results indicate that NIH-7519 is a potent analgesic in man. Since a dissociation between analgesic and abstinence-suppressive potencies might be present, human experiments were undertaken.

In 8 nontolerant former morphine addicts, 3-4 mg. of NIH-7519 subcutaneously induced marked morphine-like subjective and behavioral effects in 12 of 17 trials. The drug is probably 5-10 times as potent as morphine as an euphoriant.

Four patients who were addicted to and stabilized on 240 mg. of morphine sulfate daily received 2 mg. (total of 6 mg. in substitution period, 4 patients) or 3 mg. (total of 9 mg., 3 patients) every six hours in 24-hour substitution tests. Abstinence was suppressed very effectively by these doses.

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The average "point-hour" score in 4 patients receiving 2 mg. every six hours was 76. The average "point-hour" score in 3 patients after 3 mg. every six hours was 83. NIH-7519 is probably at least 5-10 times as potent as morphine in suppressing abstinence in man.

Two patients have undergone short direct addiction experiments. The dose of NIH-7519 was increased from 5 mg. to 24-36 mg. daily over the course of 19 to 24 days. Marked morphine-like behavioral changes were observed in these patients who also reported intense morphine-like subjective effects. Both patients were somewhat toxic on this dosage schedule. 5 mg. of nalorphine precipitated mild abstinence in both instances. Following withdrawal both patients had definite, though mild, abstinence.

NIH-7519 definitely is an addictive drug. However, like NIH-7525, the degree of addictiveness cannot be assessed precisely until other experiments which are underway are completed. Of greatest interest to us at the moment are the quantitative discrepancies between suppressive potencies in man and the monkey, and the mildness of abstinence observed after short direct addiction in man. Evaluation of the latter point will, of course, depend on a comparison of the intensity of abstinence after these drugs with that after administration of morphine for a comparable period of time.

Metabolic Fate of Normorphine

You will recall that, in our patients, normorphine is, in single dose, far less potent than morphine. Yet when small doses (10 mg. subcutaneously) are given, sedative effects of normorphine accumulate to such an extent that the dosage of normorphine cannot be elevated as rapidly or to as great a degree as is the case with morphine. Following withdrawal of normorphine, abstinence was much milder in intensity than was abstinence from morphine. For this reason, a comparison of the metabolic fate and rates of urinary excretion of normorphine and morphine in man was undertaken by our biochemists, Mrs. Jewell Sloan and Dr. A. J. Eisenman.

The method used was a modification of that of Axelrod and Cochin (3). It depends on extraction of the normorphine from urine at pH 9.3 into a mixture of 20 per cent amyl alcohol in ethylene dichloride followed by re-extraction of the normorphine into aqueous solution using 0.05N HCl, after which a blue color is developed by silicomolybdate reagent as described by Fujimoto, et al. (4). Morphine was estimated by the method of Fujimoto (4). The method for normorphine gives consistent and reproducible recoveries of added normorphine. The material being determined has been identified with a high degree of certainty as being authentic normorphine by means of paper chromatography and counter-current distribution.

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As is true of morphine, normorphine is excreted in two forms — "free" or readily extractable and "bound," or extractable only after application of some hydrolytic procedure such as heating with strong acid or incubating with beta-glucuronidase. There is, however, a marked difference in the degree of "binding" of normorphine as compared with morphine. You will notice in the following slide (Table I) that "free" morphine accounted for only 11.4 per cent of the total morphine recoverable from the urine of 3 patients who received 70 mg. of the drug, whereas "free" normorphine accounted for 51 per cent of the total excreted. These data confirm those previously reported on other patients.

Not only is the degree of binding of normorphine far less than is the case with morphine, but normorphine seems to be conjugated differently. The principal conjugate of morphine is known to be the phenolic glucuronide. When urine containing "bound" morphine is incubated with 400 units of beta-glucuronidase per cc. of urine at pH 6.2 for 65 to 70 hours, hydrolysis of "bound" morphine is nearly as complete as with drastic acid hydrolysis. On the other hand, incubation of urine containing "bound" normorphine with beta-glucuronidase under the same conditions causes no or very little hydrolysis of the "bound" normorphine. These data suggest that in man normorphine is not conjugated as a phenolic glucuronide.

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Current work in this field consists of efforts to determine the nature of "bound" normorphine and to isolate it.

The meaning of these differences between the metabolism of morphine and normorphine are still obscure. One hypothesis might be framed as follows: The "free" forms of normorphine and morphine are the active forms of these drugs; normorphine is inherently a weaker drug than morphine; under conditions of chronic administration, less normorphine is bound so that more free and, presumably, active drug accumulates in brain than is the case with morphine. Obviously this hypothesis can only be tested in animals and, before we can test it, we must find an animal that metabolizes morphine and normorphine in the same way as does man.

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Psychotomimetic Drugs

We have long been interested in and have carried out a great many investigations dealing with drugs that induce psychoses. Interest in these compounds stems, in part, from the fact that two of the drugs controlled by the narcotic laws -- cocaine and marihuana -- are, in a sense, psychotomimetics and, in part, from our interest in the relationship of these materials to larger problems of mental disease. As you know, a number of hypotheses have been formulated which relate psychosomimetic effects to a deficiency of, or to an excess of the so-called neurohumors, epinephrine, norepinephrine, acetylcholine and serotonin (Deficiency or excess is thought of in terms of pharmacological effect rather than concentration). Greatest emphasis has been placed on serotonin.

During the year, we completed an examination of a number of congeners of diethylamide of lysergic acid, which were made available to us through the kindness of Dr. R. Sircher of the Sandoz Company. The potency of these drugs in blocking serotonin-induced contractions is compared with their psychotomimetic potencies in Table 2. Unfortunately, time does not permit a description of the methods by which the psychotomimetic potencies were determined, so the figures must be taken on faith. You will notice that high potency as an antiserotonin

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is not necessarily correlated with high potency as a psychomimetic. BOL-148, BOL-61, and TLA-74 are all more potent than LSD as serotonin blockers yet are not nearly as potent as psychotomimetics. On the other hand, there is no instance of a compound in this group that is a potent psychotomimetic that is not also a potent antiserotonin. Thus the data, while not favoring the serotonin-deficiency hypothesis of the LSD psychosis, do not disprove it.

Another interesting finding during the year was the detection of potent hypnotic effects in compounds related to LSD (Figure 3). The drugs in which we have detected this sort of activity are all compounds in which the acid amide group of LSD has been replaced by alkyl and hydroxyl groups. The compounds we have studied are agroclavine and dihydroagroclavine (Takeda Co., Japan) and a closely similar compound known as Lilly 2313%. The Lilly drug is the most potent hypnotic of the three, so we will present only the data on that drug. In animals both agroclavine and Lilly 2313% were excitant, whereas dihydroagroclavine was a depressant drug.

In our patients, however, these compounds did not induce excitation or a psychosis. Rather they caused somnolence, drowsiness and sleep. A comparison of hypnosis after 2 and 4 mg. of Lilly 2313% (our number Y-1-71) and after 100 and 200 mg. of secobarbital is presented in Table 3.

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The method used in evaluating hypnosis was as follows: Patients entered the ward the night before and slept through the night as usual. On the following morning they were given, in randomized "double-blind" fashion, 2 or 4 mg. of V-A-21, 100 or 200 mg. of sodium secobarbital, or a placebo. Nine patients received all five treatments. Drugs were given with the patients fasting and coffee was not permitted. Patients were observed at half-hour intervals from 8 a.m. to 4 p.m. to determine if they were asleep. Looking at the table it is evident that both V-A-21 and secobarbital caused a significant increase in sleep as compared with placebo. The greatest increase was in the hours from 8 a.m. to noon. It is also evident that, although no clear-cut dose effect was obtained, that V-A-21 is roughly 50 times as potent as secobarbital as a hypnotic under these conditions.

We have experiments in progress in which we are attempting to block the LSD psychosis by concomitant administration of V-A-21. Although the experiment is not complete, it is already evident that V-A-21 does not attenuate the LSD psychosis but actually enhances it.

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I see that I have used all the time talking about some of the clinical aspects of our program and no time is left for a discussion of the important and interesting basic researches carried on by our neurophysiological and psychological sections. I hope that at the next meeting Dr. Wikler and his co-workers can cover these aspects of our work for you.

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2. Winter, C. A. and Flataker, L.: Studies on heptazone (6-morpholino-4,4-diphenyl-3-heptanone hydrochloride) in comparison with other analgesic drugs. J. Pharmacol. & Exper. Therap., 98: 305-317 (Mar.) 1950.

3. Axelrod, J. and Cochin, J.: The inhibitory action of nalorphine on the enzymatic N-demethylation of narcotic drugs. J. Pharmacol. & Exper. Therap., 121: 107-112 (Sept.) 1957.

4. Fujimoto, J. M., Way, E. L. and Nine, C. H.: A rapid method for the estimation of morphine. J. Lab. & Clin. Med., 44: 627-635 (Oct.) 1954.

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LEGEND FOR FIGURE 1.

Figure 1. Relationship of dose of morphine to intensity of abstinence in 24-hour substitutions.

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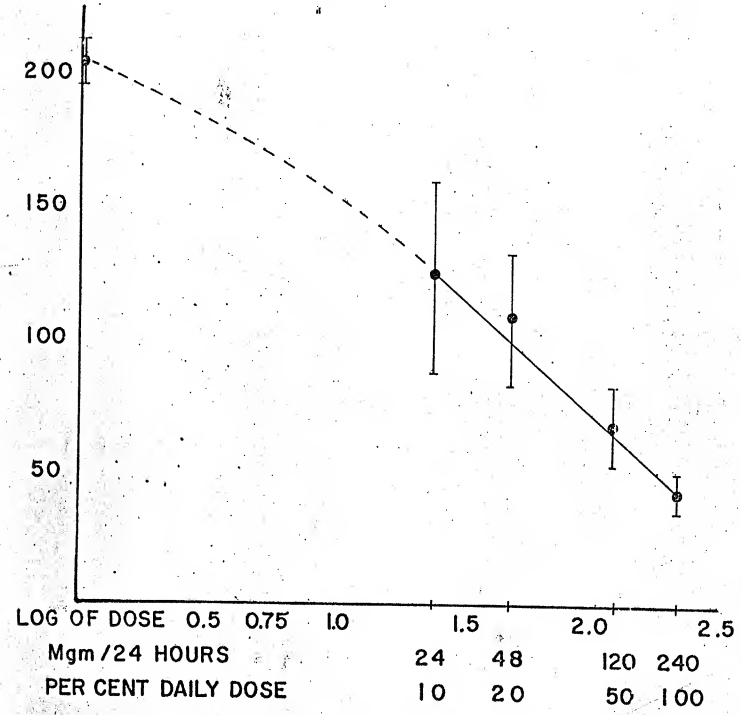
200
150
100
50
LOG OF DOSE 0.5 0.75 1.0 1.5 2.0 2.5
Mgm/24 HOURS 24 48 120 240
PER CENT DAILY DOSE 10 20 50 100

LEGEND FOR FIGURE 2.

Figure 2. Suppression of abstinence by Ethyl 4-phenyl -1[3-(phenylamino)-propyl]-4-piperidine carboxylate ethane sulfonate (WIN 14,098, NIH-7599).

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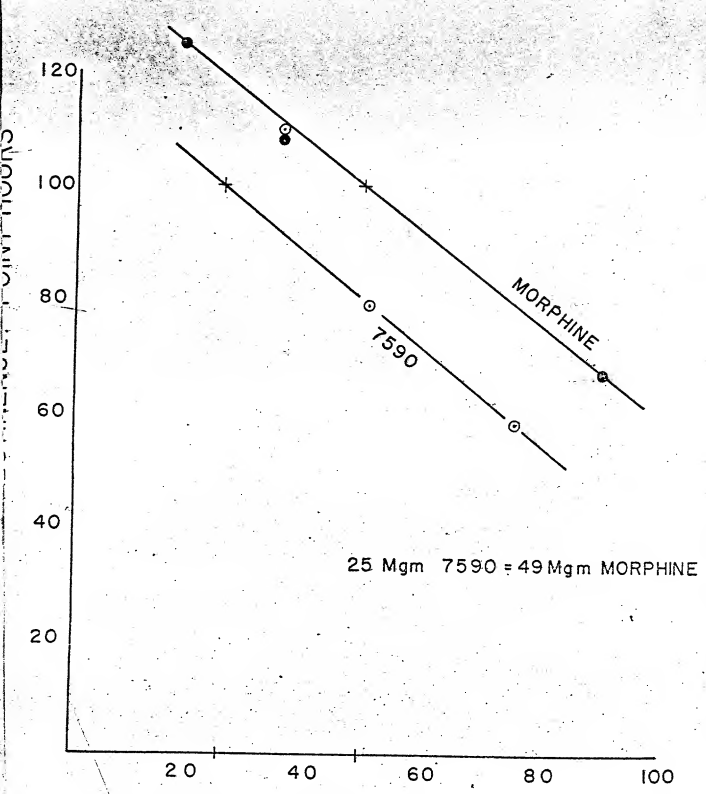
120
100
80
60
40
20
MORPHINE
7590
25 Mgm 7590 = 49 Mgm MORPHINE
20
40
60
80
100
DOSE DURING SUBSTITUTION PERIOD

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LEGEND FOR FIGURE 3.

Figure 3. Structural formulae of congeners of LSD with hypnotic effects.

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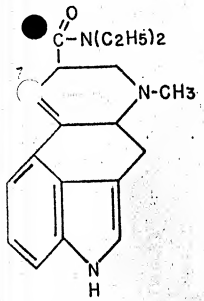
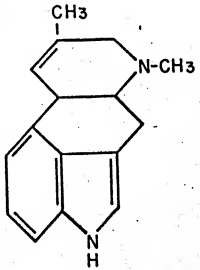
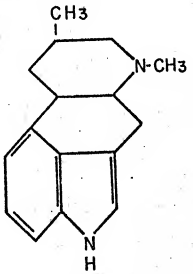


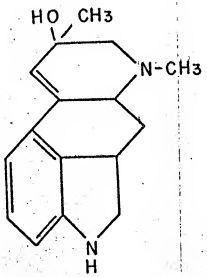
LYSERGIC ACID
IFTHYLAMIDE



AGROCLAVINE



DIHYDRO-
AGROCLAVINE



LILLY
23194
(ARC VA-21)

LEGEND FOR TABLE 1.

Table 1. Comparison of excretion and conjugation of morphine and normorphine after administration of 70 mg. of both drugs.

PERCENTAGE OF DOSE EXCRETED IN 24 HOURS					
MORPHINE			NORMORPHINE		
% AS "FREE"	% AFTER ACID	% AFTER ENZYME	% AS "FREE"	% AFTER ACID	% AFTER ENZYME
11.4 (8.9-15.1)	60.6 (55.9-63.3)	54.6 (41.2-62.1)	51 (48.8-53.2)	73.1 (68.8-77.5)	56.2 (48.8-64.7)

FIGURES ARE AVERAGES OF DATA ON THREE SUBJECTS.
RANGE SHOWN IN PARENTHESES.

LEGEND FOR TABLE 2.

Table 2. Comparison of psychotomimetic and antiserotonin potencies of congeners of LSD.

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CODE	COMPOUND	DOSE APPROXIMATELY* EQUIVALENT TO 1.0mcg/Kg OF LSD-25	RELATIVE PSYCHOTOMIMETIC ACTIVITY (LSD_{25}=100)	RELATIVE** ANTISEROTONIN ACTIVITY (LSD_{25}=100)
	A. STEREOISOMERS			
[illegible]-25	d-LYSERGIC ACID DIETHYLAMIDE	1.0	100	100
L-LSD	l-LYSERGIC ACID DIETHYLAMIDE	>70	0	0
[illegible]-LSD	d-ISO-LYSERGIC ACID	>50	0	0
	B. VARIATIONS IN AMIDE GROUP			
DAM-57	d-LYSERGIC ACID DIMETHYLAMIDE	10	10	23
[illegible] 32	d-LYSERGIC ACID MONOETHYLAMIDE	20	5	12
LPD-824	d-LYSERGIC ACID PYRROLIDIDE	10	10	5
LSM-775	d-LYSERGIC ACID MORPHOLIDE	9	11	2
	C. SUBSTITUTIONS IN RING SYSTEM			
MLD-41	d-l-METHYL LYSERGIC ACID DIETHYLAMIDE	3	33	370
ALD-52	d-l-ACETYL LYSERGIC ACID DIETHYLAMIDE	1	100	210
BOL-148	d-2-BROM-LYSERGIC ACID DIETHYLAMIDE	>86	< 2	103
MBL-61	d-l-METHYL-2-BROM-LYSERGIC ACID DIETHYLAMIDE	>175	<1	533
	D. SUBSTITUTIONS IN RINGS AND VARIATIONS IN AMIDE			
[illegible]LA-74	d-l-METHYL-LYSERGIC ACID MONOETHYL-AMIDE	25	4	835
[illegible]LA[illegible]	d-l-ACETYL-LYSERGIC ACID MONOETHYL-AMIDE	15	7	39
[illegible]PD-75	d-l-METHYL-LYSERGIC ACID PYRROLIDIDE	> 20	< 5	130

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* SEE TEXT FOR METHOD OF ESTIMATION

** TAKEN FROM DATA OF CERLETTI AND DOEPFNER

LEGEND FOR TABLE 3.

Table 3. Comparison of hypnotic effects of V-A-21 and seconbarbital.

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TIME PERIOD	DRUG	HOURS SLEPT	DIFFERENCE ± SE FROM PLACEBO	SIGNIFICANCE OF DIFFERENCE
AM-12M	PLACEBO	1.5	—	—
	VA-21 2Mg	2.8	+1.3 ± 0.25	< 0.01 **
	VA-21 4Mg	3.0	+1.5 ± 0.05	< 0.01 **
	SECONAL 100Mg	2.2	+0.7 ± 0.39	N S
	SECONAL 200Mg	2.3	+0.83 ± 0.3	>0.01 <0.05 *
12:30PM-4PM	PLACEBO	1.5	—	—
	VA-21 2Mg	0.6	-0.9 ± 0.55	N S
	VA-21 4Mg	1.5	0	N S
	SECONAL 100Mg	1.5	0	N S
	SECONAL 200Mg	2.2	+0.7 ± 0.5	N S
8AM-4PM	PLACEBO	3	—	—
	VA-21 2Mg	3.4	+0.4 ± 0.64	N S
	VA-21 4Mg	4.5	+1.5 ± 0.8	>0.05 NS
	SECONAL 100Mg	3.7	+0.7 ± 0.41	NS
	SECONAL 200Mg	4.5	+1.5 ± 0.7	< 0.05 *

** HIGHLY SIGNIFICANT
* SIGNIFICANT
NS NOT SIGNIFICANT

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DRUG	HOURS AFTER DRUG															
	0	1/2	1	1 1/2	2	2 1/2	3	3 1/2	4	4 1/2	5	5 1/2	6	6 1/2	7	7 1/2
SECONAL 200 Mg	0	2	6	7	8	8	8	5	2	6	6	7	6	5	5	2
SECONAL 100 Mg	1	5	7	6	7	8	0	3	4	4	4	5	4	2	1	0
PLACEBO	0	2	6	6	7	4	2	0	1	5	4	5	4	4	3	1
VA-21 2 Mg	4	8	9	9	8	7	6	0	1	1	2	2	2	1	1	1
VA-21 4 Mg	2	8	9	7	8	9	9	2	5	6	4	4	4	2	2	0

FIGURES SHOW NUMBER OF SUBJECTS OF 9 ASLEEP AT THAT PARTICULAR INTERVAL

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DRUG	HOURS AFTER DRUG															
	0	1/2	1	1 1/2	2	2 1/2	3	3 1/2	4	4 1/2	5	5 1/2	6	6 1/2	7	7 1/2
SECONAL 200 Mg	0	2	6	7	8	8	8	5	2	6	6	7	6	5	5	2
SECONAL 100 Mg	1	5	7	6	7	8	0	3	4	4	4	5	4	2	1	0
PLACEBO	0	2	6	6	7	4	2	0	1	5	4	5	4	4	3	1
VA-21 2 Mg	4	8	9	9	8	7	6	0	1	1	2	2	2	1	1	1
VA-21 4 Mg	2	8	9	7	8	9	9	2	5	6	4	4	4	2	2	0

FIGURES SHOW NUMBER OF SUBJECTS OF 9 ASLEEP AT THAT PARTICULAR INTERVAL

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PERIOD	HOURS OF SLEEP			
	AFTER PLACEBO*	AFTER VA-21*	DIFFERENCE ± S.E.	SIGNIFICANCE
8AM-12:00M	1.1	2.8	1.7±0.26	< 0.01 **
12:30PM-4 PM	0.5	0.5	0	N S
8AM-4PM	1.6	3.3	1.7±0.34	< 0.01 **

* FIGURES ARE MEANS OF OBSERVATIONS ON 5 SUBJECTS
** HIGHLY SIGNIFICANT

PERIOD	HOURS OF SLEEP			
	AFTER PLACEBO*	AFTER VA-21*	DIFFERENCE ± S.E.	SIGNIFICANCE
8AM-12:00M	1.1	2.8	1.7±0.26	< 0.01 **
12:30PM-4 PM	0.5	0.5	0	N S
8AM-4PM	1.6	3.3	1.7±0.34	< 0.01 **

* FIGURES ARE MEANS OF OBSERVATIONS ON 5 SUBJECTS
** HIGHLY SIGNIFICANT

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