THE BLACK VAULT

[redacted]

21 January 1952

(1)

DROMORAN PROJECT

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NR 113-149
Ser. 31540

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II. WORK ACCOMPLISHED TO DATE

The recruitment and training of personnel began in July. The training of personnel was completed in late September and an additional research ward was opened in October 1951. The work on the human pharmacology and toxicity of 3-methoxy-n-methylmorphinan, as well as the work on the detection of euphoria, was completed during the summer. Work on the relief of abstinence and substitution of this compound for morphine was completed in December 1951.

The results to date can be summarized as follows: Doses of less than 30 mg. dl-methoxy-n-methylmorphinan produced no untoward toxic effects in former morphine addicts. Doses of 20 to 30 mg., either hypodermically or orally, induced euphoria similar to and equal in intensity to that seen after the administration of 30 mg. morphine. Other morphine-like effects, such as nausea, vomiting, miosis and respiratory depression, were observed with the larger doses. The compound was found to induce its effects more quickly when administered orally as compared with hypodermic administration. It relieved abstinence from morphine and could be substituted for morphine in addicted persons. Substitution was complete as contrasted with codeine, which will not support physical dependence on morphine completely. Following withdrawal of 3-methoxy-n-methylmorphinan after substitution for morphine, a typical morphine-like abstinence syndrome appeared. For further details of these studies see the reports to the Drug Addiction Committee, National Research Council, which are attached.

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ADDICTION LIABILITY OF SYNTHETIC ANALGESICS WHICH MIGHT SERVE AS SUBSTITUTES FOR CODEINE.

I. BACKGROUND INFORMATION

In late June of 1951 $30,000 was made available by the Department of Defense for determining the addiction liability of dl-3-methoxy-n-methylmorphinan (methoxy-dromoran) in the hope that this drug might represent an adequate synthetic substitute for codeine. This grant was made following the submission of a project description entitled "The Determination of the Addiction Liability of Synthetic Analgesics of the Codeine Type." The project was supported for the following reasons:

Due to the currently disturbed international situation, it was possible that the United States might be cut off from all its usual sources of opium. Synthetic analgesics are available which are entirely adequate for the replacement of morphine. However, none of the available synthetic analgesics are as safe for general use as is codeine. More than 60 per cent of the Armed Forces' requirements for narcotics is for codeine rather than for morphine. Finding a synthetic substitute for codeine is, therefore, of considerable importance and it was hoped that methylation of 3-hydroxy-n-methylmorphinan, a synthetic drug of morphine-like structure, would produce such a compound. The facilities of the Addiction Research Center were not sufficient to carry out the work unless additional funds could be obtained.

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It is obvious that [redacted] has addiction liability equivalent to that of morphine, and for this reason, cannot be regarded as being as safe as codeine for general use. We, therefore, have not carried out Part Five of our original experimental procedure which deals with direct addiction of former morphine addicts to the new drug. It was felt that the time would be better spent in screening a number of other compounds in the hope of finding a drug which gave promise of being more codeine-like than is dl-3-methoxy-n-methylmorphinan. Work along these lines is now going on with the dextrorotatory and levorotatory isomers of methoxy-dromoran and with some valerates in the methadone series. The isomers of 3-methoxy-n-methylmorphinan are being studied because the dextrorotatory isomer is said to be an excellent antitussive agent in dogs (as judged by a newly developed technic) and probably will have very low addiction liability. Later, it is hoped that additional derivatives of dromoran with substituents other than methyl in position Number 3 will be studied. The reason for investigating these additional drugs in the dromoran series is that the activity of dromoran was altered in the proper direction by methylation, but the addiction liability of the derivative was not reduced sufficiently for it to be regarded as being innocuous as codeine. Substitution of ethyl, propyl or other groups in position 3 might yield a drug with sufficient reduction in addiction liability.

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Since the remainder of the time available under the current grant from the Department of Defense must be spent in screening, it is hoped that an additional grant can be obtained for continuation of the work during the fiscal year 1953. If a promising drug is revealed by the screening test, intensive work with it will begin as soon as possible during fiscal year 1953. If so such drug is found, screening should continue.

III. EXPERIMENTAL PROCEDURES

Drugs being screened will be subjected to the following types of investigation:

A. Human Pharmacology and Toxicity. This involves the administration of progressively increasing doses of the drug under study to human volunteers, chiefly former morphine addicts. Observations on respiratory minute volume, pupillary size, blood pressure and pulse rate, etc., are made following the administration of the drugs.

B. Administration to Human Volunteers of Single Doses of the Drugs Being Screened for the Detection of Euphoria. This experiment is conducted in exactly the same way as the studies on human pharmacology, except that detailed observations on the physiological effects of the drug are not made, because taking of observations tends to negate the pleasurable effects of the drugs. Two methods are used for gauging the "euphoria" induced by the drugs. These are, 1) unobtrusive clinical observations for the appearance of behavior resembling that seen after the administration of morphine, and 2) the administration of projective psychological tests.

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C. The Administration of Single Doses of the Drug Under Study to Patients Showing Signs of Moderate to Marked Abstinence from Opiates. Any drug which, on the basis of the screening test, appears to be promising as a potential substitute for codeine will be subjected to additional studies: 1) substitution of the drug for morphine in strongly addicted persons, followed by abrupt withdrawal of the new drug, 2) direct addiction of former morphine addict volunteers, under two conditions, (a) very high-dose levels, such as would be expected in "natural" addiction under conditions of abuse, (b) conditions of low-dosage, such as would be expected during long continued clinical administration of the drug.

D. Evaluation of Data. The drug we are seeking should have the following characteristics: 1) it should be a weak analgesic, as judged by animal experimentation; 2) The ratio of toxicity to therapeutic effect should be favorable in both animals and man; 3) it should be a good antitussive agent; 4) should relieve abstinence from morphine only partially; 5) should not substitute for morphine completely; 6) should induce only a mild grade of physical dependence in direct addiction tests under conditions of high dosage.

Information submitted to the Drug Addiction Committee by the pharmaceutical companies and universities will be sufficient to evaluate the actions of the drug in animals.

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Studies on addiction liability will yield information on the toxicology, pharmacology and euphoric potency of the drug in man and on its ability to produce and support physical dependence. From these data a satisfactory evaluation of the addiction liability of the compound can be made.

E. Location of the Project. The experiments described above will be carried out in the Addiction Research Center, U. S. Public Health Service Hospital, Lexington, Kentucky. This hospital is devoted entirely to the treatment and study of drug addiction and is the only place in the world where a study such as those described above can be satisfactorily carried out. The institution provided the two necessary facilities for this type of work: 1) a large pool of patient volunteers, 2) strict environmental control which prevents the introduction of drugs other than those under study into the situation.

F. Experimental Personnel. The work will be carried out under the direction of Harris Isbell, M.D., Director of the Addiction Research Center. This investigator has had almost eight years experience in narcotic drug addiction and has many publications in this field. He will be assisted by two other experienced Medical Officers, Dr. H. F. Fraser and Dr. Abraham Wikler, both of whom have had extensive experience in research in addiction and have many publications in this field.

In addition to the medical personnel, the part-time services of a Biochemist and a Psychologist will be made available. Sub-professional personnel include 5 Psychiatric Aides, a Medical Technician, Biological Aide, Security Aide and Clerk-Stenographer.

A special ward for conducting these studies has already been set up and is in operation.

G. Estimate of Cost.

1. Personnel

5 Psychiatric Aides GS-5	[redacted]
1 Clerk-Stenographer GS-4	[redacted]
1 Security Aide CPC-5	[redacted]
1 Medical Technician GS-4	[redacted]
1 Biological Aide GS-5	[redacted]

2. Reserve for night differential and overtime pay, within-grade raises, etc [redacted]

3. Miscellaneous expenses ---------- [redacted]

It should be noted that personnel cost for the fiscal year 1953 will be higher due to the recent salary increase granted government employees. Item for miscellaneous expenses includes money for the purchase of drugs, chemicals, glassware, electroencephalographic and photographic paper, etc.

Harris Isbell, M.D.
Director of Research

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Attachments 2
4 January 1952

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