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THE ADDICTION LIABILITIES OF SYNTHETIC SUBSTITUTES FOR CODEINE

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To develop synthetic substitutes for codeine which are less addictive than codeine.

Testing for addictiveness was completed or is in progress on the following nine compounds during the reporting year: (1) 1,2'-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I-H-2); (2) 1,2-Hydroxy-5,9-dimethyl-2(2-phenethyl)-6,7-benzomorphan (I-H-1) given orally; (3) 1-Hydroxyethoxyethyl-4-phenyl-4-propionyl-piperidine (I-D-22); (4) Methotrimeprazine (levomepromazine, VI-C-5); (5) 1-Dimethylamino-3-phenylindane (I-N-1); (6) 2-Amino-indane (I-N-2); (7) mixture of I-H-1 (see above) and II-C-1 (N-allylnorphenazocine); (8) 2'-Hydroxy-5,9-dimethyl-2(3,3-dimethylallyl)-6,7-benzomorphan (II-C-2); (9) 2-Cyclopropylmethyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan (II-C-3).

Of these, I-H-1 (orally) and the mixture of I-H-1 and II-C-1 proved to have addictiveness greater than codeine and have been dropped from further consideration.

I-D-22 (an antitussive) and II-C-2 had less addictiveness than codeine. II-C-2 deserves further investigation as an analgesic.

I-N-1, I-N-2 and VI-C-5 had no addictiveness. I-N-1 and I-N-2 are probably too toxic for clinical use. VI-C-5, a chlorpromazine congener, deserves extensive investigation in chronic pain.

II-C-2 has considerable theoretical interest, since it is morphine-like behaviorally and creates mild physical addiction but will not suppress abstinence from morphine.

II-C-3 is still being studied.

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PLANS FOR FUTURE

(a) Long range. Work will be continued but will be finished after 1 October 1962 by the National Institutes of Health rather than by Office of Naval Research.

(b) Immediate. Drugs to be tested during the coming year include II-C-3 (see above), 14-hydroxy-N-allyl-dihydromorphine, and such other compounds as are recommended by the Committee on Drug Addiction and Narcotics, National Research Council.

CURRENT REPORTS AND PUBLICATIONS

(a) Fraser, H. F., Zasig, C. F., and Wolbach, A. B. (1961), "Evaluation of carisoprodol and phenyramidol for addictiveness." Bull. Narcotics, 13, 3-7.

(b) Wolbach, A. B. and Fraser, H. F. (1962), "Addiction liability of Ethyl-1-(2-carbamethyl)-4-phenylpiperidine-4-carboxylate hydrochloride." Bulletin Drug Addiction and Narcotics, National Research Council, Washington, D.C. (Bull. Narcotics, [illegible]).

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