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

Objective. 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.

SUMMARY OF RESULTS

1. Since Start of Project. This portion of the summary covers the period from 1 July 1951 to 31 December 1956. As stated above, the objective of the project is to find a synthetic drug which would be as effective and as safe from the point of view of human toxicity and addictive properties as is codeine. Although adequate synthetic substitutes for morphine are available, such a codeine substitute is needed because no single drug which would completely replace codeine is known. Seventy-five per cent of the country's needs are for drugs of the codeine type rather than for drugs of the morphine type. This means that the United States must continue to stockpile opium until adequate substitutes for codeine have been developed. The role of the NIMH Addiction Research Center in this investigation consists of the determination of the addictive properties of new drugs. The evaluation of the analgesic and antitussive effects as well as of clinical toxicity must necessarily be made elsewhere.

The methods used for studying the addiction liabilities of new analgesics have been described in detail in the project descriptions and in previous progress reports, and will not be repeated.

During the period 1 July 1951 to 31 December 1955, 35 drugs or mixtures of drugs have been tested. For detailed information concerning these substances see Annual Reports for 1954 and 1955. Among these drugs, two substances which appear to be outstanding as possible substitutes for codeine for suppression of cough were found:

(1) D-3-methoxy-N-methylmorphinan, (dextromethorphan).

(2) Narcotine.

Clinical reports continue to indicate that dextromethorphan is an antitussive agent of some value. Since it is less toxic than codeine and possesses no addiction liability it seems a very satisfactory codeine substitute for antitussive purposes. It is already available and on sale in the United States. Narcotine, which is not a synthetic drug, would extend the narcotic supply since it has heretofore been a waste product of opium. Reports of clinical trials with narcotine are not as yet available.

In the last report we pointed out that, although the program had developed two drugs which appeared to be potentially useful codeine substitutes for suppression of cough, no compound was available for relief of mild grades of pain which was as safe as codeine, and seven drugs with some possibility as potential codeine substitutes were listed. Report for 1955 also contained information concerning alpha-d-2-Propionoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane (propoxyphene). Preliminary clinical trials continue to indicate that both the racemate and the dextrorotatory isomer of this compound are as effective as codeine in relieving mild grades of pain. The addictive properties of these substances are quite low. Addicts could not inject them readily because of the large dose required and because they have severe irritant properties. When taken orally, they do not induce a full spectrum of morphine-like subjective effects. While in a very high dose they suppress abstinence from morphine slightly, they do not create a significant degree of addiction when administered to persons not physically dependent on morphine. They, therefore, are very promising substitutes for codeine for relief of pain, but further data on efficacy and toxicity must be obtained from clinical trials before a decision is made that they would be completely satisfactory codeine substitutes.

2. Results During the Current Reporting Period. During the current reporting period (1 January to 31 December 1956) the addictive properties of 11 new synthetic drugs were evaluated wholly or in part. The results are presented below under individual headings.

a. dl-alpha-1,3-Dimethyl-4-phenyl-4-propionoxy-piperidine (alphaprodine, NIH-3402). This compound in doses of 50 to 100 mg. subcutaneously induces definite but short-lived subjective effects resembling those caused by meperidine. 150 mg. of the drug every four hours partially suppresses abstinence from morphine in strongly addicted patients. The drug, therefore, has addiction liability approaching that of meperidine and is not regarded as a promising codeine substitute.

b. dl-beta-1,3-Dimethyl-4-phenyl-4-propionoxy-piperidine (betaprodine, NIH-3403). Twenty-five to 30 mg. of this substance subcutaneously induces marked morphine-like subjective effects in former addicts. In doses of only 50 mg. every four hours, it suppressed almost completely signs of abstinence from morphine in strongly addicted patients. Its addiction liability is too high for it to be regarded as a promising codeine substitute.

c. dl-beta-1-Methyl-3-ethyl-4-phenyl-4-propionoxy-piperidine (NIH-7315). In doses of 20 to 30 mg., this compound induces marked morphine-like euphoria in former morphine addicts. Fifty mg. of the drug every four hours suppresses symptoms of abstinence from morphine completely. Its addiction liability is, therefore, equal to that of morphine and it is not a promising codeine substitute.

d. d-4,4-Diphenyl-6-piperidine-3-heptanone (d-piperidylmethadon, NIH-7343). In doses of 100 to 150 mg. subcutaneously this drug induced a partial pattern of morphine-like effects consisting essentially of lethargy and drowsiness. 100 to 125 mg. of this compound subcutaneously every four to six hours caused partial, but definite, suppression of abstinence in 5 strongly addicted patients. This is a very interesting result since dextrorotatory isomers in the methadone series generally are inactive. Since the possibility exists that the drug has been contaminated with small amounts of a very potent levorotatory isomer, it will be reinvestigated using specially purified lot of material.

e. 1[2-/orpholinoethyl]-4-Phenyl-4-carbethoxy-piperidine (NIH-7289). NIH-7289 in doses of 50 to 100 mg. subcutaneously induced a definite train of morphine-like subjective effects in nontolerant former morphine addicts. 100 mg. of the drug every four hours suppressed abstinence from morphine almost completely. Its addiction liability is too high for it to be regarded as a promising codeine substitute.

f. l-3-Methoxy-N-phenethyl-morphinan (NIH-7362). This drug is a codeine analogue of l-3-Hydroxy-N-phenethyl-morphinan which was described in the previous annual report as being one of the most potent morphine-like compounds ever discovered. In doses of as little as 5 mg. it induces intense, long-lasting morphine-like euphoria in former morphine addicts. Five to 10 mg. of the compound either subcutaneously or orally suppressed abstinence from morphine almost completely when given every six to eight hours to strongly addicted patients. The compound, therefore, has very marked addictive properties and cannot be regarded as a codeine substitute.

g. d-3-Methoxy-N-phenethyl-morphinan (NIH-7296A). This compound was too insoluble to be injected subcutaneously. In oral doses of 100 to 300 mg. no definite evidence of morphine-like effects was observed, other than dizziness. When 333 to 400 mg. were administered orally every four hours to strongly addicted patients, abstinence from morphine was partially but definitely suppressed. The amount of material available was sufficient for conducting tests in only 5 patients. Since contamination with only 1% of the very potent l-isomer would account for this unexpected result, the compound must be reinvestigated using specially purified material.

h. d-3-Hydroxy-N-phenethyl-morphinan (NIH-7295A). Like the preceding compound, this drug is too insoluble and too irritating to be injected. In doses ranging up to 250 mg. orally it did not induce any definite subjective effects of morphine-like nature. Doses of 333 mg. orally every six hours had no effect on the intensity of abstinence from morphine in strongly addicted patients. These findings indicate a low degree of addiction liability. If the compound is either an effective antitussive or an effective analgesic, it would be a potential codeine substitute.

i. d-2,2-Diphenyl-3-methyl-4-morpholino-butyl-pyrrolidine (NIH-7492). Doses of 5 to 10 mg. of this substance subcutaneously induced intense subjective effects which were described by former morphine addicts as resembling those caused by a mixture of heroin and cocaine. Fifteen to 20 mg. of the drug subcutaneously every four hours completely suppressed abstinence from morphine. The compound, therefore, has very high addiction liability which is at least equal to that of morphine, and is not a potential codeine substitute. It is, however, theoretically interesting since it is the first dextrorotatory drug known to have such high potency.

j. l-[illegible]-Hydroxy-beta-phenyl-ethyl-4-phenyl-4-carbethoxy piperidine (NIH-7292). This compound is very insoluble and caused intense irritation when a solution made in propolyne glycol was injected subcutaneously. No morphine-like effects were seen with doses ranging between 5 to 150 mg. subcutaneously in 15 patients. No suppression of abstinence was observed when 200 mg. were given subcutaneously at the twentieth hour of abstinence from morphine to 9 strongly addicted patients. Addiction liability of this compound is, therefore, quite low. In all probability, it is a completely inert drug.

k. d-alpha-4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxy butane (d-propoxyphene). This is the most active of the isomers of propoxyphene, and was mentioned above. It is fairly insoluble, quite irritating, and cannot be injected. In doses of as much as 400 mg. orally it does not induce a typical train of morphine-like subjective effects. Doses of 400 mg. three times daily suppressed slightly, but definitely, symptoms of abstinence from morphine. Administration of as much as 400 mg. of the compound three times daily for 30 days did not induce a significant degree of physical dependence in nontolerant former addict volunteers. On this basis, it was reported to the Drug Addiction Committee of the National Research

Council that the compound had very low addiction liability. Since preliminary clinical reports indicate that it is as effective as codeine as an analgesic, further studies were requested by the Drug Addiction Committee in order to determine more exactly the addiction-sustaining potency of the compound. This is being accomplished, using a "double blind" crossover design in which former addict volunteers are addicted to morphine, after which they are given either codeine or d-propoxyphene in coded capsules so that the identity of the drugs is unknown to the observers. After ten days of substitution and without the knowledge of the observers identical placebo capsules are substituted. Patients will be withdrawn once from codeine and once from propoxyphene. Results of this experiment should be available within the next sixty days.

PLANS FOR THE FUTURE

Immediate Plans. During the coming six months we hope to complete studies on NIH-7295A and NIH-7292A. The experiment with d-propoxyphene will be completed and, unless additional drugs are forwarded by the Drug Addiction Committee of the National Research Council, we intend to return to direct testing of addictive liabilities of some of the morphine antagonists particularly N-allylnorhercin and N-cyclopropylmethyldihydronormorphine.

Long Range Plans. We intend to continue the search for an adequate synthetic substitute for codeine until a drug or drugs are found which are judged by the Committee on Drug Addiction and Narcotics, National Research Council, to fulfill all necessary requirements.

REPORTS AND PUBLICATIONS (During current report period).

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