THE BLACK VAULT

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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 from the point of view of toxicity and addiction liability as is codeine.

ABSTRACT (OR SUMMARY) OF RESULTS:

a. Since start of project:

This portion of the summary covers the period from 1 July 1951 to 1 November 1958. The project was originally undertaken because no synthetic analgesic drug was available which was as safe and which had as low addictiveness as codeine. Adequate substitutes for the potent analgesics of the morphine type were available, but 75 per cent of the civilian and military consumption of narcotic drugs was in terms of codeine. Since this consumption amounted to 16 to 20 tons yearly, it meant that the United States had to continue to stockpile opium since access to the opium producing areas might be lost in event of war. Therefore synthetic substitutes for codeine were badly needed. The role of the NIMH Addiction Research Center in this investigation, which was initiated at the request of the Committee on Drug Addiction and Narcotics of the National Research Council, has consisted of the determination of the addictive properties of new potential codeine substitutes. The clinical evaluation of the analgesic, antitussive, and antidiarrheal properties of such new drugs must necessarily be made elsewhere.

The methods used for studying addiction liabilities of new drugs have been described in detail in the project description and in previous reports and need not be repeated here.

During the period 1 July 1951 to 1 November 1958, 51 new drugs or mixtures of drugs were tested for addictive potentialities. Detailed information concerning these substances can be found in the annual reports submitted between 1954 and 1957. Original object of the project has been partly solved since two substances which were outstanding as possible substitutes for codeine for suppression of cough were discovered. These substances were (1) d-3-Methoxy-N-methylmorphinan (dextromethorphan), and (2) narcotine. Continuing clinical investigations indicate that both drugs are as effective as codeine as antitussives. Both drugs are on sale in the United States.

Although satisfactory compounds for relief of cough have been developed, some doubt still remains that drugs which are as effective in relieving pain as codeine are available. Some eight compounds with definite promise were uncovered in past work. The drug, d-propoxyphene (Darvon, Lilly), has received the most attention and appears to be the most promising. This drug was shown to have fewer addictive properties than codeine. It is now being actively marketed by the Eli Lilly Company both as the pure material and in combination with aspirin. Further detailed studies on its analgesic effectiveness are underway.

b. During the current reporting period:

During the current reporting period (1 November 1957 to 1 November 1958) the addictive potentialities of 6 drugs were evaluated wholly or in part and the metabolic fate of normorphine investigated. The results are presented below under individual headings:

1. Norcodeine. Work with norcodeine was undertaken because normorphine had been shown to possess considerably less addictiveness than morphine. It was therefore thought of interest to extend the work to norcodeine. In doses of 75 mg. norcodeine induced subjective effects in former morphine addicts similar to those caused by codeine. It also caused mild respiratory depression and pupillary constriction. It suppressed abstinence from morphine effectively when substituted for morphine in patients addicted to that drug. Patients who took the drug, in doses increasing to 1,000-1,500 mg. daily over a period of 60 days, developed marked sedation and other morphine-like side effects. When the drug was withdrawn, definite but very mild abstinence occurred.

Since this drug is effective orally and since abstinence is milder after withdrawal than is abstinence from codeine, it is regarded as a potentially promising substitute. It, unfortunately, is not a synthetic drug.

2. d-Methadone. This drug was reinvestigated at the request of the Committee on Drug Addiction and Narcotics, NRC. It induced no subjective effects in doses of 200 mg. parenterally or orally, but did suppress abstinence almost completely when 650 mg. daily were substituted for morphine in patients who had been receiving 240 mg. of that drug every 24 hours. On withdrawal of d-methadone, after substitution for morphine for 10 days, extremely mild abstinence was observed. If d-methadone has any addictiveness it is of quite a low order. Direct addiction experiments are now underway and will be completed within the next six months.

3. N-(3-Oxo-3-phenyl-propyl)-normorphine. Twenty to 30 mg. of this drug induced subjective effects in former morphine addicts which appeared to be equivalent to those caused by 30 mg. of morphine. The drug was a very effective suppressor of abstinence from morphine. It is regarded as having a high addictiveness and is being dropped from further consideration.

4. N-Phenethyl-morphine. Fifteen mg. of N-phenethyl-morphine subcutaneously induced objective and subjective effects in nontolerant former addicts equivalent to those caused by 30 mg. of morphine. 140 mg. of the compound every 24 hours effectively suppressed abstinence in patients addicted to morphine. The drug is regarded as having high addictiveness and is being dropped from further consideration.

5. 1-3-Hydroxy-morphinan. No subjective effects were seen after single doses ranging up to as much as 100 mg. of this compound hypodermically or orally. When, however, patients were given 25 mg. of the drug hypodermically three times daily mild morphine-like effects did appear. 360 mg. of the drug daily suppressed abstinence partially in patients who had been receiving 240 mg. of morphine. This drug definitely will have low addictiveness, and more complete exploration by formal 10-day substitution and direct addiction is indicated.

6. 1-(3-Diphenyl-3-carbonitril-propyl)-4-phenyl-4-carbethoxypiperidine (R-1132). This compound is a derivative of meperidine, developed at the Eupharma Laboratories in Belgium, and was part of a program designed to develop a drug with constipative effects but without central nervous system effects. The drug has been shown to suppress abstinence in monkeys; a single dose being effective for a period of as long as 30 days.

Since the drug is insoluble all studies were carried out orally. No subjective or objective effects were observed in nontolerant morphine addicts who received 20 mg. or less of the compound orally. Doses of 50 to 90 mg. caused, in the majority of the patients, pupillary constriction, sedation, nausea, vomiting, and subjective effects resembling those seen after oral or hypodermic administration of morphine.

180 mg. of R-1132 daily suppressed abstinence nearly completely when substituted for morphine for 24 hours in patients who had been receiving 240 mg. of morphine daily.

R-1132 also suppressed abstinence effectively over a 10-day period when 180 mg. were substituted for 240 mg. of morphine in 5 patients. When R-1132 was discontinued, definite but mild abstinence was observed.

In direct addiction experiments the dosage of R-1132 was elevated quite slowly to 135 to 285 mg. daily in 5 subjects. With such a dosage schedule the subjective effects were mild and consisted primarily of sedation. The patients were quite constipated. Nalline precipitated mild but definite abstinence in these patients. When the drug was discontinued after 60 days, definite but mild abstinence was seen in 4 of the 5 subjects.

This is a very interesting and possibly important drug which might have definite military usefulness. It is possibly the most effective and safest constipating agent known, and therefore might be of value in the symptomatic treatment of diarrhea, especially in tropical areas. It has been reported to actually be a life-saving agent in treating cases of infantile diarrhea in the Belgian Congo.

The drug must be regarded as having definite addiction liability since it induces morphine-like subjective effects, suppresses abstinence, and abstinence is seen on withdrawal; but its addictiveness is definitely less than that of codeine or of morphine. Work with this compound is still in progress and investigations of the butyl-ester will also be carried out.

7. Metabolism of Normorphine. Studies on the excretion and metabolic fate of normorphine were undertaken because this drug was found to have definitely less addictiveness than either morphine or codeine, although it was a more potent sedative than either of these drugs. All studies have been conducted in man. An analytical method for normorphine has been developed which is based on extraction of the normorphine from aqueous solution at pH 8.5 into a mixture of amyl alcohol and ethylene dichloride. Normorphine is returned to aqueous solution by extracting with 0.05 normal hydrochloric acid, after which the silico-molybdic acid reaction is applied. The method gives reproducible results, and consistent recoveries of added normorphine. To our surprise, it was found that 50% of normorphine recoverable from urine was present in the "free" or readily extractable form. This contrasts with morphine in which only 10 to 15% is present in the free form. About 70% of the total

dose of normorphine is recoverable in the urine within 48 hours. Treatment of the urine with heat and strong acid liberates additional normorphine (so-called bound normorphine). Bound normorphine, however, does not appear to be a glucuoronide, since incubation with glucuoronidase does not elevate amount of normorphine which is extractable. In contrast, glucuoronidase readily liberates bound morphine. Both free and bound normorphine have been identified by means of counter-current distribution and paper chromatography.

Work so far suggests that normorphine may be effective because less of the drug is bound than is the case with morphine. In effect, more free normorphine would be present, leading to a higher concentration of free normorphine in brain than is the case with morphine. In order to test this hypothesis, animal work with refined techniques will be necessary.

Similar studies are to be carried out on l-3-Hydroxymorphinan.

PLANS FOR FUTURE

Immediate: During the coming year we intend to complete further direct addiction studies on the important constipating drug, R-1132. Preliminary work with the butyl-ester corresponding to R-1132 will also be carried out. Work on d-methadone and d-3-Methoxy-N-phenethylmorphinan will be completed. We will

also study the addictiveness of one compound in the benzmorphan series, and one compound in the morphinan series. Both of the latter two drugs have been reported to be nonaddictive in monkeys. We will also continue working on the metabolism of the demethylated congeners of morphine and morphinan.

Long Range: We intend to continue the search for substitutes for codeine until drugs are found which are, in the opinion of the Committee on Drug Addiction and Narcotics, completely satisfactory substitutes for codeine.

REPORTS AND PUELICATIONS (during the current report period).

1. Fraser, H. F., Isbell, H., Eisenman, A. J., and Van Horn, G. D.: Studies of Normorphine in Man. J. Pharmacol. & Exper. Therap., 122: (1) 22A (Jan.) 1958. (Abstract)

2. Fraser, H. F., and Isbell, H.: Human Pharmacology and Addiction Liability of Certain Compounds Related to Morphine or Codeine. I. Normorphine. II. Norcodeine. Min. 19th Meet., Comm. on Drug Addiction & Narcotics, Nat'l. Res. Council, 29-30 March 1958.

3. Fraser, H. F., Wikler, A., Van Horn, G. D., Eisenman, A. J., and Isbell, H.: Human Pharmacology and Addiction Liability of Normorphine. J. Pharmacol. & Exper. Therap., 122: 359-369 (Mar.) 1958.

4. Fraser, H. F., Isbell, H., and Van Horn, G. D.: Norcodeine in Man. Federation Proc., 17: (1) 367 (Mar.) 1958.

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