NARCOTIC ANALGESICS AND ANTAGONISTS 6512

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Introduction

This account covers important work reported since the last review of the subject in this series (1), and in general the literature is surveyed for the period July 1966–April 1970. Certain aspects of the subject have been fully covered in recent reviews (2–4) or Symposia (5–9) and are only briefly mentioned here. Attention has been particularly paid to recent methods for the study in animals of drugs with potential abuse liability and the factors governing tolerance, drug dependence, and relapse. New chemical agents of potential use as analgesics and reported since January 1969 are described, those reported previously being adequately covered in *Annual Reports in Medicinal Chemistry* (10). Analgesics showing a clear potential for use in medicine are discussed in greater detail with coverage of the literature over the whole period of the review.

Animal Screening for Drug Dependence

Terminology.—The semantic difficulties encountered in differentiating between "drug addiction" and "drug habituation" have culminated in an Expert Committee of the World Health Organization (11) recommending the use of the term "drug dependence'" for general drug abuse. The nature of the dependence can be specified by reference to a known drug, e.g. "drug dependence of the morphine type."

Dependence on morphine is an adaptive state characterized by severe disturbances of the neuromuscular, autonomic, and endocrine systems when administration of the drug is abruptly suspended, or its action is counteracted by a specific antagonist (12). Since no overt manifestation of physical dependence is evident if an adequate dosage is maintained, the extent of dependence can only be judged in relation to the intensity of these disturbances at the height of the abstinence syndrome.

Other features of the phenomenon of drug dependence include the development of tolerance (13–16), which requires an increase in dose to sustain the initial pharmacodynamic effect and, in certain individuals, the emergence of psychological dependence which manifests itself as a compulsion to continue taking the drug for its pleasurable subjective effects (17–20).

Screening for physical dependence.—In view of the many authoritative works already established in the literature as standard references on the laboratory assessment of physical dependence of opioid analgesics (13, 21–23), the present survey will merely itemize the traditional procedures, but will emphasize those techniques that have been developed over the last five years.

The methodology for evaluating the existence of physical dependence in new compounds in monkeys (16, 24–28)—single dose suppression, substitution, and primary physical dependence tests, respectively—is similar to that routinely used with the interned population of former opiate addicts at the Addiction Research Center at Lexington, Kentucky, U.S.A. (17, 18, 21, 29–34). In a new test, Holtzman & Villarreal (35) have investigated the effect of chair restraint on the rectal temperature of morphine-dependent monkeys. Body temperature fell by as much as 8°C if the primates were restrained in chairs within 3–7 hours after a maintenance dose of morphine; however, the hypothermic effect was corrected by a further injection of morphine. In contrast, chair restraint produced a mean temperature decrease of only 0.6°C with nondependent monkeys. Administration of nalorphine to morphine- or ketobemidone-dependent monkeys at a dose (1.0 mg/kg) which produced no change of temperature in nondependent monkeys, also elicited a hypothermic response from morphine-dependent monkeys. Interestingly, the lowest temperatures were recorded after the abstinence syndrome had declined. The mechanism of the restraint-induced hypothermia is uncertain. The fact that shivering was totally absent suggests a displacement in the 'set point' temperature of the thermoregulatory system.

A valuable application of this phenomenon may be in the evaluation of morphine-like physical dependence liability. Preliminary results (36) have been encouraging in that restraint-induced hypothermia is reversed only by those drugs that specifically suppress the manifestations of morphine withdrawal.

The sensitivity of the spontaneous blinking rate in nondependent monkeys to the effects of centrally active drugs has recently been investigated (37). Morphine, profadol XXXIV, and levallorphan markedly reduce the blinking rate (38). This effect is reversed by 2 mg/kg of nalorphine in the case of morphine and profadol, but with levallorphan, an antagonist with negligible physical dependence capacity in the monkey, only a partial reversal takes place with a dose of nalorphine four times higher.

In this context, Villarreal has suggested that evaluation of the susceptibility to antagonism by nalorphine may provide a more meaningful measure of dependence capacity for analgesics with mixed agonist-antagonist activity than the single dose suppression test, which appears unsatisfactory for this type of compound. This proposition is analogous to that of Blumberg and colleagues (39, 40) and Blane & Dugdall (41) who have ranked the analgesic effects of partial agonists in rodents on the basis of their interaction with the pure antagonists naloxone Va, and diprenorphine (R&S 5050-

M) XX using phenyl-benzoquinone (42) or bradykinin (43) as the nociceptive stimulus.

Effects on the contraction of the longitudinal muscle of the electrically-stimulated guinea pig isolated ileum have been used to measure agonist-antagonist properties (44–46). Kosterlitz (45) has suggested that compounds have only a small liability to cause morphine-like dependence when, in this test, agonist activity is absent (e.g. naloxone), or low (e.g. codeine, pentazocine XXIa, profadol), or when high agonist potency is associated with high antagonist potency (e.g. nalorphine, cyclazocine XXIe). However, Fennessy et al (47) do not recommend this preparation for dependence correlations.

Several workers (24, 48–56) have assessed dependence liability in the dog, despite the sometimes erratic abstinence syndrome and the high incidence of narcotic-induced constipating and emetic effects in this species. Utilization of the physically dependent spinal dog (57–59) seems a possibility in the screening of opioids but this procedure suffers from inherent technical difficulties.

Although a low level of dependence can be demonstrated in the cat (60), rabbit (61), and guinea-pig (62), these species have generally been found unsatisfactory for routine screening. The rat, however, has been used extensively and the numerous reports characterizing the abstinence syndrome (63–71) have provided a reasonable basis for the assessment of abuse liability (72, 73) when facilities for primate studies have not been available.

The Straub-tail reaction in mice (74, 75) is of doubtful value in screening in view of its nonspecific nature. It has been contended that the behavioral repertoire of the mouse during opiate withdrawal is too limited and variable to justify using this species in the evaluation of dependence (13, 22, 70, 76–80). The work of Huidobro and colleagues (81–86) describing the production of an intense and reproducible abstinence syndrome in mice implanted subcutaneously with pellets of morphine base has recently been successfully elaborated into a cheap, reliable, and rapid method for predicting dependence liability and tolerance (87–89, 91).

The quantitative assay (88) involves injecting naloxone into a group of 10 narcotic-pelleted (90) mice and scoring the most characteristic sign of abstinence, an uncontrollable urge to jump. An index of physical dependence can be obtained at any interval after implantation by estimating the dose of naloxone which induces half the mice to leap off a circular platform within 15 minutes. If the pellet is removed, usually after 3 days, signs of withdrawal are maximal 6–8 hours later and objective measurement is again obtained by noting the percentage of animals that leap off the platform within the time period. The response can be suppressed with morphine and its surrogates, e.g. GPA 1657 XXIIa, methadone, and pethidine, but not with a variety of other centrally active compounds.

The implantation technique has been tested in young chicks, birds with an ill-defined blood brain barrier, and the preliminary results with reference

analgesics appear promising (91). Three components of the nalorphine-precipitated abstinence syndrome in 5-day pelleted chicks are reproducible and can easily be quantified—the stereotyped head twitching in the horizontal plane, the excessive yawning, and the high incidence of soft stools. The syndrome is rapid in onset, intense, and of short duration, the first signs being apparent within one minute of antagonist injection but are declining after 7–10 minutes.

Psychological approaches to opiate dependence and self-administration by laboratory animals.—Research techniques derived from the behavioral principles of operant conditioning are playing an increasingly important role in the analysis of physiological and psychological dependence (92–96). Investigations involving the self-administration of water-soluble drugs through indwelling intravenous catheters by relatively unrestrained rats (97–100) and monkeys (101, 102) have been designed to determine whether subjects will preferentially press bars for the drug under test rather than a series of alternatives. Applications of this procedure have shown that opioids such as dihydromorphinone, methadone, and codeine may be substituted for morphine with continued maintenance of dependence, whereas dependent animals will inject themselves at a much higher rate when either the opioid is decreased, or a short infusion of nalorphine is given (103, 104). In these studies the assumption has been made that the drug acts as a reinforcer, because it prevents the occurrence of, or attenuates the aversive withdrawal state. The method is potentially useful, not only in the prediction of abuse liability of new compounds, but also for the study of the modifying effects of drugs on behavioral aspects of dependence, tolerance, and withdrawal.

Several workers (105) have used animals previously made physiologically dependent upon the test drug, so that interpretation of subsequent self-administration data in terms of subjective drives has been rather complicated. Recently, it has been established that physical dependence is not a necessary antecedent condition for some monkeys to self-inject morphine (106), or again for some rats to accept morphine-contaminated food (107) and water (108–110). Deneau et al. (111) used naive rather than dependent monkeys and reported that physiological dependence developed towards morphine, codeine, pentobarbitone, cocaine, d-amphetamine, ethanol, and caffeine, since the animals voluntarily initiated and maintained self-administration of these drugs. With particular reference to abuse liability, it is pertinent to note that all of these drugs except caffeine produced psychotoxicity (altered behavior with or without physical deterioration). The monkeys exhibited little desire for nalorphine, chlorpromazine, and mescaline—drugs seldom abused by man—but would self-administer profadol (38) and pentazocine (112).

It is evident that these techniques afford an important advance in the understanding of psychological aspects of dependence which, until lately,

have not been amenable to scientific investigation. Operant behavioral procedures may also have a role to play in the testing for hallucinogenic activity in narcotic antagonists (113). These compounds can bring about dysphoric effects in man such as uncontrolled racing thoughts, inability to concentrate, feelings of irritability, and either pleasant or unpleasant delusions (2). At present there is no satisfactory animal model that allows a confident prediction as to whether or not a new compound will cause these disturbing subjective effects when given to man. Harris & Rosenberg (114) have speculated on the possibility of selecting a suitable narcotic antagonist analgesic on the basis of its effect on animal somatic reflexes (33, 58, 59, 115–117). Collier & Schneider (118, 119) have shown that high doses of cyclazocine, levallorphan, and perhaps pentazocine, compounds known to cause hallucinations in man (2, 120–123), induce bizarre behavior in the rat consisting of side to side head movements, pivoting on the hind feet, and walking backwards. This syndrome did not occur with morphine, profadol, or naloxone. Nalorphine gave a low score, an observation that is consistent with the finding of Jacob and colleagues (124, 125) that this compound differs from a variety of other psychotomimetics in not causing hyperthermia in the rabbit. Nalorphine is also inactive, along with morphine and etorphine, XIIc, in the rabbit reserpine reversal test (126) whereas hallucinogens such as cyprenorphine XVIIIf, LSD, and atropine cause a reversal of ptosis and a recovery of the righting reflex (127).

An intriguing report describing the disruptive effect of LSD, mescaline, and amphetamine compounds on the nest-building behavior of mice has recently appeared (128). Interesting results might ensue from a comparison of narcotic antagonists in this test situation.

Factors Influencing Relapse to Opioids

The persistence of opioid-seeking behavior has often been explained on the basis of drug-induced euphoria on the one hand, and fears associated with abstinence on the other. Wikler (129, 130) has proposed that in opioid-dependent persons the environmental stimuli that accompany withdrawal from opioids may, in themselves, and at a later date, evoke signs of withdrawal thus providing an unconscious motivation for relapse and renewal of the cycle. The term 'relapse' implies the reinitiation of the self-administration of drugs after a period in which the organism has been drug-free. Wikler's hypothesis has been partially confirmed in experiments with rats (103, 130–133), and monkeys (134–136). Furthermore, in morphine-dependent rats subjected to abrupt drug-withdrawal, relapse tendencies have been apparent almost one year later, which is indicative of a long-term derangement of homeostasis (137). Such a picture has been reported by Martin and his colleagues (138, 139) for man, where the persistence of minor physiological abnormalities from pre-dependence base-line levels in blood pressure, pulse rate, temperature, pupil size, and sensitivity of the respiratory center to CO_2, became evident 6–9 weeks after morphine withdrawal and, with

respect to certain signs, lasted for 26 to over 30 weeks. These changes constitute the protracted or secondary withdrawal syndrome (69, 132) in man, and may be correlated with a reduced ability to withstand physiological stress (140), a possible predisposing factor for relapse.

Recent Theories on Tolerance and Dependence of the Morphine Type

Several explanations have been advanced to account for the phenomena of tolerance to and dependence on the narcotic analgesics (15, 16, 51, 88, 141–148) since the formulation of the dual-action theory by Tatum, Seevers & Collins in 1929 (24). The proposition by Himmelsbach (149) that tolerance and physical dependence are a consequence of the recruitment of contra-adaptive forces which antagonize the actions of morphine has been developed by Martin (2, 59, 138, 150, 151) and expressed in terms of a *homeostatic theory*. Martin envisages a component of these counter-responses being simply the homeostatic reactions to abnormally intense physiological stimuli, for example, excessive retention of carbon dioxide. He has also presented a theory based on the concept of *pharmacological redundancy* (138, 151, 152) which assumes that morphine-sensitive and morphine-resistant pathways in the CNS run in parallel. When the former pathways are depressed, a negative feedback system initiates enhanced activity in the morphine-resistant pathways and tolerance results. On drug withdrawal the depressed pathways return to their normal level of sensitivity but the morphine resistant pathways remain hyper-active and the symptoms of withdrawal are observed.

The *disuse hypothesis* of Jaffe & Sharpless (153–159) shares a common assumption with Martin's theory—that physical dependence represents an adaptation of nervous tissue to the altered pattern of nervous activity produced by the drug, rather than to the presence of the drug per se. The two theories contrast markedly, however, in that Jaffe & Sharpless consider that disuse in certain neural circuits is a primary causative factor in the pathophysiology of physical dependence. These authors postulate the emergence of 'denervation hypersensitivity' in central effector systems as a consequence of continued disuse or depression of neuronal activity by analogy with that which develops in peripheral neuroeffector junctions after pharmacological or anatomical denervation (160, 161). Whereas this hypothesis supposes that the narcotic (or hypnotic) induces supersensitivity of the nerve cell by reducing its supply of transmitter, Collier in his *supersensitivity theory* suggests that dependence may result from drug-induced changes in the number of receptors available for the endogenous humoral transmitter (162–165). Tolerance is thought to arise from a decrease in the number of pharmacological receptors (166) or an increase in the number of silent receptors (162), so that the response to a previously effective dose of drug is reduced.

The *surfeit theory* of Paton (167, 168) is also based on modifications that might occur at nerve terminals as a consequence of opiate administration. If it is assumed that opiates depress the release of transmitter at central sites as they do at peripheral synapses (see 168 for refs.), then a build-up in the concentration of transmitter (acetylcholine) in the terminal axon is possible. Paton suggests that as a result of this accumulation, the fraction of transmitter released by subsequent nerve impulses is sufficient to overcome the opiate blockade, so that effective synaptic transmission takes place and tolerance results. On the termination of opiate administration an exaggerated release of transmitter would bring about the excitatory signs of withdrawal.

Narcotic Analgesics and Antagonists in the Treatment of Heroin Dependence

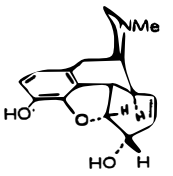
Because most heroin addicts following withdrawal are unable to remain free from drugs, methadone treatment has become increasingly popular, and may be continued for several months or years after heroin withdrawal (169). At an average oral maintenance dose of 100 mg a methadone "blockade" is established in which the patient is buffered from the effects of heroin and other narcotics (170). Methadone thus administered is said to be not euphorigenic and challenge with a very large (80 mg) intravenous dose of heroin (171) produces no euphoria. Success rate in 871 reported cases was greater than 80% (172); similar findings have been reported by other workers (169, 173, 174).

The use of narcotic antagonists to achieve a similar blockade has also been investigated. Because it is long-acting, cyclazocine, which has potent antagonist and agonist actions, was first tried (175, 176). At a daily dose of 4–6 mg some unpleasant subjective effects were experienced, but tolerance to these changes developed rapidly without affecting the narcotic antagonist action. In careful studies by Freedman and his colleagues (174, 177, 178), a maintenance dose of 4 mg per day was reached after fifteen days. After this, heroin challenge produced no euphoria in most patients. The effective duration of a 4 mg dose on chronic administration is at least 20 hours with a peak at 6–8 hours. Success rate from the original Freedman program at July 1968 was only 26 out of 74. As a spin-off from this program, clinical antidepressant activity comparable to that of imipramine was established for cyclazocine (179) and it has been suggested that this activity may contribute to its efficacy in the management of narcotic addiction (180).

The pure antagonist naloxone has also been used. Complete blockade of heroin administration (20 mg) was achieved at a maintenance dose of 200 mg/day (181). To withstand a 50 mg heroin challenge eighteen hours after administration, a dose of naloxone of the order of 1 g is needed (182). The relatively short length of action and high cost of naloxone seems likely to limit its use.

Newer Agents

Morphine derivatives.—B/C *Trans*-Morphine I has been prepared from isoneopine by Japanese workers (183), and surprise has been expressed that this base is a less potent analgesic than morphine III, whereas the reverse had been confidently expected to be the case since isomorphinan (B/C *trans*) derivatives II are more potent than those of morphinan (B/C *cis*). This apparent anomaly may be attributed to the fact that, as a result of the mode of fusion in *trans*-morphine I of the oxygen-containing ring, which is undisturbed during the sequence of reactions starting from isoneopine, ring C is constrained as a boat, and the shape of the molecule is much more similar to that of morphine III than to that of isomorphinan II in which ring C is a chair. The *trans*-1-bromo-dihydrocodeinone prepared by Gates & Shepard (184) undoubtedly has the ring-C chair structure IV (185), and a *trans*-morphine isomer prepared from this base would be of great interest.



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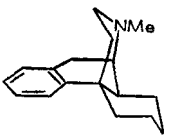

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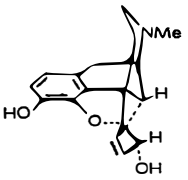

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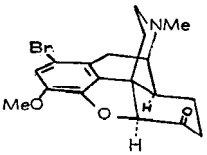
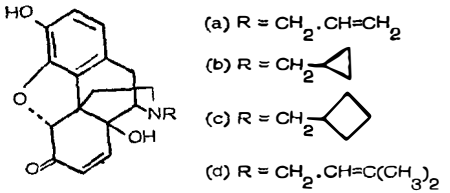


IV

The most important derivative of morphine in the period under review is N-allyl-7,8-dihydro-14-hydroxynormorphinone (naloxone) Va a powerful narcotic antagonist (15–30 × nalorphine) (186). It has no analgesic activity in the rat tail flick and phenylquinone-writhing tests (186, 187). In man it antagonises the respiratory depressant effects of narcotic analgesics but has no respiratory or circulatory effects (188). Lasagna reported (189) that in man naloxone produces no psychotomimetic effects but has some analgesic activity of a biphasic nature; at 5 mg the effect was less than placebo whereas at 2 mg an effect approaching that of morphine was observed. It is completely lacking in any potential for physical dependence (190) and has been studied as an agent to prevent relapse in the treatment of narcotic addiction (181). In addition to antagonising the effects of morphine-like compounds, naloxone in the phenylquinone writhing test antagonises the an-

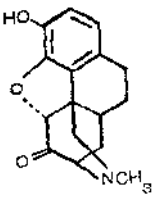
algesic effects of the partial agonists pentazocine, nalorphine, cyclazocine, cyclorphan, and levallorphan (191). Analogous findings in man have been reported (192, 193).



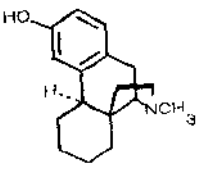
V

Analogs Vb–Vd of naloxone have morphine antagonist activity but are also analgesic (40). The cyclopropylmethyl derivative Vb has highest antagonist activity (40 × nalorphine) but is a weak analgesic. The cyclobutylmethyl compound Vc has potent analgesic and antagonist actions whereas the dimethylallyl derivative Vd, EN1620A, is moderately active in both types of test. The latter compound has been shown to have one-seventh of morphine's potency in man (194).

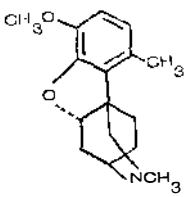
A positional isomer VI of dihydromorphinone has low analgesic activity (195) as does its analog VIII [0.5 × codeine] (197) and metamorphinan VII [0.1 × morphine] (196). The thebainol derivative IX is a potent antitussive (14–55 × codeine) with analgesic properties (2–4 × codeine) but low physical dependence effects in rats (198).



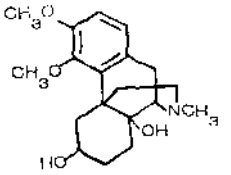
VI



VII



VIII

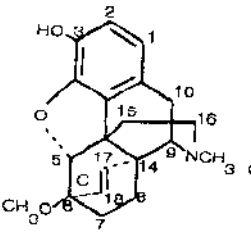


IX

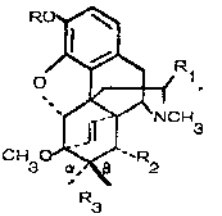
Oripavines.—Though the chemistry of this series is very extensive, and brief details of structure-activity relationships have appeared (199–217), a

collated account of the latter has not been published in a freely available form. We therefore take this opportunity to present the main principles that have so far emerged.

1. The parent of the series, 6,14-*endo*ethenotetrahydro-oripavine X is 40 times more potent than morphine.



X



XI

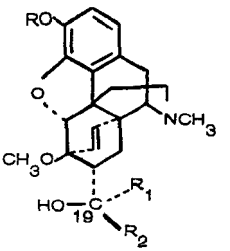
2. In the series of bases of structure XI

(*a*) Oripavine derivatives (R = H) are approximately 10–50 times more potent than corresponding thebaine derivatives (R = CH_3).

(*b*) A C_{16}-alkyl group (R_1) considerably reduces analgesic potency (218).

(*c*) A methylene group ($-CH_2-$) in the $C_{8\alpha}$ position (R_2) gives a significant increase in analgesic potency whereas an unsaturated group (e.g. $-CO_2C_2H_5$) in the same position results in a drastic decrease (215).

3. The most easily achieved and widest range of substitutions (R_3) can be made at C_7. In cases where both C_7 epimers have been studied, relatively small differences of potency have been observed. But it is in the series of tertiary alcohols XII that greatest interest has been found. These alcohols,



(a) R = CH_3, R_1 = CH_3, R_2 = C_2H_5

(b) R = CH_3, R_1 = C_2H_5, R_2 = CH_3

(c) R = H, R_1 = CH_3, R_2 = nC_3H_7

XII

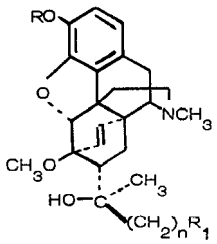
as prepared, are pure epimers so that study of the effects of changes in R_1 and R_2 has been possible. Increase in R_2 from methyl through n-pentyl is

TABLE 1. ANALGESIC ED50 [MG/KG; RAT TAIL PRESSURE (225)] FOR BASES OF STRUCTURE XVIIIa [MORPHINE = 2.0]

R_2 \ R_1	CH_3	C_2H_5	C_3H_7
CH_3	0.45	5.1	2.8
C_2H_5	0.15	1.5	
C_3H_7	0.034	0.26	0.6
C_4H_9	0.036	0.34	

associated with increase in analgesic potency with a maximum at C_3-C_4. Similar increase in R_1 results in a definite decrease in potency (Table 1). In the diastereoisomeric pair of methyl ethyl carbinols, XIIa is 30 times more potent than XIIb; there is a similar potency difference between etorphine XIIc (1000 × morphine) and its diastereoisomer (20 × morphine). In each case the more potent isomer has the R-configuration at C_{19}.

The "peaking" effect in the potency of the homologous series of tertiary alcohols XIIIa is very much more distinct in the analogous series XIIIc in which a phenyl group is sited at the end of the alkyl chain. There is a 2000-



(a) $R=R_1=CH_3$

(b) $R = H$, $R_1 = CH_3$

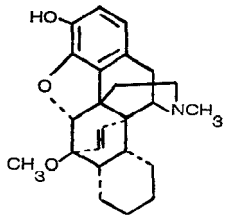
(c) $R = CH_3$, $R_1 = C_6H_5$

XIII

fold increase in potency in changing phenyl (n = 0) to benzyl (n = 1), a further fourfold increase to phenylethyl (300 × morphine) and then a 270-fold decrease to the phenylpropyl carbinol. The magnitude of these changes lies outside conceivable differences in brain concentrations so that specific receptor interactions must be postulated.

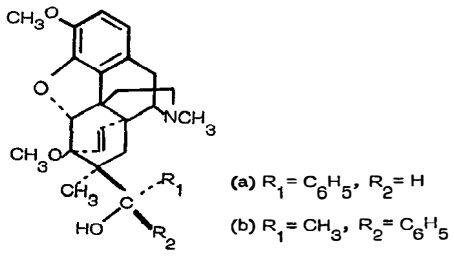
For the homologous series XIIIa Bentley & Lewis (219) suggested that the alcoholic hydroxyl group forms a point of specific binding to the receptor. However the presence of a hydroxyl group at C_{19} is not a requisite for

high analgesic potency since the cyclohexano derivative XIV (220) has been found to be 1000 times more potent than morphine. Nevertheless the



XIV

case for a lipophilic site on the receptor which can interact with the alkyl chain in the earlier series, and particularly with the phenyl group in the new series, is extremely strong. Taking the peak of activity in the phenylpropyl group as representing the most complete interaction, it can be deduced that the lipophilic site does not extend more than approximately 6 Å from C_7, and bearing in mind the high activity of the cyclohexano-compound XIV it seems probable that the site is also fairly close to C_8. The presence of a lipophilic site on the receptor surface also offers a rational explanation for the unexpectedly large difference in analgesic potency between secondary alcohol XVIIa (40 × morphine) and the related tertiary alcohol XVIIb (0.4 × morphine) (221). The alcohols are of different stereochemical se-

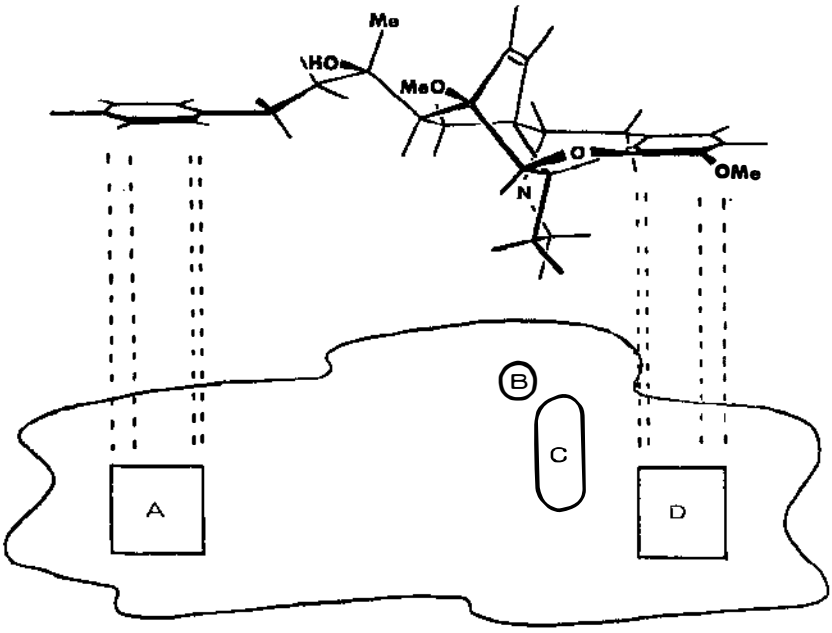


XVII

ries [XVIIa-19R; XVIIb-19S] and only the secondary alcohol can achieve substantial interaction of the side chain phenyl group with the proposed lipophilic site. The $C_{7\alpha}$ tertiary alcohol XIIIc (n = 0) isomeric with XVIIa but with considerably different stereochemistry is less potent than XVIIa by an even greater factor (10^3).

Interaction of XIIIc (n = 2) with the analgesic receptor (222) may be as depicted in Figure 1 to include the new lipophilic site. The molecule may, however, interact with the receptor in quite a different conformation in which the phenyl group in the phenylpropyl side chain occupies the flat surface of the original Beckett receptor which in morphine interacts with the aromatic ring of the phenanthrene nucleus (223).

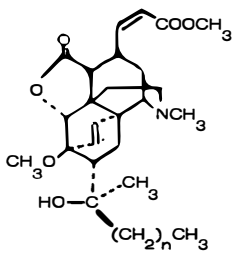
The possibility of an alternative conformation for binding is strength-



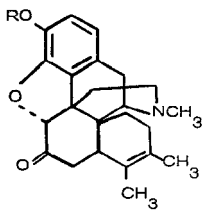
A. Lipophylic site
B. Anionic site
C. Cavity for C-15 and C-16
D. Flat surface for aromatic ring

FIGURE 1

ened by the finding that ozonolysis of carbinols of structure XIIIa, which destroys the aromatic ring, does not result in complete loss of analgesic activity in the products XV (213).



XV



XVI

(a) R = H

(b) R = CH_3

In the 6, 14-*endo*ethenotetrahydro-oripavine series no examples of N-

TABLES 2, 3, 4, 5. ED50 (MG/KG; RAT TAIL PRESSURE) FOR BASES OF STRUCTURE XVIII

TABLE 2

Structure XVIIIb

R_2 \ R_1	CH_3	C_2H_5	n-C_3H_7	n-C_4H_9
CH_3	1.45[b]	2.5[b]	>100[b,a]	9.0[a]
C_2H_5	10[b]	70[b]		
C_3H_7	0.3[a]			
C_4H_9	0.95[a]			

TABLE 3

Structure XVIIIc

R_2 \ R_1	CH_3	C_2H_5	n-C_3H_7
CH_3	110[a]	>100[b,a]	>100[b,a]
C_2H_5	15[a]	44[a]	
n-C_3H_7	2.7[a]		
n-C_4H_9	1.05[a]		

TABLE 4

Structure XVIIId

R_2 \ R_1	CH_3	C_2H_5	n-C_3H_7	n-C_4H_9
CH_3	0.01[b]	0.06[b]	0.52[b]	0.35[a]
C_2H_5	0.02[b]	0.26[b]		
n-C_3H_7	0.002[a]			
n-C_4H_9	0.026[a]			

TABLE 5

Structure XVIIIe

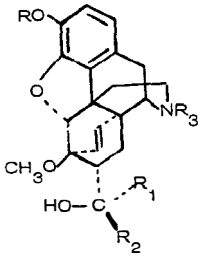
R_2 \ R_1	CH_3	C_2H_5
CH_3	0.21[b]	0.42[b]
C_2H_5	4.2[b]	0.48[b]
n-C_3H_7	0.033[a]	

[a] Analgesia [b] Morphine antagonism [Nalorphine = 0.5]

methyl compounds having demonstrable morphine antagonism have been found, but in the series of cyclohexenodihydromorphinones, which are rearrangement products of the etheno-oripavines XIIIb (203), the dimethyl derivative XVIa with one-tenth of nalorphine's potency is one of most active N-methyl morphine antagonists so far described (224). The analogous codeinone XVIb is a weaker antagonist which does not suppress abstinence in monkeys (38).

Replacement of the N-methyl group in the bases of Table 1 by propyl, allyl and substituted allyl, and cyclopropylmethyl groups has been carried out in most cases. The activities in the tail pressure test in rats (225) of the N-cyclopropylmethyl and N-allyl derivatives are shown in Tables 2 and 3; only in the former series are morphine antagonists found. Archer & Harris (226) showed that over a wide range of morphine, morphinan, and benzomorphan derivatives there is a direct relationship between the analgesic po-

tency of an N-methyl compound and the antagonist potency of the corresponding N-allyl derivative. This relationship does not hold for the bridged thebaine and oripavine derivatives since the more potent N-methyl analgesics have N-allyl and N-cyclopropylmethyl analogs which are themselves potent analgesics.



(a) R = CH_3, R_3 = CH_3
(b) R = CH_3, R_3 = CH_2-cyclopropyl
(c) R = CH_3, R_3 = CH_2.CH=CH_2
(d) R = H, R_3 = CH_2-cyclopropyl
(e) R = H, R_3 = CH_2.CH=CH_2
(f) R = H, R_1=R_2=CH_3, R_3 = CH_2-cyclopropyl
(g) R = H, R_1 = CH_3, R_2 = nC_3H_7, R_3 = CH_2-cyclopropyl
(h) R = H, R_1 = CH_3, R_2 = nC_3H_7, R_3 = CH_2.CH=CH_2

XVIII

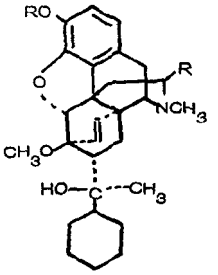
Of the diastereoisomeric pair of N-cyclopropylmethyl methyl-ethyl carbinols (Table 2), the 19S compound is a morphine antagonist (0.2 × nalorphine) whereas the 19R derivative (R&S 5205-M) is an analgesic (0.2 × morphine). However, in the tail-flick test (227) in rats R&S 5205-M shows weak morphine antagonism.

Demethylation of the bases of structure XVIIIb,c gives oripavines XVIIId,e the activities of which are shown in Tables 4 and 5. The weakly analgesic N-allyl thebaines are converted to oripavines, which are strong morphine antagonists. There is a sharp contrast in both N-allyl and N-cyclopropylmethyl series for R_1 = methyl between the bases where R_2 = ethyl and R_2 = n-propyl. The ethyl carbinols are powerful antagonists but the propyl carbinols (etorphine series) are extremely potent analgesics. N-Cyclopropylmethylnoretorphine XVIIIg (R&S 289-M) in the tail pressure test is an analgesic 1000 times more potent than morphine whereas its diastereoisomer (19S series) is a morphine antagonist of nalorphine's potency. However the etorphine derivative is remarkable in that in the tail-flick test it shows morphine antagonism (0.3 × nalorphine).

N-Allylnoretorphine XVIIIh (R&S 218-M) is 50–100 times more potent than morphine as an analgesic in rats but shows very much lower depression of respiration at an equianalgesic dose (228). However this separation of effects does not seem to hold for mice (229). In single dose studies in withdrawn morphine-dependent monkeys R&S 218-M shows some signs of depression but others of exacerbation (38) indicating a partial agonist character though no antagonism of morphine can be demonstrated in the usual animal tests.

Etorphine XIIc has been shown in dogs to be well absorbed sublingually

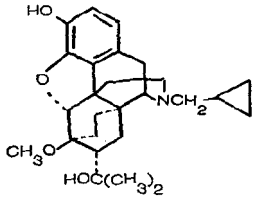
(230); in man (231) 0.5–1.5 μg/kg by this route is equivalent to 5–10 mg of morphine when given by intramuscular or intravenous injection. The cyclohexyl carbinol XIXa which is approximately equipotent with etorphine in rats has been shown to produce its biochemical and pharmacological effects by similar mechanisms to morphine (232). The related C_{16}-methyl-



(a) R = H
(b) R = CH_3

XIX

ated compound XIXb is only a weak analgesic (0.5 × codeine) but is a potent antitussive in guinea pigs (12 × codeine) (218). Etorphine causes immobilisation of animals at very low doses and with a considerable margin of safety; this has led to its use in the capture of game animals in Africa (233–235). Wallach (236) has reported the use of etorphine for immobilisation of many species of captive as well as free-ranging animals. A neuroleptanalgesic mixture of etorphine and metho-trimeprazine has been described (237, 238) and the results of its use in veterinary trials have been reported (239). In this procedure diprenorphine, R&S 5050-M XX, is the antagonist instead of the closely related but more depressant cyprenorphine, M285 XVIIIf, which has been used in game immobilisation.

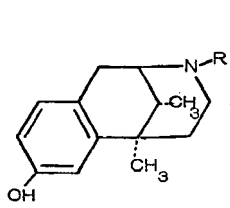


XX

Diprenorphine is a very potent morphine antagonist (100 × nalorphine) which shows no antinociceptive properties in the mouse-writhing and rat-

bradykinin tests (43) and itself can antagonise the analgesic effect of nalorphine, levallorphan, and pentazocine (41). In contrast Kosterlitz & Watt found that it shows some agonist character in the isolated guinea-pig ileum (45) and this action can be antagonised by high doses of the purer antagonist, naloxone (240).

Benzomorphans.—During the period under review the benzomorphans have attracted a great deal of attention. Pentazocine XXIa marketed for parenteral use in 1967 and for oral use in 1969 has been extremely well received and reports of its utility in new situations continue to appear (241–245). A small number of reports of its hallucinogenic (121) and de-



(a) R = $CH_2.CH{=}C(CH_3)_2$

(b) R = $CH_2.CH{=}C(CH_2OH)(CH_3)$

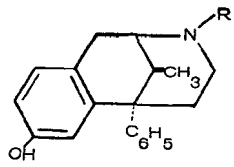
(c) R = $CH_2.CH{=}C(CH_3)(CO_2H)$

(d) R = $CH_2.CH{=}C(CH_3)(CH_2OH)$

(e) R = CH_2-cyclopropyl

XXI

pendence producing effects have appeared (246–249); a total of 57 cases of the latter were known up to mid-1969 (250). There are indications that some individuals may develop a psychological as well as a physical dependence on pentazocine. However, the withdrawal syndrome in these patients is relatively mild and in most cases discontinuation of pentazocine can be accomplished with little difficulty (251). In a direct addiction study Martin (252) found that nalorphine challenge failed to precipitate abstinence but naloxone did produce a moderately severe abstinence syndrome. Abrupt withdrawal of pentazocine produced milder abstinence than similar withdrawal of profadol XXXIV and GPA 1657 XXIIa. The pentazocine absti-



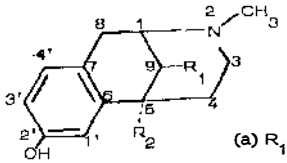
(a) R = CH_3

(b) R = $CONH_2$

XXII

nence syndrome differs significantly from both the morphine and nalorphine syndromes in that there is only minimal blood pressure increase (cf morphine) and lower fever and higher hyperpnea. It was concluded that pentazocine has a lower abuse potential than codeine, propoxyphene, profadol, or propiram since it does not produce the same level of morphine-like subjective effects as these agents and will not suppress abstinence in morphine-dependent subjects.

The metabolism of pentazocine in man has been the subject of a number of recent studies. Investigation of blood levels of the drug after intravenous, intramuscular, and oral administration have been reported (253–255). The drug has a plasma half-life of 2–2.5 hours in man and is capable of passing the placental barrier (254). Using tritium-labelled pentazocine, 50% of an administered dose was found to be excreted in the urine after 12 hours (256). In monkeys about 25% of pentazocine was excreted unchanged together with comparable quantities of oxidative metabolites XXIb and XXIc; the geometrical isomer XXId of the alcohol was identified in small amount (257). Preliminary studies in man indicate a similar pattern (258, 259).



(a) $R_1=R_2=C_2H_5$

(b) $R_1=R_2=CH_3$

(c) $R_1=CH_3$, $R_2=nC_3H_7$

XXIII

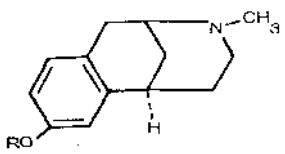
There has also been great interest in certain N-methyl benzomorphans for the differences that have been found between enantiomers in both the α (cis) XXIII and β (trans) e.g. XXII series. In both series the l-isomers have been shown to have weak morphine antagonist properties resulting in low dependence liability whereas the d-isomers are weaker analgesics but show no morphine-antagonist character and have higher dependence potential (260–263). These compounds were the first N-methyl compounds for which morphine antagonism could be demonstrated (260). Casy has shown that the l-isomers in the α- and β-series have the same configuration (R) at C_5 (264) and suggests that higher analgesic activity in these isomers and of the isomorphinans over morphinans may be due to high population of skew-boat conformations for the piperidine ring (265).

The l-isomers, l-metazocine XXIIIb and GPA 1657 XXIIa, precipitated signs of abstinence in withdrawn morphine-dependent monkeys and produced no evidence of morphine-like dependence in direct addiction studies in monkeys (38) but in man they show subjective signs, which are mor-

phine-like and not nalorphine-like (*266, 267*). Moreover they suppress abstinence in man though with lower activity than would be expected from acute effects in normal subjects (*266*). In direct addiction studies in man (*252*) with orally-administered GPA 1657 a morphine-like abstinence syndrome is established either by direct challenge with nalorphine or following abrupt withdrawal.

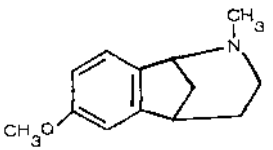
In post-partum (268),) post-operative (*269, 270*), and cancer (*270*) patients, GPA 1657 has been shown to be an effective analgesic with about twice the potency of morphine; orally, a 10 mg dose provides analgesic protection at least comparable to 90 mg codeine (*270*).

The N-carbamoyl analogue XXIIb of GPA 1657 has low dependence liability and in clinical trials 40 mg showed similar oral activity to 60 mg codeine (*271, 272*). Benzomorphans XXIV lacking a substituent at C_5 (and C_9) are as effective analgesics as the C_5-methyl compounds (*273*). Newly synthesized B-norbenzomorphan XXV is similar in analgesic potency to codeine (*274*), but introduction of a methyl group at C_3, or C_8 into XXIII destroys analgesic activity (*275*).



R = H or CH_3

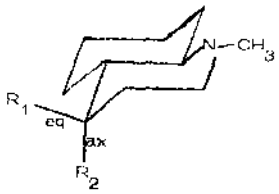
XXIV



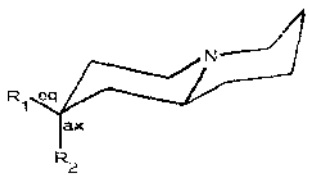
XXV

Piperidines.—The relationship of absolute stereochemistry to analgesic activity in the enantiomers of α- and β-prodine has been investigated (*276*). A number of conformationally restricted analogs of meperidine and α-prodine have been prepared. In the decahydroquinolines XXVI (*277*), and quinolizidines XXVII (*278*) and XXVII ($COOC_2H_5$ replaces $OCOC_2H_5$) (*279*), the differences in analgesic potency between epimers with axial and equatorial phenyl groups are very small. A similar result was found for the azanorbornanes XXVIII in which the difference in potency between *endo*- and *exo* phenyl epimers is due to a difference of brain concentrations (*280*).

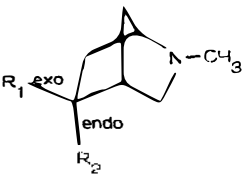
Replacement of the phenyl group by 2-pyridyl and 3-thienyl in the reversed ester series XXIXa gives retention of analgesic activity (*281*) but replacement of the C_3-methyl group in the prodine series XXIXb by halogen XXIXc destroys activity (*282*). Enhancement of the activity of meperidine is achieved by introduction of a C_3-methyl group; the β-epimer XXX (**cis** CH_3/C_6H_5) is the more potent as in prodine series (*283*). Structure-



XXVI



XXVII

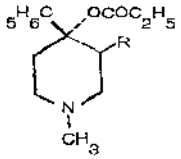


XXVIII

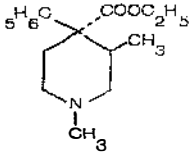
(a) $R_1 = C_6H_5$, $R_2 = OCOC_2H_5$

(b) $R_1 = OCOC_2H_5$, $R_2 = C_6H_5$

activity relationships in the 4-anilinopiperidine analgesics XXXI have been investigated (*284*).



XXIX

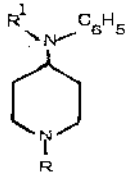


XXX

(a) R = H

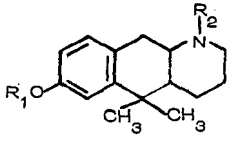
(b) R = CH_3

(c) R = Cl or Br

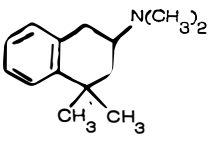


XXXI

Weak narcotic antagonist activity has been found in the series of N-substituted octahydrobenzquinolines XXXII (*285*) while the related 2-dimethylaminotetralin XXXIII showed 2.5 times the analgesic potency of meperidine (*286*).



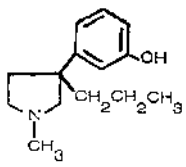
XXXII



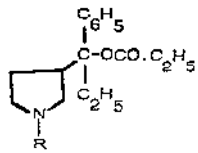
XXXIII

Pyrrolidines.—A number of pyrrolidine derivatives have recently emerged as potentially useful analgesics. Profadol XXXIV is an analgesic four times more potent than meperidine in rats (287) and this action is antagonised by nalorphine. In man it is about one-quarter as potent as morphine when administered intramuscularly to post-operative (288, 289) and cancer patients (290). Morphine antagonist properties have been demonstrated in morphine-dependent monkeys (291). Analogous exacerbation of withdrawal effects are found in man at a potency 40–50 times less than that of nalorphine; subjective effects, however, are similar to morphine and not nalorphine (267). The antagonist actions are more pronounced in the dextro-rotatory enantiomer (291). Abstinence effects of mild to moderate intensity followed abrupt withdrawal of profadol from monkeys to which the drug had been administered for 40 days. The abstinence syndrome produced by challenge with nalorphine or naloxone was more severe (38).

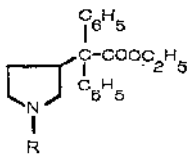
From the above observations it is clear that profadol, like nalorphine, pentazocine, and the l-isomers of the N-methylbenzomorphans, is a partial agonist. The "intrinsic activity" of such agents (and their maximum capacity to produce physical dependence) is related to their susceptibility to antagonism by nalorphine (292); an agonist like morphine is most easily antagonised. By this criterion, profadol has higher "intrinsic activity" than nalorphine or pentazocine (which is not antagonised by nalorphine) but lower than the benzomorphans XXIII which suppress abstinence in man.



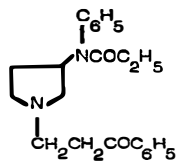
XXXIV



XXXV



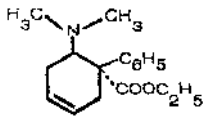
XXXVI



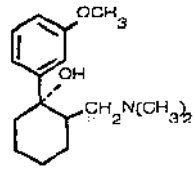
XXXVII

Esters of 3-pyrrolidinemethanols e.g. XXXV and α-phenyl-3-pyrrolidine-acetic acids XXXVI generally having propoxyphene-level activity have been described (293, 294); one example (AHR 1767) XXXV has been studied in depth. The analgesic action is not antagonised by nalorphine so that low dependence liability can be predicted (295). Analogous 3-pyrrolidinyl-anilides were more active (e.g. XXXVII; 3 × morphine) but at higher doses caused excitement, piloerection, and Straub tail (296).

Miscellaneous.—Members of two new series of cyclohexane derivatives have proved interesting and are undergoing clinical evaluation. They are the unsaturated derivative XXXVIII (W5759) which has a low capacity for producing tolerance and has morphine-like potency as an analgesic (*297*), and the less potent dimethylaminomethyl derivative XXXIX (U-26, 225A) (*272*).

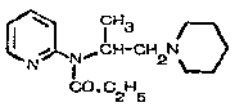


XXXVIII

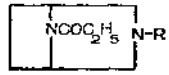


XXXIX

The basic anilide Propiram XL is a very weak morphine antagonist in animals (298, 299) and in man (291) but with analgesic activity (*272*) and respiratory depression (*269*) at approximately one-fifth of morphine's potency. It does not suppress abstinence in morphine-dependent monkeys (291) and in man (300). However it shows morphine-like subjective effects in man, and in direct addiction studies definite abstinence effects are shown following abrupt withdrawal or nalorphine challange; the level of these effects is similar to that for pentazocine (300).



XL



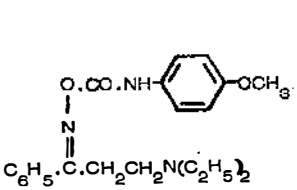
XLI

(a) R = CH_3
(b) R = $CH_2.CH{=}CHC_6H_5$

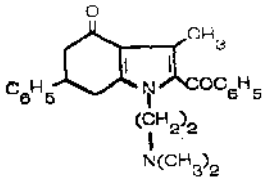
Two 8-propionyl-3,8-diazabicyclo (3, 2, 1) octanes XLI have proved to be effective analgesics in man. The 3-methyl derivative XLIa (L2774) is a mild analgesic (301) whereas the 3-cinnamyl derivative XLIb (L3060) is several times more potent than morphine (302). The β-aroylethylamine XLII is an analgesic twice as effective as morphine (303); the carbamyl

$C_6H_5CO.C(CH_3)_2.CH_2N(CH_3)_2$

XLII



XLIII



XLIV

oxime XLIII (USVP-E142) of a closely related ketone is equipotent with morphine and low physical dependence capacity is claimed (304). First reports have appeared (305) of a new series of 4-oxo-indoles, some members of which, e.g. XLIV (EN2186) are equipotent with morphine.

LITERATURE CITED

1. Fraser, H. F., Harris, L. S. 1967. *Ann. Rev. Pharmacol.* 7:277
2. Martin, W. R. 1967. *Pharmacol. Rev.* 19:463
3. Phillipson, R. V., Ed. 1970. *Modern Trends in Drug Dependence and Alcoholism.* London: Butterworths. 311 pp.
4. Portoghese, P. S. 1970. *Ann. Rev. Pharmacol.* 10:68
5. Way, E. L., Ed. 1967. *New Concepts in Pain and its Clinical Management.* Philadelphia: Davis. 224 pp.
6. Wikler, A., Ed. 1968. *The Addictive States. Res. Pub. Assoc. Nerv. Ment. Dis.* 46. Baltimore: Williams & Wilkins. 520 pp.
7. Soulairac, A., Cahn, J., Charpentier, J., Eds. 1968. *Pain.* London: Academic. 562 pp.
8. Steinberg, H., Ed. 1969. *Scientific Basis of Drug Dependence.* London: Churchill. 429 pp.
9. *New Concepts and Approaches to the Study of Drug Dependence and Tolerance.* 1970. *Fed. Proc.* 29:2
10. Cain, C. K., Ed. 1966, 1967, 1968. *Annual Reports in Medicinal Chemistry.* New York: Academic.
11. W. H. O. Expert Committee on Addiction-Producing Drugs. 1964. *World Health Organ. Tech. Rep. Ser.* 273:3
12. W. H. O. Scientific Group. 1964. *World Health Organ. Tech. Rep. Ser.* 287:3
13. Eddy, N. B. 1941. In *The Pharmacology of the Opium Alkaloids,* Part 1:687, ed. H. Krueger, N. B. Eddy, M. Sumwalt. U.S. Pub. Health Rep. Suppl. 165
14. Wikler, A. 1950. *Pharmacol. Rev.* 2:435
15. Seevers, M. H., Woods, L. A. 1953. *Am. J. Med.* 14:546
16. Seevers, M. H., Deneau, G. A. 1963. In *Physiological Pharmacology.* 1: 565, ed. W. S. Root, F. G. Hofman. London: Academic
17. Fraser, H. F., Isbell, H. 1960. *Bull. Narcotics* 12:(2)15
18. Fraser, H. F., Van Horn, G. D., Martin, W. R., Wolbach, A. B., Jr., Isbell, H. 1961. *J. Pharmacol. Exp. Ther.* 133:371
19. Hill, H. E., Haertzen, C. A., Wolbach, A. B., Jr., Miner, E. J. 1963. *Psychopharmacologia.* 4:184
20. Martin, W. R. 1966. In *International Encyclopedia of Pharmacology* 1: 155, ed. C. Raduoco-Thomas, L. Lasagna. London: Pergamon
21. Halbach, H., Eddy, N. B. 1963. *Bull. World Health Org.* 28:139
22. Fraser, H. F. 1966. In *Methods in Drug Evaluation,* p. 297, ed. P. Mantegazza, F. Piccinini. Amsterdam: North-Holland
23. Cochin, J. 1968. In *Selected Pharmacological Testing Methods* 3:121, ed. A. Burger. London: Arnold
24. Tatum, A. L., Seevers, M. H., Collins, K. H. 1929. *J. Pharmacol. Exp. Ther.* 36:447
25. Kolb, L., DuMez, A. G. 1931. *U.S. Pub. Health Rep.* 46:698
26. Seevers, M. H. 1936. *J. Pharmacol. Exp. Ther.* 56:147
27. Deneau, G. A., Seevers, M. H. 1964. In *Evaluation of Drug Activities: Pharmacometrics* 1:167, ed. D. R. Laurence, A. L. Bacharach. London: Academic
28. Seevers, M. H., Deneau, G. A., Yanagita, T. 1966. In *Pain,* p. 197, ed. R. S. Knighton, P. R. Dumke. London: Churchill
29. Kolb, L., Himmelsbach, C. K. 1938. *Am. J. Psychiat.* 94:759
30. Himmelsbach, C. K. 1939. *J. Pharmacol. Exp. Ther.* 67:239
31. Eddy, N. B., Lee, L. E., Jr., Harris, C. A. 1959. *Bull. Narcotics* 11: (1)3
32. Fraser, H. F., Isbell, H. 1960. *Bull. Narcotics* 12:(1)9
33. Martin, W. R., Fraser, H. F., Gorodetzky, C. W., Rosenberg, D. E. 1965. *J. Pharmacol. Exp. Ther.* 150:426
34. Fraser, H. F. 1968. In *The Addictive States, Res. Pub. Assoc. Nerv. Ment. Dis.* 46:176, ed. A. Wikler. Baltimore: Williams & Wilkins
35. Holtzman, S. G., Villarreal, J. E. 1969. *J. Pharmacol. Exp. Ther.* 166:125
36. Holtzman, S. G., Villarreal, J. E. Private communication
37. Villarreal, J. E. 1966. *Pharmacologist* 8:210
38. Villarreal, J. E. Private communication
39. Blumberg, H., Dayton, H. B., Wolf, P. S. 1966. *Proc. Soc. Exp. Biol. Med.* 123:755

40. Blumberg, H., Dayton, H. B., Wolf, P. S. 1967. *Toxicol. Appl. Pharmacol.* 10:406
41. Blane, G. F., Dugdall, D. 1968. *J. Pharm. Pharmacol.* 20:547
42. Blumberg, H., Wolf, P. S., Dayton, H. B. 1965. *Proc. Soc. Exp. Biol. Med.* 118:763
43. Blane, G. F. 1967. *J. Pharm. Pharmacol.* 19:367
44. Gyang, E. A., Kosterlitz, H. W. 1966. *Brit. J. Pharmacol.* 27:514
45. Kosterlitz, H. W., Watt, A. J. 1968. *Brit. J. Pharmacol.* 33:266
46. Doxey, J. C. 1970. *Brit. J. Pharmacol.* In press
47. Fennessy, M. R., Heimans, R. L. H., Rand, M. J. 1969. *Brit. J. Pharmacol.* 37:436
48. Plant, O. H., Pierce, I. H. 1928. *J. Pharmacol. Exp. Ther.* 33:329
49. Eddy, N. B., Reid, J. S. 1934. *J. Pharmacol. Exp. Ther.* 52:468
50. Scott, C. C., Kohlsteadt, K. G., Robbins, E. B., Israel, F. W. 1947. *Fed. Proc.* 6:370
51. Wikler, A. 1948. *Am. J. Psychiat.* 105:329
52. Martin, W. R., Eades, C. G. 1961. *J. Pharmacol. Exp. Ther.* 133:262
53. La Barre, J. 1965. *Ann. Soc. Roy. Sci. Med. Natur. Bruxelles* 18:5
54. Carter, R. L., Wikler, A. 1954. *Fed. Proc.* 13:342
55. Desmarez, J. J. 1957. *C. R. Soc. Biol.* 151:1988
56. La Barre, J. 1959. *Bull. Narcotics* 11:(4)10
57. Wikler, A., Frank, K. 1948. *J. Pharmacol. Exp. Ther.* 94:382
58. Wikler, A., Carter, R. L. 1953. *J. Pharmacol. Exp. Ther.* 109:92
59. Martin, W. R., Eades, C. G. 1964. *J. Pharmacol. Exp. Ther.* 146:385
60. Gold, H. 1929. *J. Pharmacol. Exp. Ther.* 35:355
61. Emerson, G. A., Phatak, N. M. 1938. *Univ. Calif. Pub. Pharmacol.* 1:77
62. Friebel, H., Jacob, R., Cros, J. 1965. *Med. Pharmacol. Exp.* 12:97
63. Joël, E., Ettinger, A. 1926. *Arch. Exp. Pathol. Pharmakol.* 115:334
64. Himmelsbach, C. K., Gerlach, G. H., Stanton, E. J. 1935. *J. Pharmacol. Exp. Ther.* 53:179
65. Kaymakcalan, S., Woods, L. A. 1956. *J. Pharmacol. Exp. Ther.* 117:112
66. Hosoya, E. 1959. *Pharmacologist* 1:77
67. Hanna, C. 1960. *Arch. Int. Pharmacodyn.* 124:326
68. Kuhn, H. F., Friebel, H. 1962. *Med. Exp., Basel* 6:301
69. Martin, W. R., Wikler, A., Eades, C. G., Pescor, F. T. 1963. *Psychopharmacologia* 4:247
70. Cros, J., Vigié, O. 1966. *Ann. Biol. Clin.* 24:487
71. Akera, T., Brody, T. M. 1968. *Biochem. Pharmacol.* 17:675
72. Buckett, W. R. 1964. *Psychopharmacologia* 6:410
73. Lorenzetti, O. J., Sancilio, L. F. 1970. *Arch. Int. Pharmacodyn.* 183:391
74. Shemano, I., Wendel, H. 1964. *Toxicol. Appl. Pharmacol.* 6:334
75. Aceto, M. D., McKean, D. B., Pearl, J. 1969. *Brit. J. Pharmacol.* 36:225
76. Fichtenberg, D. G. 1951. *Bull. Narcotics* 3:(3)19
77. Mercier, J. J., Etzensperger, P., Chatain, R. A. 1957. *Ann. Pharm. Fr.* 15:701
78. Hano, K., Kaneto, H., Kakunaga, T. 1963. *Jap. J. Pharmacol.* 13:207
79. Buckett, W. R. 1967. *Brit. J. Addict.* 62:387
80. Seevers, M. H. 1967. In *New Concepts in Pain and its Clinical Management*, p. 115, ed. E. Leong Way. Philadelphia: Davis
81. Maggiolo, C., Huidobro, F. 1961. *Acta Physiol. Lat. Am.* 11:70
82. Huidobro, F., Maggiolo, C. 1961. *Acta Physiol. Lat. Am.* 11:201
83. Huidobro, F., Maggiolo, C., Contreras, E. 1963. *Arch. Int. Pharmacodyn.* 144:196
84. Huidobro, F., Maggiolo, C. 1965. *Arch. Int. Pharmacodyn.* 158:97
85. Huidobro, F. 1967. *Arch. Biol. Med. Exp.* 4:155
86. Huidobro, F., Huidobro, J. P., Larraín, G. 1968. *Acta Physiol. Lat. Am.* 18:67
87. Way, E. L., Loh, H. H., Shen, F. 1968. *Science* 162:1290
88. Way, E. L., Loh, H. H., Shen, F. 1969. *J. Pharmacol. Exp. Ther.* 167:1
89. Marshall, J., Weinstock, M. 1969. *Brit. J. Pharmacol.* 37:505P
90. Gibson, R. D., Tingstad, J. E. 1970. *J. Pharm. Sci.* 59:426
91. Cowan, A. Unpublished
92. Weeks, J. R., Collins, R. J. 1964. *Psychopharmacologia* 6:267
93. Holtzman, S. G., Villarreal, J. E. 1968. *Pharmacologist* 10:204
94. Schuster, C. R., Villarreal, J. E.

1968. In *Psychopharmacology: A Review of Progress* 1957–1967, p. 811, ed. D. H. Efron, J. O. Cole, J. Levine, J. R. Wittenborn, U.S. Pub. Health Ser. Pub. 1836
95. Deneau, G. A. 1969. In *Scientific Basis of Drug Dependence*, p. 199, ed. H. Steinberg. London: Churchill
96. Schuster, C. R., Thompson, T. 1969. *Ann. Rev. Pharmacol.* 9:483
97. Weeks, J. R. 1962. *Science* 138:143
98. Weeks, J. R. 1964. *Sci. Am.* 210:46
99. Collins, R. J., Weeks, J. R. 1965. *Arch. Exp. Pathol. Pharmakol.* 249:509
100. Collins, R. J., Weeks, J. R. 1967. *Psychopharmacologia* 11:287
101. Thompson, T., Schuster, C. R. 1964. *Psychopharmacologia* 5:87
102. Yanagita, T., Deneau, G. A., Seevers, M. H. 1965. *Excerpta Med. Int. Congr. Ser.* 87:453
103. Weeks, J. R., Collins, R. J. 1968. In *The Addictive States, Res. Pub. Assoc. Nerv. Ment. Dis.* 46:288, ed. A. Wikler, Baltimore: Williams & Wilkins
104. Goldberg, S. R., Woods, J. H., Schuster, C. R. 1969. *Science* 166:1306
105. Wikler, A., Martin, W. R., Pescor, F. T., Eades, C. G. 1963. *Psychopharmacologia* 5:55
106. Woods, J. H., Schuster, C. R. 1968. *Int. J. Addict.* 3:231
107. Madinaveitia, J. 1969. In *Scientific Basis of Drug Dependence*, p. 155, ed. H. Steinberg. London: Churchill
108. Claghorn, J. L., Ordy, J. M., Nagy, A. 1965. *Science* 149:440
109. Kumar, R., Steinberg, H., Stolerman, I. P. 1968. *Nature, London* 218:564
110. Stolerman, I. P., Kumar, R. 1970. *Psychopharmacologia* 17:137
111. Deneau, G. A., Yanagita, T., Seevers, M. H. 1969. *Psychopharmacologia* 16:30
112. Woods, J. H., Schuster, C. R. Private communication
113. Lowe, G., Williams, D. I. 1969. *Nature, London* 224:1226
114. Harris, L. S., Rosenberg, F. J. 1967. *Arch. Biol. Med. Exp.* 4:136
115. Harris, L. S., Pierson, A. K. 1964. *J. Pharmacol. Exp. Ther.* 143:141
116. Harris, L. S., Pierson, A. K., Dembinski, J. R., Dewey, W. L. 1967. *Arch. Int. Pharmacodyn.* 165:112
117. McClane, T. K., Martin, W. R. 1967. *Int. J. Neuropharmacol.* 6:89
118. Schneider, C. 1968. *Nature, London* 220:586
119. Collier, H. O. J., Schneider, C. 1969. *Nature, London* 224:610
120. Jasinski, D. R., Martin, W. R., Sapira, J. D. 1968. *Clin. Pharmacol. Ther.* 9:215
121. DeNosaquo, N. 1969. *J. Am. Med. Assoc.* 210:502
122. Edison, G. R. 1969. *N. Engl. J. Med.* 281:447
123. Potter, D. R., Payne, J. P. 1970. *Brit. J. Anaesth.* 42:186
124. Jacob, J., Lafille, C. 1963. *Arch. Int. Pharmacodyn.* 145:528
125. Jacob, J., Lafille, C., Loiseau, G., Echinard-Garin, P., Barthelemy, C. 1964. *Encéphale* 53:520
126. Maxwell, D. R., Palmer, H. T. 1961. *Nature, London* 191:84
127. Leslie, G. B. Private communication
128. Schneider, C. W., Chenoweth, M. B. 1970. *Nature, London* 225:1262
129. Wikler, A. 1961. *Brit. J. Addict.* 57:73
130. Wikler, A. 1965. In *Narcotics*, p. 85, ed. D. M. Wilner, G. G. Kassebaum, New York: McGraw-Hill
131. Thompson, T., Ostlund, W. 1965. *J. Comp. Physiol. Psychol.* 59:388
132. Wikler, A., Pescor, F. T. 1967. *Psychopharmacologia* 10:255
133. Nichols, J. 1968. In *The Addictive States., Res. Pub. Assoc. Nerv. Ment. Dis.* 46:299
134. Irwin, S., Seevers, M. H. 1956. *J. Pharmacol. Exp. Ther.* 116:31
135. Goldberg, S. R., Schuster, C. R. 1967. *J. Exp. Anal. Behav.* 10:235
136. Goldberg, S. R., Schuster, C. R. 1969. *Fed. Proc.* 28:512
137. Wikler, A., Pescor, F. T. 1970. *Psychopharmacologia* 16:375
138. Martin, W. R., Jasinski, D. R., Sapira, J. D., Flanary, H. G., Kelly, O. A., Thompson, A. K., Logan, C. R. 1968. *J. Pharmacol. Exp. Ther.* 162:182
139. Martin, W. R., Jasinski, D. R. 1969. *J. Psychiat. Res.* 7:9
140. Eisenman, A. J., Sloan, J. W., Martin, W. R., Jasinski, D. R., Brooks, J. W. 1969. *J. Psychiat. Res.* 7:19
141. Way, E. L., Adler, T. K. 1960. *Pharmacol. Rev.* 12:383

142. Goldstein, D. B., Goldstein, A. 1961. *Biochem. Pharmacol.* 8:48
143. Grumbach, L. 1961. In Ref. 156
144. Shuster, L. 1961. *Nature, London* 189:314
145. Seevers, M. H., Deneau, G. A. 1962. *Arch. Int. Pharmacodyn.* 140:514
146. Maggiolo, C., Huidobro, F. 1966. *Nature, London* 211:540
147. Cochin, J. 1970. *Fed. Proc.* 29:19
148. Cox, B. M., Osman, O. H. 1970. *Brit. J. Pharmacol.* 38:157
149. Himmelsbach, C. K. 1943. *Fed. Proc.* 2:201
150. Martin, W. R., Eisenman, A. J. 1962. *J. Pharmacol. Exp. Ther.* 138:113
151. Martin, W. R. 1968. In *The Addictive States. Res. Pub. Assoc. Nerv. Ment. Dis.* 46:206
152. Martin, W. R. 1970. *Fed. Proc.* 29: 13
153. Sharpless, S. K., Halpern, L. 1962. *Electroencephal. Clin. Neurophysiol.* 14:244
154. Jaffe, J. H., Sharpless, S. K. 1963. *Pharmacologist* 5:249
155. Sharpless, S. K. 1964. *Ann. Rev. Physiol.* 26:357
156. Jaffe, J. H., Sharpless, S. K. 1965. *J. Pharmacol. Exp. Ther.* 150:140
157. Sharpless, S. K., Jaffe, J. H. 1966. *J. Pharmacol. Exp. Ther.* 151:321
158. Jaffe, J. H., Sharpless, S. K. 1968. In *The Addictive States. Res. Pub. Assoc. Nerv. Ment. Dis.* 46:226
159. Sharpless, S. K., Jaffe, J. H. 1969. In *Scientific Basis of Drug Dependence,* p. 67, ed. H. Steinberg. London: Churchill
160. Emmelin, N. 1961. *Pharmacol. Rev.* 13:16
161. Trendelenburg, U. 1963. *Pharmacol. Rev.* 15:225
162. Collier, H. O. J. 1965. *Nature, London* 205:181
163. Collier, H. O. J. 1965. In *Hashish: its Chemistry and Pharmacology,* p. 83, ed. G. E. W. Wolstenholme, J. Knight. London: Churchill
164. Collier, H. O. J. 1966. *Advan. Drug Res.* 3:171
165. Collier, H. O. J. 1968. *Nature, London* 220:228
166. Gaddum, J. H. 1962. In *Enzymes and Drug Action,* p. 441, ed. J. L. Mongar, A. S. V. de Reuck. London: Churchill
167. Paton, W. D. M. 1963. *Can. J. Biochem. Physiol.* 41:2637
168. Paton, W. D. M. 1969. In *Scientific Basis of Drug Dependence,* p. 31, ed. H. Steinberg. London: Churchill
169. Jaffe, J. H., Zaks, A. 1968. In *Proceedings of the First National Conference on Methadone Treatment,* p. 23. New York: Rockefeller Univ.
170. Dole, V. P., Nyswander, M. E. 1966. *N.Y.J. Med.* 66:2011
171. Dole, V. P., Nyswander, M. E. 1968. *Brit. J. Addict.* 63:55
172. Dole, V. P., Nyswander, M. E., Warner, A. 1968. In *Proceedings of the First National Conference on Methadone Treatment,* p. 11. New York: Rockefeller Univ.
173. Wieland, W. 1968. In *Proceedings of the First National Conference on Methadone Treatment,* p. 31. New York: Rockefeller Univ.
174. Freedman, A. M., Fink, M., Sharoff, R., Zaks, A. 1967. *J. Am. Med. Assoc.* 202:191
175. Martin, W. R., Gorodetzky, C. W., McLane, T. K. 1966. *Clin. Pharmacol. Ther.* 7:455
176. Jaffe, J. H., Brill, L. 1966. *Int. J. Addict.* 1:99
177. Freedman, A. M. 1966. *J. Am. Med. Assoc.* 197:878
178. Zaks, A., Bruner, A., Fink, M., Freedman, A. M. 1969. *Dis. Nerv. Syst.* 30:89
179. Fink, M., Simeon, J., Turan, M. I., Freedman, A. M. 1970. *Clin. Pharmacol. Ther.* 11:41
180. Fink, M., Freedman, A. M. 1970. In *Modern Trends in Drug Dependence and Alcoholism,* p. 49, ed. R. V. Phillipson. London: Butterworths
181. Fink, M., Zaks, A., Sharoff, R., Mora, A., Bruner, A., Levit, S., Freedman, A. M. 1968. *Clin. Pharmacol. Ther.* 9:568
182. Zaks, A., Fink, M., Freedman, A. M. Private communication
183. Kugita, H., Takeda, M., Inoue, H. 1969. *Tetrahedron* 25:1851
184. Gates, M., Shepard, M. S. 1962. *J. Am. Chem. Soc.* 84:4125
185. Bentley, K. W. 1970. In *The Alkaloids* XIII, ed. R. M. F. Manske. New York: Academic. In press
186. Blumberg, H., Dayton, H. B., Rapoport, G. M., Rapoport, D. N. 1961. *Fed. Proc.* 20:311
187. Pearl, J., Harris, L. S. 1966. *J.*

Pharmacol. Exp. Ther. 154 :319
188. Foldes, F. F., Lunn, J. N., Moore, J., Brown, I. M. 1963. *Am. J. Med. Sci.* 245 :23
189. Lasagna, L. 1965. *Proc. Roy. Soc. Med.* 58 :978
190. Jasinski, D. R., Martin, W. R., Haertzen, C. A. 1967. *J. Pharmacol. Exp. Ther.* 157 :420
191. Blumberg, H., Dayton, H. B., Wolf, P. S. 1966. *Proc. Soc. Exp. Biol. Med.* 123 :755
192. Martin, W. R., Jasinski, D. R., Sapira, J. D. 1967. *Pharmacologist* 9 :230
193. Kallos, T., Smith, T. C. 1968. *J. Am. Med. Assoc.* 204 :932
194. Forrest, W. H. Private communication
195. Sargeant, L. J., Joshi, B. C. 1968. *J. Med. Chem.* 11 :336
196. Gates, M., Klein, D. A. 1967. *J. Med. Chem.* 10 :380
197. Mokotoff, M., Sargeant, L. J. 1968. *J. Org. Chem.* 33 :3351
198. Kobayashi, S., Hasegawa, K., Mori, M., Takagi, H. 1970. *Arzneim.-Forsch.* 20 :43
199. Bentley, K. W., Hardy, D. G. 1967. *J. Am. Chem. Soc.* 89 :3267
200. Bentley, K. W., Hardy, D. G., Meek, B. 1967. *J. Am. Chem. Soc.* 89 : 3273
201. Bentley, K. W., Hardy, D. G. 1967. *J. Am. Chem. Soc.* 89 :3281
202. Bentley, K. W., Hardy, D. G., Meek, B. 1967. *J. Am. Chem. Soc.* 89 : 3293
203. Bentley, K. W., Howell, C. F., Fulmor, W., Lancaster, J. E., Brown, J. J., Morton, G. O., Hardy, R. A., Jr. 1967. *J. Am. Chem. Soc.* 89 : 3303
204. Bentley, K. W., Hardy, D. G., Crocker, H. P., Haddlesey, D. I., Mayor, P. A. 1967. *J. Am. Chem. Soc.* 89 :3312
205. Lewis, J. W., Readhead, M. J. 1968. *Tetrahedron* 24 :1829
206. Bentley, K. W., Hardy, D. G., Lewis, J. W., Readhead, M. J., Rushworth, W. I. 1969. *J. Chem. Soc.* (C) 826
207. Bentley, K. W., Crocker, H. P., Walser, R. 1969. *J. Chem. Soc.* (C) 2225
208. Bentley, K. W., Hardy, D. G., Meek, B., Taylor, J. B., Brown, J. J., Morton, G. O. 1969. *J. Chem. Soc.* (c) 2229
209. Bentley, K. W., Meek, B. 1969. *J. Chem. Soc.* (C) 2233
210. Bentley, K. W., Hardy, D. G., Smith, A. C. B. 1969. *J. Chem. Soc.* (C) 2235
211. Bentley, K. W., Bower, J. D., Lewis, J. W., Readhead, M. J., Smith, A. C. B., Young, G. R. 1969. *J. Chem. Soc.* (C) 2237
212. Bentley, K. W., Bower, J. D., Smith, A. C. B. 1960. *J. Chem. Soc.* (C) 2241
213. Bentley, K. W., Hardy, D. G., Mayor, P. A. 1969. *J. Chem. Soc.* (C) 2385
214. Bentley, K. W., Bower, J. D., Lewis, J. W. 1969. *J. Chem. Soc.* (C) 2569
215. Lewis, J. W., Rushworth, W. I. 1970. *J. Chem. Soc.* (C) 560
216. Lewis, J. W., Readhead, M. J. 1970. *J. Med. Chem.* 13 :525
217. Lewis, J. W., Readhead, M. J., Smith, A. C. B. 1970. *J. Chem. Soc.* (C) In press
218. Boura, A. L. A., Haddlesey, D. I., Harry, E. J. R., Lewis, J. W., Mayor, P. A. 1968. *J. Pharm. Pharmacol.* 20 :961
219. Bentley, K. W., Lewis, J. W. 1970. Quoted by P. S. Portoghese in *Ann. Rev. Pharmacol.* 10 :71
220. Bentley, K. W., Lewis, J. W. Unpublished
221. Lewis, J. W., Readhead, M. J. 1970. *J. Chem. Soc.* (C) In press
222. Beckett, A. H., Casy, A. F. 1954. *J. Pharm. Pharmacol.* 6 :986
223. Portoghese, P. S. 1965. *J. Med. Chem.* 8 :609
224. Lewis, J. W., Smith, A. C. B. Unpublished
225. Green, A. F., Young, P. A. 1951. *Brit. J. Pharmacol. Chemother.* 6 : **572**
226. Archer, S., Harris, L. S. 1965. *Progr. Drug Res.* 8 :261
227. D'Amour, F. E., Smith, D. L. 1941. *J. Pharmacol. Exp. Ther.* 72 :74
228. Blane, G. F., Boura, A. L. A., Leach, E. C., Gray, W. D., Osterberg, A. C. 1968. *J. Pharm. Pharmacol.* 20 :796
229. Bousfield, J. D., Rees, J. M. H. 1969. *J. Pharm. Pharmacol.* 21 :632
230. Dobbs, H. E., Blane, G. F., Boura, A. L. A. 1969. *Eur. J. Pharmacol.* 7 :328
231. Lister, R. E. Private communication
232. Blane, G. F., Boura, A. L. A., Fitzgerald, A. E., Lister, R. E. 1967. *Brit. J. Pharmacol. Chemother.* 30 :11

233. Harthoorn, A. M. 1966. *J. Am. Vet. Med. Assoc.* 149:875
234. King, J. M., Carter, B. H. 1965. *E. Afr. Wildlife J.* 3:19
235. Wallach, J. D. 1966. *J. Am. Vet. Med. Assoc.* 149:871
236. Wallach, J. D. 1969. *Vet. Med.* 64:53
237. Blane, G. F., Boura, A. L. A., Dobbs, H. E. 1968. *J. Physiol. London* 196:26P
238. Alford, B. T., Wozniak, L. A. 1970. *J. Am. Vet. Med. Assoc.* 156:208
239. Crooks, J. L., Whiteley, H., Jenkins, J. T., Blane, G. F. 1970. *Vet. Rec.* In press
240. Kosterlitz, H. W., Watt, A. J. Private communication
241. Norris, W., Telfer, A. B. M. 1970. *Brit. J. Anaesth.* 42:151
242. Kwan, Y. W. 1970. *J. Am. Med. Assoc.* 211:1544
243. Laroche, G., Remy, J. M. 1970. *Therapie* 25:73
244. Halpern, G. M. 1968. *Lancet* I:1205
245. Brown, A. S. 1969. *Proc. Roy. Soc. Med.* 62:805
246. Hart, R. H. 1969. *Lancet* II:690
247. Sandoval, R. G., Wang, R. I. H. 1969. *N. Engl. J. Med.* 280:1391
248. Schoolar, J. C., Idänpään-Heikkilä, P., Keats, A. S. 1969. *Lancet* I:1263
249. Keup, W. 1968. *Dis. Nerv. Syst.* 29:599
250. Mungavin, J. M. 1969. *Lancet* II:56
251. Rees, R. M., Bird, J. G. Private communication
252. Martin, W. R., Jasinski, D. R., Hoeldtke, R. Private communication
253. Berkowitz, B. A., Asling, J. H., Shnider, S. M., Way, E. L. 1969. *Clin. Pharmacol. Ther.* 10:320
254. Beckett, A. H., Taylor, J. F. 1967. *J. Pharm. Pharmacol.* 19:505
255. Beckett, A. H., Taylor, J. F., Kourounakis, P. 1970. *J. Pharm. Pharmacol.* 22:123
256. Flavell Matts, S. G., McCready, V. R., James, K. W., Gwyther, M. M., Hammersley, P. A. G. 1967. *Clin. Trials J.* 4:842
257. Pittman, K. A., Rosi, D., Cherniak, R., Merola, A. J., Conway, W. D. 1969. *Biochem. Pharmacol.* 18:1673
258. Pittman, K. A. Unpublished
259. Berkowitz, B., Way, E. L. 1969. *Clin. Pharmacol. Ther.* 10:681
260. May, E. L., Eddy, N. B. 1966. *J. Med. Chem.* 9:851
261. Eddy, N. B., May, E. L. 1966. In *Synthetic Analgesics*, Part IIB, p. 138, ed. D. H. R. Barton, W. von Doering. London: Pergamon
262. Ager, J. H., Jacobson, A. E., May, E. L. 1969. *J. Med. Chem.* 12:288
263. Block, F. B., Clarke, F. H., Yokoyama, N. 1970. *J. Med. Chem.* 13:488
264. Casy, A. F., Parulkar, A. P. 1969. *J. Med. Chem.* 12:178
265. Casy, A. F., Parulkar, A. P. 1969. *Can. J. Chem.* 47:3623
266. Fraser, H. F., Rosenberg, D. E., Isbell, H. Private communication
267. Jasinski, D. R., Martin, W. R., Sapira, J. D. Private communication
268. Sevelino, H., McCoy, J., Merrill, J. A., Colemore, J. P. Private communication
269. Keats, A. S., Telford, J., Fenstermacher, J. M. Private communication
270. Sunshine, A., Laska, E., Kantor, T. G., Sharkey, I., Hopper, M. Private communication
271. Block, F. B., Clarke, F. H. 1969. *J. Med. Chem.* 12:845
272. DeKornfield, T. J., Finch, J. S. Private communication
273. Kanematsu, K., Takeda, M., Jacobson, A. E., May, E. L. 1969. *J. Med. Chem.* 12:405
274. Jacobson, A. E., Mokotoff, M. 1970. *J. Med. Chem.* 13:7
275. Ziering, A., Malatestinic, N., Williams, T., Brossi, A. 1970. *J. Med. Chem.* 13:9
276. Portoghese, P. S., Larson, D. L. 1968. *J. Pharm. Sci.* 57:711
277. Smissman, E. E., Steinman, M. J. 1966. *J. Med. Chem.* 9:455
278. Sam, J., England, J. D., Temple, D. 1969. *J. Med. Chem.* 12:144
279. Beckett, A. H., Lingard, R. G., Theobald, A. E. E. 1969. *J. Med. Chem.* 12:563
280. Portoghese, P. S., Mikhail, A. A., Kupferberg, H. J. 1968. *J. Med. Chem.* 11:219
281. Sabih, K., Wiley, R. A. 1969. *J. Med. Chem.* 12:922
282. Carabateas, P. M. 1970. *J. Med. Chem.* 13:167
283. Casy, A. F., Chatten, L. G., Khullar, K. K. 1969. *J. Chem. Soc.* (C) 2491
284. Casy, A. F., Hassan, M. M. A., Simmonds, A. B., Staniforth, D.

1969. *J. Pharm. Pharmacol.* 21: 434
285. Michne, W. F., Albertson, N. F. 1969. *J. Med. Chem.* 12:402
286. Martin, A. R., Parulkar, A. P., Gusseck, D. J., Anderson, L. J. 1969. *J. Pharm. Sci.* 58:340
287. Winder, C. V., Welford, M., Wax, J., Kaump, D. H. 1966. *J. Pharmacol. Exp. Ther.* 154:161
288. Parkhouse, J., Wright, V. 1968. *Can. Med. Assoc. J.* 99:887
289. Pearson, J. W., Landesman, R. K., Lasagna, L. Private communication
290. Beaver, W. T., Wallenstein, S. L., Houde, R. W., Rogers, A. 1969. *Clin. Pharmacol. Ther.* 10:314
291. Seevers, M. H., Villarreal, J. E. Private communication
292. Ariëns, E. J., Simonis, A. M., Van Rossum, J. M. 1964. In *Molecular Pharmacology; The Mode of Action of Biologically Active Compounds* 1:119, ed. Ariëns, E. J. New York: Academic
293. Helsley, G. C., Richman, J. A., Lunsford, C. D., Jenkins, H., Mays, R. P., Funderbunk, W. H., Johnson, D. N. 1968. *J. Med. Chem.* 11:472
294. Cale, A. D., Jr., Lunsford, C. D. 1968. *J. Med. Chem.* 11:470
295. Funderbunk, W. H., Foxwell, M. H., Johnson, D. N., Ward, J. W. 1969. *Arch. Int. Pharmacodyn.* 178:446
296. Helsley, G. C., Lunsford, C. D., Welstead, W. J., Boswell, R. F., Jr., Funderbunk, W. H., Johnson, D. N. 1969. *J. Med. Chem.* 12:583
297. Sätzinger, G. 1969. *Ann. Chim.* 728: 64
298. Hiltmann, R., Wollweber, H. 1968. *Mitt. Deut. Pharm. Ges.* 38:34
299. Hiltmann, R., Wollweber, H., Hoffmeister, F. 1968. *Pharm. Ztg. Ver. Apoth.-Ztg.* 113:1157
300. Jasinski, D. R., Martin, W. R., Sapira, J. D., Hoeldtke, R. Private communication
301. Nicolis, F. B., Bonollo, L., Bonadonna, G., Leoni, E. 1968. *J. Clin. Pharmacol.* 8:322
302. Diena, A., Banfi, S., Maffii, G. 1969. *Chim. Ther.* 4:425
303. Atwal, M. S., Bauer, L., Dixit, S. N., Gearien, J. E., Megahy, M., Morris, R., Pokorny, C. 1969. *J. Med. Chem.* 12:994
304. Glassman, J. M., Rauzzino, F. 1969. *Pharmacologist* 11:257
305. Schoen, K., Finizio, M., Pachter, I. J. 1969. *Abstr. Pap. Am. Chem. Soc.* No. 158, Med. 126