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The toxicity of some of the newer narcotic analgesics

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THE toxic manifestations of the newer narcotic analgesics are in many ways similar to those of the older established agents used for the relief of pain but there are some well established quantitative and qualitative differences. A full description of the pharmacology, clinical usage and side-effect liability of the narcotic analgesics was published for the World Health Organisation between 1954 and 1957 by Braendon, Eddy, Halbach & Wolff (1954, 1955, 1956, 1957) and this review will deal mainly with drugs which have been brought on to the market or introduced for clinical trial since 1957; some recent information of the toxic effects of the older established drugs will also be included. A number of critical reviews dealing with the pharmacology and clinical applications have appeared since the publication of the WHO review (Reynolds & Randall, 1957; Murphree, 1962; Martin, 1963; Foldes, Sverdlow & Siker, 1964; Lasagna, 1964; de Stevens, 1965) and these have been used extensively in the preparation of this paper. When dealing with narcotic drugs the question of toxicity is difficult to define because of the broad spectrum of effects of many of these drugs. What may be considered an undesirable or toxic effect under one set of circumstances, e.g. constipation, may be the desired effect under different circumstances. There are also additional well marked species differences in the responses to this class of drugs and extrapolation of toxic effects from experimental animals to man cannot always be justified.

In 1957 when the review by Eddy, Halbach & Braendon (1957) was published, the pharmacology, toxicology and clinical indications of most naturally-occurring, semi-synthetic or synthetic analgesics was qualitatively similar to morphine, the only exceptions to this generalisation being the narcotic antagonists nalorphine and levallorphan. Despite vast efforts by the pharmaceutical industry throughout the world no significant separation of the clinically desirable properties from the undesirable toxic effects had been achieved. All the effective analgesic drugs possessed some degree of addiction liability and in doses within the therapeutic range frequently produced unwanted effects on the central and peripheral nervous systems and adversely affected the cardiovascular, respiratory, gastrointestinal and other systems. The generalised occurrence of these effects in all the effective analgesics led many workers to believe that these effects could not be dissociated, but recent work, which will be cited in detail later, has shown that this concept is no longer tenable. This work has shown that physical dependence capacity, which is a measure of abuse or addiction liability, can be divorced from analgesic activity. Hence the term "narcotic analgesic" may be something of a misnomer, but it is retained in this context to define analgesic agents which produce

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pain relief primarily by an action on the central nervous system without producing loss of consciousness. The exact mechanism of action of this class of drugs has not yet been elucidated but the recent review by Martin (1963) gives an up-to-date account of present theories. Analgesics may be classified according to their chemical or pharmacological properties but for a logical approach a combination of the two appears to be most appropriate for dealing with the newer developments of the last few years. New drugs which have a pharmacological and toxicological profile similar to morphine will be covered first, then the group of derivatives having a chemical affinity with nalorphine will be discussed, and finally the toxicity of a miscellaneous group of drugs all of which have been found to produce pain relief in man will be mentioned briefly.

A. Morphinomimetic drugs

As their name implies these derivatives have pharmacological properties qualitatively similar to those of morphine (I) itself. When given in therapeutic doses many of these drugs produce mild toxic effects which become progressively more severe as the dose is increased. The symptoms resulting from overdosage are well characterised; respiratory depression can be demonstrated in doses only slightly larger than those required to produce pain relief (Eckenhoff & Oech, 1960) and nausea and vomiting are common; with increasing doses circulatory collapse supervenes. Central nervous system (CNS) effects are frequent and result from both excitation and depression; they include dizziness, vertigo, sedation and restlessness. Skin reactions, such as urticaria and pruritis, and sneezing are common in the less potent analgesics and appear to result from the liberation from the skin of histamine and other naturally occurring substances. True allergic reactions are uncommon in patients but occur frequently in workers who come into daily contact with the drugs. Epigastric pain, acute urinary retention and biliary colic have all been reported in these cases.

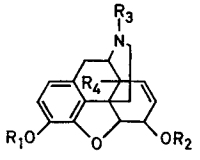
All the narcotic analgesics produce miosis in man which is thought to be the result of stimulation of the pupilloconstrictor centre or depression of an inhibitor centre. Weinstock and her colleagues (Weinstock, Stewart & Butterworth, 1958) have demonstrated that narcotic analgesics with a wide range of potencies can produce a clouding of the lens in mice and rats but this has not been reported in man. Similarly large repeated doses of narcotic analgesics are capable of producing a marked degree of corneal opacity in a variety of experimental animals (Lister, 1963, unpublished) which is reversible, but this condition has not been reported in man. Fuller details of the toxic effects of the morphinomimetic drugs will be found in a number of monographs, e.g. Reynolds & Randall (1957); Foldes, Sverdlow & Siker (1964); de Stevens (1965).

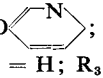
The best known and best-documented toxic effect of the narcotic analgesics is their ability to produce a condition of drug dependence commonly known as addiction. A detailed description of this toxic phenomenon is outside the scope of this review but it has been the subject of a number of recent reviews (Seevers & Deneau, 1963; Halbach & Eddy, 1963).

The degree of addiction liability of each new drug described will be indicated where it exists. Up-to-date accounts of the addiction liability of new drugs are to be found in the Minutes of the Annual Meeting of the Committee on Drug Addiction and Narcotics of the National Academy of Sciences—National Research Council.

1. DERIVATIVES OF PHENANTHRENE

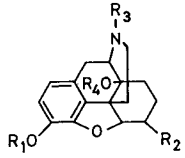
This group embraces the naturally occurring analgesics morphine (I) and codeine (II), a large group of semisynthetic derivatives ranging in potency from derivatives with an analgesic potency less than one hundredth that of morphine to the recently described derivatives of thebaine (Bentley & Hardy, 1963; Lister, 1964) some of which have analgesic potencies approaching 10,000 times that of morphine, and completely synthetic drugs of the morphinan series.



I. Morphine. $R_1, R_2, R_4 = H$; $R_3 = Me$.
II. Codeine. $R_2, R_4 = H$; $R_1, R_3 = Me$.
III. Normorphine. $R_1, R_2, R_3, R_4 = H$.
IV. Nicomorphine. $R_1, R_2 = CO$  ; $R_3 = Me$; $R_4 = H$.
V. 14-Hydroxymorphine. $R_1, R_2 = H$; $R_3 = Me$; $R_4 = OH$.
VI. Nalorphine. $R_1, R_2, R_4 = H$; $R_3 =$ allyl.

(a) *Oxymorphone* (dihydrohydroxymorphinone). This compound (VII) and its related codeinone, oxycodone (VIII), are the only examples of analgesics, derived by substitution in the morphine nucleus, to be widely introduced into clinical practice during the last decade; they are included in the review of Eddy & others (1957) but much more work has been reported since then and the drugs have been introduced on to the world market. Oxymorphone synthesised by Weiss (1955) was shown by various workers (Coblenz & Bierman, 1956; Eddy & Lee, 1959; De Kornfeld, 1961; Keats & Telford, 1960) to be a powerful analgesic with a potency approximately ten times that of morphine. Tullar (1961) found that oxymorphone had an acute LD50 in mice 1·6 times that of morphine and suggested that it might offer a wider safety margin than morphine. Unfortunately the clinical results do not support this hypothesis. No evidence can be found to support this claim for man and there is much evidence to the contrary. Oxymorphone has been shown to be a powerful respiratory depressant in man (Resnick, Berkowitz, Rodman & Close, 1960; Lasagna, 1964) and may produce more respiratory depression than equianalgesic dose of morphine (Eddy & Lee, 1959; De Kornfeld, 1961). Keats & Telford (1960) gave reputed equianalgesic doses of morphine (10 mg/10 kg) and oxymorphone (1 mg/10 kg) to patients before operation,

and found that oxymorphone produced a statistically higher incidence of nausea and vomiting than morphine and that the incidence of other undesirable responses was also higher in the oxymorphone treated group. Oxymorphone produced marked euphoria in many patients (De Kornfeld, 1961) and possesses a high physical dependence capacity (Fraser & Isbell, 1955).



VII. Oxymorphone. $R_1, R_4 = H$; $R_2 = O$; $R_3 = Me$.
VIII. Oxycodone. $R_1, R_3 = Me$; $R_2 = O$; $R_4 = H$.
IX. Naloxone. $R_1, R_4 = H$; $R_2 = O$; $R_3 = allyl$.
X. Hydromorphinol. $R_1, R_4 = H$; $R_2 =$  ; $R_3 = Me$.

(b) *Oxycodone* (dihydrohydroxycodeinone). This compound (VIII) bears the same relationship to oxymorphone as codeine does to morphine; it has been known for many years and Falk (1917) first reported on its clinical use. It has a potency and duration of action similar to that of morphine and its addiction liability and toxic effects are similar. A combination of oxycodone with a pectinate base (Proladone) has been introduced on to the British market as a long acting analgesic but there is no evidence that this combination has in any way reduced the toxicity of the oxycodone.

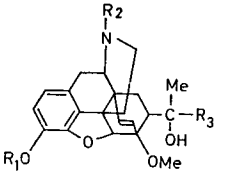
(c) *Other* 14-*hydroxy derivatives of morphine.* Weiss & Daum (1965) reported the synthesis of 14-hydroxymorphine (V) and hydromorphinol (X). The first was similar in potency and duration of action to morphine; the reduced derivative was about twice as potent as morphine with a prolonged duration of action in man. However no details of their toxicity or side-effect liability are yet available. Esterification of the 14-hydroxy group of oxycodone has been shown to produce an increase in analgesic potency in mice with a marked reduction in acute toxicity when compared with the parent compound (Buckett, Farquharson & Haining, 1964), but no clinical data are yet available.

(d) *Normorphine* (III). This is derived from morphine by *N*-demethylation and has been demonstrated to occur in the liver and brain of rats following the injection of morphine (Misra, Mule & Woods, 1961; Milthers, 1962) and it has been suggested as the active metabolite of morphine (Beckett, Casy & Harper, 1956). Clinical evaluation in man has shown that it is a weak analgesic possessing a potency rather less than one third that of morphine (Fraser, Wikler, Van Horn, Eisenman & Isbell, 1958). These authors also found that repeated doses of normorphine led to accumulation of toxic effects the most noticeable of which was excessive sedation. Normorphine substitutes adequately for morphine in addicts but the withdrawal symptoms are mild and it is

judged to have low physical dependence capacity (Eddy, 1959). As it offers no obvious advantages over other well established drugs it has not been used extensively.

(e) *Esters of morphine.* The nicotinic acid bis-ester of morphine (IV; nicomorphine) has been shown to possess a longer duration of action than morphine in animals and to be free of spasmogenic effects on the gut (Zirm & Pongratz, 1960). These authors have also claimed that this drug does not induce tolerance to the analgesic effects (Zirm & Pongratz, 1959). It has been suggested that it may be free from addiction liability but studies in man suggest that this is not the case.

(f) *Derivatives of thebaine.* In 1963, Bentley & Hardy (1963) showed that thebaine, an alkaloid occurring in opium but with no analgesic properties, could be used as the starting point for a series of highly potent analgesics and analgesic antagonists. These 6,14-*endo*-ethenotetrahydro-oripavine derivatives can be looked upon as bridged ring derivatives of morphine. Despite a very marked increase in potency over morphine and a marked reduction in toxicity relative to their analgesic potency in laboratory animals (Lister, 1964), the members of this series which have been tested in man show no significant qualitative advantages over morphine and in equi-analgesic doses produce probably more respiratory depression (Campbell, Lister & McNicol, 1964). These authors showed that with the derivative tested (XII; M183) there was some reduction in



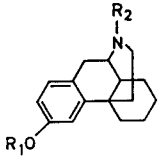
XI. M 99. $R_1 = H$; $R_2 = Me$; $R_3 = Pr$.
XII. M 183. $R_1 = COMe$; $R_2 = Me$; $R_3 = Pr$.
XIII. M 285. $R_1 = H$; $R_2 = CH_2CH\langle^{CH_2}_{CH_2}$; $R_3 = Me$.

nausea and vomiting in human volunteers and a complete absence of any histamine release, but these clinical advantages are outweighed by the undesirable respiratory distress produced. Blane (personal communication) has recently shown that M99 (XI), which is believed to be the active metabolite of M183, produced a higher neonatal mortality in rats than did morphine or pethidine when these drugs were injected into pregnant rats at term. Measurement of the oxygen consumption of the caesarean-delivered neonates indicated that respiratory depression was not necessarily the cause of death, and the author suggests that death may be associated with maternal cardiovascular disturbances during the intrauterine existence. M99 and morphine both produced a marked reduction in neonatal oxygen consumption but the neonates from the pethidine-treated mothers

showed a higher survival rate and less depression of respiration. The results suggest that in neonates there may be differences in the permeability of the brain to different drugs. Support for this view is obtained from a recent study by Way, Costley & Way (1965) who demonstrated a similar difference between the respiratory depression produced in infants after the injection of morphine and pethidine. These findings suggest that the new-born may show both quantitative and qualitative differences in their sensitivity to the toxic effects of narcotic analgesics and that this factor should be born in mind when evaluating new drugs of this type.

2. MORPHINANS

Levorphanol (XIV) was synthesised in an attempt to find a synthetic morphine-like drug devoid of some of the undesirable toxic effects of morphine, but although it had a potency about ten times that of morphine it showed no qualitative difference from morphine. Many analogues of levorphanol have been synthesised, frequently with an improvement in potency over the parent compound, but these improvements have not been matched by any significant reduction in the relative toxicity. One such drug, (–)-3-hydroxy-*N*-phenacylmorphinan methanesulphate (XV) (NIH 7525, Ro 4-0288/1) was shown to be 20 to 25 times as active as morphine in laboratory animals but only about four to five times as active in relieving post-operative pain in patients. In equi-analgesic doses no significant difference in the incidence of side-effects was found between NIH 7525 and morphine (De Kornfeld, 1960) but there is some evidence that the physical dependence capacity of this drug may be lower than that of morphine (Eddy, 1959).



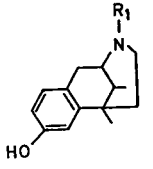
XIV. Levorphanol. $R_1 = H$; $R_2 = Me$.
XV. NIH 7525. $R_1 = H$; $R_2 = CH_2COC_6H_5$.
XVI. Levallorphan. $R_1 = H$; $R_2 =$ allyl.
XVII. Cyclorphan. $R_1 = H$; $R_2 = CH_2CH\begin{smallmatrix}CH_2\\|\\CH_2\end{smallmatrix}$.

3. BENZOMORPHANS

This series of synthetic analgesics represents a further simplification of the morphine molecule. Derivatives based on this nucleus have aroused wide interest because they first provided evidence for a possible dissociation of analgesic activity and addiction liability (Eddy, 1959). Both morphine-like drugs and morphine antagonists have been developed in this series.

(a) *Phenazocine.* The initial studies on this drug (XVIII) gave rise to a great deal of optimism because, although a powerful morphine-like

drug, it was only a poor substitute for morphine in monkeys (Tedeschi, Tedeschi & Fellows, 1960) and possessed a marked separation of analgesia from cardiovascular and respiratory depression (Shemano, Wendel & Ross, 1961). However the promising results in animals have not been borne out in man. Phenazocine has been shown to be a potent respiratory depressant and when given in equi-analgesic doses it depresses respiration more than morphine or oxymorphone (Berkowitz, Rodman & Close, 1961). In man, phenazocine has been shown to substitute for morphine in addicts. Direct addiction can be induced but the physical dependence liability is less than morphine although still significant (Eddy, 1959). Sadove & Balagot (1961) reported that when used as an adjunct to anaesthesia, phenazocine produced less cardiovascular disturbance than morphine but respiratory depression and facial pruritus were observed in patients given the drug. The position of phenazocine in clinical practice has not yet been fully established. Some workers claim that it possesses a low degree of clinical toxicity (Sadove, Schiffrin & Heller, 1959; Sadove & Balagot, 1961) but others take the opposite view (Berkowitz, Rodman & Close, 1961; York, Campbell & Gordon, 1962).



XVIII. Phenazocine. $R_1 = CH_2CH_2C_6H_5$.

XIX. Pentazocine. $R_1 = CH_2\ CH = C\begin{matrix}Me\\Me\end{matrix}$.

XX. Cyclazocine. $R_1 = CH_2CH\begin{matrix}CH_2\\|\\CH_2\end{matrix}$.

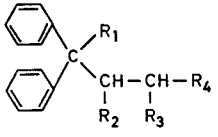
4. DIPHENYLMETHANE SERIES

Initial hopes that the synthetic analgesic methadone (amidone) (XXI) might not produce addiction soon proved unfounded but this drug has served as a model for a wide range of derivatives, a few of which have reached the stage of clinical trial and marketing.

(a) *Noracymethadol* (XXII). This congener of methadone is an effective analgesic with a more favourable oral to parenteral dose ratio than morphine and most other analgesics. Gruber & Baptisti (1963) showed that noracymethadol produced salivation, ataxia and nalorphine-reversible respiratory depression but they claimed that for an equal degree of pain relief noracymethadol produced less nausea, dizziness and drowsiness than morphine. Noracymethadol is capable of supporting physical dependence in monkeys and is thus liable to abuse.

(b) *Dextromoramide* (XXIII). Janssen & Jageneau (1957) reported on the pharmacology of dextromoramide, a new and potent analogue of methadone. Studies in the rat showed that tolerance to the analgesic

effect of dextromoramide developed slowly and that cross tolerance to morphine did not develop. As a result of this work and their own clinical observations, Soupalt and his colleagues (Soupalt, Caroli, Renon, Schops & Charbonnier, 1957) and Alvarez-Ude (1958) suggested that this drug might not prove addicting. Subsequent studies (La Barre, 1959) indicated that dextromoramide possessed an addictive potential at least equivalent to morphine. Dextromoramide is a powerful respiratory depressant (Cahal, 1958; Keats, Telford & Kurosu, 1960) and some patients appear to be unusually sensitive to this effect, many developing apnoea with analgesic doses (Black, 1966). A fatality has been reported (La Barre, 1959) from a total dose of 45 mg of dextromoramide; death was thought to be due to respiratory and cardiovascular collapse.



XXI. Methadone. R_1 = COEt; R_2 = H; R_3 = Me; R_4 = NMe_2.

XXII. Noracymethadol. R_1 = CH·O·COMe·Et; R_2 = H; R_3 = Me; R_4 = NHMe.

XXIII. Dextromoramide. R_1 = CON⟨ ⟩; R_2 = Me; R_3 = H; R_4 = N⟨ ⟩O.

XXIV. Dextropropoxyphene. R_1 = COEt; R_2 = Me; R_3 = H; R_4 = NMe_2.

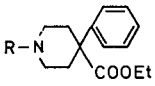
(c) *Dextropropoxyphene* (XXIV). This is a much less potent congener of methadone with an analgesic activity similar to that of codeine. Initial hopes that this compound would not be capable of supporting addiction (Gruber, 1957) have not been realised, and cases of primary physical dependence have been reported (Elson & Domino, 1963) although the incidence of drug abuse appears to be low relative to the number of doses prescribed. McCarthy & Keenan (1964) recently reported a fatality due to an overdose of propoxyphene, death being due to cardiovascular and respiratory failure accompanied by convulsions. At post-mortem generalised oedema and marked brain necrosis were found.

This drug is a mild analgesic which is effective by oral or parenteral routes but its overall toxicity and addiction liability appear to be no different from codeine (Van Bergen, North & Karp, 1960).

4. PETHIDINE DERIVATIVES

During the early 1950's organic chemists in a number of countries devoted much time and energy attempting to synthesise a safer and more potent analogue of pethidine (XXV). A number of derivatives have been made and tested, and at least four introduced clinically, but despite an increase in potency over pethidine the major toxic effects of respiratory and cardiovascular depression and emesis have invariably increased in direct proportion to the increase in analgesic activity.

(a) *Anileridine* (*Leritane*) (XXVI). This is an *N*-substituted derivative of pethidine with an analgesic potency approaching that of morphine. Pharmacological studies in dogs indicated that this drug was not emetic (Orahovats, Lehman & Chapin, 1957) but in man it was found to produce a significantly higher incidence of nausea and vomiting than equi-analgesic doses of pethidine (Chang, Safar & Lasagna, 1958). Other workers showed that it was a potent respiratory depressant and that patients found it a more unpleasant drug than pethidine, possibly because of the higher incidence of nervousness, restlessness and stimulation that followed its administration (Keats, Telford & Kurosu, 1957). Anileridine is effective by mouth but otherwise its toxic and pharmacological effects are similar to those of pethidine with an abuse liability of the same order.



XXV. Pethidine. R = Me.

XXVI. Anileridine. R = CH_2CH_2  NH_2.

XXVII. Etoxeridine. R = $CH_2CH_2OCH_2CH_2OH$.

XXVIII. Piminodine. R = $CH_2CH_2CH_2NHC_6H_5$.

XXIX. Benzethidine. R = $CH_2CH_2OCH_2C_6H_5$.

XXX. Furethidine. R = $CH_2CH_2OCH_2$  .

XXXI. Phenoperidine. R = $CH_2CH_2CHOHC_6H_5$.

(b) *Etoxeridine* (XXVII). The pharmacology and toxicology or etoxeridine were described by Merlevede & Levis (1958), and it was found to be a potent analgesic some two to 40 times as potent as pethidine depending on the route and species used.

Initial uncontrolled clinical studies (Merlevede, 1958) indicated a low degree of clinical toxicity but in a more closely controlled study, Crawford & Foldes (1959) showed that this drug was a powerful respiratory depressant in man, producing respiratory arrest in almost every patient at a dose of 0·25–0·30 mg/kg, which was equivalent in analgesic potency to the relatively safe dose of 1 mg/kg of pethidine; cardiovascular depression was also noted by these authors. Merlevede (1958) reported three cases of drug dependence and seven cases of tolerance to etoxeridine out of 64 patients treated for carcinomatoses.

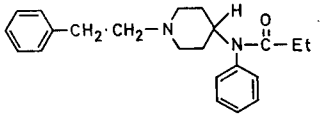
(c) *Piminodine* (XXVIII). This is a further *N*-substituted derivative of pethidine with an analgesic potency rather greater than that of morphine, but in other respects its pharmacology and toxicology resemble that of pethidine. It has a high physical dependence capacity (Woods, Deneau, Bennet, Domino & Seevers, 1961) but there is some evidence that the respiratory depression may be less than that of morphine (De Ciutiis, 1961; Lasagna, 1964).

(d) *Benzethidine* (XXIX) *and furethidine* (XXX). These are two more pethidine derivatives showing some definite advantages over pethidine when tested in animals (Lister, 1960). Both derivatives had only one

hundredth of the potency of pethidine as histamine liberators and in view of the suggestion that histamine liberation was responsible for many of the undesirable effects of pethidine (Gershon & Shaw, 1958) these compounds were tried in man. Neither drug showed any marked clinical advantage over pethidine (Masson, personal communication) and clinical trials were discontinued.

(e) *Phenoperidine* (XXXI). Rollason & Sutherland (1963) reported on the clinical pharmacology of phenoperidine. This is a potent analgesic in man but because of the unpredictability of action and incidence of side-effects in the therapeutic dose range these authors did not recommend its use. Total doses of 4 mg produced long lasting respiratory depression in some patients; others lost consciousness, although respiration appeared adequate and during this stage marked athetoid movements occurred. Catatonia with lead pipe rigidity was also reported. Vertical nystagmus was reported in 66% of the patients and there was a high incidence (17%) of nausea and vomiting and respiratory depression (20%). This drug has also been used in neuroleptanalgesia (Ingvar & Nilsson, 1961) but this combination has now been replaced by newer and safer preparations.

(f) *Fentanyl* (R 4263) (XXXII). Fentanyl can be looked upon as a pethidine analogue; it is a highly potent, short acting analgesic with an activity some 200 times that of morphine (Janssen, 1962; Gardocki & Yelnosky, 1964). In mice the therapeutic index of 775 compares very favourably with that for morphine of 31 but insufficient evidence is available to show if this favourable ratio applies to man. Because of its high potency and short duration of action it has been used in combination with droperidol for neuroleptanalgesia under the trade name of Innovar (Holderness, Chase & Dripps, 1963). The advantages and disadvantages of neuroleptanalgesia with drug combinations of this type have recently been discussed in a symposium devoted to this topic (Shepherd, 1965).



XXXII. Fentanyl.

Apnoea requiring ventilation is commonly observed with this treatment and muscular rigidity and laryngospasm, making ventilation difficult, has also been reported (Foldes & others, 1964). The technique of neuroleptanalgesia is still experimental and further work is required before a full evaluation of the hazards associated with it can be fully appraised.

B. Narcotic antagonists

Substitution of the methyl group on the tertiary nitrogen atom of many analgesics by unsaturated three carbon moieties, e.g. allyl, frequently

gives a competitive antagonist to the original analgesic. Much interest has been aroused recently by the findings that some of the antagonists are analgesics in their own right with pharmacological spectra which differ in many respects from that of the original parent compound. These antagonists are usually devoid of addiction liability and if taken by a narcotic-dependent subject precipitate an intense withdrawal syndrome.

1. DERIVATIVES OF PHENANTHRENE

(a) *Nalorphine* (VI). Early studies on nalorphine indicated that this drug was an effective antagonist to the narcotic actions of morphine (Hart, 1941; Unna, 1943). It was capable of reversing the analgesia, respiratory depression and miosis produced by morphine, and found a ready use as an antagonist to the narcotic analgesics in cases of overdosage. Nalorphine has been shown to be free of addiction liability (Isbell, 1956) and Lasagna & Beecher (1954) showed that it was a powerful analgesic with a potency similar to that of morphine. However, because of the high incidence of toxic side-effects which develop in many patients following an effective analgesic dose, it has not proved to be a practical proposition as an analgesic. When nalorphine is given alone it frequently produces marked psychotomimetic effects (Lasagna & Beecher, 1954; Woods, 1956; Keats & Telford, 1956) which have been attributed to a CNS stimulant effect. The psychotomimetic effects described include anxiety, dysphoria and visual hallucinations with occasional panic due to a sense of impending death. Morphine has little effect on these psychic disturbances but they can be abolished by pentobarbitone or chlorpromazine. Nalorphine shows other stimulant actions on the CNS; it can cause emesis, myosis and bradycardia and give rise to convulsions in experimental animals (Woods, 1956). Excessive doses of nalorphine given after morphine have induced convulsions in a female patient (Wolfe, 1955). Nalorphine alone is a powerful respiratory depressant (Foldes & others, 1964) and although effective in antagonising the respiratory depression produced by morphine overdosage, it may, if the existing depression is severe, fail to antagonise and even potentiate the depression (Campbell, 1965, personal communication). Nalorphine can produce hypotension which may be severe in some patients (Eckenhoff, Elder & King, 1952).

(b) *Naloxone* (IX). This is a newly introduced derivative of oxymorphone. It is a powerful narcotic antagonist approximately 30 times as potent as nalorphine as an antagonist (Foldes, Lunn, Moore & Brown, 1963) and shows some degree of group specificity against oxymorphone (Sadove, Balagot, Hatano & Jobgen, 1963). Naloxone has recently been shown (Lasagna, 1965) to possess some analgesic properties, 2 mg naloxone giving pain relief similar to that observed with 10 mg morphine. Strangely, higher doses produced less effect and 8 mg produced less pain relief than expected from a placebo. There have been no reports of psychotomimetic effects with this drug and it appears to be free from addiction liability (Foldes & Torda, 1965).

(c) *M*285 (XIII). This is one of a series of potent and long lasting analgesic antagonists derived from thebaine and related to M99 (XI) described by Bentley, Boura, Fitzgerald, Hardy, McCoubrey, Aikman & Lister (1965). It is a weak analgesic of the nalorphine type but possesses powerful and long lasting psychotomimetic properties (Eddy, 1965 and Campbell & Lister, 1965, unpublished observations).

(d) *Levallorphan* (XVI). Levallorphan is a more specific narcotic antagonist than nalorphine and even in large doses has no analgesic or psychotomimetic effects. Although it may produce mild respiratory depression (Foldes & Torda, 1965), no other toxic effects have been reported. It is free of addiction liability but is capable of precipitating the withdrawal syndrome in narcotic addicts. Levallorphan has been combined with narcotic analgesics, especially pethidine, with the object of antagonising the respiratory depression of the narcotic without reducing the analgesia to the same extent. Studies in volunteers (Herxheimer & Sanger, 1957) and patients (Foldes, McNall, Koukal & Tanaka, 1959) indicated that this might be possible, but recent controlled studies have shown that it is unlikely (Telford & Keats, 1961; Campbell, Masson & Norris, 1965). These latter authors showed that in some circumstances levallorphan may potentiate the respiratory depression due to pethidine. Differences in the duration of action of the analgesic and the antagonist may lead to a dangerous state of renarcotisation in a patient previously thought to be free from respiratory depression.

(e) *Cyclorphan* (XVII). This morphinan derivative is a powerful analgesic with similar properties to cyclazocine, but may prove to be even more potent as an analgesic (Deneau & Seevers, 1964; Lasagna, 1965). Like cyclazocine and pentazocine, cyclorphan can produce psychic disturbances.

(f) *Pentazocine* (XIX). Substitution of the tertiary nitrogen in the benzomorphan nucleus by allyl and other unsaturated groups gave a series of narcotic antagonists (Archer, Albertson, Harris, Pierson, Bird, Keats, Telford & Papadopoulos, 1962; Harris & Pierson, 1956, 1964). Pentazocine was found to be a weak narcotic antagonist with significant analgesic properties when tested against post-operative pain in man (Telford, Papadopoulos & Keats, 1961; Keats & Telford, 1964; Stoetling, 1965). These authors found that 10–20 mg/70 kg of pentazocine produced analgesia equivalent to that of 10 mg/70 kg of morphine. The incidence of subjective side-effects was qualitatively and quantitatively similar to those produced by morphine; only one of 75 patients described any nalorphine-like effects and these were minimal. Pentazocine produced significantly less nausea than morphine and the incidence of vomiting was also low. On the other hand pentazocine produced a high incidence of hypertension and tachycardia, conditions not observed after morphine although these conditions could not necessarily be attributed to the drug treatment (Sadove, Balagot & Pecora, 1964). Both morphine and pentazocine induced respiratory depression although that produced by pentazocine could not be antagonised by nalorphine. Restlessness, pruritis and signs of histamine release were observed in patients given

pentazocine but the incidence appeared to be no greater than with morphine.

Fraser & Rosenberg (1964) demonstrated that the addiction liability of pentazocine was low, approximating to that of dextropropoxyphene. It would not substitute for morphine in addicts and, when given by chronic administration to post-addicts, only one subject elected to continue taking the drug when offered the chance to discontinue it, even though he showed a severe inflammatory reaction at the injection site. When the drug was stopped this subject showed a mild abstinence syndrome. Thus pentazocine has been shown to be the first clinically potent analgesic with minimal psychotoxicity and addiction liability, and gives hope for the future development of a safe potent analgesic which may be free of addiction liability and the other distressing side-effects so long associated with the narcotic analgesics.

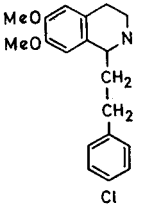
(g) *Cyclazocine* (Win. 20,740) (XX). This compound is a potent narcotic antagonist with powerful anticonvulsant, sedative and muscle relaxant properties (Harris & Pierson, 1964; Weiss & Laties, 1964). It has been found to be a highly effective analgesic when given either orally or parentally in doses as low as 0·25 mg, which can produce pain relief equal to 10 mg morphine (Lasagna, De Kornfeld & Pearson, 1964), but it is capable of producing mental confusion, depersonalisation and dysphoria reminiscent of nalorphine. Although it can give rise to respiratory depression the slope of the dose response curve is not parallel to, and is shallower than that found for morphine, and the ceiling effect appears to be much lower; thus the possibility of dangerous respiratory depression due to overdosage with this drug appears to be less than with the older analgesics. These authors also pointed out that this drug, like pentazocine, had minimal addiction liability. An abstinence syndrome has been precipitated in experimental subjects given repeated doses of cyclazocine (Lasagna, 1965). These subjects who were all post-addicts found that the initial and subsequent subjective effects of this drug were so unpleasant that there would appear to be little chance of abuse of this agent by potential or established addicts.

C. Miscellaneous analgesics

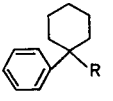
This group comprises a heterogenous collection of drugs which have been reported to produce pain relief in man but which have no direct chemical affinity with the established narcotic analgesics. However, as they all seem to act on central nervous structures they have been included.

(a) *Methopholine* (Versidyne, Ro4-1778/1) (XXXIII). This drug is an isoquinoline derivative chemically related to the analgesically inactive opium alkaloid papaverine. Methopholine has an analgesic activity similar to that of codeine (Sadove, Schiffrin & Ali, 1961). The addiction liability of this drug is very low and probably less than that of codeine (Fraser, Martin, Wolbach & Isbell, 1961). In man, methopholine produces respiratory depression which is accompanied by a mild degree of cardiovascular depression. There is evidence that the respiratory depression produced by this drug is not antagonised by levallorphan but instead the

two drugs produce an additive depression of respiration (Foldes, Moore & Suna, 1961). These workers also reported a severe atopic allergic reaction in a patient, which was relieved by hydrocortisone. This drug produces pain at the injection site and is usually given orally and often in combination with aspirin, but a high percentage (30%) of patients reported nausea with this mixed dose regimen (Cass & Frederik, 1964).



XXXIII. Methopholine.

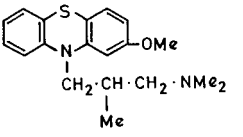


XXXIV. Phencyclidine.

R = N

XXXV. Cl 400.

R = NHEt.



XXXVI. Methotrimeprazine.

(b) *Phencyclidine* (XXXIV) and *Cl* 400 (XXXV). These drugs are closely related members of a series of cyclohexylamines which are capable of producing a high degree of sensory blockade at the sub-cortical level. Profound analgesia sufficient for minor surgical procedures can be induced with doses of 0·25 mg/kg body weight (Johnstone, Evans & Baigel, 1959; Collins, Gorospe & Rovenstine, 1960). Unlike the morphinomimetic drugs the cyclohexylamines do not give rise to respiratory or cardiovascular depression and may even stimulate these functions, nor do they substitute for morphine in addicts.

Despite these apparent advantages, the high incidence of toxic effects associated with the administration of these drugs has precluded their widespread clinical use. These effects were mainly the result of stimulation of the CNS which took the form of marked agitation and hallucinosis and in many cases a state of catatonic stupor developed. Hypertension and tachycardia frequently accompanied the hallucinatory state and appeared to be secondary to it as termination of the hallucinations with barbiturates abolished both effects. The hallucinations were usually unpleasant and often accompanied by nausea and salivation and the effects showed a marked similarity to those seen in chronic schizophrenics (Cohen, Rosenbaum, Luby & Gottlieb, 1962). The incidence of psychotomimetic effects may approach 50% in adult patients treated with these drugs but there is a lower incidence of undesirable effects in the elderly. Phencyclidine provided adequate analgesia in 78% of infants being treated for burns (Muir, Evans & Mulcahy, 1961) but these authors reported a 50% incidence of hallucinations and crying in the children.

This drug has been withdrawn from clinical use but it has demonstrated that profound analgesia can be produced without necessarily incurring the risks of addiction and respiratory depression.

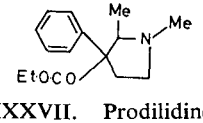
(c) *Methotrimeprazine* (XXXVI). Methotrimeprazine is a phenothiazine derivative which has been found to be an analgesic with a potency when given parentally similar to that of morphine (Lasagna & De Kornfeld, 1961; Motilla, 1963). It appears to be devoid of addiction liability (Fraser & Rosenberg, 1963) and respiratory depression (Pearson & De Kornfeld, 1963). It is ineffective when given orally but when given parenterally it may give rise to pain at the site of injection; marked sedation and giddiness have been reported in volunteers (Pearson & De Kornfeld, 1963). As this drug is a phenothiazine, its toxicity is likely to resemble that of this group of drugs rather than the narcotics and a careful watch must be kept for toxic effects such as blood dyscrasias and hepatic involvement. Hollister (1965) recently reviewed the toxicity of this group of drugs and stresses the need for care in prescribing these potent agents.

(d) *Prodilidine* (Cogesic) (XXXVII). This drug can be regarded as having some chemical affinity with pethidine but it is a much weaker analgesic. Cass & Frederik (1963) found prodilidine to be only one half as potent as codeine on a weight basis.

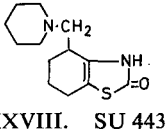
Doses of 50 mg prodilidine produced pain relief in 69% of ambulatory patients studied by Batterman, Mowratoff & Kaufmann (1964), but when the dose was increased to 75 mg the increased incidence of undesirable side effects led to a reduced patient acceptance and pain relief was found in only 61% of patients.

The physical dependence capacity of prodilidine is low, reflecting its weak analgesic properties, and no clinical evidence of abuse has been reported to date.

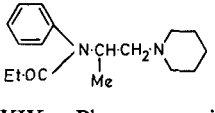
(e) *SU*4432 (XXXVIII). This compound was found to be an analgesic of similar potency to codeine when tested in man against post-operative pain. Clinical trials were terminated because a small percentage of patients complained of blurred vision believed to be due to inflammation of the optic nerve (de Stevens, 1965). Normal vision returned on cessation of the drug treatment.



XXXVII. Prodilidine.



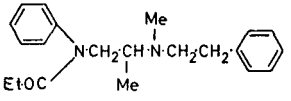
XXXVIII. SU 4432.



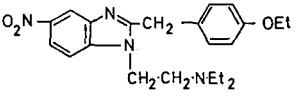
XXXIX. Phenampromide.

(f) 2-*Amino-indane* (*SU* 8629) (XLII). This simple indane derivative was found to have an analgesic potency about 20% that of morphine when tested in animals (Witkin, Heubner, Galdi, O'Keefe, Spitaletta & Plummer, 1961). These authors found the drug to have certain similarities to amphetamine, it was not antagonised by nalorphine and further studies indicated that it would not substitute for morphine in morphine-tolerant monkeys. Although found to be effective as an analgesic when given orally in man it produced an undesirable incidence of central stimulation and hypotension which led to the abandonment of further clinical studies (de Stevens, 1965).

(g) *Benzimidazoles.* These form a group of highly potent analgesics, of which an example is etonitazine (XLI). Although these compounds are effective analgesics in man they produce marked respiratory depression in analgesic doses and have a high addiction potential. These disadvantages were sufficient to warrant termination of clinical trials (de Stevens, 1965).



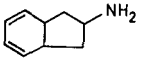
XL. Diampromide.



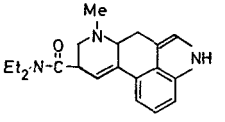
XLI. Etonitazine.

(h) *Phenampromide group.* A series of basic anilides were reported to have analgesic action by Wright, Brabander & Hardy (1959). Of this series two derivatives, phenampromide (XXXIX) and diampromide (XL) were tested clinically and found to have analgesic activity similar to pethidine and morphine respectively. Both compounds possessed morphine-like properties but possessed no obvious clinical advantages over morphine and have not been marketed.

(i) *Lysergic acid diethylamide* (LSD 25) (XLIII). This drug is a powerful psychotomimetic agent producing euphoria in some subjects. Kast & Collins (1964) tested it as an analgesic agent in patients with severe pain and found that 0·1 mg LSD 25 produced significantly greater pain relief in the third hour after administration than either 2 mg dihydromorphinone or 100 mg pethidine.



XLII. SU 8629.



XLIII. Lysergic acid diethylamide.

Three patients out of 50 reported nausea and vomiting with LSD 25; psychotic reactions occurred in most of the patients but these were not judged to be sufficiently severe to warrant their termination with chlorpromazine. Despite prolonged pain relief eight patients refused a second dose of the drug because of the unpleasant psychic effects. There was no evidence of cardiovascular or respiratory depression with this drug and it does not support morphine dependence. There is, however, increasing evidence that this drug is liable to abuse, but evidence of true drug dependence is lacking.

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Discussion

Mr. A. W. Lessin. Dr. Lister, you talk about separation of analgesic properties and addiction liability, but on looking at the examples you have given, the addiction liability seems to be related to the potency in all cases except pentazocine, and I wonder whether the confidence with which you stated that there was a separation might not be shaken.

Dr. H. O. J. Collier. I think it is agreed that, if the rate of onset of analgesia is the same for two drugs, potency in inducing dependence about equals analgetic potency. Where potency is high, the social danger of a drug is high, because its illicit exchange is easier. Heroin is thus more dangerous socially than morphine, and a compound a thousand times more potent would be very much more socially dangerous. This raises an important question. Should we seek analgetics of high potency, if these are liable to be equally highly addictive? Wisely or luckily, the very potent analgetics recently discovered have not so far been introduced into medicine.

Dr. Cicely Saunders. Much of the toxicity of this group of drugs depends not only on their chemistry but also on the way in which the drug treatment is managed. The toxic features of this group of drugs include dependence, and we may take diamorphine as one which at least has the reputation of being more likely than any other drug to cause dependence. Yet of the last 48 patients who were with us for longer than three months, only nine ever needed more than 10 mg doses; for 20 patients the 10 mg dose was the maximum, while 19 received less than 10 mg dosage. So that over many weeks this drug has been used without producing this type of toxicity. Whatever new drug is introduced its management forms a major part of the treatment. So many trials have been single dose studies, and as Lasagna and others have pointed out, dependence is usually assessed on addicts or post-addicts and other side-effects on normal volunteers. Just as it is difficult to transfer toxicity effects from animals to man, it is also very diffcult to transfer observations made on addicts or volunteers, to patients with chronic pain. There is a need for trials which are patient-centred rather than drug-centred, in which the long-term effects and side-effects are assessed.

Dr. R. E. Lister. I did point out that the physical dependence capacity of pentazocine was virtually zero, similarly with cyclazocine, and also a drug which I have examined, M285. These three compounds are narcotic antagonists of different potencies, and none of them support morphine-type physical dependence: in fact in every instance they would precipitate withdrawal symptoms in addicts who tried to use them. Therefore these are examples in which dissociation of analgesia and physical dependence is possible. There is no evidence that some of the other compounds, for example methotrimeprazine and phencyclidine and drugs like the two SU compounds produce physical dependence. But there is increasing evidence that it is possible to dissociate the clinical analgesia from physical dependence capacity. I agree with Dr. Collier.

The assumption that diamorphine, for example, is a more potent drug of addiction than say morphine has been questioned by Isbell and some of his colleagues, who claimed that if the drugs were given in equi-active doses there was no evidence that diamorphine was a stronger drug of addiction than morphine in addicts and post-addicts.

I think the assessment of the addiction potential and dependence capacity in patients raises an ethical question, and it has been suggested that patients are perhaps not the best subjects for this kind of study because the actual incidence of narcotic addiction in patients is low compared with the rate of dependence in so-called normal people, and there may well be a relation between dependence and the actual physical process of introducing a euphoric agent into the body.

Chairman's Summary

There is a strong impression that these drugs can produce toxic effects, and I think the onus is on the people who are using them, or those who prescribe them for their patients, to be aware of this and perhaps to act on the assumption that toxic effects can be produced until it has been clearly shown not to be so.