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QUARTERLY REPORT

July 1 - September 30, 1953.

Section on Addicting Drugs, Laboratory of Pharmacology
NIMH Addiction Research Center, PHS Hospital
Lexington, Kentucky.

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A. GENERAL

During the last of June and the first part of July, 1953, the processing of purchase vouchers and of personnel payrolls was transferred from the hospital's administrative division to the National Institute of Mental Health. This administrative change has functioned very well and only minor difficulties have been encountered. Uncertainties with respect to the budget for the current fiscal year have hampered purchasing to some extent. The project being carried on for the Department of Defense was reactivated during the month of July. The project is still concerned with the development of a synthetic substitute for codeine.

Clinical studies during the quarter were largely concerned with continuing search for codeine substitutes, the addiction liability of mixtures of morphine and Nalline, addiction to meperidine, with the clinical endocrinology of addiction, and with chronic intoxication with the diethylamide of lysergic acid (LSD-25). Another phase of studies on the clinical endocrinology of addiction was completed during the quarter. It was found that the adrenals and the testes will respond to stimulation by the specific adrenocorticotropic and gonadotropic hormones of the anterior pituitary during maintained morphine

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addiction. Insofar as can be determined by the measures employed, responses during addiction are in the normal range. This suggests that the reason for decreased 17-ketosteroid excretion during addiction is due to a block at the pituitary level.

The Neurophysiological Section has been concerned with preliminary experiments on the development of a test for physical dependence liability in dogs, with meperidine addiction in dogs, and with the interrelationships of morphine and Nalline.

The Psychological Section has shown a marked reduction in conditioned inhibition in rats while under the influence of morphine.

Four papers by members of the unit were published in the quarter and two lectures were presented before scientific societies. Motion pictures concerned with addiction were exhibited to twelve audiences.

B. CLINICAL STUDIES OF ADDICTION

1. Ward Studies

a. Addiction Liability of New Substances.

(1) l and d 2,N-dimethyl-3-hydroxymorphinan hydrochloride (No. Ro 1-7360 and No. Ro 1-7361). These substances are being examined as potential synthetic substitutes for codeine. Single doses of the l isomer varying between

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2.5 to 60 mg. were administered to 17 nontolerant addicts. Definite evidence of morphine-like euphoria began to appear at the 30-mg. level. Euphoria was distinct and pronounced at the 60-mg. level. Euphoria was also observed when 60 to 75 mg. were administered orally. No untoward toxic reactions were observed. Sixty to 75 mg. of the levo isomer every four hours caused marked suppression of abstinence when substituted for morphine in 2 strongly addicted patients. No evidence of morphine-like euphoria was seen with the dextro compound, and no suppression of abstinence was observed during a short substitution for morphine. Although the number of patients tested is too small to draw definite conclusions, the results indicate that the levo isomer will possess addiction liability which will exceed that of codeine.

(2) 6-Methyl-Δ-6-desoxymorphine (MK-57). It has previously been shown that this drug produced intense euphoria in former morphine addicts and was very effective in suppressing abstinence from morphine. The human pharmacology of the drug has now been studied in greater detail. In 10 patients it induced marked pupillary constriction and marked respiratory depression. The peak of these effects was observed 15 minutes after administration of the drug and was associated

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with the development of intense euphoria. One patient was directly readdicted to MK-57 for a period of 17 days. The dose was increased from 2 mg. every three hours to 6 mg. every three hours. Even after this very short period of addiction, definite abstinence appeared on abrupt withdrawal. Abstinence was evident in four hours, severe by eight, and had subsided after forty-eight hours. The results confirm our impression that this drug has high addiction liability.

(3) di-1-methyl-4-phenyl-4-carbethoxy azacyclo-heptane (No. 5835). Only preliminary work with this compound, which is in the meperidine series, has been completed. Single doses varying between 25 to 120 micrograms have been administered to 22 nontolerant former addicts. Evidence of morphine-like euphoria was observed in only 2 of these patients. No untoward toxic reactions have been encountered and the dose is still being elevated.

(4) 4-4-diphenyl-6-dimethylamino-hexanone-3 (No. 10588). This compound, a member of the methadone series, is being examined at the request of the Drug Addiction Committee, since it is being marketed in Germany. The manufacturer has indicated that a combination of this drug plus Suprifen (p-hydroxy ephedrine) does not possess addiction liability. As yet only preliminary data are available. Single doses have been administered to 7 nontolerant morphine addicts. Evidence of mild

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[redacted] morphine-like euphoria was evident at the 30-mg. level. Further studies are in progress.

b. Addiction Liabilities of morphine-Nalline Mixtures. Two of the patients who were addicted to the 1-to-5 mixture of morphine-Nalline have been readdicted to morphine and to Nalline in separate experiments, using the same dosages of both drugs that were present in the mixture. Following withdrawal of morphine, abstinence was far more intense than following withdrawal of the mixture. Following withdrawal of Nalline, no clear-cut evidence of abstinence was observed.

c. Meperidine (Demerol) Addiction.

This study is being undertaken as a cooperative project with the clinical staff of the hospital. The study was initiated because the President and President-elect of the American Medical Association approached the Surgeon General and expressed concern about the increasing incidence to meperidine in private practice. Following receipt of letters from headquarters concerning this matter it was decided that a project concerning meperidine addiction be initiated and carried out immediately. This project will include, on the part of the hospital, a survey of the records of all patients giving histories of meperidine addiction. The information gathered from the records will include data on age, sex,

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occupation, geographical location, stated reason for addiction, other drugs used, etc. In addition to surveying the records, the psychiatric staff of the hospital will undertake intensive case studies of a number of meperidine addicts. The NIMH Addiction Research Center's part of the program is to establish the presence of physical dependence in "primary" addicts and to study meperidine addiction in dogs. The method for proving that abstinence occurs in "primary" meperidine addicts utilizes the standard technic of Himmelsbach. Patients with histories of addiction to meperidine but of addiction to no other drug are selected for study. These patients are stabilized on meperidine for a period of 7 to 10 days, then the meperidine is abruptly withdrawn, and observations for signs of abstinence are carried out. At the height of abstinence from meperidine, doses of meperidine are to be administered and the relief of withdrawal symptoms observed. Where possible, attempted precipitation of abstinence from meperidine with Nalline will be carried out. Confirmation of the patient's story of addiction to meperidine only is necessary for inclusion in the series, and will be obtained by interviewing or writing to the patient's relatives and physician. To date, 6 suitable patients have been studied. All showed very definite abstinence on withdrawal of meperidine. Toxic manifestations, while

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receiving large amounts of meperidine, were apparent in all 6 cases. One patient who was receiving 300 mg. of meperidine every three hours had a convulsion. Practically all patients exhibited involuntary jerking and twitching of muscle groups. Abstinence could not be precipitated with Nalline in any of these patients.

Studies on meperidine addiction are described in the Neurophysiological Section.

d. Chronic Intoxication with the Diethylamide of Lysergic Acid (LSD-25).

This drug is a semi-synthetic member of the ergot series which produces a toxic psychosis in doses of only 20 to 60 micrograms. The effects of single doses of the drug have been extensively studied both in the United States and Europe, using both psychotic and nonpsychotic patients. Many psychiatrists have described the mental effects produced by the drug as resembling those seen in schizophrenia and some have gone so far as to call LSD-produced psychosis "experimental schizophrenia." No human experimentation on chronic intoxication with this interesting compound has been carried out. It was, therefore, felt that the study of chronic intoxication with the compound was extremely important.

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Six patients, all negro male former addicts, volunteered for the experiment. In July, control observations were obtained. These included physical, psychological, psychiatric examinations, clinical observations three times daily, electrocardiograms, electroencephalograms, blood chemistry, and liver function tests. Following the control period, an attempt was made to determine the threshold dose (dose which would just induce mild subjective effects) for each patient. In this preliminary experiment, the drug was given daily. Initially, doses of 20 to 40 micrograms were administered and the dose was increased each day. Very few effects were observed until the dose had been increased to 100 micrograms. At this point, mild subjective effects were observed which, however, were not present when additional doses were given on subsequent days. Administration of 100 to 120 micrograms to patients who had not been receiving the drug daily induced powerful subjective effects. It was, therefore, felt that patients might have developed tolerance during the preliminary period. Daily administration of LSD-25 was therefore discontinued without the patient's knowledge, and, after six days, begun again. Immediately, very striking reactions were observed. For this reason it was necessary to obtain data on the effect of single isolated doses which were spaced at least three days apart.

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Under these conditions a very consistent pattern of drug effect emerged. The degree and duration of the reactions were related to the dose. The amount of drug necessary to elicit the effect varied widely in different patients, the range extending from 90 to 300 micrograms.

The objective effects of LSD-25 include elevation of systolic and diastolic blood pressure, dilatation of pupils (measured in controlled light), increased tendon reflexes, and decreased abdominal skin reflexes. Gooseflesh, fine intention tremor of the fingers, ankle clonus, and tremor of large muscle groups were less consistently observed.

The mental effects of LSD-25 were very striking and varied from person to person. No obvious correlation with personality patterns was apparent. The mental effects consistently included anxiety, a feeling of unreality, and various haptic sensations (formication, feelings of electric shocks on the skin, tingling sensations, choking). Taste and smell appeared to be unaffected; noises were reported to be loud and difficult to distinguish; changes in the patient's body image, and in the body image of other persons were frequently reported; the patient's hands and feet appeared to grow, or decrease in size. Marked changes in visual perception were reported. These included blurring of vision, abnormal coloration of familiar objects (hands turning purple, green, etc), daubs of paint on the wall, flickering

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shadows, dancing dots of light, and spinning circles of color. Frequently, inanimate objects were distorted and changed in size. Occasionally, patients reported seeing visions consisting of rapidly changing fantastic scenes which resembled "Walt Disney Movies." Patients had difficulty in describing these sensations while under the influence of LSD-25 (blocking?) and were much more likely to give good descriptions the day following the experiment. They complained of difficulty in concentration and of a "rush of thoughts." Patients were usually apathetic and somewhat withdrawn during the height of the psychosis. Insight was always maintained.

The effects usually began 30 minutes to one hour after administration of the drug and peak effect was usually reached in one and one-half to three hours; thereafter, effects gradually subsided and were completely dissipated after eight to sixteen hours. Occasionally patients reported "hangovers" lasting for one to several days.

Electroencephalograms were not greatly changed by LSD-25, but synchronization of the electroencephalogram by rhythmic photic stimulation was enhanced. Photic stimulation also appeared to enhance perception of colors, patterns, etc., following administration of LSD-25.

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We cannot agree that the LSD-psychosis resembles schizophrenia. Certain isolated symptoms that are observed in schizophrenia, such as depersonalization, derealization and hallucinations are observed under LSD. However, insight is always maintained and affect is usually appropriate. The total picture of LSD-intoxication constitutes a distinct and recognizable clinical entity, which we feel could be confused only with intoxication with mescaline. In fact, LSD-intoxication resembles intoxication with cocaine more than schizophrenia.

The experiment on chronic intoxication has been completed in 3 patients. One patient withdrew after six days chronic intoxication and the experiment is still in progress in the 2 remaining patients. A rapid decline in the effect when one dose of LSD-25 was given daily was observed in all 3 patients who completed the experiment. Initial doses were 1.5 to 2 mcg./kg. (90 to 130 micrograms total dose) administered once daily. The first dose induced the usual changes in mentation, perception, blood pressure, pupillary size, and tendon reflexes. Partial tolerance to this dose was evident by the second day of administration and appeared to be complete after four days administration. At this point the dose was increased, and after 7 to 10 days, tolerance appeared to be complete to 3 mcg./kg. (total dose of about 180 micrograms). The diminished effect

included not only a decline in the mental effects but also decreases in the effects on blood pressure, pupillary size and deep tendon reflexes. No abstinence occurred on withdrawal of LSD-25 after 14 days administration. Development of tolerance to LSD-25 occurs more rapidly and appears to be more complete than with any drug we have ever studied. The rapidity of the return of the effects remains to be determined.

2. Biochemical Studies

a. Clinical Endocrinology of Addiction.

The phase of this particular project described in the last quarterly report was completed during this quarter. In general, the excretion of 17-ketosteroids following 8-hour infusions of International units of ACTH during maintained addiction was less in terms of milligrams than prior to addiction. However the increase in terms of percentage of the usual daily excretion was greater during maintained addiction. In addition, 17-ketosteroids increased after infusions of only 5 and 2.5 International units of the preparation of ACTH used in these experiments. With the exception of one test on one man, the increase of 17-ketosteroid excretion after ACTH fell within the normal range. Increase in excretion of uric acid after infusions of ACTH appeared to be as great during maintained addiction as prior to addiction. The decline in eosinophil

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count during timed ACTH infusions was somewhat slower during maintained addiction, but always fell to zero (or nearly so) in eight hours.

Increase in excretion of 17-ketosteroids after the injection of 1000 international units of chorionic gonadotropin for five consecutive days was as great in terms of milligrams and in terms of percentage change from the usual excretion during addiction as during the control period.

The data definitely show that the testes and the adrenal glands are capable of responding to the specific pituitary hormones during addiction to morphine. Nevertheless, excretion of 17-ketosteroids is markedly reduced during addiction and enhanced during withdrawal. Dr. Dorfmann, of the Worcester Foundation for Experimental Biology, kindly analyzed a few samples of urine for us on patients who were addicted to morphine, and during acute withdrawal of morphine. The excretion of corticoids is much lower during maintained addiction. The most reasonable hypothesis explaining the facts known to date is a block at the pituitary level during morphine addiction.

Future work will include determination of total adrenal-corticoid excretion (provided a suitable method can be developed); a fractionation of urinary corticoids by Dr. Dorfmann; and chorionic gonadotropin determinations (to be done by the National Cancer Institute, provided certain technical difficulties

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[redacted] at Lexington can be overcome. We also hope to evaluate thyroid status during maintained addiction, using serum-protein bound iodine and BMRs as the indices.

b. Serum Electrophoretic Patterns.

These studies have been extended and more patterns have been collected on former addicts and on nonaddicts. All determinations are being done in barbital buffer, rather than phosphate buffer, as heretofore. The difference in the ratio of beta globulin to gamma globulin previously reported (ratio greater than 1 in addicts; less than 1 in nonaddicts) has been confirmed and is statistically significant of a p-level of less than 0.01. There is, however, an overlap, some former addicts showing "normal" patterns and some nonaddicts showing "addict" patterns. The significance of the changes in serum-protein pattern remains obscure.

C. EXPERIMENTAL NEUROPSYCHIATRY

1. Neurophysiological Studies

a. The relation of morphine-Nalline dose proportions to degree of antagonistic effects. The degree of antagonism of morphine by Nalline has been studied in the ipsilateral flexor reflexes of 4 spinal dogs, using doses of Nalline ranging between 0.03 to 15 mg./kg. Although more experiments need to be done at

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at the various dose levels, the experiments so far indicate that a large dose of Nalline antagonizes the depressant effects of morphine more than does a small dose. Conversely, a large dose of morphine antagonizes the effects of a fixed dose of Nalline more than does a small dose.

b. Addiction of Chronic Spinal Dogs to morphine-Nalline Mixtures. Two chronic spinal dogs were given 3.75 mg./kg. of morphine and 1.25 mg./kg. of Nalline (mixture of 3-to-1). After three weeks addiction to this mixture, there was no evidence of tolerance to the depressant effects of the mixture on the flexor reflex. This is a striking observation since, with morphine alone, marked tolerance would have been expected. In all dogs hyperreflexia and spontaneous running movements began to appear between the 9th and 10th days, immediately after each dose of the mixture. Above the level of section, mydriasis, tremor, rhinorrhea, salivation, etc, appeared sooner than did hyperreflexia or running movements in the hindlimbs. Findings in the dogs confirm those heretofore observed in man. They indicate that chronic use of morphine-Nalline mixtures would be associated with the development of unpleasant side effects (precipitation of mild abstinence by each injection of the mixture).

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c. Determining Addiction Liability in Dogs, Using Nalline. We are studying the possibility of developing a short test for addiction (physical dependence) liability in dogs, using Nalline. We have carried out preliminary experiments using two methods. The first method involves the injection of large amounts of the drug under study once daily for three to five days after which 15 mg./kg. of Nalline are administered. After injection of 50 mg./kg. of morphine for three to five days, Nalline caused definite changes in the behavior of dogs. After administration of Nalline the dogs became restless, sometimes vomited, developed tremors, and consistently would dig a hole at the foundation of the building and lie in it. These changes were not observed after either morphine or Nalline separately. Erratic results were seen after injection of single doses of methadone for three to five days. In the other method, drugs were given several times daily. When 5 mg./kg. of morphine was administered four times daily, Nalline precipitated digging and other changes after three to seven days of addiction. Intensity of the changes has been steadily increasing as morphine addiction proceeded. When 3 to 5 mg./kg. of methadone were administered four times daily, Nalline precipitated the digging and other changes after three to seven days of addiction. Such changes have not been observed in dogs that are being experimentally addicted to 10 mg./kg. of meperidine every three hours for 30 days.

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d. Addiction to Meperidine in Chronic Spinal Dogs. In 2 nontolerant spinal dogs single doses of 10 mg./kg. of meperidine produced effects on the hindlimb reflexes which were similar to those produced by 0.75 mg./kg. of morphine. After a week on 10 mg. of meperidine every six hours, tolerance to the depressant effects was evident. At this time 15 mg./kg. of Nalline did not precipitate running movements. On the contrary, the flexor reflex was depressed and the dog appeared to be sedated after Nalline. When the number of doses of meperidine increased from four to eight daily, peculiar changes were observed in the paralyzed hindlimbs. These changes included marked hyperactivity of the ipsilateral, flexor and crossed extensor reflexes, irregular spontaneous tremors, and twitches and massive extensor reflexes elicited by tapping any bony-proof protuberance below the level of cord section. After sixteen days of addiction, abrupt withdrawal was carried out for 24 hours. The changes observed persisted with increased intensity for 6 to 12 hours, then subsided moderately before the dogs were replaced on meperidine. At the moment, we are unsure whether the changes seen in the dogs addicted to meperidine represent toxic effects or abstinence symptoms.

e. Effects of Diethylamide of Lysergic Acid (LSD-25) on the Human Electroencephalogram. In 6 subjects, single doses of LSD-25 varying from 90 to 150 micrograms produced little

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change in the EEG. Synchronization of the electroencephalogram by photic stimulation appears to be enhanced after LSD-25 but the statistical significance of the changes observed remains to be evaluated. However, photic stimulation definitely enhanced perception of optical pseudo-hallucinations.

2. Experimental Psychology

a. Effects of Morphine on Conditioned Inhibition in Rats ("pain anxiety"). The purpose of this experiment was to attempt to develop an analgesic testing method in rats, based on the same principle as that demonstrated in man -- the reduction of anticipatory anxiety associated with pain. The method used was as follows: Adult rats were fed 70 per cent of the amount of food required to maintain their body weight. Rats were then placed in a modified Skinner box and trained to press a bar which released small pellets of food. Motivation under these conditions was, of course, hunger. After the rats had been trained and had attained a constant rate of bar pressing, rats were conditioned by sounding an electric buzzer terminated by an electric shock. After conditioning occurred, the rate of bar pressing became far less during the period of the buzz, but after the electric shock the rat would proceed to press the bar and obtain food pellets at his normal rate. Once stable conditioning had been established, morphine was

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given every 7 to 10 hours in the following order: 3, 10, 6, 11, 4, 5, 14, 12 and 11 mg./kg. It was found that the administration of morphine markedly affected the degree of inhibition of bar pressing. As the dose of morphine was increased the rate of bar pressing during the sounding of the buzzer tended to approach the control rate. An almost linear dose-effect was obtained between 5 and 10 mg.kg. of morphine. The data obtained are consistent with the hypothesis previously developed in human studies; morphine relieves pain by reducing anticipatory anxiety caused by painful stimuli. Following further improvement in our apparatus, we intend to study the effects of other drugs, such as pentobarbital, amphetamine, aspirin, etc., and to study the effects of morphine on extinction.

b. Effects of Diethylamide of Lysergic Acid on Psychological Tests. Six subjects have been tested before and after the administration of LSD-25. Tests used have been the Rorschach, Wechsler Bellevue, Goldstein-Scheerer and the Minnesota Multiphasic Personality Inventory. Although the records have not been completely analyzed, the following trends are being observed: Performance on those sub-tests of the Wechsler-Bellevue scale which requires sustained concentration and attention is consistently lower after LSD-25. The Goldstein-Scheerer test shows no measurable impairment of abstract thinking ability. No systematic changes have been seen in the Rorschach

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tests, except for an increase in the total number of responses, and an increase in indicators of anxiety. In the MMPI tests, elevation of all clinical scales was observed, the greatest increases being in the "schizophrenia" and "paranoia" scales.

C. BIOPHYSICAL STUDIES

Considerable time was spent in installing apparatus for photic stimulation in the electroencephalographic room. At first, photic stimulation induced artifacts but this was eliminated by elevating the light. We are still working on the problem of increasing the intensity of light to compensate for the greater distance.

The apparatus for measuring the concentration of alcohol in the breath was received from the manufacturer after overhaul and was still found to be performing poorly. After correspondence with the manufacturer, the entire instrument was gone over, circuits traced and the valves checked. The chief difficulty appeared to be a bad exciter lamp.

A photographic copy stand was constructed with scrap material.

The usual services on instruments and apparatus for the entire unit were rendered.

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D. DISSEMINATION OF INFORMATION

1. Papers Published

Hill, H. E., and Belleville, R. E.: Effects of Chronic Barbiturate Intoxication on Motivation and Muscular Coordination. Arch. Neurol. & Psychiat., 70: 180-186 (Aug.) 1953.

Wikler, A., Fraser, H. F., and Isbell, H.: N-Allylnormorphine: Effects of Single Doses and Precipitation of Acute "Abstinence Syndromes" During Addiction to Morphine, Methadone or Heroin in Man (Post-addicts). J. Pharmacol. & Exper. Therap., 107: (1) 8-20 (Sept.) 1953.

Wikler, A., and Carter, R. L.: Effects of Single Doses of N-Allylnormorphine on Hindlimb Reflexes of Chronic Spinal Dogs During Cycles of Morphine Addiction. J. Pharmacol. & Exper. Therap., 107: (1) 92-101 (Sept.) 1953.

Wikler, A.: Recent Experimental Studies on Pain and Analgesia. Neurology, 3: (9) 656-660 (Sept.) 1953.

2. Papers or Lectures Presented

Medical Director Harris Isbell:

"N-Allylnormorphine and Other Antagonists to Narcotic Drugs." University of Illinois College of Medicine, Chicago, Ill., July 29, 1953.

Medical Director H. F. Fraser:

"Use of Measurements of Miotic Effects in Evaluating Analgesic Drugs in Man." Interim Meeting, Soc. Pharmacol. & Exper. Therap., New Haven, Conn., Sept. 7-9, 1953.

3. Meetings Attended

Medical Director H. F. Fraser attended the Interim Meeting, Society for Pharmacology and Experimental Therapeutics, New Haven, Conn., Sept. 6-8, 1953.

Medical Director Abraham Wikler attended meetings of International Congress of Electroencephalography and Clinical Neurophysiology, Cambridge, Mass., August 16-21, 1953, and the Annual Meeting of Kentucky Psychiatric Association, Louisville, Kentucky, September 21, 1953.

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C. Dissemination of Information [redacted]

3. Meetings Attended (continued)

Biochemist Anne J. Eisenman attended meeting of International Physiological Congress, Montreal, Canada, August 30-Sept. 4, 1953, and the Interim Meeting, Society for Pharmacology and Experimental Therapeutics, New Haven, Conn., Sept. 6-9, 1953.

4. Motion Picture Showings

a. "Clinical Manifestations of Drug Addiction"

University of Nebraska College of Medicine, Lincoln, Neb.

Dept. of Pharmacy, Harvard Medical School, Boston.

State Hospital, Yankton, S. D.

Central State Hospital School of Nursing, Norman, Okla.

Commissioner of Narcotics, Washington, D. C.

b. "Chronic Barbiturate Intoxication"

State Hospital School of Nursing, Yankton, S.D.

Central State Hospital School of Nursing, Norman, Okla.

Dept. of Pharmacology, Harvard Medical School, Boston, Mass.

c. "Treatment of Methadone Poisoning with N-Allylnormorphine"

University of Illinois, College of Medicine, Chicago, Ill.

d. "Lower Limb Reflex Changes During a Cycle of Addiction in Spinal Man."

University of Illinois College of Medicine, Chicago, Ill.

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E. PERSONNEL HONORS

Isbell, H.: Conducted Seminar, University of Illinois Medical School, Chicago, Ill., July, 1953.

Wikler, A.: Elected Councilor of Kentucky Psychiatric Association, September, 1953.

Harris Isbell, M.D.
Director of Research

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date 4 FEB 1977