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TITLE OF PROJECT: Addiction Liabilities of Synthetic Substitutes for Codeine.

Objectives: To find a synthetic analgesic and antitussive drug which would be as safe as codeine with regard to toxicity and addiction liability.

ABSTRACT (OR SUMMARY) OF RESULTS:

a. Since start of project: See annual reports for 1952 through 1958.

b. During the current reporting period:

Continued from the period covered by Annual Progress Report for 1 November 1957-1 November 1958, were the following investigations:

1. d-Methadone. The results of studies on this drug indicate that although it possesses low abuse liability, it can produce toxic effects on chronic administration in high doses. At non-toxic dose levels it may be useful as a substitute for codeine as an antidiarrheal agent. Its analgesic potency appears to be very low, while its antitussive activity has not been investigated adequately.

2. 1-(3-Diphenyl-3-carbonitril-propyl)-4 phenyl-4 carbethoxy-piperidine (R-1132, Diphenoxylate). Further studies revealed that while subcutaneous doses of 10-50 mg did not produce significant effects in postaddicts, intravenous doses in this range did produce definite morphine-like changes in behavior. These observations, as well as the results of

"direct addiction" studies confirm the opinion previously expressed, that this compound does possess addictive properties, but the order of its abuse liability is somewhat less than that of codeine. It is anticipated that R-1132 will be marketed in the near future as an antidiarrheal agent.

3. Metabolism of Normorphine. Further studies were made to determine the nature of the conjugated form of urinary normorphine. Results thus far indicate that this form is not a glucuronide nor an ethereal sulfate.

Studies on postaddicts were completed on nine new compounds. Of these, seven were found to possess abuse liability comparable to that of morphine, and therefore to be unsuitable as substitutes for codeine.

1. (-) 3-Hydroxy-N-phenacylmorphinan methane sulfonate (NIH-7525, Levophenacylmorphan). The euphorogenic and morphine abstinence-suppressing potency of this compound is about ten times that of morphine, though the intensity of the abstinence syndrome in "direct addiction" studies was somewhat less.

2. dl-2'-Hydroxy-5,9 dimethyl-2 (2-phenethyl)-6,7 benzmorphan HBr (NIH-7519, Phenazocine). Euphoria, equivalent to 20-30 mg of morphine (subcutaneously) is produced by 3-4 mg of this drug by the same route. With respect to suppression of morphine-abstinence phenomena, 1 mg of this compound is equivalent to 8.1 mg of morphine (in striking contrast to results obtained by others in the monkey, which indicated that it was only one-sixth as potent as morphine in this regard), though the intensity of the abstinence syndrome in "direct addiction" studies was somewhat less than that of morphine.

3. Ethyl 4-phenyl-1 [3(phenylamino)-propyl]-4-piperidine carboxylate ethane sulfonate (NIH-7580). In doses of 15-20 mg this drug produces euphoria equivalent to 20-30 mg of morphine, and is about twice as potent as morphine in suppressing morphine-abstinence phenomena.

4. 1-(Beta-diethylaminoethyl)-2-(benzyl-4-chloro)-5-nitrobenzimidazole (NIH-7586). In oral doses of 100 mg this drug produces euphoria and 2.62 mg are equivalent to 1 mg of morphine in suppressing morphine-abstinence phenomena.

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5. 1-(Beta-diethylaminoethyl)-2-(p-ethoxybenzyl)-5-nitrobenzimidazole methane sulfonate (NIH-7607). On oral administration this compound is 80-120 times as potent as morphine in euphorogenic potency, and about 60 times as effective as morphine in suppressing morphine-abstinence phenomena. After "direct addiction" to this drug, the intensity of the abstinence syndrome is comparable to that of morphine.

6. 1-3-Hydroxy-N (3,3-dimethylallyl)-morphinan HBr (NIH-7446). The potency of this drug, with respect both to its euphorogenic and morphine abstinence-suppressing activity, is comparable to that of morphine.

7. N-(2-[(Methyl)-phenethylamino]-propyl)-propioanilide (NIH-7603, Diampromid). Though its duration of action is much shorter (two to three hours), this compound produces euphoria in doses of 75 mg subcutaneously equivalent to that of 20 mg of morphine, and at daily dose levels of 625 or 750 mg (in four divided doses per day), it substitutes adequately for morphine in suppressing morphine-abstinence phenomena, for the relatively short period of its action.

Two other new compounds proved to have considerably less abuse-liability than morphine:

1. D-3-Methoxy-N-phenethylmorphinan (NIH-7296A). This compound was investigated for theoretical reasons. In single doses on oral administration, up to 1,000 mg did not produce euphoria consistently, though 3 of 4 subjects reported morphine-like effects while receiving 500 mg four times daily. It appears to be about 1/25th as potent as morphine in suppressing morphine-abstinence phenomena, and in "direct addiction" studies at daily dose levels equivalent to 48 mg of morphine, no abstinence phenomena were observed. However, there is no evidence at present that this compound will be useful clinically.

2. N-(1-Methyl-2-piperidinoethyl)-propionanilide . Hcl (NIH-7602. Phenampromid). In single doses subcutaneously, this compound produces definite morphine-like effects, and at daily dose levels of 1135 mg (in three equally divided doses per day), it suppresses morphine-abstinence phenomena partially. However, at such levels, disturbing side-effects occurred which were compared by the subjects to those of d-lysergic acid diethylamide (LSD-25), cocaine or marihuana. For this reason, and also because it does possess definite abuse liability, it is not likely that this compound will prove to be an adequate substitute for codeine.

Currently under investigation are three other new compounds differing basically in chemical structure from both the opiate derivatives and synthetic analgesics studied heretofore. 1-(p-Chlor-phenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline Hcl (NIH-7672A) has been found in preliminary clinical trials elsewhere to exert analgesic effects in man comparable to those of codeine, and in monkeys it does not suppress morphine-abstinence phenomena. 2-(Beta-hydroxyphenethylamino)-pyridine . Hcl (Phenyramidol) and N-Isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate (Carisoprodol) are currently marketed as "muscle relaxants" (ascribed to internuncial blocking activity) and are said to relieve certain types of pain. At present the data obtained in addictive studies on post-addicts are insufficient to warrant statements about their abuse liabilities.

In addition, studies of a basic methodological nature were made during the period of the present report to improve standards of comparison of abuse liability of new compounds primarily intended for oral administration with that of morphine. The results indicate that with respect to suppression of morphine abstinence phenomena, 1 mg of morphine subcutaneously is equivalent to 2.86 mg of morphine orally, 14.7 mg of codeine orally, and 35 mg of d-propoxyphene orally.

PLANS FOR FUTURE

Immediate: Studies on the addiction liabilities of NIH-7672A, phenyramidol and carisoprodol will be completed. In addition, similar studies will be made on a butyl ester of R-1132, the methyl analogue of phenazocine (the counterpart of codeine in this series), and on l-3-Hydroxy-N-propargyl-morphinan hydrobromide (NIH-6045), an analgesic which is a morphine-antagonist, and hence probably of low addiction liability.

Long Range: The search will be continued for synthetic compounds with therapeutic properties similar to those of codeine which, in the opinion of the Committee on Drug Addiction and Narcotics, are completely satisfactory substitutes for codeine.

REPORTS AND PUBLICATIONS (during the current report period).

1. Fraser, H.F. and Isbell, H.: Addiction Liabilities of (a) dl-2'-Hydroxy-5,9-dimethyl-2(2-phenethyl)-6,7-benzmorphan HBr (NIH-7519), and (b) l-3-Hydroxy-N-phenacylmorphinan methane sulfonate (NIH-7525). Addendum 3, Min. 20th Meet., Comm. on Drug Addiction and Narcotics, Natl. Res. Council, Washington, D.C. Natl. Acad. Sci. (Jan.) 1959.

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2. Fraser, H.F., Isbell, H. and Van Horn, G.D.: Human Pharmacology and Addiction Liability of Norcodeine. J. Pharmacol. & Exper. Therap. (in press).

3. Fraser, H.F. and Isbell, H.: Pharmacology and Addiction Liability of dl- and d-propoxyphene. Bull. on Narcotics, 12: (1) in press.

4. Fraser, H.F. and Isbell, H.: Human Pharmacology and Addictiveness of Ethyl 1-(3-Cyano-3, 3-phenylpropyl)-4-phenyl-4-piperidine carboxylate hydrochloride (R-1132, Diphenoxylate). Bull. on Narcotics (in press).

5. Fraser, H.F., Isbell, H. and Wolbach, A.B.: Addictiveness of New Synthetic Analgesics. I. Benzimidazole Derivatives: (a) 1-(Beta-diethylaminoethyl)-2-(benzyl-4-chloro)-5-nitrobenzimidazole (NIH-7586, ARC I-G-1), (b) 1-(Beta-diethylaminoethyl)-2-(p-ethoxybenzyl)-5-nitrobenzimidazole methane sulfonate (NIH-7607, ARC I-G-2). II. (-)-3-Hydroxy-N-(3, 3-dimethylallyl)-morphinan hydrobromide (NIH-7446, ARC I-B-19), III. N-(1-Methyl-2-piperidinoethyl)-propioanilide hydrochloride (Phenampromid, NIH-7602, ARC I-I-1 and, N-[2-([Methyl]-phenethylamino)-propyl] -propioanilide sulfate (Diampromid, NIH-7603, ARC I-J-1). Addendum, 21st Meet., Comm. on Drug Addiction and Narcotics, Natl. Res. Council, Washington, D.C. Natl. Acad. Sci. (Jan.) 1960.

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6. Fraser, H. F. and Isbell, H.: Human Pharmacology and Addiction Liabilities of Phenazocine (dl-2'-Hydroxy-5,9-dimethyl-2-(2-phenethyl)-6,7-benzmorphan HBr, NIH-7519) and Levophenacylmorphan (l-3-Hydroxy-N-phenacylmorphinan methane sulfonate, NIH-7525). Bull. on Narcotics, 12: (2) in press.

7. Fraser, H. F., Van Horn, G. D., Martin, W. R. and Isbell, H.: New Methods for Evaluating Addiction Liability of Morphine-Like Drugs. I. Attitude of Opiate Addicts Towards Drugs. II. Short-Term Direct Addiction Procedure. Non-quotable Section, Min. 21st Meet., Comm. on Drug Addiction and Narcotics, Natl. Res. Council, Washington, D. C. Natl. Acad. Sci. (Jan.) 1960.

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