THE BLACK VAULT

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THE ADDICTION LIABILITY OF SYNTHETIC SUBSTITUTES FOR CODEINE

(Project Description)

Request to the Office of Naval Research for Renewal of

Contract NR 101-149
NAonr-11-57
(ONR:441:MJG:set)

1. Background Information.

Since July 1951 a project designed to develop a synthetic drug which would be as safe as codeine with respect to toxicity, antitussive activity, and addiction liability has been carried on within the National Institute of Mental Health Addiction Research Center, U. S. Public Health Service Hospital, Lexington, Kentucky. This project has been financed in large part by funds from the Office of Naval Research, and this description constitutes request for renewal of the project for the period 1 July 1958 to 30 June 1959.

A synthetic substitute for codeine is badly needed since opium, or morphine derived from opium, constitute the only sources of codeine. Unless a synthetic substitute for codeine is found the United States must continue to stockpile opium in order to provide adequate supplies of codeine for both the civilian and military population in the event of war. Facilities of the NIMH Addiction Research Center are not sufficient to carry out this work, in addition to routine drug testing required

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for the evaluation of all new analgesics, unless additional funds are supplied through the Department of Defense.

2. Work Accomplished to Date.

Previous work has been summarized in the annual progress report sent to Captain F. H. Quimby and Captain T. K. Roebush, Head of the Physiology Branch, Office of Naval Research.

Two drugs have been developed which are promising substitutes for codeine for relief of cough. These drugs are: 1) dextro-methorphan, and 2) narcotine. Neither drug possesses any significant addiction liability and both have relatively low toxicity. Continuing reports to the Committee on Drug Addiction and Narcotics, National Research Council, and clinical reports appearing in the literature indicate that these drugs are effective cough suppressants. The antitussive phase of the problem has, therefore, in a sense been solved.

Although the antitussive problem is no longer as pressing there are still no compounds available which are known to be as effective and as safe as codeine for the relief of mild grades of pain. Over 46 new drugs or mixtures of drugs have been screened for this purpose. The outstanding substances so far developed are dl- and d-alpha-4-dimethylamino-1,2-diphenyl-3-methyl-4-propionoxybutane, or dl- and d-propoxyphene. The addictiveness of these compounds is so low that the Committee on Drug Addiction and Narcotics has ruled that they need not be

subjected to the controls imposed by the Harrison Act. Preliminary clinical data indicated that they were nearly as effective as codeine for the relief of pain. Complete data on toxicity and clinical use are still not available, and more recent reports indicate that their analgesic potentialities may not be as great as was originally claimed.

During the past 18 months important leads have been developed concerning the demethylated derivatives of morphine and morphinan. Normorphine has been shown to be an active agent for inducing sedation in man. It suppresses abstinence from morphine completely, but, unlike morphine, abstinence following withdrawal after direct addiction is quite mild. These studies are now being extended to include norcodeine, l-3-hydroxy-morphinan (l-nordromoran) and l-3-methoxy-morphinan. Evidence of some activity in d-isomers in the methadone series has also been obtained. We hope to develop and complete studies on these compounds within the next 18 months.

3. Need for Continuation of the Project.

The chief need for continuation of the project is related to conflicting reports concerning the analgesic potency of dl- and d-propoxyphene. Original clinical trials for relief of chronic pain were promising. More recent trials against post-partum pain and chronic pain due to cancer have not been

favorable. There is also insufficient information concerning the toxicity of propoxyphene. It is, therefore, uncertain that a satisfactory substitute for codeine for relief of pain has been found. For this reason, it is essential to continue the search for other synthetic substitutes. In addition, the larger the number of compounds tested the greater would be the chance of finding a completely adequate substitute for codeine.

4. Work Proposed.

During the period from 1 July 1958 to 30 June 1959 we propose to test the clinical pharmacology and addictive properties of narcodeine, l-3-methoxy-morphinan, d-methadone, d-piperidyl methadone, d-3-methoxy-N-phenethylmorphinan, and to undertake preliminary examination of some compounds in the meperidine series. In addition, studies of other substances regarded as potential codeine substitutes by the Committee on Drug Addiction and Narcotics will be carried out, as advice concerning possible compounds for testing is received.

5. Methods.

Methods used are the standard addiction-liability testing methods of the NIMH Addiction Research Center. The methods are accepted as standard by the Committee on Drug Addiction and Narcotics and have been described in previous project descriptions, which should be consulted for details.

6. Evaluation of Data.

Evaluation of data obtained in the addiction-liability program has also been discussed in previous project descriptions.

7. Location of Project.

The work will be carried out in the NIMH Addiction Research Center, PHS Hospital, Lexington, Kentucky. This institution provides the two necessary facilities for the type of work to be undertaken: 1) a pool of patients who will volunteer for experiments with drugs, and 2) strict environmental control which prevents the introduction of drugs other than those under study in an experimental situation.

8. Experimental Personnel.

Work will be carried out under the direction of Harris Isbell, M.D., Director, NIMH Addiction Research Center. This investigator has had 14 years of experience in research on narcotic drug addiction and has published many papers in the 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 on drug addiction, with many publications. The part-time services of a biochemist, neuropharmacologist, and research psychologist are also available. A special ward for the conduct of these studies is currently in operation.

9. Estimated Cost.

The estimated costs are shown on the attached sheet. It will be noted that the amount of money requested is higher than in past years. The increase is due to increased costs in the personnel services account; to within-grade promotions for persons who have been with the project since its inception in 1951; need to provide money for Civil Service retirement (which was formerly not paid from operating funds); and to provide for Civil Service pay raise anticipated during the current fiscal year (1958). If the Civil Service pay raise does not eventuate, this item could be eliminated from the budget. On the other hand, if the raise is greater than that provided for in the budget (6%) the figure will need to be increased accordingly.

Harris Isbell, M.D.
Director

Attachment

27 January 1958

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