The Chemopharmacological Approach to the Addiction Problem

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There are now available one or more opiate antagonists structurally based on the benzomorphan nucleus which, in those fields where they have been tried, can relieve pain without producing unusual or bizarre side reactions or physical dependence. The question of tolerance to the analgesic effect of these compounds has not yet been explored.

THE following historical or chronological account of efforts to obtain a less addicting or nonaddicting analgesic drug during the past 80 years or thereabouts concludes with recent observations on opiate antagonists structurally based on the benzomorphan nucleus.

Although morphine was discovered and named as the active principle of opium 150 years ago (*1*), it had to await technological developments and the chemists' ingenuity in their application for the determination of its intimate structure and configuration. The accepted formula today is that of Gulland and Robinson (*2*), confirmed eventually by total synthesis (*3*). Early chemical manipulations of morphine were concerned mainly with its physical properties and tests for its identification. Even during the last half of the 19th century, when derivatives of morphine were first described, there was much uncertainty about the nature and purity of the compounds and little evidence adduced on their pharmacological action.

The introduction of heroin (*4*, *5*) can, I think, be fairly pinpointed as the first of the claims for a nonaddictive potent analgesic, and, therefore, the first claim of significant dissociation by chemical modification of the good and bad features of the morphine pharmacological picture. In 1898, Dreser (*5*) and others claimed specific and unique effects of heroin on the respiratory mechanism and hence superiority as an antitussive. Other writers, in 1899 and 1900, said that there was no danger of becoming dependent on the drug (*6*, *7*), and that, during the withdrawal treatment of addicts to morphine, heroin was a safe temporary substitute (*8*).

Both the early impression and claim of relative safety for heroin and the switch within a few years to a belief of high addictiveness, came about, I think, through ignorance or disregard of facts with which we should now be very familiar.

A repetition of the heroin mistakes, at least for the same reasons, should not be possible today. Cross-tolerance and the ability of one narcotic to substitute for another, preventing the appearance of abstinence phenomena and maintaining physical dependence, could not have been realized. The morphine-dependent patient showed no withdrawal distress when heroin was substituted. As the patient enjoyed symptomatic relief while the heroin was continued, there was no reason to discontinue it. Until the heroin was discontinued there was no

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opportunity for the physician to discover that his patient was in the same state of dependence as when morphine was being given. Heroin was introduced also as an oral medicament but soon after it was injected hypodermically. Unfortunately, the relative effectiveness by the two routes of administration was not considered and the subcutaneous doses, as large as those taken by mouth, were two or three times as much as was optimal. We are now well aware that excess amounts of narcotic beyond symptomatic need speed the development of physical dependence, and hence heroin's bad name was easily acquired.

The heroin experience was discouraging but chemists nevertheless made other modifications of morphine during the next 25 years without notable improvement. The discovery of Pohl in 1914 (*9*) was an exception to which great attention should have been paid. However, medicine was not ready to realize and build upon its significance, which is discussed later in this paper.

In 1929 a really intensive effort was begun to determine the relationship between the components of the morphine molecule and its useful properties and disadvantages by additions to and subtractions from the parent molecule. This cooperative, chemical-pharmacological-clinical program continued for 10 years under the direct supervision of the National Research Council. Interestingly, though it matters little now, this program was based upon almost completely erroneous hypotheses.

A great deal of abuse of cocaine had existed in this country but had diminished and largely disappeared following the synthesis and introduction of novocain, a much simpler molecule with similar local anesthetic properties. Although cocaine was defined legally as addicting, its acute and chronic intoxications were not at all like those of morphine and it produced no physical dependence. Also, although novocain lacked the ability to produce some of the central effects of cocaine, the decrease in cocaine abuse stemmed much more from its decreased availability than from the production of a powerful local anesthetic with less central action. Nevertheless, it was said that since cocaine abuse had been ameliorated by the chemical success exemplified by novocain, possibly the addiction liability and analgesic action of morphine might be separated by chemical modification.

Almost 150 modifications of the morphine molecule were prepared and studied in the Research Council's cooperative program. Much was learned about quantitative modification of morphine-like effects by chemical change (*10*), but throughout almost complete parallelism between analgesic potency and addiction liability persisted.

One approach to partial success in the original objective was the discovery of a new type of chemical change, the introduction of a new substituent at a new position in the morphine molecule. The best example was metopon (methyldihydromorphinone). It was more potent than morphine as an analgesic (about three times), more potent orally especially, and much more potent than morphine by this route relative to parenteral effectiveness. Extensive clinical trials indicated a lower incidence of side effects (*11*). But these effects were not controlled by crossover or even parallel observations with equally effective morphine doses, and the lower incidence of side effects was not confirmed in such controlled studies (personal communication, R. W. Houde, 1957). Tolerance and physical dependence developed less rapidly with metopon than with morphine and tolerance was lost more rapidly, but at best the difference was not great (*12*).

The next major step in the history of analgesics was an accidental discovery. German chemists, seeking a synthetic atropine, made a phenylpiperidine which was spasmolytic under some circumstances but strikingly morphine-like in many ways and effectively analgesic (*13*). The compound, of course, was pethidine (meperidine, Demerol, Dolantin, and many other names). Pethidine was marketed and its popularity grew rapidy. It was a synthetic, which could be used at first without the restrictions applied to morphine and morphine-related analgesics. It would relieve pain in many cases as effectively as morphine, if its dose was large enough. Unfortunately, however, tests revealed that pethidine would also produce morphine-like subjective effects, that it would substitute for morphine, though never quite completely, in an established morphine

addiction, and that its continued administration would produce a primary physical dependence.

Despite the evidence, the producer was loathe to admit pethidine's addicting qualities until cases of addiction in clinical use were reported. The compound was brought under narcotics control quite promptly in Germany but only several years later in this country, and to this day impressions of its greater safety persist. Actually, the compound, relative to its analgesic potency, is no safer than morphine.

Thousands of phenylpiperidines related to pethidine have been made, with degrees of analgesic potency ranging from none to thousands of times greater than that of morphine. Analysis and comparison of the members of this large group is now underway and again will show the relation of analgesic potency to chemical modification, but again dissociation of analgesic action and disadvantageous properties is conspicuously lacking.

One example of dissociation, in the wrong direction one might say, is the compound known as diphenoxylate. It consists of the pethidine structure with a rather massive substituent attached to the nitrogen of the molecule. It has no analgesic action, but possesses the ability of morphine to control intestinal activity and is being used as an antidiarrheic. Diphenoxylate is almost insoluble but when absorption into the organism can be obtained it can support more or less a morphine addiction. In other words, analgesic effectiveness has been lost but addiction liability and some other morphine-like properties have in some degree been retained (*14*).

German chemists made another important discovery, which came to our attention in 1946 (*15*), when they were carrying out a planned research program on potential analgesics. The study resulted in the synthesis of methadone and its derivatives. This group of compounds was reviewed recently by Dr. Janssen of Belgium (*16*).

Methadone duplicated the effects of morphine in practically all respects qualitatively and in many respects quantitatively, but important time differences occurred in its action in man. One difference, which has been put to practical use, is the time course of the abstinence syndrome which followed abrupt withdrawal of methadone from an addicted person and the effect of methadone on the course of the abstinence phenomena after substitution in persons addicted to other narcotics. The methadone abstinence symptoms are not apparent until about 48 hours after the last dose of the drug, never reach more than low intensity, and are prolonged up to about 2 weeks. Similarly, if methadone is substituted for another narcotic when physical dependence has developed, the subsequent withdrawal sequence is slow in onset, attenuated in intensity, and prolonged. This change can be attained by substitution of one or two 20-mg. doses of methadone orally per day. Such substitution constitutes in most instances a satisfactory management of the withdrawal phase of addiction.

The production of methadone, even more morphine-like in its effects than pethidine, was an added stimulus to the chemist to manipulate the molecule, as he was manipulating and modifying the pethidine molecule. It stimulated also much speculation on structure-action relationships and the postulation of an essential molecular form to fit a receptor site for the production of morphine-like analgesia (*17*).

There followed an increased awareness of differences in analgesic activity demonstrated when the racemic synthetic analgesic was resolved into its optical antipodes, such action occurring largely, often solely, with one isomer only. But again in the methadone as in the pethidine series the many chemical modifications did not result in useful dissociation of analgesic action and addiction liability.

The resolution and study of the isomers of active racemates had, however, one interesting byproduct, apparent dissociation of antitussive action. Cough-suppressant action of useful degree was demonstrated in animals and man with the isomer which had no analgesic effect and no ability to substitute for morphine or to produce primary physical dependence. Dextromethorphan is a good example (*18–20*).

Meanwhile another German chemist, working on the synthesis of morphine, carried his work up to a morphinan structure (*21*), and this in turn was developed to the clinically useful product, levorphanol, by Schnider and Grüssner (*22*). Although 3-hydroxy-N-methylmorphi-

nan (levorphanol, Dromoran) represented an incomplete morphine synthesis, it demonstrated that some features of the morphine structure could be omitted without impairment of the characteristic morphine effects. Again the chemists modified the levorphanol molecule as had been done previously with the morphine molecule, and again, unfortunately, essential parallelism between analgesic action and physical dependence properties was demonstrated (*23*).

One interesting development, however, shown first in the morphine series and repeated for morphinan derivatives, was the disproof of the long-held belief that a methyl group on nitrogen was the optimal structure for analgesic action (*24*, *25*). Of particular note were the observations that analgesic action in members of both series, which diminished when the group on nitrogen was changed from methyl to ethyl to propyl, was restored to or surpassed that of the parent N-methyl compound when the substituent was amyl or hexyl. Also the substitution of methyl by some aralkyl groups, particularly phenethyl, greatly enhanced analgesic effect. N-substitution in potent analgesics is discussed later in this paper.

Profiting by the demonstration that the complete morphine molecule was not necessary for morphine-like analgesic action, Dr. May, in 1952, began the synthesis of a new series. He made first phenylmorphans and then benzomorphans, both only partial morphine structures. One of the phenylmorphans in its racemic form showed an analgesic effect in animal experiments almost as great as that of morphine, but greater interest developed in the benzomorphan series and more than 100 modifications have now been made (*26*).

A number of parallels between the effect of modifications in the benzomorphan series and the effect of similar modifications of morphine or morphinan derivatives have been established. For example, substitution of phenethyl for methyl on nitrogen again increased analgesic potency. The racemate, 2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan, phenazocine, has 10 times the analgesic potency of morphine in laboratory animals and 3 to 7 times its potency in man.

According to established practice the more interesting benzomorphans were submitted to a monkey screening program at the University of Michigan for testing physical dependence capacity, and some were tested in man. The monkey experiments test the ability of a compound to suppress the morphine abstinence syndrome and are considered to indicate at least qualitatively the ability of the compound to produce physical dependence. The predictiveness of the test had been good for many compounds of several chemical types.

With the benzomorphans, however, even those with high analgesic potency, very low effectiveness was seen regarding the suppression of the signs of morphine withdrawal. With phenazocine, for example, analgesic effectiveness was reported as 10 times and abstinence suppressant potency as less than one-fifth that of morphine. This was encouraging and seemed to represent a major dissociation of analgesic and physical dependence properties, if the difference carried over to man, or unless there was a much greater species difference in sensitivity to the benzomorphans than had been seen in any other group of compounds.

The carryover to man was not as good as hoped for, and consequently the difference described above was in part at least the result of species difference. Again taking phenazocine as the example, as has been said, its analgesic potency in man is three to seven times that of morphine, depending upon the situation in which it is employed. Fraser and Isbell (*27*) reported that phenazocine was 3.2 times more potent than morphine in the production of morphine-like subjective effects in postaddicts and eight times more potent than morphine in suppression of the abstinence syndrome during 24-hour substitution in morphine addicts. In direct addiction experiments the daily dose of phenazocine could not be increased as rapidly as was done commonly with morphine (slower rate of development of tolerance). Following abrupt withdrawal of phenazocine in such experiments definite morphine-like abstinence phenomena appeared, which tended to be less severe than abstinence following withdrawal of equivalent amounts of morphine.

Another illustration of the effect of a benzomorphan in man was even more interesting. The morphine analog in the benzomorphan se-

ries, (-) 2′-hydroxy-2, 5, 9-trimethyl-6, 7-benzomorphan, had an analgesic potency in the morphine range slightly more effective in animals and slightly less effective in man. Its physical dependence capacity in monkeys was quite low, since it produced almost no suppression of the morphine abstinence syndrome up to 10 to 15 times the suppressant dose of morphine, amounts which caused the appearance of signs of toxicity.

In postaddicts this benzomorphan was the equivalent of morphine in the production of morphine-like subjective effects. In 24-hour substitution experiments, even an amount of the benzomorphan twice that of the dose of morphine on which the subjects were stabilized had little effect. It was estimated that in these experiments this benzomorphan was only one-eighth as effective as morphine. In direct addiction attempts, the subjects (former opiate addicts) did not regard the drug as being as desirable as morphine, and on withdrawal the abstinence syndrome was definitely less intense than after withdrawal of morphine in other trials in the same subjects.

From the above observations, it seems that in the benzomorphan series some dissociation of morphine-like properties in the direction of less addictiveness is beginning to appear.

To go back now to the neglected work of Pohl in 1914. Pohl succeeded in substituting an allyl group for methyl on the nitrogen making N-allylnorcodeine, and he claimed that it antagonized the respiratory depressant effect of morphine. This was the most important lead to dissociation of analgesia and addictiveness that we have to date. Almost 30 years later, Merck chemists (*28*) made the morphine analog, N-allylnormorphine (nalorphine), which could antagonize most of the morphine-like effects whether produced by morphine or another morphine-like analgesic.

Nalorphine on chronic administration does not produce physical dependence (*29*). Given to an animal or a man, after the development of physical dependence on another opiate, nalorphine promptly precipitates a typical abstinence syndrome. This has been used to advantage in tests for the development of physical dependence under clinical conditions, and it is the basis of the Nalline test to detect the use of opiate drugs. Nalorphine does not show significant analgesic action in animal tests.

The structural relationship between morphine and morphinan led naturally to the preparation of the N-allylmorphinan analog (levallorphan) which proved to have specific antagonistic properties several times greater than those of nalorphine. In both series, compounds with a wide variety of substituents on nitrogen have been prepared and a wide range in antagonistic properties with these variations has been demonstrated. Generally, but not always, there has been no analgesic effect demonstrable in animals.

In 1952 Fromherz and Pellmont (*30*) reported that levallorphan in a ratio of 1:100 abolished the respiratory depressant effect of morphine and morphine-like drugs in rabbits, but that even when the ratio was 1:20 analgesic effect was not abolished. This suggested to us the possibility that a ratio of nalorphine (or levallorphan) to morphine might be found which could be administered clinically as a mixture with a resulting decrease in respiratory and other side effects without interfering with the pain relief. We therefore arranged for clinical testing of this hypothesis.

Lasagna and Beecher, in 1954, conducted such a study in patients with postoperative pain, using mixtures of morphine-nalorphine, 5:1 and 3:1, and controlled their observation by administration of morphine alone and nalorphine alone (*31*). They found that 10 mg. of morphine plus 2 mg. of nalorphine produced analgesia and side effects indistinguishable from those achieved with 10 mg. of morphine alone. A combination of 15 mg. of morphine with 5 mg. of nalorphine produced respiratory depression and subjective side effects similar to those with 15 mg. of morphine.

Although our objective was not attained at these ratios, a surprising result was seen. Ten mg. of nalorphine alone produced as much analgesia as 10 mg. of morphine. These were crossover observations on the same patients who received alternating doses of the two drugs on a double-blind randomized basis. Unfortunately, side effects with nalorphine were as frequent as with morphine and they often were most unpleasant to the patient. In 1956 Keats and Telford confirmed the analgesic

effect of nalorphine in man as well as the incidence and unpleasantness of the side effects (*32*).

Modification of antagonistic potency by changing the nitrogen substituent had begun (*24*), and in some instances the compounds which were poor antagonists showed some analgesic action in the laboratory. The work of Lasagna and Beecher and of Keats and Telford had showed that the results of testing opiate antagonists for analgesic action in animals could be false negatives. Therefore, we thought there might be found among the opiate antagonists one with a combination of antagonistic and analgesic properties which would give adequate clinical analgesia without excessive and disturbing side effects.

A search for a compound with a suitable combination of antagonistic and analgesic properties has been underway for a number of years. An added incentive was the previous observation that nalorphine did not produce physical dependence, and the compound we sought hopefully would retain sufficient antagonistic potency to be similarly unable to produce physical dependence. The search was carried out by Dr. Keats and associates under the sponsorship of the Committee on Drug Addiction and Narcotics of the National Academy of Sciences-National Research Council.

Initially, three compounds in the morphine series and three in the morphinan series were tested (*33*). One compound of the morphinan series, with the substituent on nitrogen, 3,3-dimethylallyl, had little antagonistic action, was as good an analgesic as morphine with a similar incidence of side effects, and as might be expected from its low antagonistic action, produced morphine-like effects in postaddicts at the Addiction Research Center. The other five compounds were effective antagonists, varying in potency, and produced some degree of analgesia in man. The most effective, with propargyl as the substituent on nitrogen, was like levallorphan as an antagonist, like morphine as an analgesic, and like nalorphine with respect to side effects.

This was the situation when Dr. May developed his promising benzomorphan, phenazocine, described above. The suspicion or suggestion of some dissociation of morphine-like properties in the benzomorphan series, as well as structural relationships, excited the curiosity of some chemists to make the N-allyl benzomorphan analog of nalorphine and levallorphan and later to make a series of compounds with different substituents on nitrogen. All of these (some 25 compounds now) were assessed in the laboratory for antagonistic as well as analgesic properties, and with some compounds examination today includes extensive clinical testing.

The preparation of the N-allyl analog, described by Gordon and associates (*34*), proved it to be like nalorphine in most respects. It showed no analgesic action in the laboratory, was not as effective an analgesic as morphine or nalorphine in man, 15 mg. was less effective against postoperative pain than 10 mg. of morphine, and it produced in some patients the disturbing psychic reactions which had been seen with nalorphine.

Four other members of this group are under study. One of these corresponds in structure so far as the antagonistic group is concerned to the morphinan derivative mentioned which was almost completely morphine-like. The others represent variations of the N-substituent or minor variations in another part of the molecule or both. The antagonistic potency of these compounds varies from a tenth the potency of nalorphine to twice the potency of levallorphan. All of them are analgesics in man, again with a varying effectiveness.

Two of these compounds are specially interesting. Both are products of the Sterling-Winthrop Research Institute. One may be identified conveniently as Win 20,228 (*35,36* and personal communications from A. L. Keats and H. F. Fraser, 1963). It has no analgesic effect in animals, but is effective against postoperative pain in man at a dose of 30 to 40 mg. as compared with 10 mg. of morphine. Win 20,228 has not produced the bizarre psychic reactions which were troublesome with nalorphine. Side effects similar to those seen frequently after morphine were seen with the 40 mg. dose. Win 20,264, similar to Win 20,228 except for substitution of an ethyl for a methyl group at one position in the molecule, was quite similar to Win 20,228 in its action in man.

Win 20,228 has been studied at the Addiction

Research Center. Its subjective effects in postaddicts were different from those of morphine. It had little effect on the morphine abstinence syndrome, and subjects on chronic administration disliked it to the extent that seven of eight subjects voluntarily discontinued the medication. Fraser and Rosenberg concluded that this compound has no significant degree of morphine-like addictiveness (personal communication, 1963).

Win 20,740, the most potent as an antagonist of the compounds studied in this series, is noteworthy for its other effects. It is remarkably effective as an analgesic in man. The dose equivalent to 10 mg. of morphine is only one-fourth to one-half milligram. At such doses its side effects are minor and not nalorphine-like. Unpleasant reactions may occur occasionally when the dose is increased to 2.0 mg., but the dose of morphine could not be safely increased as much in a nontolerant patient. The effects in postaddicts of Win 20,740 are not too different from those of Win 20,228.

Win 20,740 is the only really potent antagonist which has shown strong analgesia in man, at least 20 times that of morphine, without nalorphine-like side effects at the effective analgesic dose. The nearest approach to Win 20,740 in potency was the compound mentioned above, N-propargylmorphinan, which was levallorphan-like in antagonistic action, morphine-like in analgesic potency, but nalorphine-like in subjective effects to such an extent as to make it quite impractical as a clinical analgesic.

These antagonists in general are not entirely devoid of respiratory depressant effect although in suitable dose ratio the more potent will antagonize the respiratory depressant effect of morphine and other opiates. This defect in the clinical usefulness of morphine-like analgesics has not been corrected, but for practical purposes, definite, almost complete dissociation of analgesic and physical dependence properties has been achieved.

The group with whom I was then associated began the study of the relationship of chemical structure to analgesic action and addiction liability more than 30 years ago. It has been a long and frustrating search and those engaged in it have been characterized frequently as dedicated individuals who would not give up. There are still many questions to be answered, but I think it is fair to say that at last there is progress.

Assuming, however, that one of the antagonists proves to be a sufficiently powerful analgesic without undue side effects and without physical dependence properties, it will be the long-sought objective of many investigators and a boon to the clinician and his patient, but it will not solve the addiction problem overnight.

We shall still have the opium-producing countries with economic needs to oppose any effort to bring about cessation of poppy cultivation. We shall still have the established machinery for illicit production and distribution of heroin which all of the efforts toward narcotics control have not suppressed. We shall still have the social and psychological forces that encourage potential addicts to dose themselves with drugs.

The chemopharmacological success which we postulate—anticipate, I am tempted to say—will help medicine and will supply a sound basis for strengthening control of addicting morphine-like agents of natural or synthetic origin. On both counts, these discoveries will contribute to the management of the addiction problem, though they are not the solution.

REFERENCES

(1) Sertürner: De la morphine et de l'acide méconique, considérés comme parties essentielles de l'opium. Trommsdorff's J Pharmazie 13: 234 (1805); Ann Chim Phys 5: 21 (1817).

(2) Gulland, J. M., and Robinson, R.: The constitution of codeine and thebaine. Mem Proc Manchester Lit Phil Soc 69: 79 (1925).

(3) Gates, M., and Tschudi, G.: The synthesis of morphine. J Amer Chem Soc 74: 1109 (1952).

(4) v. Mering, J.: Physiological and therapeutical investigations on the action of some morphine derivatives. Merck's Jahresb 1:5 (1898).

(5) Dreser, H.: Über die Wirkung einiger Derivate des Morphins auf die Athmung. Arch Ges Physiol 72: 485 (1898).

(6) Medea, E.: L'impiego terapeutico dell'eroina. Morgagni 41 (pt. 1): 381 (1899).

(7) Daly, J. R. L.: A clinical study of heroin. Boston Med Surg J 142: 190 (1900).

(8) Morel-Levalée, A.: La morphine remplacée par l'heroine pas d'euphorie, plus de toxicomanes traitement héroique de la morphinemanie. Rev Med 20: 872 (1900).

(9) Pohl, J.: Über das N-Allylnorcodein, einen Antago-

nisten des Morphins. Z Exp Path Therap 17: 370 (1914–15).

(*10*) Small, L. F., Eddy, N. B., Mosettig, E., and Himmelsbach, C. K.: Studies on drug addiction, with special reference to chemical structure of opium derivatives and allied synthetic substances and their physiological action. Supplement No. 138 to Public Health Reports. U.S. Government Printing Office, Washington, D.C., 1938.

(*11*) Eddy, N. B.: Metopon hydrochloride; an experiment in clinical evaluation. Public Health Rep 64: 93 (1949).

(*12*) Lee, L. E., Jr.: Studies of morphine, codeine and their derivatives. XVI. Clinical studies of morphine, methyldihydromorphinone (metopon) and dihydrodesoxy-morphine-D (desomorphine). J Pharmacol Exp Ther 75: 161 (1942).

(*13*) Eisleb, O., and Schaumann, O.: Dolantin, a new antispasmodic agent. Deutsch Med Wschr 65: 967 (1939).

(*14*) Fraser, H. F., and Isbell, H.: Human pharmacology and addictiveness of ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenyl-4-piperidine carboxylate hydrochloride (R–1132, diphenoxylate). Bull Narc 13 (No. 1): 29 (1961).

(*15*) Scott, C. C., and Chen, K. K.: The action of 1,1-diphenyl-1-(dimethylaminoisopropyl) butanone-2, a potent analgesic agent. J Pharmacol Exp Ther 87: 63 (1946).

(*16*) Janssen, P. A. J.: Synthetic analgesics. Part 1. Diphenylpropylamines. *In* International Series of Monographs on Organic Chemistry. Pergamon Press, London, 1960, vol. 3.

(*17*) Beckett, A. H., and Casey, A. F.: Synthetic analgesics: stereochemical considerations. J Pharm Pharmacol 6: 986 (1954).

(*18*) Benson, W. M., Stefko, P. L., and Randall, L. O.: Comparative pharmacology of D-, DL-, and L-Dromoran and related ether derivatives. Fed Proc 11: 322 (1952).

(*19*) Cass, L. J., and Frederik, W. S.: Evaluation of a new antitussive agent. New Eng J Med 249: 132 (1953).

(*20*) Fraser, H. F., and Isbell, H.: Effects and addiction liabilities of the isomers of the 3-methyl ether of Dromoran. J Pharmacol Exp Ther 106: 397 (1952).

(*21*) Grewe, R.: Synthetic drugs with morphine action. Ang Chem, A 59: 194 (1947).

(*22*) Schnider, O., and Grüssner, A.: Synthese von Oxy-morphinanen. Helv Chim Acta 32: 821 (1949).

(*23*) Eddy, N. B., Halbach, H., and Braenden, O. J.: Synthetic substances with morphine-like effect; relationship between analgesic action and addiction liability, with a discussion of the chemical structure of addiction-producing substances. Bull WHO 14: 353 (1956).

(*24*) Winter, C. A., Orahovats, P. D., and Lehman, E. G.: Analgesic activity and morphine antagonism of compounds related to nalorphine. Arch Int Pharmacodyn 110: 186 (1957).

(*25*) Eddy, N. B., Besendorf, H., and Pellmont, B.: Synthetic analgesics; aralkyl substitution on nitrogen of morphinan. Bull Narc 10 (No. 4): 23 (1958).

(*26*) May, E. L., and Eddy, N. B.: Synthetic analgesics. Part II, B. 6,7-benzomorphans. *In* International Series of Monographs on Organic Chemistry. Pergamon Press, London, 1963. In press.

(*27*) Fraser, H. F., and Isbell, H.: Human pharmacology and addiction liabilities of phenazocine and levophenacylmorphan. Bull Narc 12 (No. 2): 15 (1960).

(*28*) Weijlard, J., and Erickson, A. E.: N-allylnormorphine. J Amer Chem Soc 64: 869 (1942).

(*29*) Isbell, H.: Attempted addiction to nalorphine. Fed Proc 15: 442 (1956).

(*30*) Fromherz, K., and Pellmont, B.: Morphinan-antagonisten. Experientia 8: 394 (1952).

(*31*) Lasagna, L., and Beecher, H. K.: The analgesic effectiveness of nalorphine and nalorphine-morphine combinations in man. J Pharmacol Exp Ther 112: 356 (1954).

(*32*) Keats, A. S., and Telford, J.: Nalorphine; a potent analgesic in man. J Pharmacol Exp Ther 117: 190 (1956).

(*33*) Telford, J., Papadopoulos, C. N., and Keats, A .S.: Studies of analgesic drugs. VII. Morphine antagonists as analgesics. J Pharmacol Exp Ther 133: 106 (1961).

(*34*) Gordon, M., et al.: A new potent analgetic antagonist. Nature 192: 1089 (1961).

(*35*) Archer, S., et al.: Narcotic antagonists as analgesics. Science 137: 541 (1962).

(*36*) Harris, H. F., and Pierson, A. K.: Further studies with antagonists in the benzomorphan series. J Pharmacol Exp Ther, 1963. In press.