THE BLACK VAULT

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THE ADDICTION LIABILITIES OF SYNTHETIC SUBSTITUTES FOR CODEINE

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To develop synthetic substitutes for codeine which are as effective as codeine for relief of pain, cough and diarrhea, but which have less addictive properties.

Testing of the addictiveness of five potential codeine substitutes was completed during the year. One of these, 1-(p-Chlor-phenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline Hcl (I-K-1), was described in last year's abstract. Further testing of this agent supported previous results -- it has little or no addictiveness even when given intravenously. Since the compound has been reported to be as effective as codeine as an analgesic, it is of great interest.

1,2-Dimethyl-3-phenyl-3-propionoxy pyrrolidine Hcl (I-O-1) also proved to be less addictive than codeine. The analgesic effects of I-O-1, however, can be questioned and clinical toxicity is high.

Ethyl 1-(2-Carbamylethyl)-4-phenylpiperidine-4-carboxylate Hcl (I-D-20), an antitussive agent, is devoid of addictiveness.

Two other drugs, 2,2-Diphenyl-4-(1-[4-(N-piperidine)-4-carboxamide]-piperidine)-butyronitrile (I-D-21) and d-3-Dimethylamino-1,1-diphenylbutyl ethyl sulfone Hcl (I-C-26) proved as, or more, addictive than codeine and are being dropped from further investigation.

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PLANS FOR FUTURE

(a) Long range. Project will be continued until the Committee on Drug Addiction and Narcotics, National Research Council, feels that adequate substitutes for codeine in all therapeutic applications are available.

(b) Immediate. Drugs to be tested during the coming year include: d-Phenampromid (I-J-3); l-2'-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan HBr (I-H-2); 1-Dimethylamino-3-phenylindane Hcl (I-N-1); 1-Hydroxyethoxyethyl-4-phenyl-4-propionyl-piperidine Hcl (I-D-22).

CURRENT REPORTS AND PUBLICATIONS

(a) H. F. Fraser and H. Isbell (1961), "Human pharmacology and addictiveness of Ethyl-1-(3-cyano-3,3-phenylpropyl)-4-piperidine carboxylate (R-1132, Diphenoxylate)." Bull. Narcotics, 13, 29-43.

(b) H. F. Fraser, W. R. Martin, A. B. Wolbach and H. Isbell (1961), "Addiction liability of an isoquinoline analgesic, 1-(p-Chlorphenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline." Clin. Pharmacol. Therap. 2, 287-299

(c) H. F. Fraser and A. B. Wolbach, Jr. (1961), "The addiction liability of Alpha-dl-3-acetoxy-4,4-diphenyl-6-methylamino heptane hydrochloride (NIH-7667, ARC I-C-25) and 6-Acetyl-3-ethoxydihydromorphine (NIH-7623, ARC I-A-38)." Bull. Drug Addiction and Narcotics, Add. 2, pp 1-3. 23rd Meet., Comm. Drug Addiction and Narcotics, Natl. Res. Council, Washington, D.C. Natl. Acad. Sci.

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ADDICTION LIABILITY OF SYNTHETIC SUBSTITUTES FOR CODEINE (Project Description)

Request to the Office of Naval Research for Renewal of Contract NAonr 21-61, NR 101-149

1. Background Information

Since 1951 the National Institute of Mental Health Addiction Research Center has been carrying on a project with the object of discovering synthetic substitutes for codeine which would be as safe as that drug with respect to toxicity and addiction liability, and which also would be as effective as codeine as antitussive, antidiarrheal and analgesic agents. The project has been financed partly by funds from the Office of Naval Research. This description constitutes a request for renewal of the project for the period 1 July 1962 to 30 June 1963.

The project was initially undertaken because codeine was the most widely used narcotic drug in both civilian and military practice. Since codeine is derived from opium, or made from morphine derived from opium, it was necessary for the United States to stockpile opium in order to insure a

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supply of codeine in the event of war. The facilities of the NIMH Addiction Research Center were not sufficient to carry out the work without further financing by the Department of Defense.

2. Work Accomplished to Date

Approximately 70 compounds have been examined in the 10 years the project has been operating. Two nonaddictive, antitussive drugs (dextromethorphan and narcotine) were developed. Three new analgesics with addictiveness lower than that of codeine have also been developed. These are ethoheptazine, d-propoxyphene and the isoquinoline drug known as I-K-1. Diphenoxylate (R-1132) is a potent antidiarrheal agent which is less addictive than codeine.

During the current year the work on the isoquinoline derivative (I-K-1) was completed. As mentioned in last year's report, this drug is of great interest. Chemically it is different from either morphine or codeine. In man it does not induce morphine-like subjective effects; it is ineffective in suppressing abstinence from morphine; and does not create physical dependence when given chronically in maximally tolerated doses. Nonetheless it has been reported to be as effective as codeine in relieving pain in well-controlled clinical studies. Unfortunately the drug is suitable only for oral use because of insolubility.

A pyrrolidine compound designated by the serial number I-O-1 was studied during the year. It induces only a partial spectrum of morphine-like effects in former addicts and is more potent when given orally than when given intravenously. It suppresses abstinence from morphine to only a slight degree. On direct addiction, toxic effects caused all patients to withdraw from the experiment. The drug therefore has low addictiveness but its toxicity may preclude clinical use.

Another compound in the meperidine series designated by the serial number I-D-20 induced no morphine-like subjective effects regardless of the route of administration. It did not suppress abstinence. It therefore is not an addictive compound and may represent the third useful antitussive developed in the program. Two of the compounds known as I-D-21 (a methadone derivative) and I-C-26 (a methadone derivative) both proved to be at least as addictive as codeine and have been dropped from further consideration in the program.

3. Need for Continuation of the Project

Although a great deal of progress has been made, we still possess no single drug which is as effective and nontoxic as codeine for all the purposes for which codeine is used. d-Propoxyphene and ethoheptazine are not as effective as

codeine in inducing analgesia, and both are more toxic. I-K-1 is suitable only for oral use. In addition, data are needed on the absorption, excretion, distribution and fate of codeine and these various synthetic drugs.

4. Work Proposed

Between 1 July 1962 and 30 June 1963 we propose to test the clinical pharmacology of four drugs: d-phenampromid (I-J-3); another meperidine antitussive known as I-D-22; an indane known as I-N-1; and a benzmorphan, known as I-H-2. In addition studies of levomepromazine will be carried out because this phenothiazine tranquilizer has been reported to be as effective as morphine in relieving pain in man.

If the gas chromatograph, which is on order, becomes available, work will be initiated on the metabolism of codeine, and eventually this work will be extended to the metabolism of I-K-1, dextromethorphan, and one of the antitussives of the meperidine type.

5. Methods

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

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methods to be used are standard and involve separation of the drug and their metabolites by extraction with differential solvents at various pHs, separation from impurities by paper chromatography, and identification by a variety of end reactions including gas chromatography, ultraviolet spectrophotometry and fluorescence measurements.

6. Evaluation of Data

Evaluation of the data has been covered in previous descriptions.

7. Location of the Project

Work will be carried out at 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 introduction of drugs other than those under study into the experimental situation. Complete biochemical facilities are also available.

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 17 years experience in research on narcotic addiction and has an extensive bibliography in this

field. He will be assisted by two other experienced physicians, Drs. H. F. Fraser and Abraham Wikler, both of whom have done research in addiction and have 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 has been made available by the hospital and has been in operation for more than nine years.

9. Estimated Cost

The estimated cost is shown on the attached sheet.

Harris Isbell, M.D.
Director

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Attachment (1)

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