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## THE ADDICTION LIABILITIES OF SYNTHETIC SUBSTITUTES FOR COLLEGE

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To davelop synthetic substitutes for codeins which are less addictive than codeins.

Testing for addictiveness was completed or is in progress on the following nine compounds during the reporting year: (1) I.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-S-1) given orally; (3) 1-Hydroxyethoxyethyl-H-phenyl-H-propionyl-piperidine (I-D-22); (4) Methotrimeprazine (levomepromazine, VI-G-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-G-1 (N-allylnorphenazocine); (8) 24-Nydroxy-5.9-dimethyl-2(3.3-dimethylallyl)-6.7-benzomorphan (II-C-2); (9) 2-Cyclopropylmethyl-21-hydroxy-5.9-dimethyl-6.7-benzomorphan (II-C-3).

Of these, I-H-1 (crally) 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 analysesic.

I-H-1, I-H-2 and VI-C-5 had no addictiveness. I-H-1 and I-H-2 are probably too toxic for clinical use. VI-C-5, a chlorpromatine 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 Mational Institutes of Health rather than by Office of Mayal Research.
- (b) Immediate. Drugs to be tested during the coming year include II-C-3 (see above), 14-hydroxy-H-ally1-dihydromorphine, and such other compounds as are recommended by the Committee on Drug Addiction and Marcotics, Mational Research Council.

## - CURRENT REPORTS AND PUBLICATIONS

- (a) Fraser, H. P., Essig, C. F., and Holbach, A. B. (1961), "Evaluation of carisoprodol and phenyramidol for addictiveness." Bull. Marcotics, 13, 3-7.
- (b) Volbach, A. B. and Fraser, H. F. (1962). "Addiction liability of Ethyl-1-(2-cartamethyl)-4-phenylpiperidine-4-carboxylate hydrochloride." Dulletin Drug Addiction and Marcotics, National Research Council, Washington, D.C. (Bull. National Research Council, Washington, D.C. (Bull. National Research Council).