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# QUARTERLY REPORT

January 1 - March 31, 1954

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

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QUARTERLY REPORT

A. GENERAL

No administrative difficulties worthy of note were encountered during this quarter. Handling of payroll and payment of vouchers by the National Institute of Mental Health is now functioning smoothly. Occasionally, minor errors have been committed because of the differences between Hospital Division and NIMH practices, but as time goes on these errors should be eliminated.

Clinical studies during the quarter were largely concerned with continuing search for codeine substitutes, the addiction liability of morphine-Nalline mixtures, studies on new morphine antagonists, intoxication with diethylamide of lysergic acid, and with the clinical endocrinology of addiction. It now appears certain that the addiction liability of L-2-N-dimethyl-3-hydroxy-morphinan and of 4-4-diphenyl-6-dimethylamino-hexanone-3 exceed that of codeine. These drugs cannot be regarded as safe codeine substitutes. It has been shown that a mixture containing 1 mg. of Nalorphine for each 10 mg. of morphine can be used for periods of 30 days, provided the dosage is held at 10 mg. every four hours. Whether pain relief by such mixtures is less than that obtained with morphine, and whether tolerance to the pain relieving effects develops as rapidly must be determined in other institutions. It is, however, certain that this mixture would not be abused by opiate addicts. Considerable work was accomplished with respect to the effects of morphine addiction on the activity of the pituitary and adrenal glands. Both these

projects are being carried out in collaboration with other laboratories (Worcester Foundation for Experimental Biology, Shrewsbury, Mass., and the National Cancer Institute, Bethesda, Maryland). The results are not yet available.

The neurophysiological section has now succeeded in demonstrating physical dependence on meperidine in dogs. This section has also been attempting to completely prevent morphine-induced depression in dogs by administration of very large amounts of Nalline at intervals of three hours. It is hoped that this experiment will constitute a test of the "adaptation" hypothesis of the development of physical dependence.

The psychological section has initiated a study on the personality characteristics of physician addicts. This project is of great theoretical importance because of the great differences with respect to availability of drugs, social, economic and educational status, and outlook on addiction in physicians, as compared with other addicts.

Two papers by members of the unit were published during the quarter. Seventeen lectures were presented before scientific audiences. One of these was a report for the entire calendar year 1953 to the Committee on Drug Addiction and Narcotics of the National Research Council. There were 36 motion picture showings.

B. CLINICAL STUDIES OF ADDICTION

1. Ward Studies

a. Addiction Liabilities of New Substances

(1) L and D 2, N-dimethyl-3-hydroxy-morphinan hydrochlorides (Rol-7362 and Rol-7363). Work previously reported with these compounds was confirmed during this quarter. Abstinence was completely suppressed in 2 patients who were strongly addicted, when 60 mg. of the l-isomer was administered every four hours. The d-isomer was completely inactive in suppressing abstinence at this dose level. It was, therefore, concluded that the levo-isomer has high addiction liability which exceeds that of codeine; whereas the d-isomer, a very inert compound, is devoid of addiction liability.

(2) 4-4-diphenyl-6-dimethylamino-hexanone-3 (10592). Work with this compound is now complete. In doses of 60 to 75 mg. every four hours, it has suppressed almost completely abstinence in 5 patients strongly addicted to morphine. It, therefore, appears to have addiction liability which far exceeds that of codeine. The combination of this compound with para-hydroxyephedrine which is being marketed in Germany under the name "Ticarda" must be regarded as having addiction liability.

(3) Benzylmorphine myristyl ester (5986-A). This compound was synthesized in France, is insoluble in water, and can be injected only in oil. For this reason, all the work carried out has been by the oral route. Doses ranging up to 600 mg. did not induce any definite morphine-like effects in nontolerant addicts.

With 600-mg. doses, transient skin eruptions consisting of blotchy erythema and wheals were observed in all patients. Sufficient data are not yet at hand to permit an evaluation of its addiction liability.

(4) Beta-d-methadol (4543). This compound is being investigated at the specific request of the Commissioner of Narcotics. Although it can readily be converted into beta-d-acetyl-methadol, a compound with known high addiction liability, it cannot itself be subjected to the controls of the Narcotic Act without proof of its addiction liability. In doses ranging between 30 to 100 mg. orally and subcutaneously, it has induced no immediate or delayed morphine-like effects in 10 nontolerant addicts. Work is not complete and as yet no definite opinion concerning its addiction liability can be rendered.

b. Addiction Liabilities of Morphine and Nalline Mixtures.

(1) 1 to 10 mixture. Six patients have been addicted in randomized order to 10 mg. morphine plus 1 mg. of Nalorphine every four hours for 30 days, and to a control experiment to 10 mg. of morphine every four hours for 30 days. This experiment was designed to determine whether or not this mixture could be used for the relief of chronic pain. The untoward side effects noted when "addicting" dose schedules of the mixture were used in previous experiments did not appear with this particular dosage schedule. Definite mild abstinence was seen after withdrawal of both the mixture and the morphine. Whether abstinence was milder following withdrawal

of the mixture is not yet known, since the data has not been completely analyzed.

c. Morphine Antagonists

(1) Levallorphan (L-60 or Rol-7700). Studies with this compound have been confirmed. It is extremely potent in precipitating abstinence from morphine in addicted patients, regardless of the route of administration (subcutaneous or oral). It also appears to be more potent and more toxic than Nalorphine.

(2) Dextro-Nallorphen (P-60). This compound is the optical isomer of Levallorphan and appears, as expected, to be quite inert. It is totally ineffective in precipitating abstinence in addicted persons in doses as high as 10 mg. subcutaneously.

(3) Levallorphan. (5759). This compound is the methyl-ether of Levallorphan and was synthesized for us by Dr. Lyndon F. Small of the National Institute of Arthritis and Metabolic Diseases in the hope that it would be orally effective and long lasting. The drug has proved to be a very effective antagonist both subcutaneously and orally. However, it appears to be more effective when administered subcutaneously and its length of action appears to be no longer than that of the parent compound, levallorphan.

(4) 3-hydroxy-n-propargyl-morphinan (Rol-7700). This is a new antagonist in the Morphinan series. It is of particular interest since, according to Dr. Nathan B. Eddy of the National Institute of Arthritis and Metabolic Diseases, it has "analgesic"

effects which are about equal to those of meperidine in mice. So far, only data concerning the side reactions in man are available. In doses of 4 to 8 mg. it induces giddiness, dizziness, pallor, nausea and sleepiness. These effects are quite marked with the 8-mg. dose. The compound appears to be much less active orally, since equivalent effects were not obtained with doses of 50 to 60 mg. orally. The antagonistic properties of the drug have not yet been tested.

d. Diethylamide of Lysergic Acid (LSD-25).

(1) Dose effect relationships. Three patients were given 0.25, 0.5, 0.75, 1.0, 1.5 and 2.0 mcg./kg. of LSD-25. Blood pressure, pupillary size, and knee jerks were measured every half-hour before and after administration of the drug over an 8-hour period. A special questionnaire was administered hourly and the degree of mental effect rated on the following basis:

Grade 1 - Anxiety without perceptual distortion

Grade 2 - Anxiety plus perceptual distortion, but without pseudo-hallucinations

Grade 3 - Anxiety, perceptual distortion and pseudo-hallucinations, but with insight retained.

Grade 4 - Same as Grade 3, but with true hallucinations plus loss of insight.

The data on pupillary size, knee jerks and blood pressure were plotted and the areas of the curve measured with a planimeter, thus reducing the total time-action course to a single area figure.

Analysis of the results indicated highly significant changes in blood pressure and pupillary size at doses of 0.5 mcg./kg. and better. Although the knee jerk data showed increases at all dosage levels, these changes were significant statistically at only three of the six dosage levels. A very good correlation between the logarithm of the dose and the degree of effect was obtained in the case of pupillary size and blood pressure. Similar curves were obtained when total number of positive answers were plotted against the log of dose or the estimated clinical grade of mental effect. A high correlation between pupillary, blood pressure and mental effects is evident in the data.

We have now studied the subjective changes induced by LSD-25 in more than 50 former morphine addicts. The symptoms observed appear to be identical with those observed in groups on noneddicts of far different composition with respect to race, age, social and economic status, and personality types. In other words, the effects of LSD-25 appear to be specific and are not related to any of the factors mentioned above. This is a matter of great interest, since the subjective effects induced by LSD-25 have been studied more intensively and more thoroughly in a greater diversity of populations than any other drug with which we are familiar, including morphine and alcohol.

(2) Tolerance to LSD-25. Tolerance experiments described in the annual report were confirmed in 2 additional patients. In addition, we have confirmed the development of tolerance in 15

other patients who were handled on an "out-patient" basis. Apparently a significant degree of tolerance can be obtained by administering 10, 20 and 30 mcg. of LSD-25 twice daily for as little as three days. Doses of this order induce only mild effects.

3. Chlorpromazine (SKF-2601). This compound is variously known as Largactil, Thorazine, and by other names. Chemically it is related to the phenothiazine group of antihistaminic drugs. It has been reported to be an adrenolytic, parasympatholytic, anti-emetic, and highly sedative drug which, in addition, markedly potentiates the effects of opiates, barbiturates and general anesthetics. It is under intensive investigation as a sedative agent for various psychiatric disorders and has been reported to greatly ameliorate symptoms of withdrawal from opiates and related drugs. Investigation of this compound has been undertaken at the request of the World Health Organization. Because of reports of the potentiation of narcotics, studies of the drug have been carried out in an extremely careful manner. The effects of single, or of repeated doses are similar to those described elsewhere. Doses of 50 mg. orally three times daily induce sensations of weakness, lethargy and drowsiness. In our patients, no marked effects in body temperature, blood pressure, pulse rate, etc., have been noted with doses of this size. No untoward effects have appeared when 30 mg. of morphine were combined with 50 mg. of chlorpromazine. Ten mg. of the drug three times daily has induced no untoward effects in individuals strongly dependent on morphine. Work with this compound is continuing.

2, Biochemical Studies

a. Clinical Endocrinology of Addiction

(1) Lack of effect of chorionic gonadotropin after withdrawal of morphine. In 2 of the patients who were given chorionic gonadotropin before and during a cycle of addiction to morphine, administration of 1000 units of chorionic gonadotropin daily for five days did not induce a significant rise in 17-ketosteroids. This was not due to decrease in activity of the preparation used, since it induced the expected rise in individuals who had not been readdicted. An additional patient was, therefore, put through a cycle of readdiction and tested with chorionic gonadotropin before, during, and after the addiction cycle. The same diminished response to chorionic gonadotropin was seen following withdrawal of morphine. The reason for this change is obscure.

(2) Effects of morphine addiction on excretion of corticoids. In collaboration with Dr. Ralph I. Dorfman of the Worcester Foundation for Experimental Biology, fractionation of the steroids excreted in the urine during cycles of morphine addiction is being carried out. The results are not yet available. Simultaneously, we are attempting to set up a method for the determination of steroids derived only from the adrenal gland. Formidable technical difficulties have been encountered with this method, which are being slowly resolved. The best data obtained to date indicate marked increase of corticoid excretion during withdrawal.

[illegible] pituitary gonadotropin excre[illegible] during cycles of addiction. In collaboration with Dr. Roy Hertz of the National Cancer Institute, determinations of pituitary gonadotropin excretion during cycles of addiction are being carried out, using 2 male subjects. The NIMH Addiction Research Center collects urines, precipitates the gonadotropin, dries the extracts and forwards them to the National Cancer Institute where the assays are made. As yet the results are not available.

b. Studies in Metabolism of Ethyl Alcohol. A considerable number of determinations of the rate at which ethyl alcohol disappears from the blood were carried out early in the quarter. Two analytical methods were used. One of these ~~methods~~ involved the determination of concentrations of alcohol in the breath; the other, determination of blood alcohol directly, using a dichromate oxidation and titration method. Technical difficulties were experienced with both methods. Unreliable results were obtained with the breathmeter, unless it was calibrated daily. Unexplained discrepancies occurred in the dichromate titration method, which were probably related to difficulties in getting quantitative distillations of the alcohol from blood. Results on the metabolic rate of alcohol obtained with the breathmeter fall within the range reported in the literature. Variations in the same individual at different times do not exceed 30 per cent, an acceptable range for biological work. Feeding of 200 grams of lean beefsteak induced no great change in the rate of alcohol metabolism.

c. Serum Electrophoretic Patterns in Addiction. Work in this field is continuing. It now appears that the ratio of gamma globulin to beta globulin tends to increase during the early phase of tolerance to morphine and to decrease following withdrawal of morphine. This phenomena may possibly be linked to the effect of addiction on the endocrine system.

C. EXPERIMENTAL NEUROPSYCHIATRY

1. Neurophysiology

a. Rebound Lowering of Threshold which Underlies Convulsions Produced by Electrical Stimulation of Thalamic Intralaminar Nuclei in Cats During Recovery from Pentobarbital Anesthesia. In cats in which bipolar electrodes were implanted in the thalamic intralaminar nuclei under deep pentobarbital anesthesia, progressive decrease in the amount of electrical stimulation required to induce convulsions was observed 20 to 30 hours after induction of the anesthesia. This lowering of threshold persisted for about 42 hours and had disappeared after 72 hours. This work is to be extended to other areas of the brain.

b. Morphine-Nalorphine Mixtures. An attempt is being made to addict chronic spinal dogs to mixtures of morphine and Nalline in such a way that depression of the ipsilateral flexor and crossed extensor reflex is never observed (except for the mild depression produced by the Nalline alone). Administration of 5 mg./kg. of Nalline every three hours and 2.5 mg. morphine every six hours appears to be a suitable schedule. After 21 days addiction, no abstinence was evident above the level of transection.

The results so far support the "adaptation" theory of physical dependence and refute the "dual action" theory.

c. Diphasic Action with Doses of Meperidine in Dogs. Single doses of 75 mg./kg. produce typical morphine-like effects in the hindlimb reflex of chronic spinal dogs. After 6 to 11 hours reversal occurs and, in addition, "strychnine-like" effects appear. These resemble in every respect the hyper-irritability seen during chronic administration of meperidine in smaller doses.

d. Meperidine Addiction in Dogs. We are now able to consistently precipitate abstinence from meperidine in dogs that were receiving meperidine chronically. This has been made possible by administering meperidine every three hours and raising the doses to the level just short of that which induces grand mal convulsions. These experiments indicate that the "dependence producing" and "toxic" doses of meperidine are very close. The same appears to be true in man.

e. Meperidine-Nalline Antagonism. Using relatively small doses of meperidine, no antagonistic action of Nalline upon meperidine effect of hindlimb reflexes could be demonstrated (see annual report, 1953). When, however, 75 mg./kg. of meperidine were given, 15 mg./kg. of Nalline antagonized the depressant effects of meperidine on the ipsilateral flexor reflex and the crossed extensor reflex.

f. Short Tests for Physical Dependence Liability In Dogs. In 2 dogs, dosage of morphine was rapidly increased from 5 to 12 mg./kg. in a 6-day period. On the 8th day of addiction, 15 mg/kg. of Nalline precipitated typical abstinence symptoms. In 2 additional dogs, dosage of methadone was increased to 17 mg./kg. in a 6-day period. On the 8th day, 15 mg./kg. of Nalline precipitated typical abstinence. These results indicate that it is very likely that a short, simple test, which could be used by pharmacological houses for a determination of physical dependence liability of new analgesics, can be developed.

g. Studies on the Relationships Between Conditioning and Extinction of Alpha Blockade and Visual-Hand Reaction Time in Man. Merrell has reported that Pavlovian "extinction" is due to cortical inhibition. The theory advanced by this investigator is based on the observation that, as alpha blockade in the EEG was extinguished by non-reinforcement, visual-hand reaction times became prolonged. Since in Merrell's technic, two variables -- non-reinforcement of EEG blockade by light and non-reinforcement of voluntary hand responses to the same stimulus -- were altered simultaneously, an experiment was designed to keep the voluntary hand reinforced, but to extinguish the alpha blockade at the same time. This involved alteration of Merrell's technic by recording, along with the EEG, hand responses to dim light (not blocking out) and hand responses to bright, flickering light (which blocked alpha), preceding the light stimuli in both cases by a low tone. This test was made on 15 subjects.

Results indicate that alpha blockade is an "orienting" response and as such cannot be conditioned. As the stimulus which induces the alpha blockade is continued, blocking of alpha gradually disappears. This is true, regardless of the nature of the stimulus -- light or sound induces the same effects. If the stimulus is discontinued, alpha blocking reappears when the stimulus is reintroduced, only to again slowly disappear.

2. Experimental Psychology

a. Hospital Project for Evaluation of Psychotherapy. The experimental psychologist was "loaned" to the clinical division of the hospital to assist in formulating plans for evaluation of the effects of psychotherapy on the relapse rate in addicts. About two and one-half months of the quarter were spent in this task. The preliminary pilot study which is being carried out by clinical division personnel and which is designed to determine the degree of amenable in all admissions is currently underway.

b. Minnesota Multiphasic Personality Inventories of Physician Addicts. The testing of a sample of physician addicts with the MMPI has been started for the purpose of determining some of the relationships between addiction and socio-economic status, special group attitudes, and availability of drugs. The physician addict appears to present a unique opportunity to study such relationships. For physicians in general, the group attitude toward addiction and antisocial behavior is negative, i.e., physicians are opposed to such behavior. On the other hand, the availability of narcotics is

positive for both addict and nonaddict physicians. Should the post-addict physicians have profiles which are similar to those of the average addict in the hospital population, it might be inferred that personality characteristics are relatively more important in the etiology of addiction than are the availability of drugs or special group attitudes. To date, 13 profiles have been obtained on physician addicts. As patients become available a group sufficient to permit significant comparison with the hospital population will be built up.

c. Psychological Data During Chronic Alcoholic Intoxication. The data obtained during the chronic alcoholic intoxication study has been fully analyzed. The most interesting finding is concerned with marked elevation of all clinical scales in the MMPI during chronic intoxication.

d. Psychological Changes During Intoxication with LSD-25. To date the most significant findings in this study have been changes in many of the MMPI scales. Twenty-five patients are currently being tested.

3. Biophysics

a. Rat Conditioning Apparatus. Numerous changes are being made in the "Skinner box" which is used for study in conditioning experiments with rats. The pellet feeder is being changed to a rotating disc type; the pressure required to throw the switch when the bar is pressed is being lowered by substituting a mercury switch for the mechanical contact switch; and better soundproofing is being added to the box.

b. Improvements have been made in the neurophysiological stimulator. It was found that the output impedance of the previous stimulators was so high that the output dropped to almost zero when the output leads were connected to the animal. Another output stage was added to the stimulator to decrease the impedance. This improved the voltage delivered to the animal, but some voltage drop still resulted when the leads were connected to the animal. This can be obviated by monitoring the stimulator with an oscilloscope.

c. Considerable equipment was constructed for use in the studies on the relationship of alpha blockade to Pavlovian "extinction."

DISSEMINATION OF INFORMATION

1. Papers or Lectures Presented

Medical Director Harris Isbell:

"Clinical Characteristics of Drug Addiction." Bluegrass Dental Association, Lexington, Ky., January 27, 1954.

"Clinical Characteristics of Important Drug Addictions. Medical and Nursing Staff, St. Joseph Hospital, Lexington, Ky. February 2, 1954.

"What to do with a Drug Addict" and "Clinical Characteristics of Important Drug Addictions. University of Cincinnati College of Medicine, Cincinnati, Ohio, March 2, 1954.

"Chronic Alcoholic Intoxication." Dept. of Pharmacol., University of Cincinnati College of Medicine, Cincinnati, Ohio, March 3, 1954.

"Clinical Manifestations of Drug Addiction." Junior Students, Cincinnati College of Medicine, Cincinnati, Ohio, March 10, 1954.

"Withdrawal Signs in Demerol Addiction." Graduate Nurse In-Service Program, PHS Hospital, Lexington, Ky. March 22, 1954.

Medical Director H. F. Fraser:

"Chronic Barbiturate Intoxication." Department of Pharmacology, Vanderbilt University, Nashville, Tenn., January 20, 1954.

Medical Director Abraham Wikler:

"Neurophysiological and Psychological Aspects of Drug Addiction." University of Cincinnati College of Med., Cincinnati, Ohio, March 2, 1954.

A series of nine lectures to Junior Students, University of Cincinnati College of Medicine, during February and March, 1954, as follows:

"An Operational View of Causal Explanations of Clinical Phenomena in Psychiatric Research."

"Pain and Analgesia - Definitions and Clinical Measurement of Pain."

"Pain and Analgesia - Neurophysiological Functions."

"Pain and Analgesia - Psychological Functions."

"Changes in Consciousness - 'Progressive Unresponsiveness' -- Classical Sensory Pathways, Diffuse Thalamic Projection System, and Reticular Activating System."

"Changes in Consciousness - 'Alteration of Selective Perception' - Anosognosia."

"Changes in Consciousness - 'Alteration of Selective Recollection' and 'Learning of Interpretations'."

"Experimental Neurosis."

"Experimental Psychosis."

2. Papers Published

Fraser, H.F., Isbell, H., VanHorn, G.D., and Nash, T.L. Use of Miotic Effects in Evaluating Analgesic Drugs in Man. (Abstract). J. Pharmacol. & Exper. Therap., 110: (1) 19 (Jan.) 1954.

Wikler, A., and Rapport, M.: Lower Limb Reflexes of a 'Chronic Spinal' Man in Cycles of Morphine and Methadone Addiction. A.M.A. Arch. Neurol. & Psychiat. 71: 160-170 (Feb.) 1954.

3. Meetings Attended

Medical Director Harris Isbell attended meeting of Committee on Drug Addiction and Narcotics, National Research Council, Rahway, New Jersey and New York City, Jan. 22-23, 1954.

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4. Personnel Honors

Medical Director Harris Isbell:

a. Invited to participate in Symposium on Alcohol, prior to meeting of International Health Congress, Toronto, Canada, 9 August 1954.

b. Invited to participate in Symposium on Alcohol, Joint Committee on Alcohol and Alcoholism, World Health Organization, United Nations, Geneva, Switzerlan September 1954.

Medical Director Abraham Wikler:

a. Promoted from Assistant Attending Neurologist, Cincinnati General Hospital, to Attending Neurologist, March 1954.

5. Motion Picture Showings

a. "Clinical Manifestations of Drug Addiction."

Vanderbilt University, Dept. of Pharmacol., Nashville, Tenn.

City of Detroit, Narcotics Clinic, Detroit, Mich.

Drake University, Des Moines, Ia.

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

Bluegrass Dental Association, Lexington, Kentucky

Vanderbilt University School of Med., Nashville, Tenn.

Dept. of Pharmacol. & Chemistry, Southern College of Pharmacology, Atlanta, Ga.

Medical College of the State of South Carolina, Dept. of Pharmacology, Charleston, S. C.

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

The Institute of Pennsylvania Hospital, Philadelphia, Pa.

U. S. Naval Station, Tongue Point, Astoria, Oregon.

DHEW, Food & Drug Administration, Minneapolis, Minn.

Mt. Sinai Hospital, New York City, N. Y.

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

University of Nebraska College of Med., Lincoln, Neb.

Stritch School of Medicine, Loyola University, Chicago

Dept. of Psychiatry, University of Cincinnati School Med., Cincinnati, Ohio

University of Cincinnati School of Med., Cincinnati, Ohio

Medical Staff and Nurses, St. Joseph Hospital, Lexington, Kentucky

b. [illegible] Barbiturate Intoxication

Narcotics Clinic, City of Detroit, Detroit, Mich.

University of Wyoming, School of Pharmacology, Laramie, Wyo.

DHEW Food & Drug Adm., Minneapolis, Minn.

University of Utah, College of Pharmacy, Salt Lake City, Utah

St. John's University College of Pharmacy, Brooklyn, N.Y.

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

Dept. of Psychiatry, Mt. Sinai Hospital, New York City, N.Y.

College of Pharmacy, Idaho State College, Pocatello, Idaho

Loyola University, Dept. of Pharmacology, Chicago, Ill

St. Anthony Hospital, Louisville, Ky.

Vanderbilt University School of Medicine, Nashville, Tenn.

c. "Precipitation of Abstinence Syndromes by use of N-allylnormorphine."

Medical Division, Merck & Company, Rahway, N.J.

Medical Division, Sharp & Dohme, Inc., West Point, Pa.

d. "Experimental Chronic Alcoholic Intoxication."

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

University of Cincinnati College of Med., Cincinnati, Ohio.

e. "Lower Limb Reflex Changes During a Cycle of Addiction In 'Spinal' Man.

Medical Division, Sharp & Dohme, Inc., West Point, Pa.

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Visitors to Research

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| Dr. Y. T. Oester<br>Dr. Donal O'Sullivan | Stritch School of Medicine; Loyola University, Chicago, Ill. January 1954. |
| Dr. Allen D. Bass, | Vanderbilt University School of Medicine, Nashville, Tenn. January 1954 |
| Dr. C. K. Himmelsbach, | Washington, D. C. |
| Dr. Victor H. Vogel, | Paris, France |
| Dr. J. B. Kahn, Jr.<br>Dr. George H. Acheson | University of Cincinnati College of Medicine. March 1954 |
| Dr. Conan Kornetsky | Long Island Biological Assn, Long Island, N.Y. March 1954 |

Harris Isbell, M.D.
Director of Research

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