THE BLACK VAULT

[redacted] PROJECT DESCRIPTION

#(4)

The Addiction Liability of Analgesics Which Might Serve as Substitutes for Codeine

Request for Renewal on NR 113-149
Ser. 31540

I. BACKGROUND INFORMATION

Since July 1951, a project designed to determine the addiction liability of synthetic analgesics which might serve as substitutes for codeine has been carried on within the National Institute of Mental Health, Addiction Research Center, at the Public Health Service Hospital, Lexington, Kentucky. During the period from July 1951 to July 1952 the project was financed by a grant of $30,000. which was transferred to the Public Health Service by the Office of Naval Research. From July 1, 1952 until January 1953, the project was financed by an additional grant of $16,142.00 also from the Office of Naval Research. From January 1953 until June 30, 1953, the project has been financed by the National Institute of Mental Health. At that time the National Institute of Mental Health will no longer be able to support the project.

The reasons for carrying on research for synthetic substitutes for codeine (which was recommended by the Drug Addiction Committee, National Research Council) are as follows:

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Due to the disturbed international situation, it is possible that the United States might be cut off from all its usual sources of opium. The single source of codeine is from opium or by synthesis from morphine derived from opium. At the time the projects were begun, there was no synthetic compound available which was as safe for general use as was codeine and, although synthetic analgesics were available which would be entirely adequate for the replacement of morphine, no synthetic was available which was as safe as codeine. Moreover, more than 60 per cent of the Armed Forces' requirements for narcotics were for codeine rather than for morphine. The importance of the project is therefore obvious, but unfortunately the facilities of the Addiction Research Center were not sufficient to carry out the work unless additional funds could be obtained and, of course, the work cannot be continued after July 1, 1953 unless additional funds are made available.

II. WORK ACCOMPLISHED TO DATE

Part of the work accomplished to date was embodied in the semi-annual progress report sent to Dr. F. H. Guimby, Head of the Physiology Branch, Office of Naval Research, in January 1953. It may be briefly summarized as follows:

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1. The racemic 3-methyl ether of N-methylmorphinan possessed too high addiction liability for it to be regarded as a safe substitute for codeine.

2. All of the addiction liability of racemic 3-methyl ether of N-methylmorphinan was found to be due to the levorotatory isomer.

3. The dextrorotatory 3-methyl ether of N-methylmorphinan is devoid of addiction liability.

Since this compound had been reported to have powerful antitussive effects in animals, extensive clinical testing in humans is being carried out elsewhere. Preliminary reports of results were made at the meeting of the Drug Addiction Committee, National Research Council, in January 1953. Unfortunately, the reports of the clinical efficacy of the drug were conflicting and the matter is not as yet settled.

4. 3-ethylmethylamino-1-1-2'dithienyl-but-1-ene. This drug was found to possess too high addiction liability to be regarded as a safe synthetic substitute for codeine. Moreover, it is rather ineffective when given orally and produces many undesirable side effects. Further investigation of this compound is not warranted.

5. dl, d, and l-2-2-diphenylamino-ethyl valerates. Work with these compounds has almost been completed. In doses

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of 75 mg., all produce weak morphine-like effects in former morphine addicts. They are also relatively ineffective in suppressing abstinence from morphine. The low potency and low addiction liabilities of these compounds suggest that preliminary clinical trials of antitussive effect and side reactions are warranted.

6. dl-2-2-diphenyl-4-dimethylamino-butyrate.

This compound has properties similar to those of the valerates and, therefore, deserves a preliminary clinical trial.

III. NEED FOR CONTINUATION OF THE PROJECT

Although the work to date has uncovered five drugs which may have possibilities as synthetic substitutes for codeine, we believe the project should be continued. The most promising of the drugs studied is the d-3-methyl ether of N-methyl-morphinan. This drug is completely devoid of addiction liability and has low toxicity. Unfortunately the reports concerning its clinical efficacy are conflicting and, at the moment, it is not certain that it will serve as an adequate substitute for codeine. The other four drugs have not been tested clinically. It is believed that they are more toxic than codeine and that untoward side reactions may be produced. for this reason, we cannot be certain that an adequate synthetic substitute for codeine is yet on hand.

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IV. WORK PROPOSED

We propose to continue testing additional drugs for a period of one year. The drugs to be tested include: 1) Normorphinan; 2) l and d 3-hydroxy-2-n-dimethylmorphinan; 3) l and d 3-propyl ethers of 3-hydroxymorphinan; 4) other agents as may be suggested after consultation with the Drug Addiction Committee of the National Research Council.

V. METHODS TO BE USED

These methods are the same as those described in previous project descriptions and in the semi-annual report to the Office of Naval Research. They include:

1. Determination of Human Pharmacology and Toxicity. This involves 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, pulse rate, etc., are made following administration of the drug.

2. Administration of Single Doses for the Detection of Euphoria. These experiments are conducted in exactly the same way as those on human pharmacology, except detailed observations on the physiological effects of the drug are not made, because the taking of physiological observations tends to negate the pleasurable effects of the drugs. New methods are used in gauging the "euphoria" produced by the drug.

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These are: 1) unobtrusive clinical observation for the appearance of overt behavior resembling that seen after administration of morphine, and 2) administration of projective and other psychological tests.

In both of the above types of testing, drugs are given in a randomized balance order and by code. The order of administration is unknown to both the subjects and the observers. Both positive and negative control drugs (morphine, codeine, and placebo) are used.

3. Administration of Single Doses of the Drug to Patients Showing Signs of Abstinence from Morphine. This type of experiment is carried out by obtaining patients who have been taking large amounts of opiates daily. After stabilization on the least amount of morphine which would just prevent the appearance of signs of abstinence, morphine is abruptly withdrawn for a period of 30 hours. At this time, a single large dose of the drug under study is administered and observations for intensity of abstinence are continued. Controls include the administration of morphine and of codeine to the same patients during other withdrawals. In this work, we are looking for drugs which have little or no effects on abstinence from morphine.

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4. Suppression of Abstinence from Morphine. This technic represents the more sensitive refinement of the one designed above. Patients with strong dependence on morphine are selected. After a suitable stabilization period, the morphine is abruptly discontinued and the administration of the test drug is begun before signs of abstinence appear. If abstinence is suppressed completely or partially, administration of the new drug is continued for a period of 10 to 14 days, after which it is abruptly withdrawn and observations for signs of abstinence are made.

5. Direct Addiction. This technic involves the administration of sufficiently large amounts of the drug under test to former morphine addict volunteers who have been abstinent for a period of at least three months before the experiment is begun. Suitable observations for the detection of tolerance are carried out during the period of administration. After 30 days or more of chronic intoxication, the test drugs are abruptly withdrawn.

VI. EVALUATION OF DATA

The drug we are seeking should have the following characteristics: 1) it should probably be a weak analgesic, as judged by animal experimentation; 2) the ratio of toxicity to therapeutic effects should be favorable in animals and in man; 3) it should have antitussive effects in animal pharmacological experiments; 4) it should be a good antitussive agent

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in many 5) it should relieve or suppress abstinence from morphine only partially, and preferably not at all; 6) it should induce only a mild grade of physical dependence under conditions of high dosage.

Information submitted by pharmaceutical firms and universities concerning drugs which should be tested will be sufficient to evaluate the actions of the drug in animals. Studies on its addiction liability will yield information on the pharmacology, toxicology and euphoric potency of the drug and on its ability to produce and support physical dependence on morphine. From these data a satisfactory evaluation of the addiction liability of the compound can be made. The determination of antitussive effect must be done elsewhere.

VII. LOCATION OF THE PROJECT

The experiments described above will be carried out in the National Institute of Mental Health, Addiction Research Center, Public Health Service Hospital, Lexington, Kentucky. This hospital is devoted entirely to the treatment and study of drug addiction and, at the current time, is the only place in the world where these studies can be satisfactorily carried out. The institution provides the two necessary facilities for this type of work: 1) a pool of patients who will volunteer for experiments of the type described above; 2) strict environmental control, which prevents the introduction of

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of drugs other than those under study into the experimental situation.

VIII. EXPERIMENTAL PERSONNEL

Work will be carried out under the direction of Harris Isbell, M.D., Director of the Addiction Research Center. This investigator has had nine years of experience in research in narcotic drug addiction and has published many papers in this field. He will be assisted by two other experienced physicians, 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 professional psychologist will be made available. A special ward for conducting these studies has already been set up and is in operation at the time this project description is being written (April 30, 1953).

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IX. ESTIMATED COST

1. Personnel:

5 Psychiatric Aides GS-5 [redacted]
1 Physical Science Aide GS-4
1 Security Aide GS-5
1 Psychologist GS-5
1 Biological Aide GS-4

2. Reserve for Night Differential, Overtime pay, Within-Grade raises, etc [redacted]

3. Miscellaneous Expenses

Total---------- [redacted]

Item 3, "Miscellaneous Expenses" includes money for the purchase of drugs, chemicals, glassware, electroencephalographic and photographic paper, needles, syringes, etc.

Harris Isbell, M.D.
Director of Research

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