25. I. S. Shklovsky, *Astrophys. Lett.* **10**, 5 (1971).
26. J. E. Felten, *J. Roy. Astron. Soc. Can.* **64**, 33 (1970).
27. I. Shklovsky, *Nature* **228**, 1174 (1970).
28. H. Gursky, A. Solinger, E. Kellogg, S. Murray, H. Tananbaum, R. Giacconi, A. Cavaliere, *Astrophys. J. Lett.* **173**, 99 (1972).
29. K. I. Kellermann, B. G. Clark, M. H. Cohen, D. B. Shaffer, J. J. Broderick, D. L. Jauncey, *ibid.* **179**, 141 (1973).
30. C. Bowyer, M. Lampton, J. Mack, F. deMendonca, *ibid.* **161**, 1 (1970).
31. E. Kellogg, H. Gursky, C. Leong, E. Schreier, H. Tananbaum, R. Giacconi, *ibid.* **165**, 49 (1971).
32. C. Wade, R. Hjellming, K. Kellermann, J. Wardle, *ibid.* **170**, 11 (1971).
33. E. Becklin, J. Frogel, D. Kleinmann, G. Neugebauer, E. Ney, D. Strecker, *ibid.*, p. 15; W. Kunkel and H. Bradt, *ibid.*, p. 7.
34. G. Fritz, A. Davidsen, J. Meekins, H. Friedman, *Astrophys. J. Lett.* **164**, 81 (1971); W. Forman, E. Kellogg, H. Gursky, H. Tananbaum, R. Giacconi, *Astrophys. J.* **178**, 309 (1972).
35. H. J. Rood, T. L. Page, E. C. Kintner, I. R. King, *Astrophys. J. Lett.* **172**, 124 (1972).
36. C. A. Muller, *Bull. Astron. Inst. Neth.* **14**, 339 (1959).
37. J. F. Meekins, G. Fritz, T. A. Chubb, H. Friedman, R. C. Henry, *Nature* **231**, 107 (1971).
38. H. Gursky, E. Kellogg, S. Murray, C. Leong, H. Tananbaum, R. Giacconi, *Astrophys. J. Lett.* **167**, 181 (1971).
39. R. C. Henry, *ibid.* **172**, 97 (1972); J. Holberg, S. Bowyer, M. Lampton, *Astrophys. J.* in press.
40. K. Brecher and E. R. Burbidge, *Nature* **237**, 440 (1972).
41. J. E. Felten and P. Morrison, *Astrophys. J.* **146**, 616 (1966).
42. M. Schmidt, *ibid.* **162**, 371 (1970).
43. A. Sandage, paper presented at the Mayall Symposium, Tucson, Arizona (1971).
44. R. Cowsik and E. J. Kobetich, *Astrophys. J.* **177**, 585 (1972).
45. T. Gold and F. Hoyle, in *Paris Symposium on Radio Astronomy*, R. N. Bracewell, Ed. (Stanford Univ. Press, Stanford, Calif., 1959), p. 104.
46. The decay scheme was $n \rightarrow p + e + \bar{\nu}$, where n is a neutron, p a proton, e an electron, and $\bar{\nu}$ an antineutrino.
47. J. I. Vette, D. Gruber, J. L. Matteson, L. E. Peterson, *Astrophys. J. Lett.* **160**, 161 (1970).
48. J. R. Arnold, L. E. Peterson, A. E. Metzger, J. I. Trombka, *Proceedings of IAU Symposium No. 55*, H. Bradt, Ed. (Reidel, Dordrecht, in press); S. V. Golenetskii, E. P. Mazets, V. N. Il'inskii, R. L. Aptekar, M. M. Bredov, Yu. A. Gur'yan, V. N. Panov, *Astrophys. Lett.* **9**, 69 (1971); R. R. Daniel, G. Joseph, P. J. Lavaklare, *Astrophys. Space Sci.* **18**, 462 (1972).
49. F. W. Stecker, *Astrophys. J.* **157**, 507 (1969); *Nature* **229**, 105 (1971).
50. M. J. Rees and J. Silk, *Astron. Astrophys.* **3**, 452 (1969).
51. J. Silk, *Space Sci. Rev.* **11**, 671 (1970).
52. R. L. Brown, *Lett. Nuovo Cimento* **4**, 941 (1970).
53. F. W. Stecker, D. L. Morgan, Jr., J. Bredekamp, *Phys. Rev. Lett.* **27**, 1469 (1971).
54. D. D. Clayton and J. Silk, *Astrophys. J. Lett.* **158**, 43 (1969).
55. H. A. Mayer-Hasselwander, E. Pfeffermann, K. Pinkau, H. Rothermel, M. Sommer, *ibid.* **175**, 23 (1972); G. H. Share, R. L. Kinzer, N. Seeman, preprint.
56. W. L. Kraushaar, G. W. Clark, G. P. Garmire, R. Borken, P. Higbe, C. Leong, T. Thorsos, *Astrophys. J.* **177**, 341 (1972).
57. K. Brecher and P. Morrison, *Phys. Rev. Lett.* **23**, 802 (1969).
58. C. S. Bowyer and G. B. Field, *Nature* **223**, 573 (1969).
59. R. C. Henry, G. Fritz, J. F. Meekins, H. Friedman, E. T. Byram, *Astrophys. J. Lett.* **153**, 11 (1968).
60. A. N. Bunner, P. L. Coleman, W. L. Kraushaar, D. McCammon, T. M. Palmieri, A. Shilepsky, M. Ulmer, *Nature* **223**, 1222 (1969).
61. T. M. Palmieri, G. A. Burginyon, R. J. Grader, R. W. Hill, F. D. Seward, J. P. Stoering, *Astrophys. J.* **169**, 33 (1971); D. J. Yentis, R. Novick, P. Vanden Bout, *ibid.* **177**, 365 (1972); R. C. Henry, G. Fritz, J. F. Meekins, T. Chubb, H. Friedman, *Astrophys. J. Lett.* **163**, 73 (1971); A. N. Bunner, P. L. Coleman, W. L. Kraushaar, D. McCammon, *ibid.* **167**, 3 (1971); S. Hayakawa *et al.*, *Astrophys. Space Sci.* **12** 104 (1971).
62. A. Davidsen, S. Shulman, G. Fritz, J. F. Meekins, R. C. Henry, H. Friedman, *Astrophys. J.* **177**, 629 (1972).
63. S. A. Ilovaisky and C. Ryter, *Astron. Astrophys.* **15**, 224 (1971).
64. J. P. Ostriker, M. J. Rees, J. Silk, *Astrophys. Lett.* **6**, 179 (1970).
65. D. McCammon, A. N. Bunner, P. L. Coleman, W. L. Kraushaar, *Astrophys. J. Lett.* **168**, 33 (1971).
66. L. Spitzer, *Astrophys. J.* **124**, 20 (1956).
67. In this expression n_e is the electron density per cubic centimeter and l is the path length.
68. J. Gott and J. Gunn, *Astrophys. J. Lett.* **169**, 563 (1971).
69. D. S. DeYoung, *ibid.* **173**, 7 (1972).
70. C. S. Bowyer, G. B. Field, J. E. Mack, *Nature* **217**, 32 (1968).
71. E. A. Boldt, U. D. Desai, S. S. Holt, P. Serlemitsos, in *Non-Solar X- and Gamma-Ray Astronomy*, L. Gratton, Ed. (Reidel, Dordrecht, 1970), pp. 309–314.
72. G. Ducros, R. Ducros, R. Rocchia, A. Tarrius, preprint.
73. P. Gorenstein, E. M. Kellogg, H. Gursky, *Astrophys. J.* **156**, 315 (1969).
74. D. W. Green, B. G. Wilson, A. J. Baxter, in *Space Research IX*, K. S. Champion *et al.*, Eds. (North-Holland, Amsterdam, 1969), pp. 222–225.
75. M. Matsuoka, M. Oda, Y. Ogawara, S. Hayakawa, T. Kato, *Can. J. Phys.* **46**, S466 (1968).
76. F. Seward, G. Chodil, H. Mark, C. Swift, A. Toor, *Astrophys. J.* **150**, 845 (1967).
77. J. A. M. Bleeker and A. J. M. Deerenberg, preprint; *Astrophys. J.* **159**, 215 (1970).
78. A. E. Metzger, E. C. Anderson, M. A. Van Dilla, J. R. Arnold, *Nature* **204**, 766 (1964).
79. D. A. Schwartz, H. S. Hudson, L. E. Peterson, *Astrophys. J.* **162**, 431 (1970).
80. E. A. Boldt, U. D. Desai, S. S. Holt, *ibid.* **156**, 427 (1967); E. A. Boldt, U. D. Desai, S S. Holt, P. Serlemitsos, *Nature* **224**, 677 (1969).
81. A. J. Baxter, B. G. Wilson, D. W. Green, *Can. J. Phys.* **47**, 2651 (1969).
82. S. Hayakawa *et al.*, in *Non-Solar X- and Gamma-Ray Astronomy*, L. Gratton, Ed. (Reidel, Dordrecht, 1970), pp. 121–129.
83. A. Toor, F. D. Seward, L. R. Cathey, W. E. Kunkel, *Astrophys. J.* **160**, 209 (1970).
84. C. Cunningham, D. Groves, R. Price, R. Rodrigues, C. Swift, H. Mark, *ibid.*, p. 1177.
85. R. Rothenflug, R. Rocchia, D. Boclet, P. Durouchoux, in *Space Research VIII*, A. P. Mitra *et al.*, Eds. (North-Holland, Amsterdam, 1968), pp. 423–429.

The Search for a Better Analgesic

After 75 years of research, solutions for morphine-type drug dependence are emerging.

Nathan B. Eddy and Everette L. May

The accepted, standard analgesic has always been morphine, the medicament without which, until recently, no one could practice medicine effectively. Morphine not only relieves pain of any origin, whether due to illness or trauma, but it may relieve anxiety and the effects of mental or physical shock, promote sleep, and evoke a general feeling of peace and well-being. Its use for any of these benefits, however, demands that a price be paid. If the dose is only a little too great in the circumstances or if the patient is very young or debilitated, the breathing may be depressed to a degree which is life threatening. Frequently nausea, vomiting, sweating, dizziness, and sluggishness occur with routine doses; the heart rate is slowed and the blood pressure may fall. When the use of morphine is repeated, the effects wane and the dose must be increased and, worst of all, morphine causes addiction (drug dependence of the morphine type), an accommodation of the cells of the body to its presence so that its use must be continued or a particular, self-limited illness, the withdrawal or abstinence syndrome, makes its appearance. The search for a better analgesic then is a search for a better morphine, a substance with morphine's beneficial properties and with attenuated or no harmful side effects including tolerance and dependence.

Morphine, as morphine, has been known for less than 200 years, but the effects of opium are the effects of mor-

The late Dr. Eddy was consultant and Dr. May is chief of medicinal chemistry, at the Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014.

phine and the properties of opium were known before the earliest medical records. Children were given poppy capsules to chew in order to keep them quiet 3500 years ago. Opium, in one form or another, was in every medical and first-aid kit for centuries and was used as a household and professional remedy for mental disorders and for aches and pains of every kind and description. Some liked the effects apart from symptomatic relief, and there were opium eaters and opium smokers, seekers after pleasure from the poppy instead of, or in addition to, the grape. This was no great problem; in the state of medical ignorance then, opium was indeed "a friend in need." But man's curiosity is unlimited and about 200 years ago, maybe earlier, he began to wonder why opium did what it did and if there were a separable active principle.

In 1803, Derosne (*1*) by extraction of opium with water and precipitation of the extract with potassium carbonate, obtained a crystalline substance which he called the "salt of opium." Shortly thereafter, Sertürner (*2*), a pharmacist of Einbeck in Hanover, described the isolation of a pure alkaloidal base which he called morphine after Morpheus, the god of sleep. He tried this morphine in dogs and showed that its effects were like those of opium (*3*). Derosne's "salt of opium" is considered to have been morphine or narcotine. Sertürner's isolation of morphine was quickly confirmed and effort for some time was directed toward the isolation and purification of morphine and other opium alkaloids—for example, narcotine in 1817 (*4*); codeine in 1832 (*5*); thebaine in 1835 (*6*); and papaverine in 1848 (*7*).

There were many attempts at elemental analysis of morphine, but such analysis was not correctly accomplished until 1847 (*8*). Chemical manipulations for the purpose of determining the structure of morphine (**1**) were not begun until nearly the last quarter of the 19th century (*9*), and the structure was not acceptably established until 1925 by Gulland and Robinson (*10*). Identification of the products of these manipulations was poor and pharmacological examination, cursory and qualitative at best; the work of Dott and Stockman (*11*) was probably the most complete. The effect of acetylation was one of the earliest approaches to the pharmacological examination of morphine and there is presumptive evidence that diacetylmorphine, heroin (**3**), was obtained in 1874 (*12*) (Fig. 1).

The potency of heroin was soon recognized. It underwent more investigation than any other product of the time, and was introduced into clinical medicine with claims of superiority to morphine in 1898 (*13*). It was a good analgesic though shorter acting than morphine. At the doses used in the laboratory it appeared to have little respiratory depressant effect; therefore, it was thought that it would be a safer antitussive. It could be substituted for morphine in chronic users without causing the appearance of withdrawal phenomena; therefore, it "cured" the addiction. That Dreser missed the greater respiratory effect of heroin is almost unbelievable. He seems to have relied mainly on change in respiratory rate, an unsatisfactory measure of respiratory activity. As to the cure of addiction, there was not yet appreciation of the phenomena of cross-tolerance and of maintenance of dependence by a substance of similar pharmacological profile, but this was soon to come. Even in the year (1898) of its introduction Strube (*14*) said, with respect to his clinical experience, that patients took the drug willingly and asked for it if it was replaced by something else. He was unable to decide whether this was a first sign of habituation but admitted that the dose had to be increased in prolonged administration.

Early Research: Derivatives of Opium Products

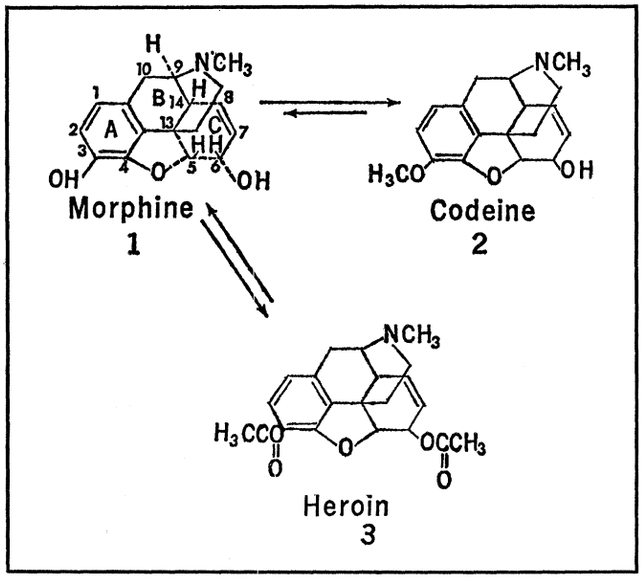
The introduction of heroin, though based on faulty observation and interpretation, and a great disappointment, undoubtedly influenced the trend and objectives of morphine research and may truly be said to mark the beginning of the search for a better analgesic. This search, emphasizing as it has from the beginning avoidance of tolerance and physical dependence and attenuation or elimination of disagreeable or dangerous side effects, has been beset by at least three extraordinary difficulties that are not yet completely overcome. Two of these difficulties concern the validity of animal procedures that are used for testing analgesia and drug dependence.

The older tests gave good indications of the pain-relieving power of substances related pharmacologically to morphine in other respects. Eventually, nalorphine, shown by the older methods to be essentially free of positive effect, was demonstrated incidentally to be analgesic in man. Since the introduction of nalorphine, new methods for measuring analgesia in animals have been described (*15*) which now seem to be fully predictive for compounds giving rise to the whole range of behavior from "pure" agonist to "pure" antagonist. Although one may still get a false negative result in the laboratory, the chance of doing so has been greatly reduced. There have been no false positive results, at least qualitatively.

With certain classes of compounds, perhaps largely because of differences in the way different species metabolize them, there have been differences in the apparent physical dependence liability in the rhesus monkey and in man. For example, many representatives of the benzomorphan group have shown little capacity to support or cause physical dependence in monkeys; some have been unexpectedly nalorphine-like, that is, antagonistic to narcotic analgesics. The few that have been tested in man have been more like morphine, qualitatively and quantitatively. In contrast, for members of the pethidine series, dependence liability has been generally less in man than predicted from results in the monkey (*16*). Qualitative comparisons, however, have been good. Again there have been no false positive results.

The third major difficulty has been that of investigators' regarding the physical dependence-producing potential of strong analgesics to be of utmost importance to the extent that they directed their greatest research effort toward eliminating it. Drug abuse patterns have changed, however. Drugs have been abused throughout; even cocaine and marihuana, for example, which do not cause physical dependence, have been abused. Gradually it has been realized that psychic factors, such as "liking" the drug effect, are paramount in the continuation of drug abuse and more progress in this area must be attained if a better analgesic is to be developed.

During the 25 years after the introduction of heroin, other morphine derivatives came into medical practice and are in use even today without clear superiority. These include (Fig. 2): dihydrocodeine differing from codeine (**2**) only in saturation of one double bond and not very different from it in activity; dihydrocodeinone, hydrocodone, or Hycodan (**6**) having, in addition, one hydroxyl replaced by oxygen



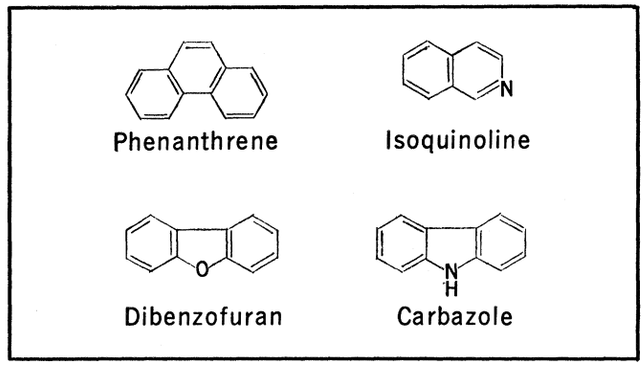
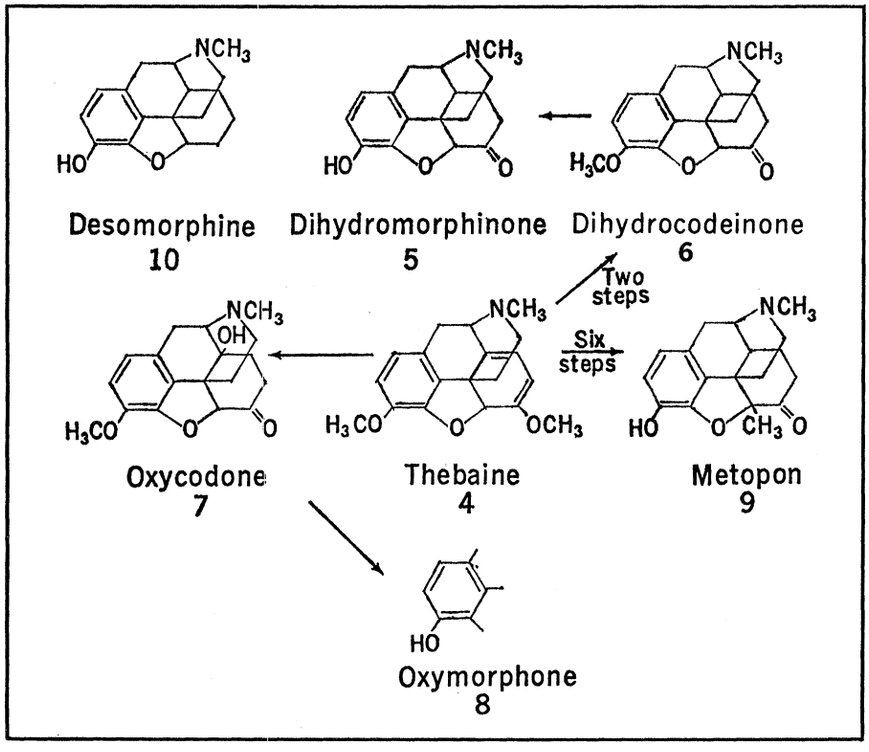


Fig. 1 (top left). Structure of morphine, codeine, and heroin. Fig. 2 (bottom left). Morphine analogs. Fig. 3 (top right). Fragments of morphine.



(Fig. 2) and an effective dose one-sixth that of codeine; and acetyldihydrocodeinone or thebacon, a product of acetylation of dihydrocodeinone and similar to it in activity. All of these were analgesics but are now used mainly as antitussives. Also new in this period was dihydromorphinone, hydromorphone, or Dilaudid (**5**) differing from morphine as dihydrocodeinone differs from codeine, and very similar to heroin in its action.

In 1929 a most significant change in analgesic research came about, the beginning of the first systematic study of structure-action relationships to dissociate, if possible, analgesic effectiveness from side-effect and addiction liability.

From 1929 to 1939 this plan was directed by the Committee on Drug Addiction of the National Research Council (NRC) with financial support from the Rockefeller Foundation. In 1939 it was taken over in principle by the National Institutes of Health. Through the first 10 years the chemical studies were conducted at the University of Virginia and consisted, on the one hand, of modification of the morphine molecule at all accessible points and, on the other hand, of syntheses from moieties of the morphine molecule or analogs, such as phenanthrene, hydrogenated phenanthrenes, isoquinolines, dibenzofuran, and carbazole (Fig. 3). More than 150 derivatives of morphine and more than 300 synthetic products were made. Each compound was tested uniformly at the University of Michigan for toxicity and for analgesic, respiratory, gastrointestinal, sedative, and other central nervous system effects. More than 20 compounds were tested for morphine-like effects and the ability to support a morphine addiction in man, and some were tested clinically for analgesic or antitussive activity. The major portion of this work was reviewed in 1938 (*17*), with a careful analysis of trends in structure-action relationships.

The National Research Council Committee thought that it had initially some basis for an optimistic outlook. It drew attention to the diminution of cocaine abuse coincident with the introduction of chemically different synthetic local anesthetics which were not abused. It also noted that codeine (**2**), the phenolic methyl ether of morphine, retained a very useful degree of analgesic and antitussive activity, but had a very low abuse potential; indeed, at the time it was considered to be essentially nonaddictive. The investigators themselves, while intensely interested in structure-action relationships, were less confident in the practical aspects of their results. After 10 years of intensive effort, no significant dissociation of strong analgesic effect and dependence-producing liability was accomplished; there were rewarding results, nevertheless. In addition to a comparison of morphine and codeine, several similar structures were examined. The effects of the simple chemical change, phenol → methyl ether, were found to be

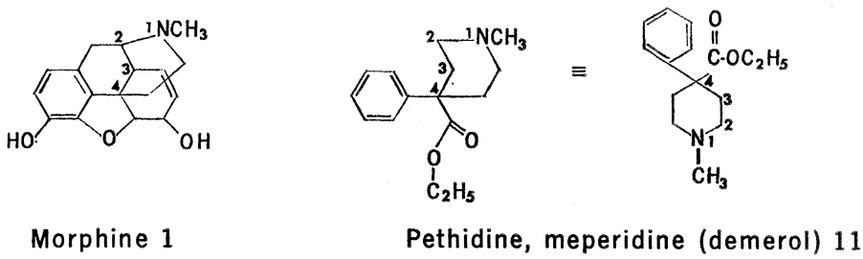


Fig. 4. Structural comparison of morphine and pethidine.

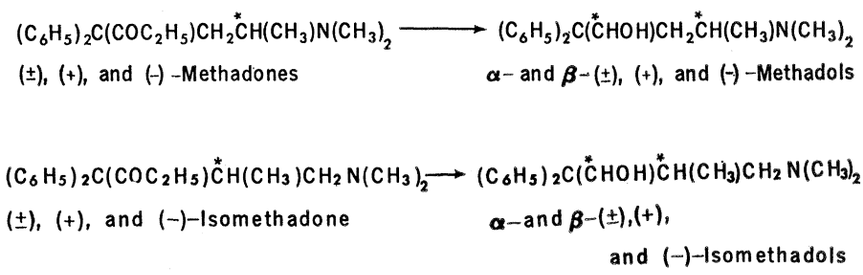


Fig. 5. Methadols and isomethadols.

remarkably uniform. The significance of the phenolic and alcoholic hydroxyls for intensity of analgesic action was established. Removal of the latter, as in desomorphine (**10**), resulted in the most rapidly acting, intense, and powerful analgesic known to that time. A new alkyl group was introduced at carbon-5 of the morphine molecule as in metopon (**9**); this was advantageous with respect to analgesic action, and there was some lessening of tolerance and dependence development. Among the synthetic products, some exhibited a certain amount of analgesic and other morphinelike properties, but these leads have not been followed. The work set a valuable pattern of systematic study and was a stimulus to alkaloid chemistry and to chemists, industrial chemists particularly, in the search for better analgesics. Particularly to be noted as an indirect result of the NRC program are the 14-hydroxy-7,8-dihydro compounds oxycodone (**7**) and oxymorphone (**8**) (Fig. 2), derived from thebaine (**4**). Both have been used successfully and have led to important antagonists that we discuss later.

Totally Synthetic Analgesics

The next milestone in analgesic research was the synthesis of pethidine [meperidine, Demerol (**11**)] and the serendipitous discovery of its morphinelike properties. In the late 1930's a German chemist-pharmacologist team (*18*) were looking for a spasmolytic substitute for atropine. Pethidine was not a success for this purpose, but routine pharmacological screening, like that done at the University of Michigan in the NRC program, revealed that it was analgesic and had other morphine-like properties in spite of its seeming chemical dissimilarity. Schaumann in 1940 (*19*) drew attention to the phenylpiperidine moiety in morphine and later (*20*) stressed other features which morphine and pethidine had in common—a benzene nucleus, a quaternary carbon attached, and a tertiary amino group two aliphatic carbons removed (Fig. 4). Pethidine supported and produced primarily a drug dependence of morphine type and had a "liking" score, relative to its analgesic potency, at least as great as that of morphine (*21*). It was the first wholly synthetic analgesic which could replace morphine in many clinical situations. Like heroin, it was introduced into medical practice with claims of nonaddictiveness and greater safety. That it was morphine-like in dependence liability was recognized very early in Germany and proved conclusively at the Addiction Research Center at Lexington (*21*). Yet, this was admitted reluctantly and the initial impression of relative safety, still prevalent to some extent, has played a significant role in the abuse of the drug by medical and paramedical personnel. Introduced in the United States in 1941, pethidine was brought under narcotics control by special congressional action in 1947, and is now generally admitted to need the same precautions as morphine in its clinical use.

Thousands of phenyl-piperidines, related to pethidine, have been synthesized in the last 30 plus years, some with tremendously increased analgesic potency. A few have been used clinically (alphaprodine or Nisentil, and anileridine are examples) and some have been developed for other purposes, for example, neuroleptics and antidiarrheal drugs. But again, significant dissociation of analgesia and dependence liability has not been attained (*22*).

Recognition of the chemical features common to morphine and pethidine initiated a systematic program of synthesis and a whole new class of analgesic agents, methadone (**12**) and its congeners (*22, 23*) was developed. The line of reasoning from pethidine to the methadone structure was never clearly revealed, but both do contain several features in common with morphine and

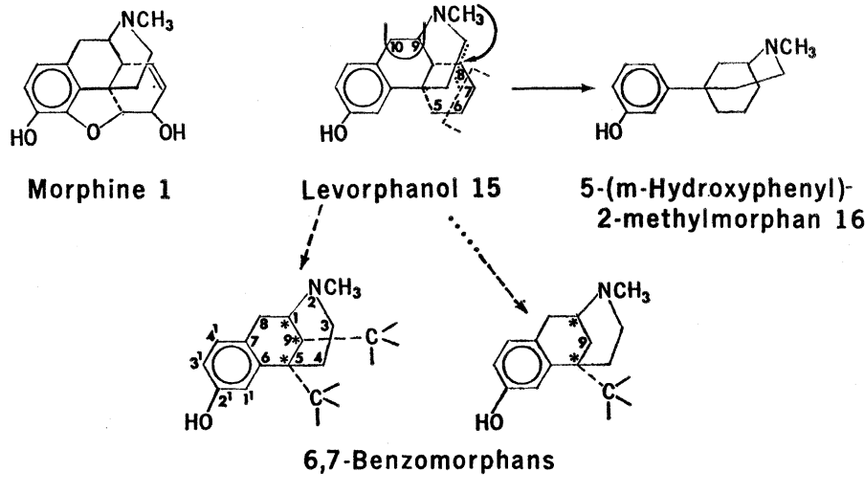


Fig. 6. Derivation of phenyl- and 6,7-benzomorphans.

with each other as noted by Schaumann (*20*). Methadone duplicated qualitatively the pharmacological profile of morphine but there were some differences in the time-courses of action. It was as effective as morphine as an analgesic, more so and longer acting when administered orally. Its repeated administration caused the development of tolerance and dependence of the morphine type, and it substituted very adequately for morphine or other narcotics. Compared with morphine or heroin, the methadone abstinence syndrome was slower in onset, longer in duration, and much less intense. It is the drug of choice to ameliorate the distress of withdrawal of other narcotics, and, because of its prolonged oral effect, for maintenance of dependence of morphine type when such is judged advisable (*24*).

A great many methadone derivatives have also been made with wide variation in analgesic potency and duration of action, but with ability to produce dependence of morphine type approximately parallel to pain relief. Two examples are dextropropoxyphene (**13**) and dextromoramide (**14**). The former, a mild analgesic of considerable popularity, substitutes poorly in dependence of morphine type but has been abused to a small extent by drug-dependent persons and others. Dextromoramide is a very effective analgesic, as effective orally as parenterally, but with a correspondingly high abuse potential (*22*).

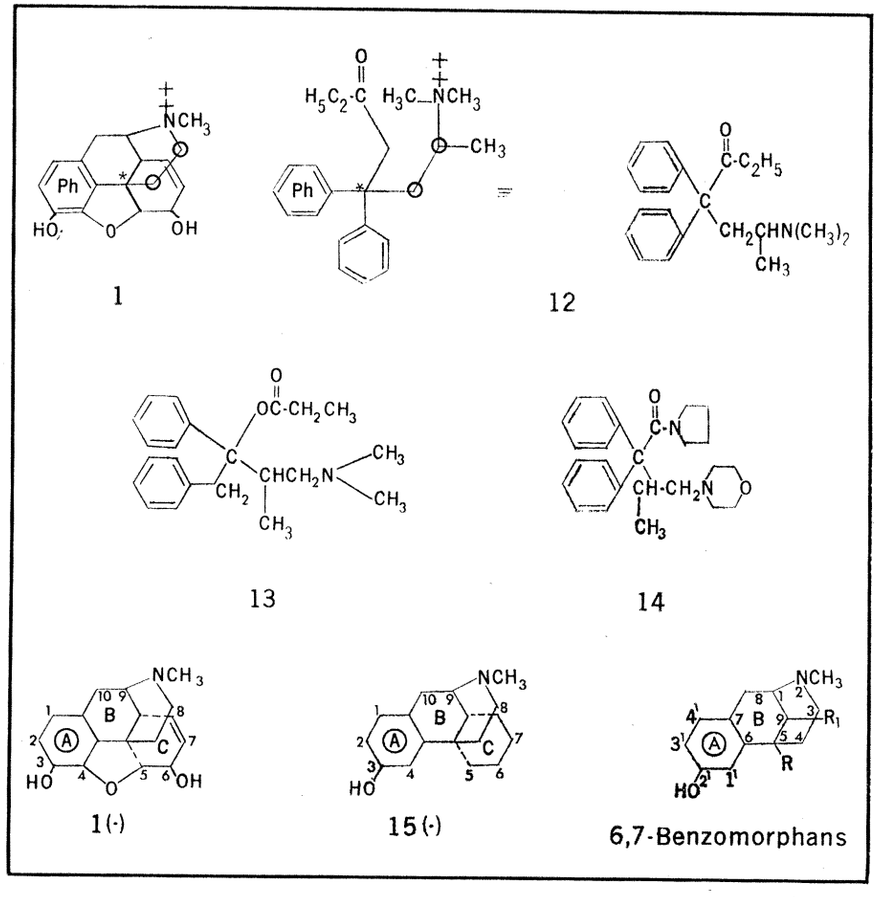
Notable in the chemistry and pharmacology of the methadone series are the synthesis and analgesic evaluation of all possible methadols and isomethadols and their *O*-acetylated analogs (*25*), 24 structural and configurational variations as illustrated in Fig. 5. If the sometimes pronounced variations in analgesic effect and duration of action in this series could be correlated with physical or chemical properties, or both, our understanding of structure-action relationships might be considerably advanced. One member of the series, *α-l*-acetylmethadol, that is as effective and twice as long-acting as methadone, is being studied for practical use in methadone maintenance programs (*26*).

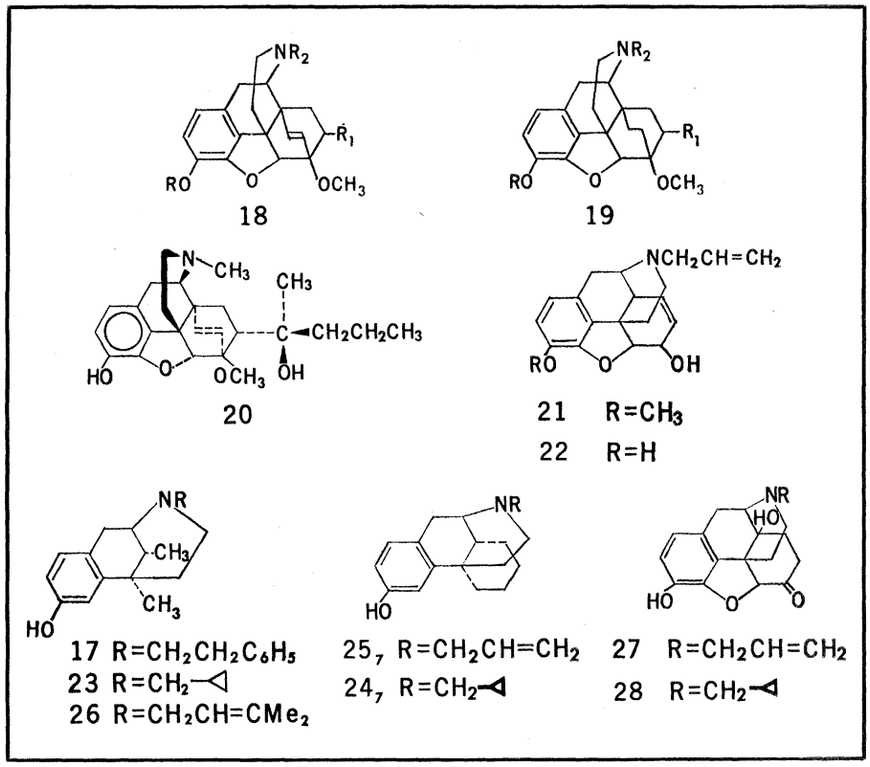
The discovery of the complete structure of morphine (*10*) led inevitably to attempts to synthesize the molecule. Initially successful only to the production of a basic skeleton [see Grewe, *27*)], the total synthesis was completed in 1956 by Gates and Tschudi (*28*); Grewe's work, continued by Schnider and his associates (*29*) yielded a most important discovery. The complete morphine structure was not essential for strong analgesic action and other morphine-like effects. *N*-Methylmorphinan (*27*) was analgesic, and (—)-3-hydroxy-*N*-methylmorphinan (levorphanol, **15**) was an effective therapeutic agent, three or four times more potent than morphine (*21, 29*). But once again analgesic potency and dependence liability appeared together and continued to do so in the many morphinan derivatives produced subsequently.

The activity exhibited by levorphanol prompted the synthesis (from 1953) of two even simpler modifications, phenylmorphans and 6,7-benzomorphans (Fig. 6). The former (*30*) was a very simple structure indeed, but it retained the alleged chemical essentials—the benzene nucleus, the quaternary carbon, and the tertiary nitrogen two methylene groups removed from the quaternary carbon. 5-*m*-Hydroxyphenyl-2-methylmorphan (**16**) (*30*) was equivalent to morphine in analgesic activity in animals. In spite of this, attention was diverted to the benzomorphans and this group has been studied extensively (*31*), particularly because for the first time, in animals at least, some dissociation of analgesia and dependence was evident.

Levorphanol has one ring less than morphine, and benzomorphan (Fig. 6) has one ring less than levorphanol, bearing hydrogen only or an alkyl group at carbon 9 and an alkyl group at carbon 5. The first of the benzomorphans to be brought to general attention was phenazocine (**17**) (*31*), which had a phenethyl group on nitrogen and methyl groups at carbons 5 and 9. It was an effective analgesic, especially orally, with definitely less dependence capacity in monkeys and somewhat less dependence liability in man (*16*). Its greatest usefulness should be orally for chronic pain but it was introduced on the American market only in a form for parenteral administration.

The attachment of phenethyl onto nitrogen was an outgrowth of another series of experiments. Methyl on nitrogen of morphine for a long time was considered optimal for analgesic action because its elimination or substitution by ethyl reduced activity. A systematic study of the role of the tertiary amine in morphine action (*32*), however, showed that although activity was re-

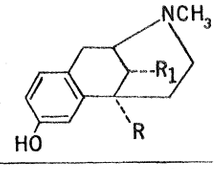




duced by *N*-ethyl substitution, it began to be restored and increased even beyond that of morphine as the *N*-alkyl group increased in length or size from *N*-propyl to *N*-amyl to *N*-hexyl to *N*-phenethyl, and to *N*-phenacyl. Studies of the benzomorphan series showed additionally that analgesic action was exhibited even with hydrogen (*33*) instead of alkyl groups on carbons 5 and 9, and some interesting differences were revealed in some of the optical isomers that we will describe later.

We have described modifications of morphine and the synthesis of related, less complex structures. In contrast, Bentley and his co-workers (*34*) reasoned that bases of more rigid and complex construction might afford selectivity for the biologic receptor and thus a separation of pharmacological actions. They prepared a large group of compounds from thebaine (**4**) with an etheno (**18**) or ethano (**19**) bridge from carbon 6 to carbon 14 and with variations at carbon 7. A most active compound of this series, M-99 (**20**) was, on a dosage basis, at least 2000 times more powerful as an analgesic than morphine and in dependence capacity in monkeys. It has proved useful for incapacitating large animals such as elephants because of the very small size of the effective dose which can be applied with a dart propelled by a crossbow or similar device. Potency based on dosage is not of itself an advantage in clinical medicine and, though members of this series have been tried in man, none has yet found favor as a practical medicament.

Table 1. Pharmacologic properties of *l*- and *d*-benzomorphans compared with morphine (**1**) and codeine (**2**). R and R_1 may be methyl (Me), ethyl (Et), or propyl (Pr) groups, or hydrogen (H); the 50-percent effective dose (ED_{50}) is expressed as milligrams per kilogram of body weight; PDC is physical dependence capacity.



Compound No.	R	R_1	Enantiomer	ED_{50}	PDC	Antagonistic potency compared with that of nalorphine
32	Me	Me	(−)	0.6	No	1/50–1/30
			(+)	Inactive	No	No
33	Et	Et	(−)	1.2	No	1/10
			(+)	7.5	Intermediate	No
33 a	Pr	Me	(−)	0.8	No	1/5
			(+)	12.3	High	No
	Et	H	(−)	0.6	No	1/40–1/20
			(+)	21.8	Low	No
	Me	H	(−)	1.8	No	1/50
			(+)	22.9	Very low	No
1			(−)	1.2	High	No
2			(−)	7.5	Intermediate	No

Narcotic Antagonists

Many years ago Pohl (*35*) made the astonishing observation that *N*-allylnorcodeine (**21**), codeine (**2**) with an allyl group replacing methyl on nitrogen, was antagonistic to the respiratory depressant effect of morphine. Almost 30 years later, the phenolic analog, *N*-allylnormorphine (nalorphine, Nalline) (**22**) was made and specific antagonistic action confirmed (*36*). In the search for a better analgesic, this was another milestone that was brought into particular prominence when it was demonstrated in the early 1950's that nalorphine was not only a potent, specific antagonist to essentially all morphine-like effects but also by itself was an analgesic equal to morphine on a milligram dose basis. It also produced morphine-like and, too often, bizarre, disturbing, psychotomimetic side effects. As an antagonist, it appeared both theoretically and in initial tests in man unlikely to produce drug dependence. More thorough study demonstrated that nalorphine could produce some degree of physical dependence of an unusual character, drug dependence of specific opiate antagonist type (*37*), but it did not cause drug-seeking behavior and there was no evidence of abuse potential. From the practical standpoint, then, if it were not for the aforementioned side effects, separation of analgesia and dependence liability had been accomplished. The important point, however, was the presence of agonist (morphine-like) and antagonist (nalorphine-like) properties, perhaps simultaneously operative, in the same compound and, according to subsequent observations, in almost all so-called morphine-like compounds. This was brought out most clearly in a number of very potent antagonists such as cyclazocine, cyclorphan, and levallorphan, and most interestingly in some *N*-methyl-benzomorphan isomers.

Cyclazocine (**23**), an *N*-cyclopropylmethyl benzomorphan (*38*) and cyclorphan, *N*-cyclopropylmethylmorphinan (**24**), (*39*) were many times more potent as antagonists than nalorphine and both were about 40 times more potent as analgesics than morphine. Both produced psychotomimetic effects to such an extent at or near the analgesic dose as to preclude their use as analgesics in man. Levallorphan, *N*-allyl-3-hydroxymorphinan (**25**), the morphinan analog (*29*) of nalorphine, was several times more effective than nalorphine as an antagonist and in the same range as morphine as an analgesic with a very flat dose-response curve.

The direct respiratory depressant effect of these antagonists alone is minimal; they never produce apnea. Administered repeatedly to man, tolerance to the psychotomimetic effects develops rapidly but antagonism to the euphoric and dependence-producing effects of morphine, heroin, and related substances persists so that administration of any of these narcotics, in a single dose or in repeated doses, to an individual tolerant to cyclazocine, for example, has no acute effect nor does physical dependence of the morphine type develop. Hence, stabilization on cyclazocine is being used clinically in order to deter relapse to abuse of heroin (*40*).

The presence of analgesic activity in compounds which may also produce some degree of specific antagonistic action is the best lead to date in the search for a better analgesic and has stimulated much research along several lines. Of particular importance is the investigation of the optimum ratio of agonist-antagonist activity that would make a compound useful as an analgesic and give it better and more prolonged antagonistic action for more effective deterrence of dependence. Pentazocine (*38*) is a product of the first part of this investigation. It has 3,3-dimethylallyl as the substituent on nitrogen of a benzomorphan (**26**) and has been marketed as Talwin. It is a weak antagonist, with only about one-fiftieth the activity of nalorphine, and a good analgesic, 30 or 40 milligrams of pentazocine being equivalent to 10 mg of morphine; it has a relatively low frequency of disturbing side effects. Tolerance to it can develop and it can cause some physical dependence with an abstinence syndrome partly like that of morphine, partly like that of nalorphine. Animals and man show some drug seeking behavior and a few cases of abuse have been reported mostly with persons who abused other drugs previously.

Naloxone (*41*), the *N*-allyl derivative (**27**) of oxymorphone, is a product of the second line of research mentioned in this area. It seems to possess no agonist property. It is short acting and poorly effective orally. Its analogs with cyclopropylmethyl (**28**) or cyclobutylmethyl on the nitrogen of oxymorphone are longer acting and better candidates for development as deterrents to relapse to heroin abuse (*42*). The ratio of effectiveness of naloxone by parenteral as opposed to oral administration has suggested a special application of this product as a general deterrent to drug dependence of morphine type. A very small amount of naloxone added to an oral dose of a narcotic, in the ratio of 1 : 20 of the usual dose of methadone, for example, would not at all antagonize or interfere with the desired effect of methadone. If the attempt were made to take a large dose or multiple doses over a short period of time, the increase in the naloxone would antagonize the methadone effect. If the attempt were made to divert the oral mixture to parenteral administration, the 100 times greater effectiveness of the naloxone would manifest itself, no narcotic effect would be experienced in the naive individual, and abstinence phenomena would be precipitated in a heroin-dependent person (*43*).

Another curious aspect of the agonist-antagonist combination of pharmacological properties was encountered in the evaluation of the optical isomers of some benzomorphans (Table 1). The relatively inactive (for analgesia) dextro isomers supported a dependence of the morphine type in the monkey. More surprisingly, the analgesically active levo isomers were antagonistic in that they increased the severity of the symptoms of withdrawal and precipitated abstinence signs in the nonwithdrawn, dependent animal (*44*, *45*). This difference for the benzomorphan isomers has not yet been demonstrated in man.

Miscellaneous Synthetic Compounds

To complete this survey of the search for a better analgesic, we will mention briefly a number of compounds that have resulted from other attempts to elaborate (or alter) Schaumann's concept of the essential features of a morphine-like analgesic. These include the thiambutenes, the profadols (Fig. 7), the benzimidazoles (**28a**), the propionanilides (**30**) and propiram, the tetrahydroisoquinolines (**29**) and other miscellaneous compounds, discovered usually in other research efforts (*44*). Many such compounds are interesting but their practical importance has been discounted or not yet proven. The thiambutenes are remotely related to methadone (**12**). Profadol is interesting because the antagonistic component in one of its optical isomers was apparent in both animals and man. Propiram, *N*-propionyl-*N*-(2-pyridyl)-1-(*1*-piperidino-2-aminopropane, as the *levo* isomer showed

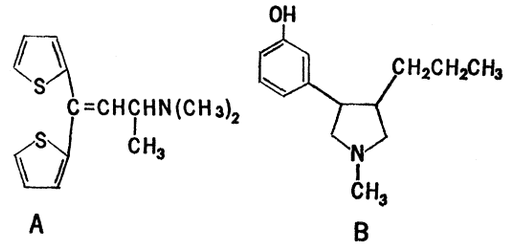
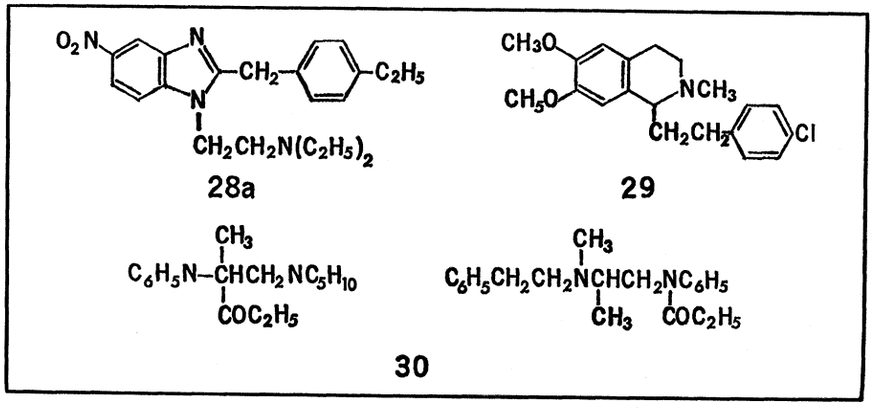


Fig. 7. Dimethylthiambutene (A) and profadol (B).



similar effects (*46*). In the propionanilides, tertiary nitrogen has replaced the quaternary carbon (*22*). The benzimidazoles are powerful analgesics unsuitable for clinical use because they cause severe respiratory depression. The tetrahydroisoquinolines were based on the reported codeine-like activity of certain 1-substituted isoquinolines (*44*).

Present Status

Where are we then in our search for a better analgesic, an understanding of structure-action relationships, and the mechanism of analgesic action? Not at the end of the road or the attainment of these goals, certainly. Schaumann's concept (*19*) of the importance of a 4-phenylpiperidine fragment of morphine, broadened (*20*) to an aromatic ring attached to a quaternary carbon separated from a tertiary nitrogen by two saturated carbon atoms, as basic for strong analgesic action still holds in a practical sense, in spite of exceptions. Recently, Jacobson *et al.* (*44*) stated that if the tertiary nitrogen was in six-membered ring formation a phenolic hydroxyl meta to the quaternary carbon enhanced pharmacological activity and that in the benzomorphans a change of the quaternary carbon to tertiary reduced analgesic activity only slightly (*44, 47*).

Since 1954 considerable attention has been paid to the topology and absolute stereochemistry of analgesic molecules and their fit on a biologic receptor. Gero (*48*) tried to equate the thiambutene and methadone structures to the classical analgesics by postulating a pseudopiperidine ring formation. Beckett and Casy (*49*) suggested specific orientation of the various pharmacophoric groups to fit a hypothetical analgesic receptor, having a flat surface, a cavity and an anionic site accommodating an aromatic ring, a hydrocarbon moiety and a protonated nitrogen, respectively. These are interesting postulates but none of them account adequately for the high analgesic potency of outstanding exceptions such as fentanyl, benzimidazoles, and tetrahydroisoquinolines. Nor is there consistent correlation between the configuration of the more active enantiomers and analgesic activity. Portoghese (*50*) has introduced a new concept of different modes of interaction with the receptor site, and others (*51*) are employing quantum chemical calculations to define the molecular mechanism of drug action and its relation to drug molecular structure and possible receptor site interaction. Finally, Pert and Snyder (*52*) claim to have demonstrated specific binding of narcotic analgesics and naloxone "to an opiate receptor of mammalian brain and guinea pig intestine" and interference with binding of the naloxone by prior treatment of the tissue with other narcotics. These studies may ultimately provide for a more intelligent scientific design of new analgesics and antagonists. Along with the research into the pharmacokinetic properties and enzyme interactions of new compounds, these studies should also lead to a better understanding of the mechanisms of analgesia, tolerance, and dependence.

Meanwhile we continue to make some progress by synthesis planned from rather superficial structure-action rationale, however pedestrian this may seem. Thus have emerged during the last 30 years a fair number of totally synthetic analgesic and antitussive agents—pethidine, methadone, levorphanol, dextrometharphan, phenazocine, propoxyphene, pentazocine (to name a few) that have proved to be useful substitutes for the narcotic products of opium. Among these, pentazocine, for moderate to severe pain, and propoxyphene, used extensively in mild pain, are deemed of sufficiently low abuse potential that they are not controlled as narcotics. In addition, orally effective, long-acting maintenance drugs (methadone, *l*-α-acetylmethadol) have been developed; they are being used beneficially, it is the consensus, in some 70,000 addicts in the United States and Canada. Finally, safe narcotic antagonists have been developed and these may prove effective in the deterrence of narcotic abuse in one of the most recent modalities of treatment under study.

References and Notes

1. Derosne, *Ann. Chim.* **45**, 257 (1803).
2. F. W. A. Sertürner, *J. Pharmazie* **13**, 234 (1805).
3. ———, *Ann. Physik.* **55**, 56 (1817).
4. P.-J. Robiquet, *Ann. Chim. Phys.* **5**, 275 (1817).
5. ———, *ibid.* **51**, 225 (1832).
6. J. Pelletier, *J. Pharmacol.* **21**, 555 (1835).
7. G. Merck, *Justus Liebig's Ann. Chem.* **66**, 125 (1848).
8. A. Laurent, *Ann. Chim. Phys.* **19**, 359 (1847).
9. A. C. Brown and T. R. Fraser, *Proc. Roy. Soc. Edinburgh* **6**, 228 (1869); A. Matthiessen and C. R. A. Wright, *Proc. Roy. Soc. London* **17**, 455, 460 (1869); *ibid.* **18**, 83 (1869).
10. J. M. Gulland and R. Robinson, *Memoirs of the Proceedings of the Manchester Literary and Philosophical Soc.* **69**, 79 (1925); *Chem. Abstr.* **20**, 765 (1926).
11. D. B. Dott and R. Stockman, *Int. Med. Congr. 9th*, Washington, D.C. (1890); *Brit. Med. J.* **2**, 189 (1890).
12. C. R. A. Wright, *J. Chem. Soc.* **27**, 1031 (1874).
13. H. Dreser, *Deut. Med. Wochenschr.* **24**, 185 (1898); *Ther. Monatsschr.* **12**, 509 (1898).
14. G. Strube, *Ber. Klin. Wochenschr.* **35**, 903 (1898).
15. J. Pearl, H. Stander, D. McKean, *J. Pharmacol. Exp. Ther.* **167**, 9 (1969); P. L. Nilsen, *Acta Pharmacol. Toxicol.* **18**, 10 (1961); T. D. Perrine, L. Atwell, I. B. Tice, A. E. Jacobson, E. L. May, *J. Pharm. Sci.* **61**, 86 (1972).
16. H. F. Fraser and H. Isbell, *Bull. Narcotics* **12**, No. 2, 15 (1960).
17. L. F. Small, N. B. Eddy, E. Mosettig, C. K. Himmelsbach, *Pub. Health Rep. Suppl.*, p. 138 (1938).
18. O. Eisleb and O. Schaumann, *Deut. Med. Wochenschr.* **65**, 967 (1939).
19. O. Schaumann, *Arch. Pharmakol. Exp. Pathol. Naunyn-Schmiedebergs* **196**, 109 (1940).
20. ———, *Pharmazie* **4**, 364 (1949).
21. N. B. Eddy, H. Halbach, O. J. Braenden, *Bull. World Health Organ.* **17**, 569 (1957).
22. R. A. Hardy, Jr., and M. G. Howell, in *Analgetics*, G. deStevens, Ed. (Academic Press, New York, 1965), chap. 5.
23. M. Bockmühl and G. Ehrhart, *Justus Liebig's Ann. Chem.* **561**, 52 (1949).
24. V. P. Dole, in *Narcotic Drugs, Biochemical Pharmacology*, D. H. Clouet, Ed. (Plenum, New York, 1971), chap. 25.
25. N. B. Eddy, E. L. May, E. Mosettig, *J. Org. Chem.* **17**, 321 (1952); E. L. May and N. B. Eddy, *ibid.*, p. 1210.
26. J. H. Jaffee and E. C. Senay, *J. Amer. Med. Ass.* **216**, 1303 (1971); A. Zaks, M. Fink, A. Freedman, *ibid.* **220**, 811 (1972).
27. R. Grewe, *Naturwissenschaften* **33**, 333 (1946).
28. M. Gates and G. Tschudi, *J. Amer. Chem. Soc.* **78**, 1380 (1956).
29. J. Hellerbach, O. Schnider, H. Besendorf, B. Pellmont, *Synthetic Analgesics* (Pergamon, London, 1966), pt. 2(A).
30. E. L. May and J. G. Murphy, *J. Org. Chem.* **20**, 1197 (1955).
31. N. B. Eddy and E. L. May, *Synthetic Analgesics* (Pergamon, London, 1966), pt. 2(B).
32. R. L. Clark, A. A. Pessolano, J. Weijlard, K. Pfister, 3rd, *J. Amer. Chem. Soc.* **75**, 4963 (1953).
33. E. L. May and M. Takeda, *J. Med. Chem.* **13**, 805 (1970).
34. R. W. Bentley, D. G. Hardy, B. Meek, *J. Amer. Chem. Soc.* **89**, 3267, 3273 (1967).
35. J. Pohl, *Z. Exp. Pathol. Ther.* **17**, 370 (1915).
36. J. Weijlard and A. E. Erickson, *J. Amer. Chem. Soc.* **64**, 869 (1942); K. Unna, *J. Pharmacol. Exp. Ther.* **19**, 27 (1943); E. L. McCawley, E. R. Hart, D. Marsh, *J. Amer. Chem. Soc.* **63**, 314 (1941).
37. N. B. Eddy and W. R. Martin, *Pharmakopsychiat. Neuro-Psychopharmakol.* **3**, 73 (1970).
38. S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, J. G. Bird, *J. Med. Chem.* **7**, 123 (1964).
39. M. Gates and T. A. Montzka, *ibid.*, p. 127.
40. M. Fink, in *Narcotic Drugs, Biochemical Pharmacology*, D. H. Clouet, Ed. (Plenum, New York, 1971), chap. 24.
41. M. J. Lewenstein and J. Fishman, U.S. patent 3,254,088 (1966).
42. H. Blumberg, personal communication.
43. I. Pachter and M. Gordon, personal communication.
44. A. E. Jacobson, E. L. May, L. J. Sargent, in *Medicinal Chemistry*, A. Burger, Ed. (Wiley-Interscience, New York, ed. 3, 1970), chap. 49.
45. N. Yokoyama, F. B. Block, F. H. Clarke, *J. Med. Chem.* **13**, 488 (1970).
46. D. R. Jasinski, W. R. Martin, R. Hoeldtke, *Clin. Pharmacol. Ther.* **12**, 613 (1971).
47. K. Kanematsu, M. Takeda, A. E. Jacobson, E. L. May, *J. Med. Chem.* **12**, 405 (1969).
48. A. Gero, *Science* **119**, 112 (1954).
49. A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.* **6**, 986 (1954).
50. P. S. Portoghese, *J. Pharm. Sci.* **55**, 865 (1966); *Annu. Rev. Pharmacol.* **10**, 51 (1970).
51. J. Kaufman, J. D. Petke, E. Kerman, *Int. J. Quantum Chem.*, in press.
52. C. B. Pert and S. H. Snyder, *Science* **179**, 1011 (1973).