THE CLINICAL EVALUATION OF MORPHINE AND ITS SUBSTITUTES AS ANALGESICS[1]

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". . . it is the mark of an educated man to look for precision in each class of things just so far as the nature of the subject admits . . ."

Aristotle, 4th Century B.C.

"A micrometer is not used to measure a football field."

Freis and Williams, 1961.

I. INTRODUCTION

There are few symptoms more urgent than severe pain, few classes of drugs more useful than the major analgesics. The world literature on morphine-like drugs is both voluminous and ancient, but until recent times one searched in vain for quantitative data on their clinical performance. The last two decades have witnessed not only the birth of many new pain-relieving compounds, but—

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more important—have seen the emergence of scientifically acceptable techniques for generating reliable and interpretable clinical data.

This review will attempt to summarize the information available on the relative merits of the individual morphine-like compounds, and on their drawbacks. Before this, however, it is necessary to discuss briefly the problems involved in evaluating the literature in this field.

II. PROBLEMS IN EVALUATING THE LITERATURE

The delineation of analgesic efficacy can be thought of at two different levels. The first, and more simple one, is exemplified in the question: "Does this drug clearly relieve human pain?" The second, more complex level—and one which is crucial if we are to evaluate side-action liability in any meaningful way—can be exemplified in a second question: "How does this analgesic drug compare with already available analgesics, especially the standard ones?"

The first question requires a comparison of drug and placebo, the second a comparison of two or more drugs. Both kinds of comparisons are optimally made by the use of clinical trials employing accepted principles of experimental design, including the randomization of subjects to reduce or eliminate bias in allocation; the "double blind" technique (in which neither subject nor observer is aware of the specific nature of the medication being exhibited at a given time) to reduce or eliminate bias in assessment; and statistical planning and analysis, to minimize the drawing of conclusions unjustified by the magnitude of differences obtained and the numbers of subjects studied.

It is no exaggeration to say that we do not, at the present time, possess an adequate amount of information for most of the compounds to be discussed. This lugubrious statement is made not so much because of our inability to answer the first question posed above, but because of problems in answering the second.

Difficulties arise from the following sources:

A. Dose-response problems

It is a truism that the evaluation of a drug in man, no less than in other species, requires knowledge of the effects achieved with a reasonably broad span of doses (114). For reasons of convenience, caution, and habit, it is still commonplace to have evaluations and comparisons of analgesic drugs made at single dose levels.

B. The semantics of "pain relief"

The inter-investigator comparisons that one might desire to make are often hampered by the use of different criteria of response. Thus one may find papers reporting on the analgesic power of a given agent with the emphasis being on complete disappearance of pain, "significant" pain relief (variously defined or undefined), or incidence of pain relief of any degree; on peak effects or total performance over a matter of hours or days; or even on scores representing a strange melange of pain relief and untoward effects, with points given for analgesia and subtracted for such things as nausea or dizziness.

C. Acute vs. chronic administration

The study of single doses of drugs is certainly simpler and tidier than the study of repeated doses, but it does not shed light on such problems as cumulation and tolerance. Fortunately, drugs like morphine are most often used on a short-term basis, so that results on single-dose studies appear readily transferable to much of clinical practice. Occasionally, problems arise even in acute studies from the prolonged effects of analgesics (*cf.* acetylmethadol) (84). There is a dearth of information on the effects of chronic dosage with morphine and its substitutes.

D. Oral vs. parenteral routes

There is evidence that most of the drugs in the category under consideration are probably much less effective by mouth than by injection. At the same time, reliable potency estimates for drug given by these two routes are rarely available for the simple reason that controlled trials of an agent given by different routes pose certain technical obstacles which, while not insuperable, constitute a significant deterrent to the investigator. For example, patients with postoperative pain are often used to assess injectable drugs, but such patients, with their recent surgery, anesthesia, indwelling tubes, *etc.*, are likely to be considered poor candidates for oral medication. Contrariwise, postpartum patients or ambulatory outpatients are candidates for oral medication, but it may be difficult to arrange to give such patients injections, or they may be unwilling to undergo the pain and apprehension caused by them. In addition, there is the difficulty of eliminating bias in oral *vs.* parenteral comparisons, since to maintain double blind conditions, it is necessary to use two kinds of placebos, one oral and one injectable.

E. Population differences

Pain occurs in many clinical situations. There is the pain of labor, the afterpains of the postpartum period, the pains after a host of different surgical procedures, the pain of cardiac infarct, the pain of biliary or renal or intestinal colic, the pain from primary or metastatic malignant invasion of soft tissues or bone. The possibility arises that analgesic data, no matter how precise, in one kind of pain may not be readily transferable to other kinds of discomfort. Fortunately, the evidence to date suggests that potency estimates in such entities as postoperative pain, postpartum pain, and pain of malignant disease are often in reasonably good agreement, although some kinds of pain (*e.g.*, of rheumatoid or gouty arthritis) theoretically and empirically are responsive to agents (such as cortisone or colchicine) which are considered of little or no use in painful states unaccompanied by inflammatory pathology of any degree. Although the concepts of specific and nonspecific pain relief (for example, atropine or nitrites *versus* morphine in relieving the pain of smooth muscle spasm) are by no means new or profound, this point is mentioned because of the fact that analgesic studies are still reported which either fail to describe patients adequately, or include varying (and often unspecified) proportions of patients (such as arth-

ritics) in whom pain relief could conceivably be more impressive with agents affecting basic pathogenetic processes rather than (or as well as) producing "central" pain relief.

Certain kinds of common clinical pain, such as headache, traumatic pain (nonsurgical), and labor pain (126a), have been the subject of extraordinarily few adequately controlled trials.

F. Individual differences in drug response

Most clinical trials are designed to measure and describe the "average" performance of a drug, rather than to answer the question of whether a given drug works better for one person than another drug. Even "cross-over" trials, unless specifically designed to study the problem, usually give only limited assurance that an individual will reproducibly prefer one agent to another for relief of pain. At present, therefore, it is usually possible to say only that if Drugs A, B, and C relieve, respectively, 90%, 60%, and 40% of a given population, one is well advised to use Drug A as the agent of choice. Such percentages do not tell us whether failures with Drug A *will* respond to Drug B or C; indeed, it is not unlikely that failures to Drug A will *not* respond to B and especially not to C.

Although it is unfortunate that we do not have reliable data on individuality of response, the practice of medicine is hardly paralyzed by the lack of such information. Indeed, even if we were sure that Drug C mentioned above would handle the pain problem of all failures on Drug A, one would not select C as the drug of first choice unless somehow there were a way of knowing in advance whether a patient was an "A-" or a "C-responder." Clinical medicine generally lacks such information, so that barring a clearcut history, from a patient, of poor analgesia (or untoward effects) from a known drug, one would still prescribe, in any given situation, the drug with the best "average" performance.

G. The delineation of side-action liability and addiction potential

The quantification of the limitations of morphine and its substitutes poses a dilemma for the clinical investigator. The most precise and careful studies on this problem are unfortunately performed under conditions considerably different from the conditions of ordinary medical usage. The potential of morphine-like drugs for producing respiratory depression, affecting pupil size, inducing nausea and vomiting, *etc.*, is often, for example, evaluated in healthy volunteers. The ability of drugs to produce physical dependence, tolerance, and euphoria is most readily studied in experienced "postaddicts," recidivist prisoner volunteers who may not even be representative of the general addict population, let alone the nonaddict patient in pain.

The reasons for preferring such volunteers to actual sick patients in evaluating side-action or addiction liability are numerous: 1) Patients are often in a state of flux because of improvement or deterioration in their basic disease, so that one is faced with the evaluation of drug-induced change superimposed on change of other sorts; 2) not only may the basic disease produce symptoms and signs, but other medications may be applied concurrently in the management of the pa-

tient's total problem (anesthetics, anticancer drugs, *etc.*); 3) the sick patient is often not as accurate or reliable an observer and reporter as the volunteer subject; 4) many of the investigations in question cannot ethically be carried out in populations other than those now used (*e.g.*, certain addiction studies).

The result of current practice is to provide the investigator with data that are in a way spuriously precise. Qualitative statements can be validly made; even crude quantitative statements are possible, such as: "When Drugs X and Y are given in equianalgesic dosage, Drug X will probably cause nausea more frequently than Drug Y." But one is hard put to go beyond this. That a drug can cause respiratory depression is easily determinable; how often it will cause *biologically significant* respiratory depression in ordinary clinical use is impossible to tell from studies in volunteers. That a drug is likely to be abused by addicts, or may produce primary addiction, is not impossible to predict, but the precise relative addiction liability of drugs under conditions of medical usage (or even illicit use) is not within our grasp. One thing seems relatively clear: facile generalizations from nonpatients to patients are likely to be accompanied by substantial error.

There have been attempts at determination of tolerance and physical dependence development in patients with chronic pain, in some instances by challenging periodically with nalorphine. These have been few, and for the most part we are left with an imperfect impression, based on "past experience," of the degree and rate of development of tolerance or the likelihood that a patient may become dependent upon a drug under conditions of prolonged clinical use.

III. INDIVIDUAL DRUGS

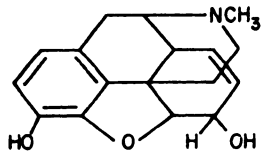
In the sections that follow, the major drugs used in the clinic for relief of severe pain will be discussed. Not all such drugs are included, and a few drugs not in the category of popular morphine substitutes will also be taken up. When one in clinical use is omitted, the reason is usually that there are no data on humans which satisfy modern criteria for a valid experiment. In addition, certain analgesics comparable to aspirin rather than morphine, or analgesics not in widespread clinical use, are discussed, usually either for theoretical reasons or in an attempt to correct widespread misconceptions about the drugs. The drugs are taken up in groups of similar molecular configuration.

The accent will be on clinical analgesic trials which appear interpretable by reason of apparently acceptable design and execution, and on the side-action liability of the drugs in man. (Of necessity, much of the interpretable literature on side effects is in healthy volunteers, as mentioned above.) No attempt is made to discuss such clinical matters as control of cough or diarrhea, *e.g.*, although the drugs to be discussed have broad applications in the management of these symptoms. Most of the so-called "mild" analgesics will not be taken up, except occasionally in statements about comparative efficacy. This omission reflects the desire to keep this review within reasonable limits, rather than a cavalier disaffection for these drugs. (Indeed aspirin—acetylsalicylic acid—remains

the standard of reference for oral analgesics in most laboratories concerned with controlled clinical assays.)

This review will not attempt to discuss addiction liability in detail, partly because of the absence of quantitative clinical data. Instead, addiction will be discussed under individual drugs when it is especially relevant to the evaluation of the compound, and very briefly for the drugs as a whole in Section IV.

Several sources should be listed for those interested in reading further in this area, either to fill in the gaps in this review, or to pursue related topics. The relationship between chemical structure and analgesic action has been summarized by Braenden *et al.* (19) and that between analgesic action and addiction liability by the same authors (43). A third and extremely useful reference by these workers deals with synthetic substances with morphine-like effect, and covers the clinical experience in regard to potency, side effects, and addiction liability (44). An additional source of references, although less satisfactory than the above, is the book on *Morphine and Allied Drugs* by Reynolds and Randall (140). A superb discussion of methods for measuring clinical pain, including related statistical problems, can be found in the review by Beecher (6); a shorter coverage of some of these problems is also available (105). Also recommended is the book by Beecher entitled *Measurement of Subjective Responses. Quantitative Effects of Drugs* (7). Those who wish to be apprised of current methods for assessing addiction liability are referred to the methodologic paper by Fraser *et al.* (49), and that by Halbach and Eddy (61).



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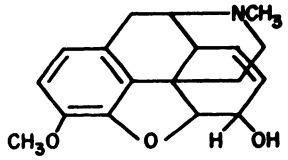

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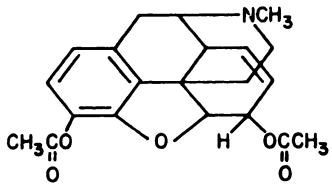

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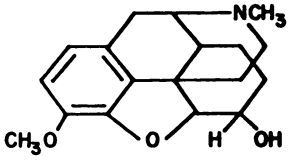
(DIACETYLMORPHINE)



DIHYDROCODEINE

A. Morphine

The beginning of the modern era in the clinical evaluation of analgesic drugs dates from 1949–1950, when a series of classic papers emerged from the Anesthesia Research Laboratory of Harvard University at the Massachusetts Gen-

eral Hospital. The key figures in this research were Henry K. Beecher, Jane E. Denton, Arthur S. Keats, and Frederick C. Mosteller.[2] Workers since that time—both in and out of the Harvard Laboratory—have modified and improved on the early protocols, but these subsequent modifications have been in the nature of refinements rather than complete reworkings. Since 1949, many papers have been published on analgesics which are as uninterpretable as those pre Beecher-Denton-Keats-Mosteller, but there has also been published an encouraging amount of data generated by experiments properly designed and executed. More important, the way is now clear for any who care to perform a properly controlled trial in this field.

The principles established by Denton and Beecher (35) were these: 1) because of inconsistencies in response of experimental pain to drugs, the proper appraisal of analgesics must be performed in humans with "natural" pain, *i.e.*, pain that is a consequence of disease or trauma, 2) the collection of data must not be biased by observers' knowledge of which drug the patient has received, 3) a dose-response curve for each drug must be determined, 4) the data collected should be subjected to statistical analysis, 5) the study of side effects in patients (postoperative, specifically) may be not sufficiently reliable to warrant recording and analysis, 6) side-action liability can be measured in healthy volunteers, 7) the performance of a good experiment in this field requires full-time attention and cannot easily be accomplished as a sideline in clinical practice, 8) appropriate measures must be taken to assure the safety of patients and volunteer subjects, 9) new agents must be compared with controls, *e.g.*, morphine, saline, or both, 10) sleep should not be confused with analgesia, 11) the comparative side-action liability of drugs, to be meaningful, must be assessed at equianalgesic doses.

In a second paper, Denton and Beecher (36) presented evidence that the analgesic dose-response curve for morphine reached a plateau at 7 to 9 mg. This dose seemed to provide acceptable relief in 90% of the patients, and further increase in dose did not improve on this performance. (In subsequent work from Beecher's laboratory, as certain kinds of surgery were eliminated from study because of the mild nature of the pain they produced, this figure changed somewhat, although the "optimal" dose of morphine remained at 10 mg per 70 kg; *vide infra.*) It was estimated that the mean interval between subcutaneous injection and onset of some degree of pain relief was 10 minutes, and the mean duration of analgesia was about 4 hours.

The paper by Keats *et al.* (85) further emphasized the reliability of clinical assays based on the principles outlined above. A study of saline, 5, 8, 10, 12, and 15 mg morphine, always pitted against 10-mg doses of morphine, produced a satisfactory dose-response curve with an assay error of approximately 10%. Further information was provided as to choice of patients, types of surgery, order of drug administration, variability in response to morphine, *etc.* The paper remains a classic one, and is a delight to read.

In 1954 Lasagna and Beecher re-examined the question of the "optimal" dose of morphine (108). They found that 10 mg of morphine per 70 kg body weight

[2] For the record: anesthetist, internist, anesthesiologist, statistician.

provided significant relief of pain in about two-thirds of patients. With 15 mg per 70 kg, a little over three-fourths of patients reported such relief. The higher dose also provided somewhat longer relief of pain. Counterbalancing the gains provided by the higher dose was a significant increase in side effects. Their review of the literature, plus the fact that the group studied by them was purposely selected as a group with severe pain, rather than the average group of patients likely to receive morphine-like compounds, led Lasagna and Beecher to conclude that 15-mg doses of morphine are probably unnecessary to relieve pain in most patients receiving this drug, and that the optimal parenteral dose is 10 mg per 70 kg body weight. (This dose has become the standard for comparison in most controlled trials.)

Houde *et al.* (74) have described their technique for the evaluation of analgesic drugs (both oral and parenteral) in man. Like the other workers described above, they present evidence for the reproducibility of analgesic effects in patients with pathologic pain (they use cancer patients with chronic pain), for the satisfactory dose-response curves obtainable with morphine, and for the performance of parenteral morphine and oral aspirin as controls.

In contrast to the excellent analgesia provided by 10 mg morphine given parenterally is the poor performance of this dose given by mouth. Beecher *et al.* (10), studying postoperative patients, found 10 mg oral morphine only 9% better than placebo capsules in relieving pain. Houde *et al.* (65), studying cancer patients, found that in terms of peak effects, oral morphine was 1/15th as potent an analgesic as parenteral morphine. Because the effects with oral morphine have a delayed peak but also a more prolonged effect, the use of "total" pain relief scores over 6 hours changes this ratio to 1/6th. Nevertheless, it is obvious that *single* doses of oral morphine are not very effective. (There are no adequate comparisons available on repeated doses of oral morphine *versus* repeated doses of parenteral drug.) Preliminary data from Houde and Wallenstein (73), on the other hand, indicate that this performance of oral morphine is nevertheless superior to that of oral codeine, milligram for milligram.

The subjective effects of morphine (nausea, vomiting, dizziness, sleepiness, "mental clouding," *etc.*) have been repeatedly reported (37, 54, 83, 88, 108, 115, 146, 156) in healthy volunteers and in patients. (Although most of these studies have been performed in males, it is perhaps worth observing that our own experience with thousands of female patients indicates that the oft-repeated canard that women are very likely to react to morphine with the excitement seen in cats and horses is another of those interesting myths that textbook writers are fond of repeating without evidence down through the years.)

The respiratory depressant capacity of clinical doses of morphine is easily demonstrable whether one simply measures minute ventilation or uses more complicated techniques such as displacement of ventilation-P_{CO_2} curves (39, 83, 118). Holford and Mithoefer (64) have presented evidence that in terms of respiratory effects healthy aged individuals respond no differently to 10 mg morphine than do healthy young adults.

Laidlaw and Read (101), and Laidlaw *et al.* (102) have stressed the greater

EEG response of cirrhotic patients to morphine, but their papers give no indication that even severely decompensated cirrhotics reacted catastrophically to 8 or 16 mg parenteral morphine. The original paper by Benedict (13) on the dangers of morphine in myxedema is unimpressive today, although its conclusions may be valid; comparative data on the effects of morphine in hypothyroid patients and matched controls are unavailable.

The effects of morphine on blood pressure and cardiovascular responses have been most easily shown in tilt-table experiments (38). Given to supine subjects intravenously, morphine produced only transient increases in cardiac rate and output. If subjects given morphine parenterally were put suddenly in a 75-degree head-up position, there was an increased incidence of fainting, when contrasted with the nonmorphine state.

The gastrointestinal effects of morphine in man are complex (155), but in general there appears to be an increase in intestinal tone different from normal coordinated propulsive activity, plus sphincteric spasm, with resultant diminution in peristalsis and the occurrence of constipation (1). The ability of morphine to produce spasm of smooth muscle also can cause increased pressure in the biliary system (52, 99), sufficient at times to produce biliary colic. Spasm may also occur in the vesical sphincter.

In summary, morphine is a good, reliable analgesic when given parenterally, but is considerably less effective when given by mouth. It can produce a variety of untoward side effects, but these are not of sufficient seriousness or frequency in most patients with severe pain to override the remarkable analgesia this drug can provide. Despite its drawbacks, and because no other established drug which can equal the analgesic performance of morphine is free of its undesirable qualities, morphine remains the standard against which all potential new morphine substitutes must be compared.

B. Codeine

Despite codeine's long use as an analgesic drug, it is amazing how little reliable information there is about its efficacy, particularly by the parenteral route. Beecher *et al.* (10) compared 60 mg codeine by mouth against placebo in the management of postoperative pain. The percent of doses providing analgesia was insignificantly higher (39%) after codeine than after placebo (34%).

Houde and Wallenstein (67) found 32 mg codeine given by mouth significantly better than placebo as an analgesic in patients suffering from pain of terminal cancer, but not significantly different from 600 mg of aspirin. Together, however, these two agents gave impressive summation of effect.

Gruber (57) studied patients with pain of various sorts: osteoarthritis, rheumatoid arthritis, cellulitis, bursitis, malignant neoplasm, peripheral neuritis, fractured femur, and "vascular" pain. Thirty-two mg codeine orally produced relief clearly superior to that seen after placebo, but 65-mg doses seemed to yield little additional benefit over that provided by the lower dose; in 3 of the subcategories of patients the pain relief scores were higher on 65 mg and in 3 lower. The lower dose of codeine in this study produced a very low incidence of nausea, vomiting,

or sleepiness; the higher dose caused a substantial increase in incidence of nausea, vomiting, anorexia, constipation, abdominal pain, dizziness, and sleepiness.

Cass and Frederik (24), in a group of patients with chronic pain, concluded that codeine by mouth in doses of 32 to 130 mg was better than either placebo or equal doses of *d*-propoxyphene.

Boyle *et al.* (18) also studied oral codeine in patients suffering from a variety of conditions causing chronic pain (arthritis, fractures, *etc.*). Sixty-five mg codeine provided pain relief significantly better than placebo or an equal dose of *d*-propoxyphene, but not better than 650 mg aspirin. The best performance was actually achieved with a combination of 32 mg codeine and 325 mg aspirin. Only one patient receiving codeine showed nausea and vomiting; "no other side effects were noted."

A study by Van Bergen *et al.* (154) examined the comparative efficacy of oral codeine (65 mg), meperidine (100 mg), *d*-propoxyphene (100 mg) and placebo. They concluded that all active drugs were better analgesics than placebo, but not significantly different from one another except in regard to side effects, codeine and meperidine having produced slightly more nausea and gastric distress than did *d*-propoxyphene. All 3 agents produced more drowsiness than did placebo. Incompleteness of crossover, dropouts, and analysis of doses only, rather than of patients, make it hard to evaluate these conclusions.

Prockop *et al.* (133) analyzed the responses of a large number of puerperal patients to oral analgesics. Most of these patients complained of uterine discomfort ("after-pains"), but others suffered from incisional pain (episiotomy or perineal tear). Thirty-two and one-half mg codeine provided complete or adequate relief of cramps for 55% of patients, as opposed to 36% of the placebo-treated group, 80% of the "ASA-compound"-treated group, and 80% who received both 32.5 mg codeine and ASA. (ASA compound = acetophenetidin 160 mg, acetylsalicylic acid 227 mg, and caffeine 32.4 mg.) Doubling the dose increased the placebo response to 43%, the codeine to 62%, and the codeine-ASA to 83%, while the ASA performance dropped to 61%. (These double-dose treatment groups were only ¼th as large as the single-dose groups, however, and were not studied contemporaneously with the latter.) The incisional pain study gave somewhat different results. The single dose phase showed only slight trends in favor of codeine and ASA compound, with no essential difference between them. A clear-cut superiority over placebo was seen only in the case of the codeine-ASA compound mixture. The double dose phase of the incisional study employed numbers of patients too small for analysis.

Side effects in this study were not impressive; codeine produced nausea, vomiting, and drowsiness somewhat more often than did placebo. A total of 28% of patients reported one or more side effects after 32.5 mg codeine, in contrast with 11% after placebo. Doubling the dose of codeine did not seem to increase the reporting of side effects, except in the case of codeine-ASA compound.

Sadove *et al.* (141) found 30 mg oral codeine better than placebo for relieving the pain of postoperative orthopedic patients.

Gruber and his colleagues (58, 59) studied two groups of patients similar to

that of Prockop *et al.* They found that ASA compound provided pain relief significantly greater than placebo, but 32 mg of codeine alone were ineffective, and when added to ASA compound yielded no additional analgesia.

Only two groups of investigators have published on the efficacy of parenteral codeine. Lasagna and Beecher (106) found 30 mg codeine considerably inferior to 10 mg morphine in treating postoperative pain. Sixty mg provided almost, but not quite as good a performance as 10 mg morphine, and 120 mg codeine also failed to equal the performance of the standard. Despite this inferior performance, codeine depressed the respiration and caused other undesirable morphine-like symptoms. [Bellville *et al.* (12) have shown that respiratory depression also occurs after codeine in healthy volunteers given 60 mg codeine by mouth.]

Houde and Wallenstein, while originally (72) suggesting that codeine and morphine had parallel dose-response curves, and that the "ceiling" for the two drugs was really not different, have indicated (65) that at high doses the curves diverge and that codeine is indeed an analgesic of lesser merit, in terms of peak or total performance, than is morphine. These high doses are, to be sure, well above the usual therapeutic doses of the two drugs, and the population studied is one with greater past exposure (and perhaps tolerance) to morphine or its substitutes than the patients studied by other groups. They found respiratory depression, nausea, vomiting, *etc.*, at least as frequent and severe after codeine as after morphine.

In summary, therefore, codeine by mouth appears to be a moderately effective analgesic, but one not superior, on the average, to aspirin when these drugs are given in usual doses. Indeed there is evidence suggesting that aspirin is a more reliable and effective agent for short-term use. Codeine plus aspirin, on the other hand, is worth trying in situations where either drug alone is ineffective. Codeine by injection, in 60-mg doses, approaches but does not equal 10 mg morphine as an analgesic. At these doses, however, codeine possesses most of the disadvantages of morphine. It would therefore seem that the use of codeine parenterally could be avoided by simply using doses of morphine smaller than 10 mg.

C. Dihydrocodeine (Paracodin)

Although dihydrocodeine has been in clinical use in Europe and Japan as an antitussive for half a century, its potential as an analgesic has been carefully scrutinized only during the last decade. Gravenstein *et al.* (54) compared the drug against morphine, giving both drugs subcutaneously, in doses calculated per 70 kg body weight, to patients suffering from postoperative pain. Fifteen mg of dihydrocodeine provided significant pain relief in 56% of patients, whereas 10 mg morphine did so in 89%. Doubling the dose of dihydrocodeine to 30 mg narrowed the difference between the drugs to 12%, but a further increase to 45 mg still left dihydrocodeine with an analgesic performance 13% less than that of 10 mg morphine. An extension of this work from the same laboratory (9) indicated that 60 mg dihydrocodeine were equal to 10 mg morphine as an analgesic at 45 minutes, but inferior 150 minutes after medication. Indeed at all dose levels studied, duration of pain relief was shorter after dihydrocodeine.

Keats *et al.* (90) also administered dihydrocodeine parenterally to postoperative patients, comparing it to morphine. Thirty mg dihydrocodeine were analgesic in 66% of doses, as opposed to 75% for morphine. At 60 mg, dihydrocodeine was indistinguishable from 10 mg morphine, but at 90 mg it was 5% less effective than the standard dose of morphine.

Seed *et al.* (143) studied dihydrocodeine in patients suffering from the pain of terminal cancer, most of whom had been on morphine-like drugs regularly, but all of whom had been receiving less than 16 mg morphine (or what the authors considered its equivalent) every 4 hours. Although these authors concluded that dihydrocodeine and morphine, given intramuscularly, yielded analgesic dose-response curves that were parallel, inspection of the data suggests another interpretation. The bulk of the pain scores in this paper is contained in their "second quartet" group, which totals 29 patients and actually includes 4 of the "remaining" 12 patients in the "first quartet" group. The mean 6-hour pain relief scores for morphine in the "second quartet" group are: 5 mg, 3.72; 10 mg, 6.06. The mean scores for dihydrocodeine in this group are: 30 mg, 4.23; 60 mg, 4.81. To this reviewer, the total impact of the data is to suggest that dihydrocodeine has a "ceiling" analgesic effect inferior to that of morphine, so that a potency ratio for the two drugs may be both pointless and invalid.

Cope and Jones (27), in an investigation not as well controlled as those already mentioned, studied patients who had undergone major gynecologic surgery or Caesarean section. They found only 35% of patients reporting "excellent" analgesia after 50 mg dihydrocodeine given subcutaneously, whereas 10 mg dextromoramide, 20 mg Pantopon, and 25 mg dipipanone provided such analgesia to 84%, 92%, and 91% of patients, respectively.

Lund (119) and Lund and Lind (121) compared dihydrocodeine, meperidine, morphine, and placebo in postoperative pain, and dihydrocodeine and meperidine in labor pain. In the former situation, 30 mg dihydrocodeine worked satisfactorily in 77% of the doses, as compared with 90% for 10 mg morphine, 87% for 100 mg meperidine, and 47% for saline placebo. In labor pain, 100 mg meperidine gave good relief in 64% of patients, whereas 30 mg dihydrocodeine worked well in only 41%.

The variable, but generally inferior, performance of dihydrocodeine makes it difficult to interpret the reported data on side effects. Gravenstein *et al.* (54) found 30 mg dihydrocodeine almost free of untoward subjective effects, as measured by spontaneous reports or questionnaires, and of respiratory depressant effect in healthy young male volunteers, but this dose is unquestionably inferior, for analgesic purposes, to the 10-mg dose of morphine used for comparison At 60 mg (9), dihydrocodeine depressed respiratory minute volume less than did 10 mg morphine, but increased the incidence of side effects, and of mood changes, over those seen with 30 mg dihydrocodeine.

Keats *et al.* (90) found that 30 mg dihydrocodeine depressed the respiration of healthy volunteers only slightly, but 60 mg produced effects comparable to those seen with 10 mg morphine. Using a check-list approach, these same authors found that a subcutaneous dose of 30 mg dihydrocodeine produced minimal

effects, whereas 60 mg clearly produced side effects, although they were in most respects less than were seen after 10 mg morphine.

Seed *et al.* (143), in an incomplete cross-over study of 2 healthy volunteers and 7 patients, concluded that the respiratory depressant effects of morphine and dihydrocodeine were roughly parallel to the analgesic potency of these drugs. These authors state that they observed drowsiness and grogginess "to roughly the same extent" following 10 mg morphine or 60 mg dihydrocodeine in their subjects, but give no actual data on this point.

In summary, dihydrocodeine provides analgesia, with a minimum of untoward effects, at parenteral doses of 30 mg. Higher doses provide some additional analgesia but substantial disadvantages in terms of side effects. The drug cannot be considered a complete substitute for morphine, and it is not clear that even the alleged advantages of the 30-mg dose cannot be readily achieved with doses of morphine smaller than the standard 10 mg.

D. Heroin (diacetylmorphine)

With few drugs is there a greater discrepancy between volume of published material and content of convincing and reliable information, than in the case of heroin. It was evident soon after the drug was placed on the market at the end of the 19th century that heroin possessed many, if not all, of the attributes of morphine, including the ability to relieve pain, suppress cough, depress respiration, and produce both euphoria and dysphoria (44).

It is unfortunate that so much emphasis has been placed on papers that are either insufficiently controlled or irrelevant. For example, one widely quoted article (144) compared heroin and morphine in trials on 8 healthy volunteers. The paper contained no placebo controls, was off in its estimate of the analgesic potency of heroin (by an experimental pain technique) by a factor of 2 to 5, and equated euphoria with "the opposite of narcosis . . . and stupefaction," although it admitted that the absence of unpleasant side effects after heroin (in retrospect, small doses were used, relative to all other drugs) may have accounted for "the pleasurable reaction to the drug." Yet the paper has become an important source of "evidence" of the high euphorigenicity and addiction potential of heroin.

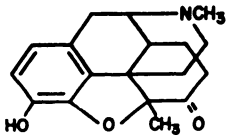
Lasagna, von Felsinger, and Beecher (115), on the other hand, employing 3 different experimental populations—healthy male volunteers, "postaddicts," and chronically ill patients—found a similarity in the responses to morphine and heroin, the prime differences being a greater euphoria after morphine in the postaddicts (in the 4:1 morphine-to-heroin ratio used) and a greater dysphoria after morphine in the healthy volunteers.

In 1962 a definitive set of experiments was published from Beecher's laboratory. First, Reichle *et al.* (136) showed that 2.3 to 5.2 mg heroin given parenterally were equal to 10 mg morphine in relieving postoperative pain. (Heroin's analgesic activity reached a peak earlier and was of shorter duration than that of morphine; this explains the range in ratios.) Next, Smith and Beecher (147), and Smith *et al.* (148) carefully compared heroin and morphine at equianalgesic doses,

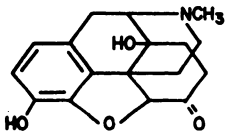
for subjective and objective effects in healthy volunteers. Again, the pattern was one of similarity between the two drugs, with heroin being, if anything, less pleasant than morphine. Work from this same laboratory suggests that heroin and morphine probably depress the respiration equally in equianalgesic doses (135). Finally, Martin and Fraser (123) have presented evidence in "postaddicts" that heroin and morphine are similar in their effects. They reported that their data did "not support the claim that addicts find heroin markedly superior to morphine" and also that "there was no indication that tolerance developed more rapidly to heroin than to morphine."

Although oral doses of heroin have not been subjected to controlled analgesic trials, early reports on this drug (122) indicated that 5 to 10 mg heroin by mouth provided little or no analgesia. This would suggest that heroin, like most other morphine-like compounds, is a considerably less effective analgesic by the oral route.

In summary, heroin seems little better or worse than morphine in its capacity to produce analgesia, respiratory depression, and other side actions, or in addiction potential. To quote from the recent report of the expert Ad Hoc Panel for the White House Conference on Narcotic and Drug Abuse: "There is a widespread misconception that heroin has effects significantly different from those of morphine. It does not, and this misconception should be dispelled permanently" (158).



METOPON



OXYMORPHONE
(DIHYDROHYDROXYMORPHINONE)

E. Metopon

In 1942, Lee reported on extensive clinical trials of metopon as an analgesic agent (116). Patients with acute pain on the emergency, medical, or surgical wards of a general hospital, and patients with chronic pain at a cancer hospital were given coded drugs (the former by injection, the latter either by injection or by mouth). Efficacy was gauged primarily by the evaluation of pain relief by nurses and physicians, rather than by the patients. It was concluded that 5 mg metopon were equivalent in pain-relieving power to 10 mg morphine, but that there was less nausea and vomiting after metopon. Although Lee reported that the mean individual oral doses for metopon and morphine were similar to those used by injection, relative efficacy of the two routes of administration cannot be assessed, since the patients on oral medication had less severe pain than those on parenteral drugs, and were also in "better general physical condition." The author himself points out that the total of 3 cases on morphine and 3 on metopon is too small to draw firm conclusions, but it seems relevant that 2 of the

patients on oral metopon and one on oral morphine had to be switched to hypodermic drug "as the pain became more severe."

In 1952, Keats and Beecher (83) subjected the same 2 drugs to comparison in a controlled trial in postoperative patients. Three-mg doses of metopon, given subcutaneously, gave adequate relief in 77% of instances, whereas 10-mg doses of morphine gave relief in 80% of cases. Six mg metopon, on the other hand, surpassed morphine by 14%. Keats and Beecher concluded that 3.5 mg metopon were equal, in analgesic efficacy, to 10 mg morphine. They also studied side-action liability in healthy male volunteers, finding that the 3-mg dose of metopon was as likely as, or more likely than, 10 mg morphine to affect respiration, pulse, temperature, and subjective responses.

Houde and Wallenstein (70) studied 42 patients with pain due to cancer, and estimated that 2.75 (95% confidence limits 2.1 to 3.6) mg metopon, intramuscularly administered, were equivalent in analgesic effect to 10 mg morphine. Raising the doses of both drugs to the level where undesirable side effects were produced showed no difference between the drugs in terms of side effects. The same investigators (71), studying the same type of patient, went on to compare the potency of metopon by the oral and parenteral routes. They found that doses of 15 mg metopon or greater were required by mouth to approach the analgesia conferred by 3 mg metopon given parenterally. Indeed, in terms of peak effects, the intramuscular form was over 11 times more potent.

In summary, 3 to 4 mg metopon are probably equivalent to 10 mg morphine when the drugs are given by injection. At these doses, the two drugs seem also equally likely, on the average, to produce untoward effects. The frequently made claim that metopon is as effective by mouth as by injection is unsupported by the available evidence.

F. Oxymorphone (dihydrohydroxymorphinone, Numorphan)

Oxymorphone was studied in a controlled trial by Eddy and Lee (45), who used subcutaneous medication in patients with chronic pain. This experiment indicated that 1 mg oxymorphone yielded pain relief similar to that provided by 10 mg morphine. Side effects after these two drugs, as reported by nurse observers, were not greatly different, although the authors suggested that perhaps oxymorphone might produce less nausea and vomiting, but more respiratory depression, than did morphine.

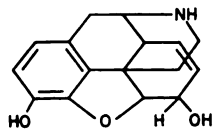
Wallenstein and Houde (157) had earlier come up with similar data in cancer patients with chronic pain. De Kornfeld (30) could detect no difference between 1 mg oxymorphone and 10 mg morphine given parenterally to patients with postoperative pain. This investigator believed that oxymorphone caused less sedation than morphine. In healthy volunteers, however, oxymorphone depressed respiration more than did morphine when both were given intravenously, and oxymorphone was said to produce more euphoria, nausea, and vomiting than did morphine.

Using the potency ratios estimated by the investigators mentioned above, Keats and Telford (88) studied the side effects of oxymorphone (1 mg per 70 kg)

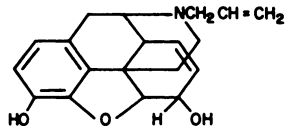
and morphine (10 mg per 70 kg) in 60 female patients awaiting elective surgery. These authors found a higher incidence of most side effects after oxymorphone, including a statistically significant higher incidence of nausea and vomiting.

Resnick *et al.* (139) examined the respiratory depressant capacity of oxymorphone in healthy young subjects and in patients with cardiovascular, pulmonary, or hepatic disease. All subjects showed respiratory depression after 1.5 mg of the drug, with marked depression (including periodic breathing) in the older patients.

In summary, 1 mg oxymorphone given by injection is equal to 10 mg morphine as an analgesic, but at this ratio oxymorphone is at least as likely, and perhaps more likely, to produce untoward effects.



NORMORPHINE



NALORPHINE
(N-ALLYLNORMORPHINE)

G. Normorphine

Normorphine has been the subject of considerable speculation because of certain theoretical considerations regarding the metabolism of morphine. It has been suggested that N-demethylation of morphine to normorphine is a crucial step in the production of analgesia, a hypothesis particularly espoused by Beckett *et al.* (5).

In 1958, Lasagna and De Kornfeld (109) compared morphine and normorphine, given subcutaneously, in patients suffering from postoperative pain. They found that 40-mg doses of normorphine were required to equal the analgesia produced by 10 mg morphine. Keats *et al.* (92) also gave normorphine and morphine by injection to postoperative patients in pain. The percent of "analgesic doses" after normorphine was lower than that after 10 mg morphine at 16 mg (24% lower), 24 mg (6% lower) or 32 mg normorphine (6% lower). Houde and Wallenstein (72) attempted a similar comparison in cancer patients with chronic pain. Their data suggest that intramuscular normorphine may have a somewhat shorter duration than morphine, but in terms of total effect, morphine was 2.6 times more potent than normorphine (95% confidence limits 1.9 to 4.3).

Fraser *et al.* (50) administered normorphine subcutaneously to volunteers from a population imprisoned for narcotic offenses. They found 30-mg single doses of normorphine produced less sedation, miosis, vomiting, and depression of respiration and rectal temperature than did equal doses of morphine, but that repeated doses of normorphine led to marked cumulation of sedative effects, a finding opposite to the experience of Houde and Wallenstein in cancer patients (72).

Because of evidence suggesting that N-demethylation occurs chiefly or exclusively in the liver (3), the clinical assays described above seemed to rule out the theory that normorphine was the active metabolite of morphine. More recent

work by Milthers (125), however, indicates that N-dealkylation of morphine occurs *in vivo* in the rat brain. Although this has revived interest in Beckett's hypothesis, some of Milthers' data in rats are themselves inconsistent with the notion that the formation of *nor*-compounds is essential to analgesia, as is the work of Jóhannesson and Schou (81).

In summary, normorphine given subcutaneously or intramuscularly is considerably less active, milligram for milligram, than morphine as an analgesic in man. Although this finding does not eliminate the possibility that normorphine might be an important active metabolite of morphine, there seems little compelling evidence for the hypothesis. A comparison of the analgesic power of the two drugs in man when given by the intravenous route would be of interest to correlate with the data of Jóhannesson and Milthers in rats (80).

H. Nalorphine (N-allylnormorphine, Nalline)

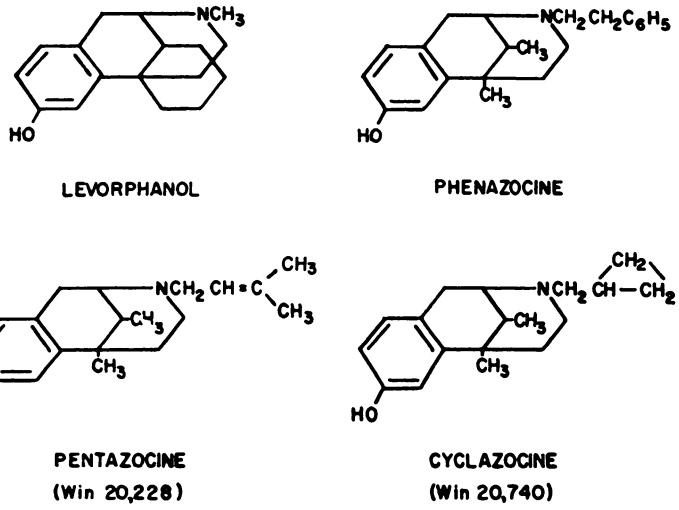
The analgesic powers of nalorphine were discovered by serendipity. Lasagna and Beecher (107) established in 1954 that the drug was, milligram for milligram, similar to morphine in relieving pain in man, despite the general impression from animal experiments that nalorphine was devoid of analgesic activity. This fact emerged accidentally during their unsuccessful attempts to find some "ideal" ratio of antagonist to analgesic which would preserve the desirable effects of morphine while decreasing the undesirable attributes. [Despite a considerable body of published opinion to the contrary, critical reviews (137, 150) suggest that this latter goal has still not been achieved.] To their surprise, nalorphine, which in most of the available animal work looked like a simple antagonist of morphine, was substantially less effective than 10 mg morphine only at doses of 5 mg (both drugs being given subcutaneously). At doses of 10 mg, nalorphine provided relief in 10% fewer postoperative patients, and at 15 mg, nalorphine was 5% more effective than 10 mg morphine.

These findings were confirmed by the work of Keats and Telford (86). Unfortunately, these latter investigators also substantiated (87) the findings of Wikler *et al.* (159) and of Lasagna and Beecher (107) that nalorphine could produce not only morphine-like subjective effects but also in some people a special type of dysphoric and hallucinatory reaction, which seems to qualify nalorphine as a depersonalizing and psychotomimetic drug. This propensity has been the chief reason why nalorphine, a nonaddicting analgesic, has never been introduced into clinical practice as a pain-reliever.

The similarity of nalorphine to morphine includes the ability to produce significant respiratory depression in both healthy volunteers and patients (42, 107, 152), a fact of considerable theoretical and practical interest in view of the drug's capacity to lighten respiratory depression in patients poisoned by large doses of narcotics. The dose-response curve for respiratory depression, however, seems to flatten out at a "ceiling" value considerably lower than that for morphine (151), and this may help to explain the paradox (104).

In summary, nalorphine is a nonaddicting analgesic in man with an unfortunate capacity for producing mental aberrations in some patients at dose levels re-

quired for pain relief. Its theoretical importance cannot be overstated, however: nalorphine has dramatically illustrated the limitations of animal testing in uncovering exciting new leads in the field of analgesics and has spurred the search for better pain-relieving drugs among compounds of the morphine-antagonist variety.



I. Racemorphan (Dromoran) and levorphanol (Levo-Dromoran)

Tidrick *et al.* (153) found 5 mg racemorphan and 10 mg morphine equally effective in relieving the pain of postoperative patients. Jaggard *et al.* (79) came to similar conclusions, giving the drugs subcutaneously to postoperative urologic patients. Keutmann and Foldes (97), giving racemorphan and morphine by the subcutaneous route in doses of 5 and 10 mg, respectively, presented evidence that racemorphan was somewhat more effective in the doses used.

Houde and Wallenstein (68) studied racemorphan, given by two routes of administration, in cancer patients. By mouth, racemorphan was a significantly less effective analgesic than when given intramuscularly.

There are a number of reports testifying to the ability of racemorphan to produce typical opiate side effects, such as nausea, itching, dizziness, and drowsiness in healthy volunteers in doses as low as 2 to 3 mg by injection or by mouth (117, 145, 160).

In patients, Tidrick *et al.* considered side effects to be as frequent after 5 mg racemorphan as after 10-mg doses of morphine. In general, Keutmann and Foldes came to the same conclusions, whereas Jaggard *et al.* thought that the overall incidence of side effects was greater after racemorphan.

There seems little reason for doubting that levorphanol, the levorotatory isomer, contributes the analgesic (and other morphine-like) activity present in the racemate (44, 76).

In summary, racemorphan in doses of 4 to 5 mg by injection is as effective as 10 mg morphine. The active levorotatory isomer, levorphanol, is effective in doses half as large as those of racemorphan. Although these drugs are said to be highly effective when given by mouth (53), the available evidence in controlled trials (68) suggests that they are probably similar to most morphine substitutes in this respect, *i.e.*, they must be given in oral doses several times larger than those given by injection to approach the efficacy of the latter. If so, then these agents possess no advantages over older morphine-like drugs.

J. Phenazocine (Prinadol)

This compound was at one time the subject of considerable publicity, when hopes were aroused that it might be relatively free of some of the disadvantages of morphine. Unfortunately, this temporary enthusiasm was founded on the optimistic "evidence" supplied by uncontrolled trials.

In properly designed experiments, the original estimate that 1 mg phenazocine was perhaps as analgesic as 10 mg morphine (41) was quickly modified. De Kornfeld and Lasagna (32), studying postoperative patients, found 0.5 and 2 mg phenazocine by injection decidedly inferior to 10 mg morphine, whereas 3 mg phenazocine gave results similar to those provided by 10 mg morphine. Houde *et al.* (75), studying cancer patients, collected data almost identical to those of De Kornfeld and Lasagna. They estimated that 2.3 to 3.1 mg phenazocine were equivalent, by injection, to 10 mg morphine, and that at equianalgesic doses the two drugs seemed to show similar incidence of untoward effects.

The claim that the drug is highly effective by mouth also seems unwarranted. Houde *et al.* (65) found that the chronic pain of cancer patients was poorly relieved by oral doses of phenazocine which were very effective by injection. The peak analgesic effects of 2 mg intramuscular phenazocine were considerably greater, for example, than those of 12 mg phenazocine by mouth.

Papadopoulos and Keats (129) examined the respiratory depressant capacity of 2.5 mg phenazocine (intramuscularly, per 70 kg body weight) in healthy volunteers. They concluded that phenazocine and morphine were equally depressant when given in equianalgesic doses. Greisheimer *et al.* (55), also using healthy subjects, found the respiratory effects of intravenous phenazocine more pronounced than those of meperidine, when the drugs were studied at a ratio of 1:40. Bellville *et al.* (11) concluded that 1.7 mg phenazocine depressed respiration as much as 10 mg morphine. This latter estimate is in line with the data of Berkowitz *et al.* (14), who studied respiratory depression in young and elderly "normals," and in patients with cardiovascular disease, emphysema, or cirrhosis. They concluded that 4 mg phenazocine depressed respiration more profoundly than did 15 mg morphine.

In summary, 3 mg phenazocine by injection can substitute for 10 mg morphine in the control of pain. By mouth, much higher doses of phenazocine are less effective than this standard dose given by injection. The drug possesses a capacity for depressing respiration which is at least as great as, and possibly greater than,

morphine, when both are given in equianalgesic dosage. Despite early hopes to the contrary, it is capable of causing addiction, being a "completely adequate" substitute for morphine in addicted persons (46a).

K. Pentazocine (Win 20,228)

This compound, 2-(3,3-dimethylallyl)-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan, has received only limited testing to date, but shows considerable promise in early trials. Keats and Telford (89) have presented evidence that postoperative pain is alleviated to a significant degree by parenteral doses of 10 mg or higher. The precise dose, equivalent to 10 mg morphine, is not yet defined, but is probably greater than 20 mg.

The side-action liability cannot, of course, be defined until more information is available on the doses required to produce analgesia of the degree produced by standard doses of morphine. At certain dose levels, the drug is capable of eliciting subjective reactions reminiscent of those produced by morphine, but is considered to have minimal addictive liability on the basis of studies on "postaddicts" (48). One instance of "nalorphine-like" symptomatology has been reported (82), but the incidence of this type of mental side effect seems low. It is said to depress respiration (in doses of 20 mg per 70 kg) to a degree similar to that seen after half this dose of morphine (2).

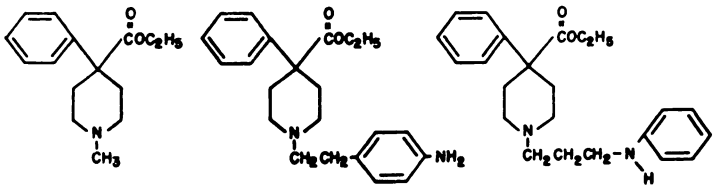
In summary, pentazocine, which in animals appears to be a weak antagonist of morphine and meperidine (2), is an analgesic in man. Further studies must corroborate early claims as to its analgesic efficacy, relative freedom from psychotomimetic effects, and minimal addiction risk, before it is known whether the drug represents an important advance, either in showing dissociation of morphine-like effects usually linked together or for clinical practice.

L. Cyclazocine (Win 20,740)

This drug, 2-cyclopropylmethyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan, is a potent antagonist of morphine and meperidine in animals (62). In man, however, the compound is an extraordinarily potent analgesic (112), being effective by mouth (against postpartum pain) and by injection (against postoperative pain) in doses as low as 0.25 mg. It depresses the respiration of volunteers (112), but the dose-response curve seems to flatten out at a lower "ceiling" than for morphine, in a manner reminiscent of other morphine antagonists (151). It is said to have little addiction liability (48), but in occasional patients produces confusion, depersonalization, and dysphoria (112). Such effects seem rare at low doses.

In summary, cyclazocine is another interesting development in the search for promising analgesics among compounds which appear to be antagonists of morphine and morphine substitutes in animals. It is very potent, on a weight basis, with 0.25 mg showing analgesic activity in man by oral and parenteral routes. Its

ultimate clinical potential remains in question until further experience is accumulated on both its pain-relieving capacity, and its side-action liability.



M. Meperidine (pethidine, Demerol, Dolantin)

Lasagna and Beecher (106) compared parenteral meperidine with morphine in patients with postoperative pain. Fifty mg meperidine were slightly less effective than 10 mg morphine, whereas 100 mg were 11% more effective. Houde and Wallenstein (71), studying the pain of cancer patients, concluded that 62 to 79 mg meperidine were equivalent to 10 mg morphine, depending on whether one focused on peak analgesic effect or total analgesic effect over 6 hours.

Masson (124), using a complex system of scoring involving elements of duration of effect, and both "subjective" and "objective" assessments, studied patients who had undergone major abdominal surgery, and came up with results similar to those described above. Although he had difficulty differentiating between saline and 10 mg morphine ($P = 0.13$ in favor of morphine) and between saline and 50 mg meperidine ($P = 0.17$ in favor of meperidine), Masson clearly showed activity with 100 mg meperidine, which was significantly better than either 10 mg morphine ($P = 0.04$) or saline ($P = 0.001$), and suggestively better than 50 mg meperidine ($P = 0.19$).

Keats *et al.* (94), in a beautifully designed comparison of meperidine, promethazine, and a mixture of the two, contributed data on the dose-response curve of meperidine. Their results indicate that 100 mg parenteral meperidine are considerably more effective than 25 mg meperidine and somewhat better (9 to 12%) than 50 mg meperidine.

Given by mouth, meperidine appears considerably less potent and reliable in its effects than meperidine by injection. This is apparent not only in controlled trials (72), but in the earlier uncontrolled trials of Batterman and others [see review by Eddy *et al.* (44)]. This is of some interest, in view of the studies of Burns *et al.* (21) suggesting that the drug is rapidly and completely absorbed in man.

Like other morphine substitutes, meperidine depresses respiration in man when given in therapeutic doses (16, 25, 91, 103, 118, 127, 132, 138). In equianalgesic doses, meperidine appears no better than morphine in this respect;

it is surprising that one continues to read statements to the contrary in textbooks and articles. (The fact that meperidine may have less effect than morphine on respiratory *rate* as opposed to tidal volume, and that rate is more readily and usually measured in the clinic may help to account for this widespread myth.) One point upon which there are few reliable data is the question of relative potential for respiratory depression in newborns delivered of mothers treated with meperidine. There is a general impression among obstetricians that meperidine carries less risk than would equianalgesic doses of morphine; but in a controlled trial by Campbell *et al.* (23a), a (mean) dose of 11 mg morphine administered to women in labor was not significantly different from a (mean) dose of 120 mg meperidine in its effect on the infant, as gauged by Apgar scores. Subjective side effects are similar to those produced by other morphine-like compounds (91), except that meperidine is, perhaps, more euphoriant than morphine (4, 77, 100).

The reports on the effects of meperidine on the gastrointestinal tract of man are conflicting [*cf.* review by Eddy *et al.* (44)]. Some authors claim that morphine increases intestinal tone whereas meperidine does not (98) or that both drugs increase tone (26) but that the effects of meperidine are less marked. It has been recently claimed again that morphine increases intraluminal gut pressure, whereas meperidine actually diminishes the number and dimensions of the pressure waves, both in healthy subjects and in patients with diverticulosis (128).

Meperidine seems to have a definite spasmogenic effect on the biliary tract (52), but it has been stated that occasional patients who have attacks of biliary colic precipitated by morphine do not do so after meperidine (28). These contradictions may be more apparent than real, however, since the work of Gaensler *et al.* (52) and that of Kjellgren and Löf (99) indicate that the rise in biliary pressure is probably somewhat greater and more prolonged, on the average, after morphine than after equianalgesic doses of meperidine. Nevertheless, Gaensler has noted that meperidine, like morphine, can precipitate typical biliary colic.

In summary, parenteral meperidine, in doses of 60 to 80 mg, can substitute for 10 mg morphine as an analgesic, but in equianalgesic doses produces many of the side effects seen with morphine, including respiratory depression. It is thought by some that it may have some advantage over morphine in regard to a decreased tendency to produce spasm of smooth muscle, but this is denied by others and is in any case counterbalanced by a risk of addiction which is substantial. [Meperidine is an extremely popular drug of addiction among doctors, nurses, and members of related professions (77, 134).] By mouth it is a relatively inefficient analgesic.

N. Anileridine (Leritine)

In 1957, Keats *et al.* measured the analgesic potency of parenteral anileridine in postoperative patients (91). Their data indicated that 20 mg anileridine were inferior to 50 mg meperidine but 40 mg anileridine were superior to 50 mg meperidine.

Houde and Wallenstein (71), studying cancer patients, estimated that in terms of total effect 39 mg (95% confidence limits 27 to 47) anileridine parenterally were equal to 100 mg meperidine, and that 31 mg anileridine were equivalent to 10 mg morphine. In terms of peak effect, 10 mg of morphine equalled 62 mg meperidine or 24 mg anileridine, suggesting that morphine had a somewhat longer duration of action.

Chang *et al.* (25), in a controlled trial on the efficacy of analgesic drugs in supplementing nitrous oxide anesthesia, estimated that 60 mg anileridine intravenously were approximately equivalent to 100 mg meperidine.

Keesling and Keats (96) studied the efficacy of anileridine and other drugs given by mouth to patients suffering from the pain of alveolar osteitis. Thirty mg anileridine were better than placebo but not significantly better than 0.6 gram aspirin, 30 mg dihydrocodeine, or a mixture of 2 mg methadone, 1 mg *d*-desoxyephedrine, and 30 mg pentobarbital sodium. Anileridine and dihydrocodeine produced more unpleasant side effects than did any of the other treatments.

Houde and Wallenstein (72) ran a comparison of oral and parenteral anileridine in cancer patients with chronic pain. Anileridine produced less peak analgesia but more prolonged pain relief when given by mouth, although it was more effective, milligram for milligram, and seemed less variable in its effects, than oral meperidine.

Keats *et al.* (91) found 40 mg anileridine as depressant to the respiration of healthy subjects as 100 mg meperidine, but the effects of anileridine were shorter lived. Chang *et al.* (25), studying similar subjects, concluded that parenteral anileridine was at least as depressant to the respiration as meperidine, when both drugs were given in equianalgesic doses.

Volunteers receiving anileridine report side effects similar to those reported after meperidine (25, 91). Chang *et al.* found nausea, vomiting, and dizziness more frequent after 60 mg anileridine than after 100 mg meperidine. Keats *et al.* found most symptoms to be reported as often after 50 mg anileridine as after 100 mg meperidine, although deep sedation was seen significantly more often, and nervousness, restlessness, and stimulation less frequently, after meperidine. In this study, both technicians and patients considered anileridine more unpleasant than meperidine.

In summary, 30 to 60 mg anileridine can probably be substituted for 100 mg meperidine (and presumably for equivalent doses of morphine and other standard morphine-like analgesics) in most clinical situations. Anileridine has only one real advantage: it is probably more efficacious by the oral route, relative to its parenteral potency, than morphine and many other morphine substitutes. It is not *as* good, milligram for milligram, by mouth as by injection, but has significant pain-relieving capacity at 30- to 60-mg doses by either route. In other respects, the drug has no superiority to older drugs, and side effects after it may possibly be greater than with equianalgesic doses of other agents.

O. Piminodine (Alvodine)

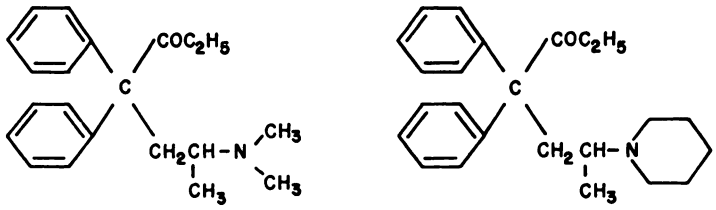
De Kornfeld and Lasagna (31) studied the efficacy of parenteral piminodine against postoperative pain. They found 5 mg piminodine inferior to 10 mg morphine, but 10 mg piminodine at least as effective as, and possibly more effective than, an equal dose of morphine. They estimated that 7.5 mg were perhaps equivalent to 10 mg morphine. There was no impressive incidence of untoward effects from piminodine, even at doses of 20 mg.

De Ciutiis (29) found that 10 to 20 mg piminodine provided pain relief that was "excellent and accompanied by minor change in vital signs" in 86% of postoperative patients, as compared with 43% for 50 to 100 mg meperidine. These doses of meperidine provided "good" pain relief in another 43% of patients, but at the cost of "significant" sedation and depression of blood pressure, pulse, and respiration. In the other 14% of patients, both drugs provided "moderate" pain relief and "moderate" change in vital signs. For preoperative sedation, piminodine was considered less effective than meperidine. In obstetrical patients, 100 mg meperidine were considered superior to 20 mg piminodine, perhaps because of the greater sedative qualities of the former. (Although this study is described as double blind, it is disturbing to read in the paper that all 4 recovery-room nurses were able to discriminate between saline, meperidine, and "new drug." Since the performance of the active drugs was such as to provide overlapping categories of response, one would at least have expected a certain confusion in deciding, for example, which drug had produced excellent pain relief and minor changes in vital signs.)

Betcher *et al.* (15) also compared piminodine and meperidine in postoperative patients, allowing nursing personnel a certain freedom in adjusting individual dosage of coded medication. Although this makes the paper a bit difficult to interpret, 10 mg piminodine appeared at least as good as, and possibly better than, 100 mg meperidine. The incidence of drowsiness was less after piminodine.

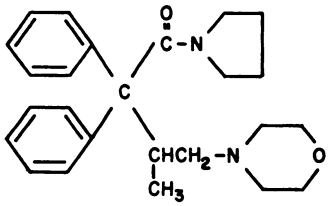
Groeber and Ziserman (56) found 10 to 20 mg piminodine given to women in labor to provide patients with as good analgesia as did 50 to 100 mg meperidine but to cause significantly less respiratory depression of newborns. The suggestion that piminodine may be intrinsically less depressing to the respiration than meperidine is supported by limited data in healthy volunteers on the respiratory effects of piminodine (66). Houde *et al.* found 5 mg piminodine as depressant, on the average, as 10 mg morphine, but 10 mg piminodine caused no further depression, whereas 20 mg morphine caused a considerably greater shift in P_{CO_2} response curves than did 10 mg morphine. These authors did not study the effects of higher doses of piminodine because of "pronounced sedation" with the 10-mg dose (66).

In summary, piminodine, when given by injection, is probably a somewhat more potent analgesic, milligram for milligram, than morphine. It is said by some to be less sedating, dose for dose, than morphine. There is suggestive evidence that the drug may be safer than morphine or meperidine in terms of respiratory depression.

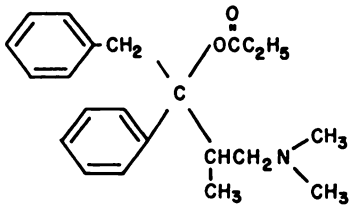


METHADONE

DIPIPANONE



DEXTROMORAMIDE



d-PROPOXYPHENE

P. Methadone (*Adanon, Amidon, Dolophin*)

Denton and Beecher (36) compared parenteral methadone with morphine (and other drugs) in patients with postoperative pain. They concluded that methadone was probably equivalent to morphine, milligram for milligram. These findings were confirmed by Beecher *et al.* (8) in postoperative and wounded patients, although there is a suggestion in their data that methadone may be slightly better than morphine on a weight basis, a finding which would be more in keeping with the bulk of the uncontrolled reports in the literature (44).

In healthy volunteers, Denton and Beecher (37) could see little difference between morphine and methadone in regard to side-action liability. Prescott *et al.* (132) found methadone as depressant to the respiration as morphine, milligram for milligram. Remy (138) showed depression of respiration after 10 mg methadone, to a degree similar to that caused by an equal dose of morphine or by 100 mg meperidine.

Gaensler and McGowan (51) presented evidence that methadone had spasmogenic effects on the human duodenum and could increase intrabiliary pressure, although Kewitz *et al.* (98) denied that methadone had morphine-like effects on the gut of man.

In summary, parenteral methadone is, milligram for milligram, as potent as, or slightly more potent than, morphine in most respects. There is a paucity of evidence on the oral efficacy of this drug, although in one trial (96) a mixture of 2 mg methadone with rather small doses of *d*-desoxyephedrine and pentobarbital was significantly better than a placebo in relieving dental pain. In addition, the drug is given orally at the United States Public Health Service Hospital in Lexington, Kentucky, during withdrawal of other narcotics, with satisfactory

effects. These facts suggest that oral methadone is deserving of more attention, although one should also anticipate cumulative effects if repeated doses are used.

Q. Dipipanone (Pipadone)

Houde, Seed, and Cochin, and Beecher and Gravenstein [results described by Eddy *et al.* (44)] have compared dipipanone and morphine by injection. Houde, Seed, and Cochin studied patients with chronic pain in 3 separate hospitals. The dose of dipipanone considered equivalent to 10 mg morphine was 20 mg, 22 mg, and 11 mg, respectively, for the 3 hospitals, with 19 mg being the best estimate from the combined data. Beecher and Gravenstein worked with patients suffering from postoperative pain. They found 15 mg dipipanone definitely inferior to 10 mg morphine, and 25 to 35 mg dipipanone essentially equal to 10 mg morphine.

Cope and Jones (27), studying women after gynecologic surgery, found 25 mg dipipanone given subcutaneously as good as 20 mg pantopon or 10 mg dextromoramide, and superior to 50 mg dihydrocodeine.

Cahal (22) evaluated the propensity of dipipanone for producing side effects in healthy volunteers. He found a steady increase in side effects as the subcutaneous dose was increased from 4 to 34 mg, with a sharp rise after 15 mg. The symptoms were those produced by most morphine-like compounds, and certain symptoms were less severe when subjects were in the recumbent position, as is the case with other morphine-like drugs.

In summary, 25 mg dipipanone, given parenterally, are probably equivalent to 10 mg morphine in most respects.

R. Dextromoramide (Dimorlin, Palfium)

Lasagna, De Kornfeld, and Safar (113) attempted to evaluate dextromoramide in patients with postpartum pain. The study had to be terminated prematurely because of a high incidence of dizziness, nausea, vomiting, drowsiness, sweating, feelings of warmth, and itching in the dextromoramide group. Enough data were collected, however, to indicate that the drug was an effective analgesic by mouth or injection in doses of 5 to 10 mg. There seemed to be no significant advantage of 10 mg over 5 mg.

Keats *et al.* (93), studying postoperative pain, also concluded that the dose-response curve for analgesia seemed to reach a plateau at 5 mg (per 70 kg in their study), and that this dose was for the most part the equivalent of 10 mg morphine, both in analgesia and in liability to produce side effects. The major difference between dextromoramide and morphine was a somewhat shorter duration of action for the former, evident in respiratory depression studies on healthy male subjects and in the 5- and 6-hour analgesia scores.

The results of Cope and Jones (27) referred to above (*cf.* sections on dihydrocodeine and dipipanone) are compatible with the estimate that dextromoramide and morphine are equianalgesic, milligram for milligram.

Houde and Wallenstein (72), studying cancer patients, estimated that 7 mg dextromoramide, given intramuscularly, were equivalent to 10 mg morphine,

and that the drug when given by mouth was approximately 90% as effective as when given by injection. Two sets of Scandinavian investigators, studying postoperative patients (40, 120) estimated that 7.5 mg dextromoramide were the analgesic equivalent of 10 mg morphine

The reports of Cahal (23), Peeters (131), and of Boudin and Barbizet (17), like those of Lasagna, De Kornfeld, and Safar (113) testify to the capacity of dextromoramide to produce nausea, vomiting, dizziness, somnolence, and other undesirable side effects. In addition, Keats *et al.* (93) observed apnea in 3 of 36 patients who received 5 mg per 70 kg dextromoramide, and Lund and Erikson (120) reported a similar experience after 10 mg of the drug.

In summary, 5 to 7.5 mg dextromoramide appear to be equal in analgesic activity to 10 mg morphine. The side-action liability of the drug, however, seems somewhat greater than that of morphine, when both drugs are given in equianalgesic doses, and the reported instances of serious respiratory depression after standard doses of the drug are somewhat disturbing. The compound has one interesting characteristic: by mouth it is almost as good as by injection, a characteristic not commonly seen in morphine-like compounds. The drug has been erroneously considered by some to be nonaddicting, but numerous cases of medical addiction to it have been seen in Europe (76a).

S. Propoxyphene and dextropropoxyphene (Darvon)

The *alpha*-racemate of 4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane has been called propoxyphene. Its analgesic activity, however, appears to reside in the *alpha-d*-isomer, which is known as *d*-propoxyphene or dextropropoxyphene.

Gruber *et al.* (60) first studied the analgesic efficacy of propoxyphene in a small number of patients with chronic pain. The technique involved giving capsules routinely every 4 hours (except during hours of sleep) and then relying on the memory of the patients at the end of 24 hours to determine how many hours of pain they had suffered, and how bad each hour of pain had been. During the placebo periods, the patients averaged higher scores (*i.e.*, more pain) than when on doses of 32.5 mg codeine, 50 mg propoxyphene, or 325 mg aspirin, but there were no significant differences among the latter three treatments. No significant incidence of side effects was observed with any drug.

Gruber (57) then reported on *d*-propoxyphene, studying 32.5- and 65-mg doses of this drug, similar doses of codeine, and a placebo, all given by mouth. The order of administration of the active agents was counterbalanced, but the placebo was always given for 3 days in the middle of the trial. Again, Gruber used the anamnestic interview technique described above and a crossover design. The trial involved seven cooperating hospitals and a total of 101 patients. Codeine and *d*-propoxyphene both performed better than placebo, the higher doses performed in general better than the lower doses, and the two drugs appeared indistinguishable except for side effects. Codeine produced more nausea, anorexia, constipation, abdominal pain, and dizziness than did *d*-propoxyphene, the major differences being observed at the 65-mg level. The two drugs appeared equally

likely to cause drowsiness, and there were slightly more rashes with the 65-mg dose of *d*-propoxyphene than with any other treatment.

Van Bergen *et al.* (154) came to similar conclusions regarding 65 mg codeine and 100 mg *d*-propoxyphene given orally (*cf.* codeine section), with both agents performing better than placebo, but insignificantly different from each other as analgesics. There were more gastrointestinal complaints with codeine, but the drugs produced an equal incidence of drowsiness.

Boyle *et al.* (18) (*cf.* section on codeine), on the other hand, considered 65 mg codeine a better analgesic than a similar dose of *d*-propoxyphene, and observed 3 of their 4 cases of severe nausea and vomiting in patients receiving *d*-propoxyphene.

Sadove *et al.* (141) compared oral *d*-propoxyphene and codeine in patients on an orthopedic surgical ward. They found a 32-mg dose of dextropropoxyphene not significantly better than a placebo (whereas a 30-mg dose of codeine was), but that 65 mg dextropropoxyphene and 60 mg codeine did not differ significantly.

Prockop *et al.* (133) (*cf.* section on codeine) found *d*-propoxyphene to be not significantly better than a placebo in relieving after-pains or incisional pain in puerperal patients, despite the production of a certain amount of nausea, vomiting, and drowsiness.

Gruber *et al.* (58), studying postpartum pain (*cf.* section on codeine) also failed to detect analgesic activity with 32 or 65 mg *d*-propoxyphene.

Sahagian-Edwards (142) studied the oral efficacy of *d*-propoxyphene in patients with pain from carcinoma, myeloma, lymphosarcoma, or herpes zoster, using a "demand" technique wherein success of medication was judged by the time elapsing between requests for medication for pain. The mean pain relief interval was shorter following 100 mg *d*-propoxyphene (5.4 hours) than after 100 mg meperidine (6.4 hours). This difference was statistically significant at the 5% level.

Cass and Frederik (24) found *d*-propoxyphene substantially inferior to codeine in relieving chronic pain.

Burget and Greene (20) measured the effects of 130 mg *d*-propoxyphene given orally to five healthy male volunteers, and failed to demonstrate any changes in ventilation-response curves.

There are a few reports available on the parenteral use of *d*-propoxyphene. Stoelting *et al.* (149) gave the drug, as well as meperidine and placebo, to a group of patients who had undergone surgery "or who had organic pain from other causes." At 25-mg doses, neither parenteral meperidine nor parenteral *d*-propoxyphene was better than placebo. At 50 mg, both drugs were better than placebo, but indistinguishable from each other. At 100 mg, meperidine was significantly better than *d*-propoxyphene. It is stated by the authors that more central nervous system depression was noted after meperidine than after *d*-propoxyphene, but the details of the data are not presented, other than an uninformative analysis of covariance table.

Lasagna and De Kornfeld (111), in a study of postoperative patients, found

meperidine to be more potent than *d*-propoxyphene, when both were given by injection, at 50- or 100-mg doses. Houde *et al.* (66) agreed with these findings on the basis of a study of the two drugs in cancer patients. They estimated *d*-propoxyphene to be ⅓rd as potent an analgesic as meperidine. Nausea and drowsiness were seen after both drugs.

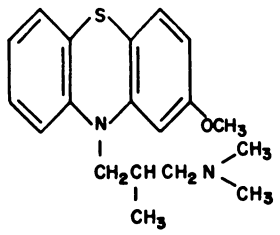
In summary, propoxyphene and *d*-propoxyphene appear to be mild analgesics when given by mouth, probably less effective than standard older oral analgesics, such as aspirin and codeine. As a compensating feature, the drugs may be less productive of side effects than more effective drugs. The parenteral form of *d*-propoxyphene would seem to have nothing to offer for clinical practice that is not already provided by other morphine-like drugs.

One is at first puzzled at the enormous popularity of oral *d*-propoxyphene in the United States, in view of its less than brilliant performance in controlled trials. This is less of a paradox than it seems, however. Like some compounds of even more dubious analgesic merit (ethoheptazine, carisoprodol), *d*-propoxyphene is sold not only alone but in combination with aspirin. Most *d*-propoxyphene is sold in combination with an "ASA" (*cf.* Section III B) preparation. Since aspirin is an excellent analgesic, and preparations containing *d*-propoxyphene can be obtained in the United States without a narcotic prescription, there are two obvious reasons for its popularity.

The narcotic status of *d*-propoxyphene is a muddled issue. The World Health Organization recommended to the Commission on Narcotic Drugs of the United Nations that governments control it as they do codeine. The U. S. Bureau of Narcotics, on the other hand, simply ruled that propoxyphene and *d*-propoxyphene did not have "addiction forming or addiction sustaining properties similar to morphine or cocaine," on the basis of comparative experiments at the U. S. Public Health Service Addiction Research Center and approximately 5 years of marketing experience on the part of the manufacturer. Propoxyphene in doses of 800 mg by mouth is considered by some postaddicts to produce effects resembling those of an opiate (47). Twelve to twenty-four hundred mg of oral propoxyphene daily suppress abstinence from morphine to a statistically significant but biologically slight degree. *d*-Propoxyphene, in doses of 355 to 600 mg, produces subjective effects termed pleasurable by postaddicts, who liken them to the effects of marihuana, heroin, morphine, and cocaine. It also reduces morphine abstinence significantly but slightly. *d*-Propoxyphene in doses of 800 mg per day does not suppress the morphine abstinence syndrome as well as 1500 mg of codeine, and attempts to use higher doses of *d*-propoxyphene have been limited by the production of toxic psychosis and other untoward effects.

There is, to be sure, little reported abuse of *d*-propoxyphene. There is also, however, essentially no abuse of codeine when it is prescribed in combination with aspirin-containing compounds (as *d*-propoxyphene usually is), probably in part because of the recognized low addiction liability of codeine, but also because abuse of aspirin or aspirin–phenacetin–caffeine preparations is likely to be limited, since toxicity from these drugs will occur before any substantial effects from overdose of codeine are manifest. One reasonably convincing case of abuse

of, and primary dependence on, *d*-propoxyphene itself has been reported (46), but the number of cases admitted to date at the U. S. Public Health Service Hospital at Lexington for abuse of *d*-propoxyphene has been small.



METHOTRIMEPRAZINE
(LEVOMEPROMAZINE)

T. Methotrimeprazine (levomepromazine, Nozinan)

There is considerable question as to whether most of the phenothiazine drugs now used in the clinic for one purpose or another are significant contributions to the management of pain except as adjuncts to control vomiting or provide sedation (69, 78, 94). Methotrimeprazine, however, seems to represent a distinct advance. Lasagna and De Kornfeld (110) demonstrated that 10 to 15 mg of this drug by injection were as effective as 10 mg morphine (in postoperative pain). De Kornfeld *et al.* (33) found 15 mg methotrimeprazine by injection indistinguishable from 75 mg meperidine in relieving labor pain.

Keats *et al.* (95), also studying postoperative pain, concluded that a 15-mg dose of methotrimeprazine by injection was definitely an analgesic, but somewhat less effective than 10 mg morphine. The data of Montilla *et al.* (126), on the other hand, from patients with a variety of types of pain, are in agreement, as are those of Houde and Wallenstein (working with cancer patients) (73), with the assessment of Lasagna and De Kornfeld (110).

By mouth, single 25-mg doses of methotrimeprazine were indistinguishable from a placebo in relieving postpartum pain (110).

The drug appears to lack morphine-like physical dependence properties (34, 48) and may have advantages over morphine in regard to respiratory depression. Pearson and De Kornfeld (130), studying healthy volunteers, found 15 mg methotrimeprazine to depress respiration when subjects were breathing room air, but not when they were breathing a CO_2-containing mixture, whereas 10 mg morphine depressed respiration under both sets of conditions.

In administering methotrimeprazine to ambulatory postpartum patients, Lasagna and De Kornfeld (110) observed symptoms of postural hypotension at doses that were not analgesic. Montilla *et al.* (126), and Houde and Wallenstein (73) were impressed by the considerably higher incidence and degree of sedation after this drug.

In summary, methotrimeprazine is a potent sedative and analgesic when given by injection in doses of 15 mg. The drug may be more sedative, and cause more

postural hypotension, dose for dose, than morphine, but its nonaddicting quality and its possible advantages in terms of decreased effect on respiration suggest that its clinical utility needs to be evaluated more fully. Its capacity to potentiate the analgesia of standard morphine-like compounds in man has not been tested adequately, although there was no evidence of synergistic effect on respiration when the two drugs were given together to healthy volunteers (130).

IV. ADDICTION LIABILITY

In the preceding discussion, reference to addiction liability has not been regularly made, in part because such information is available elsewhere (43, 44), and also because precise quantification of the addiction risk attendant on the *clinical* use of morphine or its substitutes is not at hand. It would seem, however, that morphine, heroin, metopon, oxymorphone, levorphanol, phenazocine, meperidine, anileridine, piminodine, methadone, dipipanone, dextromoramide, alphaprodine, and dihydromorphinone—all the compounds which are on the market and can more or less substitute for one another as analgesics—are substantially similar in their addiction liability. Analgesic drugs that appear less addicting than these—for example, codeine (63)—are also less effective as analgesics. Only in the case of nalorphine and of certain experimental drugs not yet freely available to physicians—pentazocine, cyclazocine, and methotrimeprazine —has there been claimed high-grade analgesic power and minimal addiction liability, and experience with the three latter compounds is inadequate to be sure of this point.

V. THE SEARCH FOR BETTER ANALGESICS

The large number of analgesic compounds now available has provided the physician with increased flexibility in his management of pain. Primarily, however, today's doctor is better off in possessing "backstop" drugs, *i.e.*, drugs which can be tried when standard, inexpensive, time-tested agents do not work well in individual patients. No new drug has come along which has made morphine obsolete. Most of the agents described above which can substitute for morphine as analgesic (and all such drugs now available on the market) are also addicting, and in some ways certain of the drugs that have been developed are perhaps more dangerous than morphine in this respect (*e.g.*, meperidine, which is so common a drug of addiction among physicians and nurses).

We must continue, therefore, to search for new agents. A truly nonaddicting morphine substitute would be a boon in a variety of ways. It would decrease the number of "medical addicts" (although addiction actually occurs infrequently when current drugs are properly utilized in the legitimate practice of medicine). It would decrease the problem (also minor) of diversion of medical stores of analgesics into illicit channels. Most important, perhaps, would be the increased comfort it would provide for patients in pain, who now suffer unnecessarily because of both legitimate and unreasonable apprehension among doctors and nurses that they will create addicts by using morphine or its substitutes as often as they are needed to control pain.

But there are other undesirable features of morphine: it can produce anorexia, nausea, vomiting, constipation, urinary retention, dizziness, sedation, respiratory depression, hypotension, and pruritus. Some of these "side effects" are, to be sure, put to good therapeutic use in certain situations—for example, the sedation is probably desirable in many cases of postoperative pain, labor pain, or pulmonary edema, and the constipating effect is used to control diarrhea. Yet a dissociation of these effects and analgesia would be highly desirable, and may indeed be seen more frequently in the future, in view of encouraging developments in the reports described above on nalorphine, pentazocine, cyclazocine, and methotrimeprazine. An achievement of great clinical importance would be the discovery of a morphine substitute to which significant tolerance did not develop on chronic use.

It would also be helpful to have additional analgesics which are truly as potent by mouth as by injection. Although a few of the current drugs are reasonably effective by mouth, many have to be given in much larger doses by this route, and the results even with these higher doses are sufficiently erratic and unpredictable as to be potentially dangerous.

VI. CONCLUDING REMARKS

In concluding this review, I should like to complement the quotations used at its beginning with the following remarks of Keats, Beecher, and Mosteller:

". . . it is not so certain to what extent conclusions from experimentally produced pain apply to naturally occurring pain. In our practice this uncertainty is avoided by the use of clinical pain.

". . . the subjectivity of the data is no serious limitation when adequate controls are used, both in the experimental design and in the collection of data. The individual variation in clinical pain is often larger, but not different in type from that found in most experimentation; this variation can be measured and accounted for . . ." (85).

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