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SYNTHETIC SUBSTANCES WITH MORPHINE-LIKE EFFECT

Clinical Experience: Potency, Side-Effects, Addiction Liability*

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CONTENTS

* This is the fourth of a series of studies on synthetic drugs with morphine-like effect, undertaken in accordance with resolution No. 505 (XVI) C, adopted at the sixteenth session (30 June to 5 August 1953) of the United Nations Economic and Social Council The first study of the series deals with " Chemical Aspects " (Braenden, O. J. & Wolff, P. O. (1954) *Bull. Wld Hlth Org.*, **10**, 1003), the second with " Relationship between Chemical Structure and Analgesic Action " (Braenden, O. J., Eddy, N. B. & Halbach, H. (1955) *Bull. Wld Hlth Org.*, **13**, 937), and the third with " Relationship between Analgesic Action and Addiction Liability " (Eddy, N. B., Halbach, H. & Braenden, O. J. (1956) *Bull. Wld. Hlth Org.*, **14**, 353).

[a] International non-proprietary name; for other designations, see *Estimated World Requirements o Narcotic Drugs in 1958* (United Nations document E/DSB/15).

SYNOPSIS

A review of effects in man of morphine-like drugs which have been brought under international narcotics control is presented in the form of individual monographs. These are based on controlled observations with quantitative data and significant reports of results obtained in medical practice. In a summarizing section, the drugs are compared with respect to effectiveness, side-effects and addiction liability. Morphine-like drugs of natural and synthetic origin now cover a wide range of potency (analgesic, antitussive), not necessarily paralleled by incidence of side-effects or addiction liability.

[a] International non-proprietary name; for other designations, see *Estimated World Requirements of Narcotic Drugs in 1958* (United Nations document E/DSB/15).

INTRODUCTION

The data in the second report in this series, on the relationship between chemical structure and analgesic action, were derived solely from experimentation on animals. Also, in the third report, on the relationship between analgesic action and addiction liability, only laboratory data were used, although the evidence on addiction liability was obtained in experiments on man. The present report will develop the problem specifically with respect to man, making use of three sources for the assembled information: reports of experience acquired in everyday medical use of a drug; controlled observations on patients, usually by means of the double-blind technique; and controlled experiments on normal human volunteers to assess in quantitative terms various aspects of a drug's action. The over-all objective is to provide a basis for evaluation of the advantages, and special uses, if any, of the many drugs which have been introduced as possible alternatives to morphine and/or codeine. The plan of presentation is a series of individual monographs arbitrarily arranged alphabetically according to international non-proprietary or other common name, followed by a discussion and summary in which the drugs as a whole will be compared. Most of the drugs considered are of practical importance in medical use, as can be seen from the *Estimated World Requirements of Narcotic Drugs in 1958.*

MONOGRAPHS ON INDIVIDUAL DRUGS *

1. Desomorphine[a] (dihydrodesoxymorphine-D)

The pharmacological action of desomorphine was reported upon in 1934 and the first trials of the drug in man were begun in April of that year. The main purpose of these early trials was evaluation of the addiction liability (see below), but other properties of the drug were also observed. In the first trial (Eddy & Himmelsbach, 1936) six hopelessly incurable cancer patients, who had had no previous narcotic experience and whose pain required treatment, were selected. Three were given desomorphine, three morphine. The initial dose of the former was 1 mg. of the latter 10 mg. All doses were given subcutaneously. The intent was to give small doses at sufficiently frequent intervals to control the pain almost continuously. As had been shown in the laboratory, the duration of action of desomorphine was short and it could not be prolonged by an increase in the dose. The attempt to do so caused an early increase in the dose and once this had occurred it was not feasible to reduce the dose again. This may have influenced the development of tolerance, so that the dose schedules must be kept in mind in

* Wherever doses are mentioned, they are the doses stated in the report quoted; usually they refer to a salt of the compound and, as a rule, no attempt will be made to identify the salt used.

[a] International non-proprietary name; for other designations, see *Estimated World Requirements of Narcotic Drugs in 1958* (United Nations document E/DSB/15).

evaluating the drug's effects. The dose schedules for the six patients were as follows:

No. 1.	Desomorphine:	Initial dose	5×	1	mg/day	increasing to	12×	5	mg/day over	57 days
No. 3.	,,	,,	5×	1	,,	,,	12×	3	,, ,,	68 ,,
No. 5.	,,	,,	6×	1	,,	,,	10×	2	,, ,,	32 ,,
No. 2.	Morphine:	,,	4×	10	,,	,,	8×	10	,, ,,	73 ,,
No. 4.	,,	,,	7×	10	,,	,,	10×	20	,, ,,	55 ,,
No. 6.	,,	,,	5×	10	,,	,,	8×	10	,, ,,	42 ,,

The prompt and complete relief of pain by the initial doses of desomorphine was striking. In retrospect one suspects that adequate relief could have been attained with a smaller dose. The effect, however, lasted only 2 or 3 hours, as compared with 3 or 4 hours for the duration of effect of morphine in the paired patients. The respiratory rate was decreased by desomorphine and by morphine; the effect persisted with the former but disappeared with the latter within the period of administrations.

Later, Lee (1942) extended the trial of desomorphine for relief of pain in cancer patients. His series consisted of 10 patients on desomorphine and 20 on morphine; the starting doses were again 1 mg and 10 mg, respectively, and again administration was subcutaneous. Satisfactory pain relief was obtained with 96.4% of the desomorphine doses and with 94.0% of the morphine doses. Relief was accomplished a little more promptly with the former but was of briefer duration. Sleep per dose was less with desomorphine. Nausea and vomiting occurred with similar frequency after both drugs. Lee also compared the effect of desomorphine (126 cases) with that of morphine (776 cases) for the relief of post-operative pain. Again 1 mg of the former was equivalent to 10 mg of the latter for pain relief. In this study of acute pain the relief per dose averaged 2 hours and 25 minutes for desomorphine, 3 hours and 7 minutes for morphine; sleep per dose averaged 2 hours and 7 minutes for desomorphine, nearly all of the pain-relief time, and 2 hours and 36 minutes for morphine, about 84% of the pain-relief time. Sleep was produced by 91.8% of the desomorphine doses and by 80.5% of the morphine doses. Nausea occurred in 28 cases (20.3%) and vomiting in 23 cases with desomorphine; nausea occurred in 160 cases (20.5%) and vomiting in 103 cases with morphine. Lee concluded that desomorphine had no advantage over morphine and that the brevity of its action was a disadvantage. Desomorphine was adequate as pre-anaesthetic medication (93 cases).

In one field of medicine brevity of action might be an advantage. Snyder & Lim (1941) have found that desomorphine in analgesic dosage has less effect on the labour mechanism and less effect on the foetus than morphine and many other analgesic agents. It should be profitable to explore further the use of desomorphine in obstetrics.

The first published report on the clinical use of desomorphine was that of Schürch & Brunner (1935). They had treated approximately 900 cases

in about a year and had obtained good results pre- and post-operatively in cases of trauma. The analgesic potency of desomorphine was 5 or 10 times that of morphine. The effect appeared more quickly but was often of shorter duration. These authors found the sedative effect of desomorphine to be less than that of morphine; the effect on intestinal peristalsis was less, and it had less effect on the vesical sphincter so that post-operative catheterization was required less frequently. Dizziness and vomiting were less frequent with desomorphine than with morphine but depression of respiration was sometimes greater. Ten years later, Schürch (1945) continued to recommend desomorphine for traumatic cases and for premedication for local anaesthesia because of its calming effect on excitement and fear. In neither of these situations would shortness of action be a particular disadvantage.

Drack (1942) also reported upon the satisfactory relief of pain of accidental injury by desomorphine. She used a dose of 2 mg intravenously and combined this with scopolamine and ephedrine. Drack employed desomorphine in connexion with 409 operations, pre-operatively in 97, during or after the operation in the others. Administration was subcutaneous in 231, intramuscular in 47 and intravenous in 131 cases. It produced quiet or light sleep but the patient responded when spoken to and was able to co-operate. Drack believed that the post-operative need for analgesic medication was reduced when desomorphine had been used pre-operatively. She also thought the drug superior to morphine in renal or biliary colic, since it gave complete relief with relaxation for 5 or 6 hours without the occurrence of nausea or vomiting. This persistence of effect is very surprising in view of the shortness of action of the drug in other situations. Christ [a] and Rapin (1945) stated that good pain relief was obtained with the drug.

Addiction liability

In the 6 cases reported by Eddy & Himmelsbach (1936) the drug being used, whether desomorphine or morphine, was withheld for 6-12 hours at about 10-day intervals throughout the course of the study. During these brief withdrawals observations for specific abstinence symptoms were made. Such signs of abstinence began to appear 10 days after the beginning of desomorphine administration. After the third week definite evidence of abstinence was seen if desomorphine was withheld for only 4 hours. No signs of addiction were observed during the short periods of withdrawal in the three patients receiving morphine. It must be remembered, however, that the dose of desomorphine had been increased more rapidly than that of morphine, and also that signs of abstinence from morphine are not ordinarily very apparent within the first 12 hours of withdrawal because of the longer duration of action of this drug.

[a] A. Christ (1942), quoted by Wolff, P. O. (1945) unpublished working document WHO/APD/54.

In Lee's (1942) chronic cases drug administration was withheld at approximately 2-week intervals, saline injections being given instead. These withdrawal periods varied from 6 to 22 hours. When the results of all withdrawal periods (16 for desomorphine, 40 for morphine) were compared, the intensity of observed abstinence phenomena was greater for desomorphine; the time of appearance of these phenomena from the beginning of drug administration was approximately the same for both drugs. Tolerance to the analgesic effect developed similarly for both drugs and manifested itself first in a shortening of the period of pain relief. In these experiments tolerance and physical dependence developed with desomorphine even when the drug was administered in minimal clinical analgesic dosage at intervals consistent with its duration of action, but desomorphine was not significantly different from morphine with respect to tolerance or physical dependence when both drugs were so administered.

In another study (Eddy & Himmelsbach, 1936), desomorphine was substituted for morphine in 5 addicts. The morphine stabilization dose was 200 mg per day in one, 400 mg per day in the others. Both morphine and the substituted desomorphine were administered subcutaneously 4 times a day. The desomorphine doses ranged from 70-160 mg per day at the start to 180-200 mg per day at the end of 8-21 days of substitution, but the interval of administration continued to be 6 hours. Substitution was nearly but not entirely complete; that is, the group were never completely stable or entirely normal in feeling and appearance during the substitution period. Again, increasing the dose did not compensate for the shortness of action of desomorphine. It is possible that, had the frequency of administration rather than the size of the dose been increased, stability, or complete satisfaction of the addiction, would have been maintained. Following abrupt withdrawal of the substituted desomorphine, abstinence syndromes developed promptly, more rapidly than after abrupt withdrawal of morphine. They were at least equal in severity to the usual morphine abstinence syndrome. The duration of the desomorphine abstinence syndrome was about the same as that of morphine, but since it appeared sooner it subsided sooner.

Binswanger (1939) described a case of tabetic crises in whom desomorphine gave better pain relief, in the patient's opinion, than dilaudid without disagreeable intestinal effects. The patient became dependent upon desomorphine as he had upon dilaudid. Knaffl-Lenz (1938) reported the prompt relief of morphine abstinence symptoms by 5 or 10 mg of desomorphine subcutaneously in a carcinoma patient clearly addicted to pantopon as the result of 6 weeks' continuous administration. Knaffl-Lenz agreed that desomorphine acted like other morphine derivatives and that its advantage of stronger action was counterbalanced by shorter duration. Tiffeneau (1938) also said that desomorphine would substitute for morphine or heroin in cases of addiction; a fifth as much desomorphine had the same

sedative effect in cancer patients as the morphine they were taking. M. Bleuler & J. E. Staehelin[a] frequently saw addiction to desomorphine, usually, however, secondary to addiction to other opiates.

SUMMARY

Desomorphine is a potent analgesic agent, up to ten times more powerful than morphine, but its potency for most purposes is largely offset by the short duration of its action, which is not much more than half that of morphine. Desomorphine may have particular usefulness for the relief of traumatic pain. If it is administered repeatedly at its minimal analgesic dosage at an interval related to its duration of action, it does not differ materially from morphine, similarly administered, with respect to tolerance, addiction liability or incidence of side-effects.

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2. Dihydrocodeine

Dihydrocodeine was introduced in Germany more than 40 years ago as an antitussive, and curiously almost no attention was paid to the possibility of analgesic action. Fraenkel (1913) said that it was twice as effective as codeine and was more sedative without other side-effects. Dahl (1913) also found it more effective than codeine. He compared 25 mg of the former with 35-45 mg of the latter. Dahl commented on the greater sedative effect of dihydrocodeine and said its side-effects were no greater than those of codeine. The drug was used orally, of course.

In 1926 Heinroth reported a few observations on the analgesic effect of dihydrocodeine. He stimulated the teeth with faradic current and continued his control observations until a similar response was obtained on stimulation of two different teeth. 20 mg of dihydrocodeine orally reduced

[a] Personal communication, 1955

the tooth sensitivity less than 10 mg of morphine but more than 50 mg of codeine. Again, dihydrocodeine seemed to have no adverse effects. Dihydrocodeine has continued to be used for its effect on cough but not to any great extent outside Germany, and not at all in America.

Quite recently interest in a possible analgesic effect of dihydrocodeine has been aroused, at the outset mainly as a matter of curiosity. H. K. Beecher et al.[a] and Gravenstein et al. (1956) tested it by parenteral administration in post-operative pain. They drew the very surprising conclusion that a dose of 30 mg subcutaneously was about as effective in relieving pain as 10 mg of morphine and yet produced no more side-effects than a placebo and did not depress respiration. The evaluation of analgesic effectiveness was by the double-blind technique of Denton & Beecher (1949). Morphine and dihydrocodeine were given alternately in the same patient and the degree of relief was recorded by an impartial observer. The criterion of effect was at least 50% reduction of pain at two check-points after administration, and was expressed as the percentage of doses giving at least that much relief:

Number of patients	*Dihydrocodeine*		*Morphine*	
	mg per 70 kg	*percentage relief*	*mg per 70 kg*	*percentage relief*
21	15	56	10	89
55	30	70	10	82
15	45	50	10	63

The duration of effect of dihydrocodeine was less than for morphine: 4.4 as against 5.1 hours when the pain was severe, 4.3 as against 5.3 hours when the pain was of moderate intensity. This difference was considered immaterial because in the absence of any side-effects there was no contra-indication to repetition of the dose at the shorter interval.

Assessment of side-effects was made by administering the approximately equal analgesic doses, 10 mg of morphine and 30 mg of dihydrocodeine, and a placebo in random order to each of 30 normal subjects. Respiratory minute volume was measured while breathing room-air and 5% carbon dioxide and the subjects filled out a questionnaire designed to elicit mood changes. With dihydrocodeine there were no significant differences in respiration or in mood from what was seen with a placebo, and no other side-effects were observed.

Because at the doses used dihydrocodeine was not quite equal to morphine in analgesic potency, Gravenstein et al. (1957) extended their work with the drug, comparing 60 mg of dihydrocodeine with 10 mg of morphine, each given alternately to the same post-operative patient by subcutaneous injection. In terms of the percentage of doses giving 50% or more relief of pain 45 and 90 minutes after injection, this dose of dihydrocodeine also was nearly but not quite equal to that of morphine, and again the duration of its effect was shorter. However, this dose of dihydrocodeine caused some

[a] Personal communication, 1956

depression of respiratory minute volume in normal subjects, especially when the subjects were breathing 5% carbon dioxide—slightly more than 60 mg of codeine, but less than 10 mg of morphine in the same individuals. Unfortunately, increasing the dose of dihydrocodeine to 60 mg increased the incidence of side-effects (except nausea) and mood changes nearly to the level of their occurrence with 10 mg of morphine.

Stimulated by the earlier report of Gravenstein et al., various workers re-examined dihydrocodeine in a number of situations. H. H. Keasling & E. G. Gross[a] compared the effect of codeine and dihydrocodeine with that of aspirin and a placebo on the radiant heat threshold in normal subjects, using their adaptation (1956) of the Wolff-Hardy-Goodell technique. The doses employed were 10 mg and 20 mg of codeine and dihydrocodeine and 300 mg of aspirin, and all were given orally in random sequence under double-blind conditions. None of the medications differed significantly in their effect from the placebo or from each other, a result which might have been expected considering the doses employed and the route of administration.

Keats, Telford & Kurosu (1957) gave doses of 30, 60 and 90 mg of dihydrocodeine per 70 kg of body-weight to post-operative patients, alternating the doses in individual patients with 10 mg of morphine per 70 kg. Administration was subcutaneous. Evaluation of pain relief was made by a technician following each dose of each drug during the first 30 post-operative hours. The difference in analgesic potency between the two drugs was expressed as the difference in the percentage of total doses which were analgesic. Only paired doses were considered. The results were as follows:

Number of patients	*Paired doses*	*Dihydrocodeine*		*Morphine*	
		dose (mg per 70 kg)	*percentage analgesic doses*	*dose (mg per 70 kg)*	*percentage analgesic doses*
54	104	30	66.3	10	75.0
51	96	60	72.9	10	72.9
41	81	90	72.8	10	77.8

The effect of 30 mg of dihydrocodeine was a little less than that of the standard dose of morphine; 60 mg of dihydrocodeine and 10 mg of morphine were alike in their analgesic effectiveness; and no increment in analgesic effect was afforded by increasing the dose to 90 mg.

The respiratory effects of 30 mg and 60 mg of dihydrocodeine, of 10 mg of morphine, and of a saline placebo were determined in seven normal subjects. Each received each of the medications in random order at an interval of not less than five days. Respiratory rate, minute volume and response to 3% carbon dioxide were measured. The 30-mg dose produced some depression of respiration which had, however, disappeared 3 hours after injection. This was no greater than with the placebo when the subjects were breathing room-air, but significant when 3% carbon dioxide was

[a] Personal communication, 1956

respired. The 60-mg dose had a depressant effect which approached but did not equal the degree of depression produced by 10 mg of morphine. The respiratory minute volume figures (in litres) were:

	Breathing room-air			*Breathing 3% CO_2*		
	control	*1 hour*	*3 hours*	*control*	*1 hour*	*3 hours*
Placebo	6.61	5.84	6.25	12.49	12.22	12.73
Dihydrocodeine, 30 mg	5.73	5.10	5.65	11.20	10.72	11.14
Dihydrocodeine, 60 mg	5.72	4.37	4.97	13.08	10.26	11.71
Morphine, 10 mg	5.83	4.12	4.66	12.01	9.76	10.29

Patients awaiting elective surgery received subcutaneously the day before operation saline, 30 mg or 60 mg of dihydrocodeine, or 10 mg of morphine to assess the incidence of subjective side-effects. The conditions were double-blind. A technician used a simple check-list as a guide and recorded any voluntary statements of the patients. No patient received more than one drug. At a dose of 30 mg side-effects with dihydrocodeine were minimal and hardly different from those seen with the placebo. At a dose of 60 mg the incidence of side-effects was greater, but in most respects less than with morphine. Nevertheless, 55% of the patients disliked the drug effect when 60 mg of dihydrocodeine were given as against 36% who disliked the effect of 10 mg of morphine.[a]

Keasling, Hinds & Keats[b] compared the effectiveness of oral medication given on a double-blind basis in random order to more than 100 dental surgical patients. Each individual was given a 24-hour supply of one medication to be taken at 4-hour intervals, was directed to report the result the next day, and was then given another drug. The medications and incidence of pain relief with each were as follows:

Placebo	62%
Aspirin, 0.6 g	71%
Dihydrocodeine, 30 mg	73%
Anileridine, 30 mg	70%
Anileridine, 60 mg	95%

The greatest number of side-effects, such as dizziness and nausea, followed the 60-mg dose of anileridine.

Wallenstein, Seed & Houde (1957) compared dihydrocodeine with morphine for its effectiveness against chronic pain. Thirty-seven patients with pain due to cancer were used, none of whom had been receiving more than 16 mg of morphine every 4 hours or its equivalent. Pain intensity was recorded in the patient's own estimate of severe, moderate, slight or none. If it was rated as moderate or severe and no analgesic medication had been given within 3½ hours, one of five coded medications was given intramus-

[a] A. S. Keats—personal communication, 1957

[b] Keesling, R., Hinds, E. C. & Keats, A. S. (1957) Thirty-fifth general meeting of the Internationa lAssociation for Dental Research, Atlantic City, N.J., USA, 21-24 March 1957 (Abstract No. 196)

cularly. These were two dose-levels of dihydrocodeine and morphine and a placebo. Each patient received each medication in randomized order. The conditions were double-blind. Hourly reports of pain severity were accumulated for 6 hours or more or until the pain returned to its premedication level. Initially, 30 mg and 60 mg of dihydrocodeine were administered in sequence with 8 mg and 16 mg of morphine; in a second series the doses of morphine were reduced to 5 mg and 10 mg. Plotting their results and calculating for equal potency, the authors estimated 68 mg of dihydrocodeine to be equivalent to 10 mg of morphine, with fiducial limits at the 95% level of 45-125 mg.

Using two normal healthy adults, three patients with lymphomas who were not receiving narcotics and five subjects who were receiving narcotics for pain due to metastatic cancer, Seed et al. (1957) assayed the respiratory effect of dihydrocodeine in comparison with that of morphine in terms of displacement of alveolar ventilation—pCO_2 response curves, which in turn were determined from an automatic record of a subject's response to re-breathing. The individuals were at rest, semi-recumbent, and the dosages were 5 mg and 10 mg of morphine and 30 mg and 60 mg of dihydrocodeine intramuscularly. Dose-response curves for the two drugs were not significantly different in slope and it was calculated that 77 mg of dihydrocodeine equalled 10 mg of morphine in degree of respiratory depression. Since this dose was well within the limits of error calculated for analgesic effectiveness, the authors concluded that equivalent analgesic doses of dihydrocodeine and morphine produce approximately equivalent amounts of respiratory depression.

Eckenhoff, Helrich & Rolph (1957) also studied the respiratory effect of dihydrocodeine and added observations on its influence on the circulation. The study was made on five healthy male volunteers, 20-30 years of age, before and after administration of 50 mg or 60 mg (in one instance, 75 mg) of dihydrocodeine intramuscularly. The subjects were connected to a closed, carbon-dioxide-absorption re-breathing system and observations were made on respiratory rate and tidal volume and end-expiratory carbon dioxide concentration. Minute volume and carbon dioxide partial pressures were calculated and the respiratory response to endogenously accumulated carbon dioxide was measured. Respiratory rate and minute volume were decreased somewhat and the respiratory response to accumulated carbon dioxide was decreased at lower carbon dioxide tensions only. The authors concluded that dihydrocodeine had some respiratory depressant action at the doses used but less than that observed with other well-known opiates and opiate-like drugs (Eckenhoff et al., 1955).

The circulatory response to dihydrocodeine was determined by observing the response to tilting before and after the drug in seven normal subjects. Again the doses were 50 mg or 60 mg, and 75 mg in one subject only. Three of the seven subjects became hypotensive and fainted on tilting after the

drug. The heart rate tended to increase during the tilt after dihydrocodeine. A bradycardia, however, occurred at the time of the faint in the three subjects who fainted. In an earlier study Drew, Dripps & Comroe (1946) reported that two of eight subjects in the same age-group fainted during tilting after 20 mg of morphine, so that the effect of dihydrocodeine on the circulation seemed to be not materially different from that of morphine.

Of the 12 subjects investigated by Eckenhoff and his associates in the two experiments, 10 noted no side-effects except brief drowsiness, and two complained of nausea. From preliminary studies in the recovery room after operation Eckenhoff considered 30 mg of dihydrocodeine inferior to 10 mg of morphine in analgesic power.

Swerdlow (1957a) determined the effect of dihydrocodeine on respiratory function on patients in good general condition about to undergo surgical operation. In the first group of 20 patients thiopentone 8 mg per kg was injected rapidly intravenously and then nitrous oxide/oxygen was given via a closed circuit. Six minutes later dihydrocodeine 0.25 mg per kg was injected intravenously. In another 20 patients the same procedure was repeated, using twice the dose of dihydrocodeine—0.5 mg per kg. Respiratory rate and minute volume after the thiopentone and at intervals after the dihydrocodeine were as follows (the changes when pethidine 0.6 mg per kg was given under similar conditions (1957b) are added for comparison):

		After thiopentone	*Minutes after narcotic* 3	5	7	9
Pethidine: 0.6 mg/kg	Respiratory rate	19.1	10.6	9.9	10.1	9.2
	Minute volume	5361	3269	3318	3648	3429
	Percentage change in alveolar ventilation		−32.4	−20.7	−0.57	−2.1
Dihydrocodeine: 0.25 mg/kg	Respiratory rate	18.3	15.2	14.4	14.0	13.8
	Minute volume	5529	5075	4985	5081	4912
	Percentage change in alveolar ventilation		+0.65	+7.3	+11.0	+7.5
Dihydrocodeine: 0.5 mg/kg	Respiratory rate	18.5	14.6	13.6	13.4	13.0
	Minute volume	5441	4644	4470	4613	4601
	Percentage change in alveolar ventilation		−3.8	−3.0	+5.3	+7.2

Even with the larger dose of dihydrocodeine evidence of respiratory depression was significantly less than with pethidine, and it is probable that this larger dose was more than equi-analgesic with pethidine. However, there was some depressant effect present due to dihydrocodeine because the administration of levallorphan 10 minutes after the dihydrocodeine in a 1 : 50 ratio consistently produced a pronounced increase in minute volume and some increase in respiratory rate.

J. D. Myers[a] sought to determine the analgesic effectiveness of dihydrocodeine in 50 normal labours. On admission all patients were given 100 mg or 200 mg of a barbiturate (Seconal) orally, and this was repeated as necessary to relieve their anxiety. The dose of dihydrocodeine was always 30 mg subcutaneously and was first given when the cervix was partially dilated. The number of doses varied from one to four, one only in 34 patients, two in 22, three in 4 patients and four in one patient only. Analgesia was noted subjectively after 56 of 65 injections (86%), usually in 20-30 minutes. The author estimated the duration of action at 2¾ hours. Objectively, attendants judged that significant pain relief was obtained with dihydrocodeine in 91% of the patients. Nearly all were relaxed and rested well between contractions. Of 26 multiparas 12 thought the relief afforded by dihydrocodeine was better, 5 considered it as good, and 9 believed it less satisfactory than the relief experienced with other agents in previous deliveries. The drug had no apparent effect on the duration of labour.

One of the 50 babies was born dead (macerated), and there was one neonatal death. This occurred in a rapid delivery (52 minutes from medication to delivery), the mother having received 100 mg of Seconal and one dose of dihydrocodeine only. The baby made only two respiratory gasps and failed to respond to resuscitative measures. Of the other 48 babies only 29 gave a normal cry and breathed normally within a minute, 8 in one to two minutes, 5 in two to three minutes, and 6 required more than three minutes to breathe normally. Other factors contributed to the depression in five of the six in the last group.

For comparison Myers observed a comparable group of 48 presumably normal deliveries in which the only difference from the dihydrocodeine group was the administration of 100 mg of pethidine intramuscularly instead of dihydrocodeine. The incidence of normal cry and respiration in the infants of the two groups at successive time intervals after birth was as follows:

	Normal cry and respiration			
	0-1 minute	*1-2 minutes*	*2-3 minutes*	*3-25 minutes*
Dihydrocodeine group . . .	29	8	5	6 (12%)
Pethidine group	25	5	7	11 (23%)

The author concluded that for the level of analgesia obtained dihydrocodeine was safer for the baby than pethidine, but one cannot say that it is entirely free of risk when only 61% of the babies cried and breathed normally within one minute.

Forty-five of Myers' obstetrical cases were given dihydrocodeine orally in doses of 15-30 mg for post-partum discomfort. Of the multiparas so treated 96% thought they were more comfortable than, or as comfortable as, on previous occasions when they had received a half-grain of codeine plus 10 grains of aspirin.

[a] Personal communication, 1957

Addiction liability

A case of primary addiction to dihydrocodeine came to the attention of one of the authors some years ago. In spite of alleged circulatory weakness the drug was withdrawn without difficulty and with general improvement in the patient's condition. Meyer (1934) described a case of morphine addiction who after withdrawal relapsed to the use of hydrocodone and then switched to dihydrocodeine, taking 30 tablets a day for 16 months. Isbell [a] found that 150 mg of dihydrocodeine subcutaneously was approximately equal to 20 mg of morphine for the production of morphine-like effects in post-addicts, and Himmelsbach (1941) said that dihydrocodeine would satisfy morphine physical dependence but that its withdrawal was definitely less severe than that of morphine. Eight addicts were stabilized on morphine and transferred to dihydrocodeine at the same interval of administration (4 doses per day). 175 mg substituted completely for each 50 mg of morphine. On abrupt withdrawal the onset of abstinence phenomena was a little slower than after the withdrawal of morphine and Himmelsbach estimated the duration of physical dependence potency as 20 hours compared with 14 for morphine. The addiction liability of dihydrocodeine would seem to lie between that of morphine and that of codeine, probably closer to the latter.

SUMMARY

Dihydrocodeine is an effective analgesic, which, however, never seems to attain quite the potency of morphine. Its optimal dose is 30 mg. At that dose very little, if any, respiratory depression occurs and no other side-effects of significance other than drowsiness. Increasing the dose to 60 mg adds little or no increment of analgesia but does cause the appearance of morphine-like side-effects and respiratory depression. The duration of action of dihydrocodeine is a little less than that of morphine. In obstetrics the analgesic effect of dihydrocodeine nearly equals that of pethidine, but there is evidence of some foetal depression. Dihydrocodeine has addiction liability between that of morphine and that of codeine, probably closer to the latter.

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3. Ethoheptazine [a] (1-methyl-4-phenyl-4-carbethoxyhexamethyleneimine)

Ethoheptazine is a homologue of pethidine, having a seven-membered heterocyclic ring, a hexamethyleneimine, where pethidine has a six-membered ring, a piperidine. Pharmacological examination (Seifter et al., 1954) revealed that it was a weaker analgesic than pethidine and differed from it in some other respects. It was submitted to preliminary clinical trial by Gittinger, Grossman & Batterman (1955) and Grossman et al. (1956). The drug was administered orally to groups of ambulatory patients with chronic pain secondary to a variety of musculoskeletal conditions. The dosage ranged from 50 mg to 250 mg every 4 hours for 1-16 weeks of continuous administration. A dose-response curve attained in over 200 trials indicated an effective safe dose of 50 mg. Although the majority of individuals tolerated three to five times that amount, the incidence of central nervous system stimulation and other side-reactions favoured the smaller dosage. No tolerance was observed. Golbey and his associates (1956) investigated further the clinical usefulness of the compound for relief of pain due to a wide variety of medical and surgical conditions. A bed-ridden group of 118 patients presented a satisfactory analgesic response to 50 mg or 100 mg orally four times a day in 58% of 139 trials. Patients with pain due to musculoskeletal conditions, early metastases from various neoplasms and neuropathology noted the most relief; 80% of an additional 35 post-partum patients experienced satisfactory analgesia. In 85 ambulatory patients 50 mg 4 times a day resulted in relief of pain in 64 (75%). Side-effects were minimal: nausea in only 4 of 238 patients, and dizziness in one.

Golbey, Gittinger & Batterman (1955) also tried ethoheptazine parenterally against acute and chronic pain of medical and surgical conditions. A satisfactory analgesic response equivalent to pethidine or morphine effectiveness was achieved with a dose averaging 100 mg. Untoward reactions with initial or occasional doses were minimal or absent, but prolonged, repeated administration resulted in cumulative toxicity which took the form of central nervous system stimulation. Respiratory and pulse rates, oxygen consumption, blood pressure and the pupil were unchanged.

[a] International non-proprietary name

Recently Cass, Frederik & Bartholomay (1957) completed a double-blind study on the clinical effectiveness of ethoheptazine in comparison with codeine and aspirin. Seventy-one patients with chronic pain due to arthritis, metastatic carcinoma, cardiovascular disease or neuropathology completed the study; two-thirds were males ranging in age from 42 to 78 years and most were semi-ambulatory. Most had received aspirin or aspirin and codeine previously for relief of their pain. All patients received each of the test medications at random, each for a period of seven days, with no rest period between. The medications were prepared in capsule form and the dosage throughout was two capsules four times a day. The patients were questioned three times a day by a disinterested observer and note was made of the degree of relief on the basis of a numerical rating: 0 for no relief to 4 for complete relief. The five medications employed were:

Aspirin, 600 mg
Ethoheptazine hydrochloride, 100 mg (equivalent to 87.8 mg base)
Codeine sulfate, 30 mg, plus aspirin, 600 mg
Ethoheptazine, 100 mg, plus aspirin, 600 mg
Placebo

The pain-relief scores for each drug for each patient were cumulated ($71 \times 3 \times 7$ observations for each drug) and subjected to statistical analysis. Ethoheptazine alone or aspirin was significantly more effective than the placebo; the addition of aspirin to ethoheptazine or of codeine to aspirin increased analgesic effectiveness; and ethoheptazine plus aspirin was as effective as codeine plus aspirin. The effectiveness of ethoheptazine was confirmed by sequential analysis of the data on a smaller group of 35 patients who received a placebo, codeine plus aspirin or ethoheptazine plus aspirin.

The Addiction Research Center at Lexington, Ky., examined ethoheptazine for morphine-like effects in post-addicts and for possible suppression of the morphine abstinence syndrome (Fraser, 1956). In doses of 25-150 mg subcutaneously or 50-300 mg orally ethoheptazine produced neither objective signs nor subjective symptoms of morphine-like effect in non-tolerant former addicts. In doses of 100 mg subcutaneously every 4 hours it was also ineffective in suppressing symptoms of abstinence in patients who had been addicted to 240-280 mg of morphine daily. However, all the addicted persons who received these multiple doses developed nervousness, insomnia, twitches and tremors which persisted for 12-24 hours after the drug was discontinued. One addicted patient developed signs of vascular collapse and pulmonary oedema after receiving 150 mg of ethoheptazine. Fraser concluded that the addiction potentiality of ethoheptazine was low or non-existent, but pointed out that the testing was necessarily incomplete because of the nervous system excitation and other toxic effects which the drug induced.

SUMMARY

Ethoheptazine is effective orally against moderate pain in doses of 50-100 mg; the former appears optimal for ambulatory patients. Its use parenterally is limited by the appearance of signs of central nervous excitation under conditions of repeated administration. Side-effects with oral doses are minimal. Ethoheptazine seems to have no addiction liability, but toxic reactions occurred with the larger doses used to test this property.

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4. Heroin (diacetylmorphine)

Heroin came on the market in 1898 after Dreser's experiments had been interpreted by him as showing greater potency with relatively less respiratory depression. Its trial as an antitussive spread very rapidly; usually oral administration and doses of 5-10 mg were employed. For the most part these doses were reported to give satisfactory cough relief but frequently were found ineffective for pain. Very early the usual morphine-like side-effects—nausea, dizziness, drowsiness and constipation—were noted, but, though it was said that these symptoms were less frequent than after morphine, no controlled quantitative comparison seems to have been made. There were very early references also to tolerance and to the possibility of addiction. Heroin was substituted for morphine in known addicts, successfully it seemed, but a stronger desire for heroin replaced the desire for morphine. The earlier reports, all within the first two years of clinical use of heroin, illustrate the enthusiasm with which the drug was received and typical estimations of its properties.

Strube (1898) said that 5-10 mg orally slowed the respiration, abolished cough and produced a feeling of weariness which led to sleep if the patient was undisturbed. There were no unpleasant side-effects. The drug was not effectively analgesic. The patients liked the drug and continued to take it when he ceased to prescribe it or changed to other medication. Strube thought this liking might foretell addiction liability. He reported on 50 cases. In the same year Manges (1898) reported that disagreeable side-effects followed the use of heroin in a few cases, yet these symptoms were milder and of less frequent occurrence than those after morphine. Manges too

found the drug useless as an analgesic in an ordinary dose, 6-10 mg orally. Two years later he summarized the experiences of himself and others in 416 cases where the indication was mainly relief of cough (Manges, 1900). He preferred oral use, starting with 5 mg, the daily dose not exceeding 15 mg or 20 mg. The drug was effective in 318, or 76.4%, a failure in 98. His own experience was slightly better for cough alone, with a good result in 84%. Constipation, drowsiness and nausea were the side-effects noted. Manges quoted a personal communication regarding 37 cases, with good effect in 89%, side-effects in 11% and recognized addiction in 8 cases, a very high incidence among only 37 cases at this early date.

Tauszk (1898) reported on 16 cases of cough promptly relieved or much ameliorated by heroin. 3 mg were effective in chronic cough where 3 mg of morphine or 60-120 mg of codeine had failed. After prolonged use the dose had to be increased to 5 mg. These were all oral doses. In 50 cases, mostly respiratory conditions but including sciatica and insomnia, Medea (1899) gave doses of 7.5-10 mg, usually subcutaneously, which were followed in 10-15 minutes by a sense of well-being, partly at least from symptomatic relief, and drowsiness leading to refreshing sleep. There were vertigo and ringing in the ears in a third of the cases but nausea in only one patient. The respiratory rate, however, diminished in most patients by 6-8 per minute. Eulenburg (1899) used 5-10 mg of heroin subcutaneously in various painful conditions with a sedative effect similar to that after a larger dose of morphine. He substituted it for morphine in several cases of addiction, usually satisfactorily. Lang (1899) preferred heroin in chronic rather than acute respiratory conditions, using 5 mg orally 3 times a day. Larger doses were unsatisfactory. Cough was reduced in frequency and intensity and pruritus was the only side-effect noted. It disappeared in a few days even when the drug was continued. The report of Rosin (1899) was distinctly adverse. He obtained good results in only 6 of 48 dispensary patients and in these the results were no better than with morphine or codeine. There were unpleasant side-effects, dizziness, nausea and headache, in 14 cases. The dosage was 8-10 mg orally. Contrariwise, Brown & Tompkins (1900) said that all but 7 of 50 patients (in 34 pain, in 16 insomnia was the indication) were relieved in 15-20 minutes with doses of 5 mg (34 cases) to 10 mg (16 cases). The drug was given subcutaneously in 31 patients.

Very early reports dealing specifically with heroin addiction were those of Leynie de la Jarrige (1902) and Pettey (1903). The former said that patients became addicted to heroin, when its use was no longer indicated for symptomatic relief, on account of its euphoric effect; the latter described the drug as another curse. Many other early references to heroin addiction are listed by Krueger, Eddy & Sumwalt (1942). Morel-Lavallée (1900) and Ahlborn (1901) substituted heroin for morphine in persons addicted to the latter, in 6 and 3 cases, respectively. One addiction was replaced by another; the patients were not cured. In 1905, Sollier was condemning the

increasing practice of substituting heroin for morphine in addicts because the resulting state, he said, was worse than the first. Individuals became rapidly addicted to heroin, tended to increase their dose more rapidly than they would with morphine, showed greater mental and physical deterioration, were more difficult to cure, and in attempted withdrawal were more liable to collapse, which was difficult to relieve by administration of heroin. Duhem in 1907 and again in 1911 condemned heroin outright as having none of the advantages claimed for it. It induced an addiction that was even more dangerous and more difficult to treat than morphine addiction. He compared the abstinence syndromes of withdrawal of each drug and said that morphine would suppress serious heroin withdrawal symptoms more easily than heroin itself. In 1915, according to Farr, 86 of 120 addicts admitted to hospital in the first two months were taking heroin, usually by snuffing. In none had the drug been prescribed by a physician.

This is a very small sampling of the early literature on heroin (see *Bull. Narcot.*, 1953, for the history of the development of heroin). More important for the present purpose are accounts of experiments designed to determine quantitatively its various effects.

Analgesic and other subjective effects

Seevers & Pfeiffer (1936) compared heroin with morphine, dilaudid and codeine for analgesic, euphoric and general depressant effects in six normal subjects. Pain thresholds were determined by means of von Frey hairs for five spots on the face; individuals were questioned as to subjective effects and observed for overt depression and side-effects. Neither the observer nor the subject knew what drug or dose was given on a particular occasion. No placebo was used. Each drug was given at two dose-levels; the attempt was to match doses producing the same peak effect. From the authors' graphs equivalent analgesic doses appeared to be morphine sulfate 10 mg, codeine phosphate 64 mg, heroin hydrochloride 1.0 mg, dilaudid hydrochloride 0.8-1.0 mg, all subcutaneously. Peak effect occurred in 30 minutes with heroin, in 30-60 minutes with codeine, in 60-90 minutes with morphine and in 90 minutes with dilaudid. The order of duration of effect was morphine (longest), dilaudid, codeine and heroin. When the drugs were given intravenously, potency was about the same for heroin, less for morphine and much less for dilaudid than for subcutaneous injection; peak effect occurred in about 20 minutes with all drugs; duration of effect was shorter than with subcutaneous injection and again was about the same for all drugs. The order of over-all narcotic or sedative effect was morphine (greatest), dilaudid, heroin and codeine, and was the same for both routes of administration. Without exception heroin was cited as producing the most pleasurable sensation, next morphine, and then dilaudid. Codeine produced very little depression or euphoria. Morphine produced nausea

in 57% of trials, dilaudid in 37%, heroin in 6% and codeine in none. After disappearance of the analgesia, especially with heroin, there was increased sensitivity to painful stimuli.

Pfeiffer and his associates (1948) compared heroin and dilaudid for their effect on different types of pain in normal subjects. The authors distinguished (1) superficial pain, from stimulation of the finger pad, (2) deep pain, from stimulation of tooth pulp, and (3) sympain, from stimulation of the nail-bed. Both drugs were administered subcutaneously at a dose of 2 mg in 7 subjects. Both increased the threshold for deep pain markedly and that for superficial pain only slightly. Dilaudid increased the threshold for sympain moderately, but heroin increased this threshold not at all. In contrast, levo-methadone, at a dose of 5 mg subcutaneously, increased all three thresholds considerably and to about the same extent.

Javert & Hardy (1951) attempted to compare pain thresholds, as determined by a radiant heat stimulus, with the intensity of pain in labour. The drugs used were heroin 5 mg, morphine 15 mg plus scopolamine 0.4 mg, and morphine 10 mg plus demerol 100 mg, all subcutaneously. None of these drugs raised the pain threshold but all had a good analgesic effect as indicated by reduction in pain intensity and restlessness.

Jackson (1952) also failed to obtain a rise in pain threshold (radiant heat stimulus) with morphine 10-15 mg, or heroin 5 mg, intravenously or by other routes in normal subjects. These doses were accompanied by severe side-reactions, particularly vomiting.

Lasagna, von Felsinger & Beecher (1955) compared the effect of morphine and heroin on subjective responses in 20 normal adult males, in 30 chronically ill individuals and in 30 former opiate addicts. The results were determined by self-scoring questionnaires filled out before and after drugging in the normals and post-addicts and by uniform questioning in the chronically ill. The dosages employed, subcutaneously, were for heroin 2 mg and 4 mg in the normals, 2 mg in the chronically ill, 4 mg and 6 mg in the post-addicts, and for morphine 8 mg and 15 mg in the normals, 8 mg in the chronically ill, 15 mg and 22.5 mg in the post-addicts. All subjects received for comparison a saline placebo. The surrounding circumstances affected the individuals' judgement of drug effect. Half of the normal subjects considered the effects of morphine and of heroin unpleasant; 8 were euphoric with morphine, 9 with heroin; 18 were sedated by morphine, 17 by heroin; only 2 after morphine and 4 after heroin would have cared to repeat the experience. Among the chronically ill the morphine effect was judged pleasant in 14, unpleasant in 8; the heroin effect was pleasant in 11, unpleasant in 3; the placebo effect was judged pleasant in 10, unpleasant in none, unchanged in 12. Among the post-addicts the effect of morphine was considered pleasant by 22, unpleasant by 3, and 17 would have liked to repeat the experience; the effect of heroin was considered pleasant by 15, unpleasant by 4, and 14 would have liked to repeat the

experience. In the normal subjects the incidence of side-effects with heroin and morphine, respectively, were: headache 6 and 9, nausea 9 and 9, dizziness 13 and 16, shakiness 9 and 9, itching 10 and 5, dryness of mouth 7 and 10, and a feeling of warmth 8 and 9. In these experiments and at the doses used, approximately four times greater for morphine, the differences between the two drugs were very small.

Although the above controlled studies indicate a potency of heroin four or five times greater than that of morphine, a technical study (League of Nations, 1939) of morphine and other addicting agents concluded the therapeutic dose of heroin to be 5 mg against 10 mg for morphine. Brouet (1953) gave the therapeutic range for heroin as 5-10 mg with a maximum daily dose of 20 mg. He believed its use should not be routine but should be justified by the complete or partial ineffectiveness of other drugs, with restriction, as a rule, to incurables who had not long to live and were in severe pain. Some at least of the European pharmacopoeias stated the therapeutic range for heroin as 5-10 mg, that for morphine up to 20 mg. Also Chopra and co-authors (1942) placed heroin below morphine in analgesic potency. They placed in decreasing order of analgesic effectiveness eucodal, morphine, heroin, codeine and dionin. Morphine and heroin were superior to eucodal in euphoric effect, codeine and dionin inferior. As a respiratory depressant heroin, they said, held topmost place.

Macht & Macht (1939) compared the effect of morphine 8 mg, codeine 20 mg, dilaudid 2 mg and heroin 2.5 mg on special senses and psychomotor functions in 30 normal subjects. At the doses used the effects of the several drugs were similar: acuity of vision was unaffected but the field of vision was decreased, most for red and green; the time taken to solve an arithmetical problem was prolonged but errors were not necessarily increased; the performance of a tapping test was retarded.

In normal subjects, one per drug, in which gastro-intestinal activity was followed by fluoroscopic examination after a barium meal, Myers & Davidson (1938) found a greater amount of barium still in the stomach and the movement of the meal through the intestine more retarded with 5 mg of heroin than with 10 mg of morphine.

Antitussive action

Although heroin was introduced or exploited in the first instance as an antitussive, and still is credited with peculiar power in this respect, there have been surprisingly few reported attempts to evaluate its action on cough under adequately controlled conditions. Hillis & Kelly (1951) were unable to demonstrate suppression of an artificially induced cough (cough provoked by intravenous injection of α-lobeline) even with substantial doses of heroin; codeine and morphine also failed to suppress the cough. In another experiment, however, using a single normal subject

and spraying a cough-inducing mist (peppermint water or ether) directly into the larynx, Hillis (1952) found that 5 mg of heroin completely suppressed the cough response in 10 trials. Morphine or methadone, each in a dose of 15 mg subcutaneously, were equally effective, while the effect of codeine, 60 mg subcutaneously, was not significantly different from that of a placebo. Heroin produced severe drowsiness in 66%, methadone in 15%, morphine in 21% and codeine in 18% of trials. Beecher and his associates (1954) also were unable to determine a significant reduction in the number of coughs artificially induced, by inhalation of ammonia or citric acid mist or by intravenous paraldehyde, with subcutaneous doses of heroin, 2.5-10 mg; with codeine, 10-20 mg orally or 30 mg intravenously; or with morphine, 5-10 mg subcutaneously. In studies on patients with cough of pathological origin, both codeine (10-15 mg orally) and heroin (5 mg orally) were effective in producing qualitative reduction; that is, a downward trend in the frequency of the cough, when results were compared with those with a placebo. The patients thought they coughed less, whereas the number of coughs was not reduced to a statistically significant degree. Perhaps, as Beecher suggested, the main effect of heroin and other antitussives is on subjective responses and not primarily on the incidence of coughing; the patients feel better and think they cough less.

Respiration

Winternitz (1899) described experiments on two normal humans. 7 mg of heroin subcutaneously decreased respiratory minute volume from 5793 ml to 4576 ml (a reduction to 78.7% of normal) and respiratory rate from 16-17 to 12-13 per minute. Whereas minute volume was 10 023 ml with 4.77% CO_2 in the expired air before heroin administration, it was 8707 ml (a reduction to 86.8%) with 6.00% CO_2 in the expired air after heroin. It required 20 mg of morphine to produce an equivalent effect. Higgins & Means (1915) also compared morphine and heroin in normal subjects, using a similar dose ratio, 16 mg of morphine (4 experiments, 3 subjects) and 5 mg of heroin (2 subjects), subcutaneously. The respiratory effects were very similar throughout for both drugs at these doses—a slight increase in respiratory rate, diminished tidal and minute volume, increased alveolar CO_2, and decreased respiratory quotient. Respiratory minute volume, the factor most affected, was decreased slightly more with heroin, to 83% of normal, than with morphine, to 91% of normal. In both these experiments the dose of heroin was in the therapeutic range (according to Brouet, 1953, 5-10 mg) while the dose of morphine used was definitely above the optimum of 10 mg (Lasagna & Beecher, 1954). The latter dose of morphine in normal subjects depressed resting respiratory rate to 87.7% of normal, resting minute volume to 87.2% of normal and minute volume response to 5% CO_2 to 85.5% of normal (Keats & Beecher, 1951). The

depression of minute volume response to CO_2 was but slightly greater when the dose of morphine was 15 mg (Lasagna & Beecher, 1954).

Effect on labour

Lund & Harris (1943) investigated the effect of heroin in 454 deliveries. Adequate pain relief was obtained in 90% of the patients following a single dose, usually 5 mg subcutaneously, and the rapid and intense analgesia thus induced persisted for 3 or 4 hours. Relief from tension and fear produced tranquillity of mind and, as a rule, the patients dozed but did not sleep. Of 17 infant deaths 6 were wholly or partially attributable to heroin; 4 were in premature infants. The incidence of asphyxia was increased about 5% by heroin alone and, according to the authors, " represents the price the infant must pay for maternal comfort ". An additional 10% of the infants were asphyxiated by the combined effects of heroin and obstetric complications.

Ross (1944) reported on the use of heroin in over 200 cases. The dosage was 10 mg subcutaneously initially, with further doses of 5 mg as necessary according to the length of labour. Pain was adequately relieved and in the majority of cases no supplemental anaesthesia was required. He said that heroin produced a euphoria unrivalled by any other narcotic drug and concluded that it was the most generally useful drug in normal labour. Venters (1944) too said that he had never found heroin to have any ill effect on the infant even though delivery followed very shortly after an injection. He used a 5-mg dose subcutaneously.

Davis & Tupper (1949) in three groups of 100 cases each compared heroin 8 mg plus hyoscine with pethidine 100 mg plus hyoscine and with pethidine alone. In each group the dose was repeated at 2-hour or 3-hour intervals. Analgesia and amnesia were satisfactory in 81% of the heroin group, in 68% and 69%, respectively, of the two pethidine groups. Medication was judged to be a factor in the occurrence of asphyxia in the infant in 8 cases in the heroin group, and in 7 and 12 cases, respectively, in the pethidine groups. De Bellefeuille (1949) preferred heroin-hyoscine over pethidine as an obstetrical analgesic and did not believe that the depressive action of heroin was dangerous to the child.

The observations of Javert & Hardy (1951) on heroin in obstetrics have been referred to above. Douville (1950) reported on 200 cases in which heroin up to 8 mg per dose together with scopolamine was used and concluded that its effects were similar to those of morphine and scopolamine.

Addiction incidence and tests of addiction liability

Some indication of the earliest statements in the literature in this connexion has already been given. A few additional authors may be quoted to show the trend from optimism and contradiction to almost universal

recognition of heroin's high potential for addiction production. McIver & Price in 1916 said that heroin was not as deleterious as morphine and could be much more easily withdrawn. They may have been influenced by comparison of heroin addictions of short duration with morphine addictions of longer standing. Bloedorn (1919) just three years later said heroin was the ideal drug for the addict, and Dixon in 1921 maintained that heroin had no advantage over morphine and that its use might be forbidden without harming a single genuine patient. In 1926 the British Ministry of Health Departmental Committee on Morphine and Heroin Addiction (*Brit. med. J.*, 1926) concluded that, " Addiction is more readily produced by heroin than by morphine and addiction to heroin is more difficult to cure ".

The committee of experts appointed by the Council of the League of Nations in 1931 to answer certain questions concerning heroin replied in part that heroin was particularly likely to produce addiction because it was more powerful than morphine and its dose was smaller, because heroin euphoria was much more pronounced than that of morphine, and because troublesome constipation did not occur in the addict. The Committee said also that the addiction-producing properties of heroin, from the medical point of view, were much worse than those of other addiction-producing drugs, that addiction to heroin progressed more rapidly than with any other addiction-producing drug and that heroin addiction was most difficult to cure. The Committee believed that heroin could be entirely dispensed with.

In 1952, Dunlop, participating in a conference on the relief of pain, compared the clinical usefulness of a number of narcotic drugs. His recommendation for the use of heroin was " in the late stages of hopeless disease ". In reply to a question he said, " The dangers of its [heroin's] use outweigh its advantages."

Lambert (1936) judged the time required for morphine to produce addiction, under conditions of regular administration, as 23-25 days, for codeine as a month to 6 weeks, for heroin as a week or 10 days and for dilaudid as a little longer than for morphine. One unit of morphine was equivalent for the addict to 8 units of codeine, $^1/_3$ unit of heroin or $^1/_4$ unit of dilaudid.

Wolff in 1928 published a general summary on drug addiction and its treatment. Among 280 replies to questionnaires which he had sent out, there were 45 reporting positively on heroin addiction, 83 positive for eucodal addiction, 17 positive for dicodid addiction, and 8 and 1 positive for dilaudid and dihydromorphine addiction respectively. In 1931 Dansauer & Rieth reviewed the records of 918 war-wounded chronic users of narcotics; 238 were classified definitely as addicts, and of these only 5 used heroin.

Two types of experiment on the addiction liability of heroin have been performed at the US Public Health Service Hospital for addicts at Lexington, Ky. In the first experiment (Himmelsbach & Isbell, quoted by Eddy, 1953),

heroin was substituted for morphine in 9 morphine addicts. These men had been stabilized on 140-400 mg (average 200 mg) of morphine daily. Heroin substituted for morphine in doses ranging from 40-120 mg (average 71 mg) daily, or a substitution ratio of 1 mg of heroin hydrochloride for each 3 mg of the stabilization dose of morphine sulfate. The heroin was subsequently abruptly withdrawn and the intensity of the abstinence syndrome which followed was comparable to the average intensity of the abstinence syndrome in a large group of morphine withdrawals. The heroin abstinence syndrome appeared more rapidly, became significant in 5 hours as compared with 13 hours for morphine. Also at the 39th hour of withdrawal the heroin abstinence intensity was already beginning to decline, while that for morphine was still rising.

The second experiment at Lexington (Wikler, quoted by Eddy, 1953) consisted of a direct addiction study on two former addicts free of drugs and non-tolerant when the experiment was started. Both subjects received heroin subcutaneously 4 times a day, 15 mg per dose for 4 weeks; 30 mg per dose for 2 weeks, and 45 mg per dose for 10 days. Morning pre-injection abstinence phenomena were observed as early as the sixth day on the 15-mg dose, the seventh day on the 30-mg dose and the fourth day on the 45-mg dose. Once pre-injection abstinence phenomena began, they increased in intensity until the dose was raised and concomitantly the subjects demanded such dose increase. Each time the dose was raised the pre-injection phenomena disappeared temporarily and reappeared as indicated. Abrupt withdrawal of heroin was followed by very severe abstinence symptoms, reaching peak intensity from the 19th to the 28th hour and largely subsiding by the 48th hour. Both subjects were eager to start another heroin experiment.

From the above and previous experience Wikler drew the following conclusions: milligram for milligram heroin is more potent than morphine in the production of " satisfaction " for the addict; its action is more rapid, hence it produces a greater sense of well-being; the duration of action is less and pre-injection abstinence phenomena appear sooner, hence more frequent injections and more rapid increase in dose are inevitable; the intensity of the heroin abstinence syndrome is as great as or greater than that of morphine and the peak is reached sooner, hence the over-all " need " for it is greater; heroin is likely to be more addicting than morphine, conditions of a non-pharmacological nature being equal.

SUMMARY

The therapeutic dose of heroin most often stated is 5-10 mg, even though it has been shown that the pain-threshold-raising dose is only 1 mg or 2 mg. Establishment of equivalence to the optimum 10-mg dose of morphine by modern double-blind, placebo-included techniques has not been attempted.

Duration of effect is shorter for heroin than for morphine. Most reports agree that nausea and vomiting and the milder side-effects occur less frequently after heroin than after morphine. Its respiratory depressant effect, however, on the basis of quantitative data, is at least as great. Most reports agree also that heroin is more addicting than morphine. Addiction to it develops more rapidly and it is the drug of choice of a very great many addicts. Bearing in mind that the usual therapeutic dose of heroin is two or more times the experimentally established pain-threshold-raising dose, it is possible that the feeling of superiority for heroin and the admittedly rapid development of dependence (addiction) on it have come about through the use of these relatively higher doses. Brouet states the prime indication for heroin to be the partial or complete ineffectiveness of other agents. One cannot help but believe that greater familiarity with and application of the broad range of analgesic and antitussive agents now available would cause this indication to diminish or perhaps disappear.

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5. Hydrocodone[a] (dihydrocodeinone)

Hydrocodone (dicodid) was prepared in 1920 and its use as an antitussive and analgesic was reported upon in a preliminary note by Rickmann in 1923. He used doses of 10 mg and 15 mg and said that good results were obtained both as an antitussive and analgesic in about 75 cases. Hecht (1923), very shortly thereafter, said that dicodid was much more effective as an antitussive than codeine, but that it always caused a striking euphoria. Tolerance developed rapidly, abstinence symptoms were seen, and it was difficult to revert to the use of codeine. These statements are not surprising since his usual starting dose was 20 mg of dicodid subcutaneously. Other early literature on the use of hydrocodone for cough or pain is summarized in Table I.

Although the early reports indicated generally good analgesic effectiveness, hydrocodone has been used much more for cough relief, and its use for this purpose has been increasing in recent years, supplanting to a significant extent the use of codeine. Stein & Lowy reported in 1946 on the use of hydrocodone, in doses of 5 mg and 10 mg orally, in 26 patients with chronic cough.

[a] International non-proprietary name; for other designations, see *Estimated World Requirements of Narcotic Drugs in 1958* (United Nations document E/DSB/15).

TABLE I. SUMMARY OF EARLY EXPERIENCE WITH HYDROCODONE (DICODID)

Author (year)	Indication	Number of cases	Dose (mg)	Route	Effect	Remarks
Crohn (1923)	Cough	28	15 20	s.c. oral	Cough suppressed	No tolerance to antitussive effect; no constipation.
Kleinschmidt (1923)	Pre- and post-operative use	250	15	s.c.	Equivalent to 10 mg morphine	Practically no side-effects; less nausea than with morphine.
Schindler (1923)	Severe pain	21	10	s.c.	Equivalent to morphine; sometimes greater	Respiratory depression and nausea less than with morphine. Completely replaced morphine in one addict.
Bing (1924)	Cough	12	3×5 per day	oral	Equivalent to 30 mg codeine per day	Hypnotic; addiction occurred; would not replace morphine in addicts.
Castelhun & Langheinrich (1924)	Cough, pain	16	15 15	oral s.c.	Equal to 10 mg morphine	Side-effects not greater than with morphine; would not replace morphine in addicts.
Herz (1924)	Sedation, pain				At least equal to morphine	No euphoria; no tolerance. Only side-effect nausea with oral administration.
Roller (1924)	Cough		2×10 per day	oral	Always effective	Slight euphoria; no other side-effects; patients requested continuation.
Schwab & Krebs (1924)	Cough, pain	40	2×10 per day	oral	Equal or superior to morphine in most cases	Euphoria and some sedation.
Rosenberg (1925)	Pain		15	s.c.	Very effective	Sedative; no tolerance; substituted for pantopon in an addict.
Schammer (1925)	Cough	Many	10 7.5	oral s.c.	Effect satisfactory with 2 or 3 doses per day	No addiction seen in one year's experience.
Schelenz (1927)	Cough					No tolerance to antitussive effect in 3 months; no difficulty in withdrawal.
Kenner (1930)	Cough	240	5–10	oral	5 mg equivalent to 30 mg codeine	Increasing dose above 10 mg or giving s.c. did not increase effect; tolerance but no dependence seen; sedative; urticaria in 2 patients.

The effect of the drug was completely satisfactory in 27%, markedly better than previous medication (codeine or dionin) in 58%, and only fair but still better than previous medication in 15% of the cases. Its effect was never less than previous medication. Hydrocodone was more effective than 30-60 mg of codeine or than 15-22.5 mg of dionin. It should be mentioned here that Davenport (1938) deplored the use of such large doses of codeine for cough, finding them rarely necessary or significantly more effective than the optimum dose of 10 mg. Stein & Lowy said that hydrocodone produced no euphoria, that it was less constipating than codeine, and that it produced no other side-effects. These authors followed closely nine additional patients through successive periods of no medication, of codeine medication, of hydrocodone medication, and again of codeine medication. It is not clear whether or not the patients knew the nature of the medication; the observers certainly did. The dose of hydrocodone was always one-third that of codeine; both drugs were always given orally. In this series hydrocodone gave at least as good cough relief as codeine; as to dose, then, it was at least three times more effective.

Curtis & Browning (1946) also used doses of 5 mg and 10 mg of hydrocodone orally in 42 cases of tubercular cough. Relief was better than with codeine. There were no side-effects and no sign of tolerance or dependence was seen.

Rudner (1947) reported adequate control of cough throughout the 24 hours in 50 cases of tuberculosis, when hydrocodone was given in doses of 5 mg or 10 mg orally 4 times a day. Again there were no side-effects and no indication of tolerance or dependence. Hydrocodone was less constipating than codeine in these patients.

Reese (1948) found that hydrocodone would control the cough in many cases which did not respond well to codeine. Hydrocodone, he said, was not constipating, and, although it might cause nausea and vertigo, these symptoms were avoided if the drug was taken after food. He recommended a 5-mg dose orally.

Hyman & Rosenblum (1953) gave hydrocodone in syrup in a dose of 10 mg 3 times a day to 44 tubercular patients. Thirty, or 68%, were relieved of their cough, 11, or 25% were partially relieved, and 3, or 7%, got no relief. The cough reflex was not completely suppressed as accumulated secretion could be eliminated without difficulty. There was no constipation or other side-effect.

The Council on Pharmacy and Chemistry of the American Medical Association (1948) judged the action and use of hydrocodone to be essentially similar to that of codeine. They found hydrocodone to be more active than codeine but also more addicting. They indicated a dose range of 5-15 mg (the top dose rarely necessary) orally 3 or 4 times in 24 hours. Seevers (1949) said that hydrocodone was incapable of replacing morphine, and it retained some of the principal disadvantages of the latter—the production

of mental sluggishness, irregularity of action after oral administration, considerable incidence of unpleasant side-effects, and capability of developing tolerance and addiction. According to Seevers addiction to hydrocodone probably would rarely be seen with the small doses used for cough relief, but the drug's addiction potentiality was somewhat greater than that of codeine. Bonyai (1952) recommended hydrocodone for the treatment of cough at a dosage of 5-10 mg orally 3 times in 24 hours.

Analgesic mixtures, containing hydrocodone as a principal component, are currently being recommended for the milder grades of pain. One such mixture also contains homatropine terephthalate, whose presence should produce unpleasant side-effects if the dose is increased unduly, and might be expected to prevent abuse of the mixture. No case of addiction to this mixture has been reported. It cannot be admitted, however, that the mixture of a potentially addicting substance with another agent which should produce unpleasant symptoms under conditions of abuse, affords complete protection. (See, for instance, the experience with Ticarda, under normethadone, page 652.)

Subjective and psychomotor responses

Heinroth (1926) stimulated the tooth pulp and repeated control observations until similar responses were obtained with two teeth. Only two experiments were done with dicodid, using doses of 5 mg and 10 mg orally. Sensitivity was decreased slightly. In experiments with codeine, 50 mg orally, a slight but not noteworthy decrease in sensitivity was observed. Römmelt (1927) used himself as experimental subject on 30 test days during a five-month period. There were 10 days of control observations and other days, on which 3 mg of dilaudid or 15 mg of dicodid were administered subcutaneously, were interspersed in irregular order. There was no constipation and no euphoria was experienced; rather nausea and vomiting sometimes occurred and a distaste for the injections developed. Attention (determined by immediate recall of letters) was decreased during the first and second hours after drugging, more with dilaudid than with dicodid, and typing speed was reduced, also more with dilaudid. Discrimination time for auditory stimuli was lengthened and errors in discrimination were increased. On the other hand, the work done, calculated from ergographic records, was increased with both drugs in comparison with control days, probably because of suppression of sensations of pain and fatigue.

According to Meyer & Pfaffenholz (1932) patients treated with dicodid for cough complained of disinclination to work and an inability to concentrate so disagreeable that they were willing to forgo the cough relief. These authors, therefore, experimented on themselves using two tests, one for co-ordination and another for mental activity. 10 mg of hydrocodone orally produced a pleasant feeling of sleepiness; one forgot to do the things

required in the experiment. With 20 mg orally the feeling of sleepiness was more marked; the subjects were unable to concentrate and disinclined to all work; any effort was unpleasant. With the 20-mg dose errors increased significantly in the co-ordination test; the speed of the arithmetic test decreased markedly, and errors in it also increased.

Addiction incidence and tests of addiction liability

As early as 1927 Müller de la Fuenta said that cases of addiction to dicodid were known; 17 of the 280 questionnaires analysed by Wolff in 1928 reported dicodid addiction; and in 1930 Richtzenhain warned that " dicodidismus " was then so often observed that one should be as cautious with dicodid injection as one would be with morphine. Dansauer & Rieth (1931) found among 238 war-wounded addicts 8 who took dicodid only, 7 of them taking the drug orally, and another who took dicodid with morphine. Sametinger (1935) reviewed 30 cases of " dicodidismus " and believed that they showed a greater susceptibility of females than of males.

Fraser and his associates (1950) carried out three types of experiment with hydrocodone: (1) 30 mg of hydrocodone subcutaneously produced the same morphine-like effects in post-addicts as 30 mg of morphine in the same individuals; (2) 45 mg of hydrocodone subcutaneously, at the 30th hour of abstinence in individuals abruptly withdrawn from stabilization doses of 480 mg of morphine per day, produced almost complete suppression of the morphine abstinence phenomena, the relief lasting 6-8 hours; and (3) hydrocodone produced direct addiction in former opiate addicts, free of drugs and non-tolerant at the time the hydrocodone was started. There were five subjects in the direct addiction experiment and the dose of hydrocodone was built up to 240 mg per individual per day. For each subject the course and symptoms during this addiction were like those of a morphine addiction. Abrupt withdrawal of hydrocodone was carried out on the 38th day and the abstinence syndrome was milder than would be expected after similar administration of morphine. The conclusion was that hydrocodone had an addiction liability greater than that of codeine, approaching that of morphine.

SUMMARY

Hydrocodone is an effective antitussive, dose for dose about twice as effective as codeine; reported side-effects, with the dose of 5 mg usually recommended, are minimal. Hydrocodone is definitely more addicting than codeine, and reports of addiction to it have been much more frequent than of addiction to the latter drug. However, restriction to the small oral dose recommended for cough relief may reduce the risk of addiction.

As an analgesic hydrocodone is less potent than morphine, and this is further offset by an addiction liability almost as great as for morphine, when the dosage required for an analgesic effect is used. The duration of its effect is not materially different from that of morphine.

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6. Hydromorphone [a] (dihydromorphinone)

Hydromorphone was introduced (under the designation dilaudid) clinically by Krehl (1926) after a relatively short pharmacological study by

[a] International non-proprietary name; for other designation, see *Estimated World Requirements of Narcotic Drugs in 1958* (United Nations document E/DSB/15).

Gottlieb (1926). Of about 70 publications evaluated for the present study, those published before 1933 have already been reviewed by Eddy (1933). These early papers still represent the majority of published investigations into the therapeutic uses of hydromorphone including its side-effects and addiction liability.

Analgesic effectiveness

In order to facilitate the review, the results of the relevant clinical descriptions and evaluations are summarized in Table II. The indications for hydromorphone were in general the same as for morphine. It was rarely given orally or rectally but mostly by subcutaneous injection, except in emergency cases where intravenous application was preferred, for example, by Rödel (1930).

Whereas the range of the effective dosage of hydromorphone was reported to be between 1 mg and 5 mg, the large majority of authors found that satisfactory pain relief was obtained with 2-2.5 mg subcutaneously. Twenty-two authors compared the analgesic effectiveness of hydromorphone with that of morphine and estimated the dose of hydromorphone equivalent to 10 mg morphine to be from 1 mg to 5 mg. Taking into account the distribution of these data, it can be stated that 2-4 mg hydromorphone have the same analgesic effect as 10 mg morphine.

Seevers & Pfeiffer (1936) using the von Frey hair method, determined in eight normal subjects with the double-blind technique the analgesic dose equivalent to 10 mg morphine to be 1 mg of hydromorphone subcutaneously. Pfeiffer et al. (1948) studied in men the influence of morphine-like analgesics on three types of artificial pain—superficial pain produced in the finger pad by a needle, deep pain by electrical stimulation of the tooth pulp, and so-called sympain by thermal stimulation of the nail bed. 2 mg hydromorphone subcutaneously raised the threshold of superficial pain by 15%—as compared to 1% by the same dose of heroin—and the threshold of deep pain and sympain to the same degree as heroin. Using the Wolff-Hardy-Goodell (1940) method in double-blind, cross-over experiments, Slaughter (1950) found 3 mg hydromorphone as effective as 16 mg morphine. In patients with a T-tube in the common bile duct, Gaensler (1951) determined quantitatively the threshold for visceral pain by increasing the hydrostatic pressure in the biliary system. 3 mg hydromorphone were somewhat less effective in raising the pain threshold than 10 mg morphine.

The results of the aforementioned experiments agree fairly well, particularly in view of the very different methods; they confirm the clinical experience that 2-4 mg hydromorphone are comparable to 10 mg morphine in their analgesic potency.

TABLE II. CLINICAL ANALGESIC DOSAGE OF HYDROMORPHONE AND ITS SIDE-EFFECTS

Author	Indication	Number of cases	Dose (mg)		Side-effects	
			effective	equivalent to 10 mg morphine	nature (degree)	number of cases
Basch (1926)	Pain of various origins		2 s.c.	2	Nausea (<morphine)	
Dittrich (1926)	Pre-anaesthetic use	42	2.5 s.c.		Intestinal paralysis (<morphine)	
Ellerau (1926)	Pre- and post-operative	300	2 s.c.		Vomiting, intestinal paralysis (<morphine)	
Fürst (1926)	Pain of various origins	50	2.5 s.c.		Vomiting, Headache, dizziness Excitation	3 4 2
Hemmerling (1926)	Pain of various origins, stenocardia	"Many"	5 s.c.	2.5–5	Same as by morphine, but less. Respiratory depression	 2
Krehl (1926)	Pain of various origins	"Numerous"	2.5 oral		Vomiting, Respiratory depression	1 2
Krüskemper (1926)	Pain of various origins			2.5–5	Slight dizziness and nausea	Occasional
Rady (1926)	Pain in tuberculosis	80	2 s.c.		Respiratory depression	
Taschenberg (1926)	Pain of various origins, heart diseases		2 s.c.		None	
Trautmann (1926)	Neurological diseases	20	5 s.c.	2	Respiratory depression Deep sleep	1 1
von Wertheim (1926)	Same as for morphine		2 (–5)	2.5–5	Nausea, headache	
Behlau (1927)	Tonsillectomy	>50		<2.5	Excitation	1
Bescht (1927)	Same as for morphine		2 s.c. 2.5 oral	2.5–3.3	Sleep, constipation (<morphine)	
Birkholz (1927)	Pre- and post-operative		2 s.c.	2	Sleep (usually)	
Burckhard (1927)	Obstetrical and gynaecological			2.5–5		
Grage (1927)	Tabes dorsalis and other nervous diseases	"Great"	2 s.c. 2.5 oral		Circulatory depression, no constipation	Many
Hartung (1927)	Pre-operative	40	2 s.c.		None, except sleep	
von Hilger (1927)	Same as for morphine		2.5 s.c.		None	

TABLE II. CLINICAL ANALGESIC DOSAGE OF HYDROMORPHONE AND ITS SIDE-EFFECTS (continued)

Author	Indication	Number of cases	Dose (mg)		Side-effects	
			effective	equivalent to 10 mg morphine	nature (degree)	number of cases
von Oettingen (1927)	Pre-operative	473	2 s.c.	2	Deep sleep; intestinal paralysis (<morphine)	57
Sachs (1927)	Obstetrical		1–2 s.c.		None	
Senderowitsch (1927)	Surgical			3.3–5	Not harmful	
Bender (1929)	Tabes dorsalis and other nervous diseases		2–2.5 s.c.		Vomiting	3
Crohn (1929)	Same as for morphine		2–4 s. c. 2.5–5 supplementary		None	
Klemperer (1929)	Same as for morphine		2.5 oral		Dizziness, nausea	
Lullies (1929)	Surgical	>1000	3–4 s.c.		Nausea Vomiting	Some 5
Paeprer (1929)	Same as for morphine		2 s.c.		None	
Simenauer & Pulfer (1929)	Surgical, pre-operative	100	4 s.c.	4	Dullness, dizziness	Some
von Hoesslin (1930)	Same as for morphine			1	Respiratory depression, circulatory depression	
Rödel (1930)	Cholelithiasis, nephrolithiasis		2 i.v.	2	Sedation	
Schäfer (1930)	Obstetrical	100	5 supplementary 3 i.m.		Prolonged labours Asphyxia of infant	22 17
Altner (1931)	Obstetrical	150	2.5 supplementary			
Wachtel (1931)	Obstetrical		2.5 oral			
Alvarez (1932)	Same as for morphine			2	Nausea (>morphine) Constipation (<morphine)	
Leyton (1932)	Same as for morphine	Several dozen	2 (–4) s.c.		Slight nausea, giddiness, no constipation	
Tollas (1932)	Obstetrical, minor surgery		2–5 s.c.		None	

TABLE II. CLINICAL ANALGESIC DOSAGE OF HYDROMORPHONE AND ITS SIDE-EFFECTS (concluded)

Author	Indication	Number of cases	Dose (mg)		Side-effects	
			effective	equivalent to 10 mg morphine	nature (degree)	number of cases
Paine et al. (1933)	Surgical, post-operative	15	2 s.c.		Respiratory depression, nausea, vomiting, intestinal paralysis	
David (1934)	Same as for morphine	74	0.6–2.5 s.c.		Itching Nausea Vomiting Constipation (Incidence of these less than after 8-15 mg morphine)	53 % 58 % 20 % 30 %
Jacobs (1934)	Obstetrical		2		None	
Ruch (1934)	Obstetrical	100	2 s.c.		Nausea (3 times more often than after morphine)	
Moench (1935)	Obstetrical	25	3 s.c.	2	Vomiting, vesical spasm, intestinal paralysis (<morphine)	
Baranger & Bodet (1938)	Pre-anaesthetic use	250	2 s.c.		Slight vomiting in 80 % of cases	
Hogan (1938)	Pre-anaesthetic use	200	1.3 s.c. ½-hourly		Vomiting, vesical spasm, intestinal paralysis (<morphine)	
Jones (1938)	Pre-operative	Several hundred		<10	None, except sleep	
Redenz (1938)	Pre-anaesthetic use	600		2.7	Intestinal paralysis (<morphine)	
Ruch (1938)	Obstetrical	755	2 s.c.		Apnoeic baby when C_2H_4 or N_2O narcosis	4 %
Saltzstein et al. (1940)	Advanced cancer	700		<10	Sleep, constipation (<morphine)	
Lee (1941)	Terminal cancer			2		
Seevers (1942)	Intractable pain			0.8–1	<Morphine	
Wayne (1948)	Same as for morphine		2–4 s.c.		Sleep; vomiting, constipation (<morphine)	
Curreri et al. (1950)	Post-operative	12	2 s.c.		Sedation	
Hammes (1952)	Post-operative			2		

Onset and duration of analgesia

Ruch (1934) compared 100 obstetrical cases receiving hydromorphone subcutaneously with 160 receiving morphine, both combined with scopolamine; with hydromorphone the onset of effect occurred within 10 minutes, with morphine after 20 minutes. Jones (1938) concluded from several hundred cases of pre-anaesthetic use that after subcutaneous administration hydromorphone had a quicker onset than morphine.

Only relatively few of the numerous clinical papers dealing with the analgesic effectiveness of hydromorphone give precise data as to the duration of this effect. From the reports of those authors (von Oettingen, 1927; Hogan, 1938; Redenz, 1938) who used hydromorphone for pre-anaesthetic purposes, its analgesic and sedative effect would seem to last at least one hour; it lasted longer when administered together with scopolamine (Baranger & Bodet, 1938). When used with the same indication as morphine (Leyton, 1932), post-operatively (Curreri et al., 1950; Paine and co-authors, 1933) or in obstetrics (Sachs, 1927), the resulting analgesia was reported to last 4-6 hours after subcutaneous administration of 2 mg and 11 hours after 5 mg subcutaneously (Hemmerling, 1926.)

Using the von Frey hair method in eight normal men, Seevers & Pfeiffer (1936) found that the analgesic effect of 1 mg hydromorphone subcutaneously lasted for a shorter time than that of the equivalent dose (10 mg) of morphine and for a longer time than that of the equivalent dose of heroin (2 mg). Similar results were obtained by the Wolff-Hardy-Goodell method (Seevers, 1942). Pfeiffer et al. (1948), when studying the analgesic effect of hydromorphone on three types of pain (superficial, deep and sympain; for details, see page 601), stated that the peak effects occurred 160 minutes after subcutaneous administration of the drug. By determining the visceral pain threshold in 11 patients by increasing hydromechanically the pressure in the common bile duct, Gaensler (1951) found 3 mg hydromorphone subcutaneously to be effective for 4 hours (as compared to 5 hours after 10 mg morphine subcutaneously) with an onset which was definitely quicker than that after 10 mg morphine under the same conditions.

The clinical and experimental data, although rather scattered, allow the conclusion that the analgesic effect of hydromorphone in doses equivalent to morphine has a quicker onset of effect and lasts a somewhat shorter time than morphine, i.e., on an average about 3-4 hours. In the same range is the duration of the antitussive effect of 2.5 mg hydromorphone (Krehl, 1926; Taschenberg, 1926).

Antitussive action

The antitussive action of hydromorphone was evaluated mostly in tuberculosis and in many cases together with its analgesic action. As Table III shows, the dosage for cough relief appears to be much more uniform than the analgesic dosage—namely, 2.5 mg orally several times a

TABLE III. ANTITUSSIVE DOSAGE OF HYDROMORPHONE

Author	Number of cases	Dose (mg)		Side-effects
		effective	equivalent to	
Basch (1926)		2.5 oral		Nausea (< morphine)
Krehl (1926)		2.5 oral 4 times a day	> 30 mg codeine	Vomiting, respiratory depression
Krüskemper (1926)		1.25-2.5 oral 3 times a day		Slight dizziness, nausea
Rady (1926)	100	2.5 oral		Respiratory depression
Taschenberg (1926)		2.5 oral 3-4 times a day		None
von Werthern (1926)		2.5 oral		Nausea, headache
Loewenthal (1927)	41	2.5 oral	10 mg morphine	None
Paulsen (1927)		2 s.c.		Respiratory depression after 4 mg s.c.
Senderowitsch (1927)		3-5	10 mg morphine	Not harmful
Schwarz (1928)		2.5 oral 1-2 times a day		Dizziness
Crohn (1929)		2-4 s.c. 2.5-5 supplementary		None
Klemperer (1929)		1.25-2.5 oral		Dizziness, nausea
Markowicz (1929)		2.5 oral	> 30 mg codeine	Dizziness, nausea, respiratory depression
Paeprer (1929)		2.5 oral		None
Bassett (1935)		1.5-3 oral		None

day—possibly indicating that the antitussive effect lasts about 3-4 hours. This dose proved itself to be comparable to 30 mg of codeine and more (Markowicz, 1929; Krehl, 1926), on the one hand, and to 10 mg of morphine (Loewenthal, 1927) and less (Senderowitsch, 1927), on the other.

The clinical investigation of the antitussive action of hydromorphone was stimulated by the experiments of Gottlieb (1926), demonstrating in rabbits the absence of tolerance to its depressing action on the respiration. How far these observations could be confirmed by clinical experience will be discussed below.

Special therapeutic uses

Special therapeutic uses different from those of morphine were not developed for hydromorphone, although the lower incidence and degree of

its side-effects as compared to morphine (see below) attracted several authors to use it instead of morphine. Thus, it was introduced into obstetrical practice by Burckhard (1927), Sachs (1927), Schäfer (1930), Altner (1931), Tollas (1932), Jacobs (1934), Ruch (1934, 1938), and Moench (1935). Tollas reported that, compared to morphine, hydromorphone had nearly no paralysing effect on the uterus. Jacobs noted no prolongation of labour after hydromorphone and apparently less narcosis in the baby. Generally, however, hydromorphone was not considered superior to morphine in obstetrical practice. Schäfer and Ruch reported on respiratory deficiencies in the newborn, which, however, might have been due to the relatively high dose as such (Schäfer) and/or to prolonged labour induced by the high dosage of hydromorphone. Finally, the latter was, like morphine, superseded in this field by pethidine.

For pre-anaesthetic and post-operative medication, hydromorphone was used by Dittrich (1926), Ellerau (1926), Birkholz (1927), Hartung (1927), von Oettingen (1927), Simenauer & Pulfer (1929), Baranger & Bodet (1938), Hogan (1938), Jones (1938), Redenz (1938), Curreri et al. (1950) and Hammes (1952). Here, too, hydromorphone was expected to be better than morphine because of its quicker onset, stronger tendency to induce sleep, and less pronounced side-effects, especially as to vomiting and intestinal paralysis. Hogan stated clearly that he preferred hydromorphone to morphine. However, in general practice, these differences were apparently not so definite as to give hydromorphone priority over other morphine-like analgesics for pre- and post-operative medication.

Side-effects

In order to facilitate the review, the observations on side-effects connected with the use of hydromorphone for analgesic and antitussive purposes are included in Tables II and III. Of 56 authors mentioned in these tables, 51 reported on the presence or absence of side-effects. Nine of these 51 authors had not seen any side-effects when using doses of between 2 mg and 5 mg subcutaneously or 1.5 mg and 3 mg orally. Nine authors reported on sedative and hypnotic effects of doses of 2 mg subcutaneously. On the other hand, excitation occurred with similar doses (Behlau, 1927; Fürst, 1926). Dizziness and/or nausea following subcutaneous administration of 2-4 mg or oral administration of 2.5 mg were seen by 14 authors, five of whom designated these side-reactions as slight and less pronounced or less frequent than after the equivalent doses of morphine. Only Ruch (1934) reported a threefold greater incidence of nausea in 100 obstetrical cases receiving hydromorphone compared to 100 cases receiving morphine, both together with scopolamine. Of the 56 authors listed in Tables II and III, 11 mentioned the occurrence of vomiting, which was often less severe than after morphine. Wayne stated in a review of the newer analgesics that hydromorphone might be used in short-term treatment of painful conditions

such as myocardial infarction and abdominal emergencies when emetic action was especially undesirable.

Constipation, abdominal distension, and gas pain were produced less (if at all) by hydromorphone than by morphine. This was the unanimous opinion of the authors who reported on these undesired side-effects. In this context, the expert report of the Technical Committee on Heroin of the League of Nations stated in 1931:

" For the relief of pain in patients in whom it is undesirable to act on the bowels, heroin is better than morphine but dilaudide offers the same advantages ... It has about the same influence as heroin in its pain-relieving properties, and, like heroin, has little effect on the alimentary canal."

Clinical experience was confirmed in normal subjects (Seevers & Pfeiffer, 1936) in whom morphine produced nausea in 57% and hydromorphone in 37% of trials; constipation occurred most often with morphine, but only occasionally with hydromorphone.

Like most of the opiates hydromorphone has the tendency to produce spasm of sphincters. Vesical spasms due to hydromorphone were reported by Hogan (1938), Maloney (1937) and Moench (1935). By means of a T-tube inserted in the common duct for biliary drainage, Butsch et al. (1936) recorded in patients the intrabiliary pressure and the pressure required to force fluid through the sphincter into the duodenum; they found that 2 mg hydromorphone subcutaneously raised both pressures as did 10 mg morphine, but the elevation by hydromorphone was less and was less swiftly produced than that produced by morphine. In 21 patients with biliary drainage Gaensler & McGowan (1950) recorded an average increase of intrabiliary pressure of 90 mm H_2O by 3 mg hydromorphone subcutaneously as compared to 115 mm H_2O by 10 mg morphine and 55 mm H_2O by 60 mg codeine. The passage of a barium meal checked by X-rays was retarded by 1.5 mg hydromorphone subcutaneously, as seen in two normal men by Myers & Davidson (1938). As with morphine this was due to an increased tonus in the pyloric and ileocolic sphincters.

The incidence of itching and pruritus was rarely reported with respect to hydromorphone (David, 1934; Maloney, 1937). The former, however, saw it in about half of 74 patients.

Gottlieb (1926) had found 1 mg morphine per kg and 0.3 mg hydromorphone per kg to be comparable doses for the production of a slight respiratory depression in the rabbit. This proportion is of the same order as that reported for the analgesic and antitussive effects of both substances in man and seems to be valid also for the situation in man regarding respiratory depression, although the latter was relatively less often reported as a side-effect than nausea, vomiting, etc. Hemmerling (1926), Paulsen (1927) and Trautmann (1926) saw respiratory depression after doses of 4-5 mg hydromorphone subcutaneously; but 2-2.5 mg orally also decreased the respiration (Krehl, 1926 ; Markowicz, 1929; Rady, 1926). In a normal volunteer,

12 mg hydromorphone intravenously diminished the respiratory volume from 5.8 litres per minute to 3.5 per minute (Zindler & Ganz, 1955). Markowicz (1929) stated that a fall in frequency of respiration from 14-17 per minute to 8-9 per minute occurred after subcutaneous administration of 2 mg hydromorphone. As with morphine, a fall in blood pressure occurred with therapeutic doses of hydromorphone (Grage, 1927; von Hoesslin, 1930).

Tolerance

From the beginning of the therapeutic use of hydromorphone clinicians have paid some attention to the development of tolerance to its therapeutic effects. However, of 11 papers published between 1926 and 1932 and stating the absence of tolerance to the pain-relieving effect of hydromorphone, eight contain no indication of the duration of administration or the admission that the time of observation was not long enough. Fürst (1926) saw no tolerance in one patient who received 5-10 mg hydromorphone *pro dosi* for four months after 10-20 mg morphine were no longer effective. Von Hilger (1927) reported on one carcinoma patient in whom hydromorphone remained effective when 18 oral doses of 2.5 mg were given per week for a year.

On the other hand, Grage (1927) said that tolerance with the usual analgesic dose (2 mg subcutaneously; 2.5 mg orally) could occur. Bescht (1927) denied the occurrence of tolerance with the above doses, but saw it after 10-12 doses of 4 mg. In cases of severe persistent pain, Crohn (1929) reported tolerance to the higher dosage of 4 mg subcutaneously. Hemmerling (1926) considered the possibility of tolerance to the analgesic action of hydromorphone to be less than with morphine. Hartung's experience (1927) that the usual dose of 2 mg, which produced no tolerance, had to be doubled if other narcotics had been used before and von Hoesslin's report (1930) that, in patients with increasing tolerance to morphine, replacing doses of hydromorphone had also to be increased are examples of cross-tolerance.

From experiments by Gottlieb (1926), demonstrating in rabbits the absence of tolerance to the respiratory depressing action of daily doses of 0.3 mg hydromorphone per kg for seven weeks, it was concluded that its chronic administration for the relief of cough would not lead to tolerance, or at least not as easily as with morphine. Yet tolerance was observed, although rarely, by Markowicz (1929). Paulsen (1927) reported on cross-tolerance in a patient who, instead of a normal daily dose of 2 mg, needed 7 mg hydromorphone after his cough had become resistant to 90 mg morphine a day.

Subjective and psychomotor responses

Such responses to hydromorphone were studied by Macht & Macht (1939) and Römmelt (1927). Since these experiments were partly interlocked

with those on hydrocodone, the results pertaining to hydromorphone are summarized in the monograph on hydrocodone (see page 598).

Addiction incidence and tests of addiction liability

Of 27 authors who between 1926 and 1942 published their practical experience regarding the addiction liability of hydromorphone, six had not seen euphoria with doses up to 4 mg subcutaneously, partly after prolonged administration (Lullies, 1929, in 1000, Simenauer & Pulfer, 1929, in 100 surgical cases; Bender, 1929; Moench, 1935; Taschenberg, 1926). On the other hand, euphoria was reported early, for example, by von Werthern (1926) (after 2.5 mg orally); Rödel (1930) (2 mg intravenously); Leyton (1932) (4 mg for several weeks); Bescht (1927) (4 mg subcutaneously, but not with lower doses). The euphorigenic potency of hydromorphone was thought to be less than that of morphine (Alvarez, 1932). Thus, Loewenthal (1927) observed some euphoric effect from 6-9 mg in a case who had taken 80 mg morphine a day. David (1934) reported a lower incidence of euphoria as compared to morphine (in 17 of 75 patients receiving 0.6-2.5 mg hydromorphone as opposed to 32 cases of euphoria in 41 patients receiving 8-15 mg morphine). This was confirmed by Seevers & Pfeiffer (1936) in normal subjects who designated heroin as " producing the most pleasurable sensation, next morphine, and then dilaudid ".

Symptoms of withdrawal after prolonged medication with hydromorphone were not observed by Paeprer (1929), Senderowitsch (1927), Taschenberg (1926), Vidoni (1927), or Klemperer (1929). The latter had administered a total of 10 000 tablets (2.5 mg), 2000 suppositories (5 mg), and 300 injections (2, 4, and 6 mg). But there are also early reports on true addiction to hydromorphone, for example, by Grage (1927) (2 cases); Müller de la Fuenta (1927) (15-18 ampoules of 2 mg a day); Richtzenhain (1930); von Hoesslin (1930). In 1928 Wolff discovered, by means of a questionnaire to medical institutions in Germany, Austria, and Switzerland, eight positive reports of addiction to hydromorphone. Of 238 war-wounded German addicts in 1931, three were using hydromorphone (Dansauer & Rieth, 1931).

In 1931 the expert report of the Technical Committee on Heroin of the League of Nations concluded that " the euphoric effects of dilaudide are weaker than those both of morphine and heroin as gauged by withdrawal symptoms ". Lambert (1936) estimated that the time required to become addicted by regular intake was a little longer for hydromorphone than for morphine. Seevers (1942) placed the euphorigenic potency of hydromorphone between those of morphine and codeine.

In their studies on seven morphine addicts, involving the substitution of hydromorphone for morphine, King, Himmelsbach & Sanders (1935) found that an average daily dose of 340 mg morphine could be replaced by 90 mg hydromorphone, both divided into 4 injections, without the subjects

becoming aware of the substitution. However, all noticed that hydromorphone was more potent and that, after a single dose, anxiety and restlessness reappeared earlier (3-3½ hours) than with morphine (5-5½ hours). When, after 12-17 days' substitution, hydromorphone was abruptly withdrawn, the abstinence syndrome developed more sharply and was more intense but less prolonged than after withdrawal of morphine. In further experiments on five morphine addicts (Himmelsbach, 1941), physical dependence was satisfied by hydromorphone when substituted for morphine in 6 daily doses of one-seventh the dose of morphine. The addiction-sustaining action of hydromorphone could therefore be considered to be seven times greater than that of morphine and to last 7 hours, i.e., half as long as that of morphine.

SUMMARY

Hydromorphone is a powerful analgesic, two to four times as strong as morphine, having the same therapeutic indications as the latter. Its antitussive potency is about four times greater than that of morphine. The duration of these therapeutic effects is 3-4 hours, a little shorter than for morphine. It has a pronounced sedative action.

The side-effects produced by hydromorphone are of the same character as those produced by morphine, but generally less severe, especially so with regard to vomiting, constipation, and paralysis of the intestine.

Tolerance to the therapeutic effects of hydromorphone may develop more slowly than with morphine.

Hydromorphone has euphoric action, although somewhat less than morphine when equi-effective therapeutic doses are compared. It produces true addiction. Hydromorphone can effectively sustain morphine addiction in a dose of one-seventh that of morphine.

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7. *l*-Isomethadone (*l*-4,4-diphenyl-5-methyl-6-dimethylamino-3-hexanone)

Isomethadone is a structural isomer of methadone; it is a hexanone, with a methyl group attached to carbon-5, instead of a heptanone; otherwise the structure of the two compounds is the same. Like methadone, isomethadone is synthesized as a racemate, and pharmacological examination has shown that practically all of the analgesic action and most other effects are produced by the levo-isomer. Hence clinical trials have been carried out mainly with the *l*-isomer.

Denton & Beecher (1949a) compared *l*-isomethadone and *dl*-isomethadone with *l*- and *dl*-methadone and with morphine, subcutaneously administered, for the relief of post-operative pain. They used a double-blind technique with an impartial observer querying the patient as to the degree of pain relief at 45 and 90 minutes after drug administration. The standard (morphine), a placebo and a dose of one of the new substances were administered in random order to the same patient, and comparison was made of the percentage of doses which gave relief—at least 50% reduction in pain at both the 45- and 90-minute checks. Doses were calculated per 150 pounds of body-weight. The results obtained are shown in Table IV.

l-Methadone produced 89.1% relief at a dose of 4-6 mg in 25 patients. *dl*-Methadone and *l*-isomethadone were milligram for milligram equivalent to morphine in analgesic power. *l*-Methadone had twice and *dl*-isomethadone only one-third the analgesic power of morphine or *dl*-methadone. There was no material difference in the duration of effect of these analgesics.

Later, Beecher et al. (1951) conducted a field trial with *dl*-methadone and *l*-isomethadone at an army evacuation hospital at Hamhung in North Korea and at an army base hospital in Tokyo. The dosage in the Hamhung trial was 15mg of *dl*-methadone, 15 mg of *l*-isomethadone and 15 mg of

TABLE IV. RELIEF OBTAINED WITH DIFFERENT DOSES OF MORPHINE, *dl*-METHADONE, *dl*-ISOMETHADONE AND *l*-ISOMETHADONE

Doses (mg)	Morphine			*dl*-Methadone			*dl*-Isomethadone			*l*-Isomethadone		
	number of patients	number of doses	percentage relief	number of patients	number of doses	percentage relief	number of patients	number of doses	percentage relief	number of patients	number of doses	percentage relief
4–6	32	85	82.4	33	90	83.3	—			40	103	78.6
7–9	42	120	93.3	40	130	89.9	—			37	159	89.9
10–12	45	144	93.7	24	71	91.5	22	49	73.5	36	143	95.1
13–15	17	69	90.5	15	55	98.2	14	50	74.0	18	71	94.4
16–20							11	27	71.4	12	62	91.9
21–25							27	64	87.5			
26–30							24	85	92.9			
31–35							15	81	92.6			
36–40							15	63	86.9			

morphine; in the Tokyo trial 10 mg of each of the drugs were used. The criterion of effectiveness, that is, the percentage of doses giving satisfactory relief as determined by 50% or more reduction in pain 45 and 90 minutes after medication, was the same as in the earlier study. The results in number of doses rated as satisfactory or unsatisfactory and percentage of relief were as follows:

Hamhung trial

	dl-Methadone 15 mg	*l-Isomethadone 15 mg*	*Morphine 15 mg*	*Placebo*
Satisfactory	9	9	7	2
Unsatisfactory . . .	0	1	2	7
Percentage relief . .	100	90	78	22

Tokyo trial

	dl-Methadone 10 mg	*l-Isomethadone 10 mg*	*Morphine 10 mg*	*Placebo*
Satisfactory	17	14	15	7
Unsatisfactory . . .	3	5	4	13
Percentage relief . .	85	74	79	35

Again methadone, *l*-isomethadone and morphine were equally potent as analgesics, even under the rugged conditions of a combat zone.

Meanwhile, Bieter & Hirsh (1948) employed *dl*-methadone, *l*-methadone and *l*-isomethadone in a limited number of cases, injecting each subcutaneously in doses of 5 mg, 7.5 mg and 10 mg. Because of the small number of cases the dose groups for each drug were combined. The numbers of cases, with the effects produced, were as follows:

	Analgesia			*Sedation*		*Nausea and vomiting*
	good	*fair*	*none*	*good*	*none*	
dl-Methadone . . .	13	1	2	1	15	2
l-Methadone	24	2		3	23	3
l-Isomethadone . .	12	3	2	4	13	1

Robbins (1949) compared methadone and isomethadone and their *l*-isomers in pre-operative medication and for post-operative pain. All pre-operative doses were given with atropine. The dosages used were:

	Pre-operatively	*Post-operatively*
dl-Methadone	5.0-7.5 mg	5.0-20.0 mg
l-Methadone	2.5-5.0 mg	2.5-10.0 mg
dl-Isomethadone . . .	7.5-15.0 mg	5.0-15.0 mg
l-Isomethadone	5.0-7.5 mg	5.0-20.0 mg

Robbins said that the doses equivalent to 10 mg of morphine in analgesic potency were:

dl-Methadone	7.5 mg
l-Methadone	3.7 mg
dl-Isomethadone	10.0-12.0 mg
l-Isomethadone	7.5 mg

In other words, both Bieter & Hirsh and Robbins found *l*-isomethadone equipotent as an analgesic with *dl*-methadone and morphine.

Hewer & Keele (1948) determined the effect of methadone and isomethadone (the racemates in both instances) on ischaemic pain, produced by contraction of the muscles of the forearm when the blood supply to the arm was occluded. The threshold intravenous dose which would arrest the rapidly rising pain intensity was 0.25 mg for methadone and 0.3 mg for isomethadone. These observations were made on normal subjects at rest.

Brown & Volpitto (1950) gave 80-190 mg (average 150 mg) of pethidine with scopolamine to 25 women in labour and 10-25 mg (average 20 mg) of *l*-isomethadone with scopolamine to 11 other patients and compared the amnesia produced. All of the pethidine cases had excellent or satisfactory amnesia; in three of the isomethadone cases amnesia was inadequate.

Denton & Beecher (1949a) maintained that accurate appraisal of the incidence of side-effects with analgesic drugs was not possible in post-operative patients because of confusion arising from the pathological condition and the after-effects of the anaesthetic. Consequently they devised a technique for determination of side-effect liability in normal subjects. All agents, including a standard (usually morphine) and a placebo, were given subcutaneously in random sequence on a double-blind basis to the same subjects, who were semi-ambulatory; i.e., they were required to walk about for a fixed portion of each hour. Equipotent analgesic doses, as determined in previous studies on post-operative patients, were used. By this technique they (Denton et al., 1948; Denton & Beecher, 1949b) compared *l*-isomethadone with *dl*-isomethadone, *dl*-methadone, *l*-methadone and morphine. They concluded that *dl*-methadone, *l*-methadone and *dl*-isomethadone, when used in comparable analgesic doses, were as toxic as morphine with respect to symptom production and duration of symptoms; *l*-isomethadone, however, produced less nausea than morphine. Both isomethadone and its *l*-isomer slowed the pulse and respiratory rates as much as morphine, but did not affect systolic or diastolic blood pressure.

Keats & Beecher (1951, 1952) repeated the determination of side-effect incidence in normal subjects following the subcutaneous administration of *l*-isomethadone, in comparison with morphine, a saline placebo and some other analgesic agents. In this study they measured also the effect of these substances on respiratory rate and minute volume, respiratory response to 5% carbon dioxide, oxygen consumption and oral temperature. All drugs were administered in random order to each subject, and observations were recorded by disinterested observers. Dosages were those determined to be equi-analgesic in post-operative patients (10 mg per 70 kg of body-weight for each drug). The kind and percentage incidence of side-effects are shown in Table V.

The other analgesics included in the study were 6-methyldihydromorphine metopon and phenadoxone. The authors said that *l*-isometha-

TABLE V. SIDE-EFFECTS FOLLOWING SUBCUTANEOUS ADMINISTRATION OF SALINE PLACEBO, MORPHINE AND *l*-ISOMETHADONE

	Saline placebo	Morphine	*l*-Isomethadone
Number of subjects	72	58	58
Drowsiness	33	91	81
Sleep	7	24	29
Difficulty in concentrating	10	43	28
Dizziness	1	41	29
Difficulty in focusing eyes	3	14	16
Thick speech	3	2	3
Ataxia, objective	3	31	19
Uneasy stomach	2	10	7
Nausea	6	34	14
Vomiting		7	5
Warm glow	3	29	17
Drunkenness	2	3	10 [a]
Headache	13	21	17
Pallor	1	16	3
Sweating	1	7	2
Hiccups		10	0
Itching		12	7
Constricted pupils	7	40	33 [a]
General numbness		3	0 [a]

[a] Based on 30 subjects

done was the only drug studied possessing advantages over morphine since it produced fewer symptoms, especially nausea and vomiting, than morphine. At its equal analgesic dose, however, *l*-isomethadone produced as much decrease in oral temperature (0.4°-0.6°F), as much decrease in oxygen consumption (about 10%) and as much effect on resting respiratory minute volume (a decrease to about 80% of normal) and on the respiratory response to 5% carbon dioxide as the same dose of morphine. Prescott et al. (1949) measured the respiratory minute volume during breathing of 5% carbon dioxide in eight medical students and compared the effect of racemic isomethadone on this minute volume with that of morphine. Both drugs were given intramuscularly to the same subjects. With the effect of morphine rated as 1, the effect of isomethadone lay between 0.4 and 0.7. Therefore, the effect of the *l*-isomer should be the same as that of morphine, the result recorded by Keats & Beecher (1952).

According to Isbell & Eisenman (1948), post-addicts who received 15-45 mg of *dl*-isomethadone subcutaneously experienced no sedation or morphine-like euphoria. The men who received the largest dose, however, complained of nervousness and said the drug had an effect like amphetamine. *dl*-Isomethadone intravenously at a dose of 30 mg or more regularly produced euphoria manifested by talkativeness, a feeling of well-being, etc.—a typical morphine-like reaction. The men seemed exhilarated rather than sedated. The pupils were constricted but nausea or vomiting did not occur. 60-90 mg of *dl*-isomethadone administered subcutaneously to men strongly addicted to morphine at the 28th to 32nd hour of abstinence produced about as much suppression of the morphine abstinence syndrome as did 30 mg of morphine. The duration of relief was 4-6 hours. Isomethadone was substituted for morphine in five strongly addicted individuals at a ratio of one mg for each 1.33 mg of the morphine stabilization dose. Substitution was not quite complete, so that mild abstinence signs appeared. After 10 days of substitution the isomethadone was stopped abruptly and in 12-18 hours a typical morphine-like abstinence syndrome appeared. Finally, 10 former morphine addicts, abstinent from morphine for three months or more, were started on *dl*-isomethadone subcutaneously 4 times a day. The initial dose was 80 mg a day and was increased as rapidly as tolerance permitted to 270-360 mg daily. The men were at first exhilarated, slept less and showed signs of nervousness but after about a week began to be sedated, but never as much so as with morphine. Nor did they show as much deterioration or neglect of their appearance as is usual during morphine addiction. The men were severely constipated and miosis persisted, but no serious toxic reactions developed. Isomethadone was abruptly withdrawn in one man after 42 days and in the others after 56 days of administration. An abstinence syndrome like that after withdrawal of morphine appeared in 12-18 hours. It was not quite as severe as after morphine but developed and subsided at about the same rate as the morphine abstinence syndrome. It began sooner, was more severe, and declined more rapidly than the abstinence syndrome after methadone addiction. Isbell (quoted by Eddy, Halbach & Braenden, 1956) on the basis of the experiments just described, estimated that 37 mg of *dl*-isomethadone were equivalent to 50 mg of morphine in physical dependence potency; that is, in ability to maintain an addiction. The equivalence for *l*-isomethadone should be, therefore, about 18.5 mg.

SUMMARY

l-Isomethadone is equivalent to morphine or *dl*-methadone in analgesic potency. The optimal dose appears to be 10 mg subcutaneously, and the duration of effect is not materially different from that of morphine. The drug produces fewer side-effects, particularly nausea and vomiting, than

morphine when administered in equipotent analgesic dosage, but it does, under the same circumstances, produce as much decrease in respiratory minute volume and in the respiratory response to carbon dioxide. *l*-Isomethadone is an addicting substance. It produces morphine-like euphoria, at least when administered intravenously; it will suppress the morphine abstinence syndrome; it will substitute for morphine in stabilized morphine addicts; and, after eight weeks of regular administration, its abrupt withdrawal results in a typical morphine-like abstinence syndrome.

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8. Methadone [a] (4,4-diphenyl-6-dimethylamino-3-heptanone)

Analgesic effectiveness

Methadone was introduced into medical practice on a wide scale in 1946. Table VI reproduces the results of clinical investigation reported by 29 authors covering observations on nearly 4000 patients. The range of single doses was, for oral and subcutaneous administration, between 2.5 mg and 20 mg and, when administered intravenously or intramuscularly, between 2.5 mg and 15 mg, the oral and subcutaneous routes being the more commonly used. The majority of the authors enumerated in Table VI judged that the optimal subcutaneous dose for severe pain of various origins which gave complete or satisfactory relief in a high proportion of trials was between 5 mg and 15 mg. Thus, Schwaiger & Bach (1949), while stressing the need for individual dosage, believed that doses below 5 mg were generally not sufficient, but that it was usually not necessary to exceed 15 mg. Bercel (1948) and Baumhoff & Schürmeyer (1950) reported that, if 15 mg were not satisfactory in cases of severe protracted pain, 30 mg

[a] International non-proprietary name for the racemic form; for other designations, see *Estimated World Requirements of Narcotic Drugs in 1958* (United Nations document E/DSB/15).

failed to afford relief. Schmitz-Helff (1953) designated 5 mg as not always sufficient, but 10 mg as effective in most cases. Kirchhof & David (1948), when administering parenterally 1080 single doses of between 10 mg and 20 mg methadone to 200, mostly post-operative, patients, found that optimal relief of pain was obtained in all cases receiving 17.5 mg.

Half of the authors entered in Table VI tried to assess the dose of methadone which was equally effective with respect to analgesia as 10 mg of morphine. Their figures range from 3.3 mg to 10 mg of methadone. Taking into account the figures for analgesic effectiveness (as percentage of cases with satisfactory relief from pain), there appears to be fairly good agreement that the average dose of methadone equally effective as 10 mg morphine is a little less than 10 mg when administered orally or subcutaneously, the figures given for the latter route being more consistent than those given for oral administration.

More precise figures for the ratio of analgesic effectiveness of morphine *versus* methadone can be expected from controlled clinical trials making use of placebo administrations and blind experiments. With this technique, Denton & Beecher (1949a) compared in 112 patients the effect of doses of 5-15 mg methadone with the effect of morphine in the same dose range, with the result that methadone was milligram for milligram equivalent to morphine in its analgesic power. The observations of Beecher et al (1951) on two groups of 29 and 28 soldiers, freshly wounded and post-operative, respectively, confirmed the aforementioned findings obtained in a civil hospital. From trials on patients with constant pain over weeks given placebos and at least 10 injections each of different dosages of methadone, Nathan (1952) concluded that on an average 10 mg of methadone were equally effective as 23 mg of morphine. Stamm (1950) administered 2500 single doses of, usually, 10 mg of methadone to 100 gynaecological patients and, by simple comparison, found them largely as effective as 10 mg of morphine in a parallel series of 100 similar cases.

It remained to be seen whether the equality of methadone and morphine as observed in clinical practice as well as in controlled trials was confirmed by experiments in normal human subjects. To this end, different types of experiments were conducted.

The thermal radiation method of Wolff, Hardy & Goodell (1940) was used by Scott, Robbins & Chen (1946), Isbell et al. (1948b) and Christensen & Gross (1948). Scott, Robbins & Chen considered 5 mg of methadone equal to 100-150 mg of pethidine and 7.5 mg of ketobemidone respectively (when orally administered), from which figures it can be deduced that 5 mg of methadone are comparable to about 10 mg of morphine. Isbell et al. found that, in 10 normal volunteers and 31 persons formerly addicted to morphine, the pain threshold was elevated as much by 5 mg of methadone subcutaneously as by 10-15 mg of morphine. Vogel, Isbell & Chapman (1948) indicated a similar proportion in the analgesic effectiveness of

methadone and morphine in respect of the elevation of the pain threshold as well as of the alteration of reaction to pain by the two drugs. By the same technique applied to 11 normal subjects, Christensen & Gross (1948) determined methadone to be three times as potent as morphine.

The method described by Harrison & Bigelow (1943), where pain of different degrees was induced and maintained by contraction of muscles of the forearm under ischaemic conditions, allowed for the application and evaluation of drugs during pain, thus imitating the clinical application of analgesics. The approximately equi-analgesic doses giving complete relief as determined with this method in four normal subjects by Hewer & Keele (1947, 1948) were 7.5 mg each of methadone and morphine when administered intravenously; the threshold doses, i.e., the smallest intravenous doses which would produce a definite effect on a certain degree of pain, were 0.35 mg of morphine and 0.3 mg of methadone in one person and 0.1 mg of each drug in another normal subject. Keele (1952) later on confirmed by the same method that both drugs were in the same range of effectiveness.

Wilson et al. (1950), applying a modification of the ischaemic pain method to five normal persons, found methadone somewhat superior to morphine (which, in view of the complicated method and evaluation, might perhaps be interpreted as meaning that methadone and morphine have the same order of analgesic potency).

In another type of experiment, in 10 patients with a T-tube in the common bile duct, quantitatively determining the pain threshold by increasing the hydrostatic pressure in the biliary tract, Gaensler (1951) found that 7.5 mg of methadone raised the pain threshold less than 10 mg of morphine but that the total analgesic effect of methadone (taking into account also the duration of analgesia) was about 20% greater than that of morphine.

Thus, the different experimental methods gave somewhat different figures for the analgesic potency of methadone: the investigations with the thermal method indicated an analgesic effectiveness about twice that of morphine whereas the results of the ischaemic and visceral pain methods revealed a similar order of effectiveness of methadone and morphine, as did the clinical evaluation in patients.

Onset and duration of analgesia

Relatively little attention has been devoted by investigators to the onset of the analgesic effect of methadone. Such data as have been given for the subcutaneous administration by Gaensler (1951) (7-15 minutes), Baumhoff & Schürmeyer (1950) (10-15 minutes), Troxil (1948) (15-20 minutes), and Houde, Rasmussen & LaDue (1948) (15-30 minutes) are within the usual time of absorption from the subcutaneous tissue and in

the same range as is known for morphine. Vogel, Isbell & Chapman (1948), however, characterized methadone as slowly acting with a tendency towards cumulation requiring repeated administration in order to develop its full effect. They considered it, therefore, not suitable for rapid pain relief by a single dose.

As can be seen in Table VI, the analgesic effect of 5 mg of methadone orally lasted on an average 5 hours (Scott & Chen, 1946; Batterman & Oshlag, 1948, 1949; Bercel, 1948; Christensen & Gross, 1948; Becker & Wulff, 1949; Magaldi & Brandão, 1949; Stamm, 1950; Schmitz-Helff, 1953). Subcutaneous or intramuscular injection of 5-10 mg of methadone gave relief for 4 hours and more (Bryan & Smyth, 1947; Scott et al., 1947; Bercel, 1948; Christensen & Gross, 1948; Jacoby, Woolf & Livingstone, 1948; Rovenstine, 1948; Troxil, 1948; Becker & Wulff, 1949; Costello & McDonald, 1949; Magaldi & Brandão, 1949; Stamm, 1950; Schmitz-Helff, 1953). Nathan (1952) stated that analgesia always lasted longer after parenteral than after oral administration.

A few authors compared methadone with morphine with respect to the duration of analgesia: Jacoby, Woolf & Livingstone (1948) and Pratt & Welch (1955) considered methadone in this respect somewhat inferior to morphine, whereas Vogel, Isbell & Chapman (1948), Gaensler (1951) and Goeck (1950) found the reverse to be the case.

Sedative action

Great attention was paid to the sedative or hypnotic—sometimes also called narcotic—properties of methadone. From the beginning of clinical evaluation, the authors who denied an appreciable degree of sedation were in the majority. Kohlstaedt et al. (1947): analgesic doses of methadone produced less sedation than equivalent amounts of morphine; Van Dyke (1949): little sedation; Bieter & Hirsh (1948): of 188 patients, 147 were relieved from pain, but only 12 were sedated; Kaae (1948): in 19 of 20 cancer patients, methadone had the same analgesic effect as morphine or a better, but notably less hypnotic, effect; Kirchhof & David (1947a): in 101 patients no noticeable sedative or hypnotic effect was produced by 5-15 mg of methadone subcutaneously; Seevers (1949): the outstanding characteristic of methadone is analgesia with a minimum of sedative action; Hammes (1952): methadone was considered useless in obstetrics or pre-anaesthetic analgesia because of lack of sedation; Stamm (1950): in 100 gynaecological cases, methadone was as effective an analgesic as morphine in a parallel series, but devoid of hypnotic effect; Schmitz-Helff (1953): in 170 patients, methadone had at least the same analgesic effect as morphine but no sedative effect. All of eight normal subjects were sedated by 10 mg of morphine, but none by 10 mg of methadone (Prescott et al., 1949). Riebeling (1950) even reported on

TABLE VI. CLINICAL ANALGESIC DOSAGE OF METHADONE AND ITS SIDE-EFFECTS

Author	Indication	Number of cases	Dosage				Side-effects	
			effective single dose (mg)	effective in percentage of cases	duration of analgesia (hours)	dose (mg) equivalent to 10 mg morphine	nature	frequency
Gentling & Lundy (1946)	As for morphine	106	5 i.v.	nearly 100 %		3.3	Dizziness	Mainly ambulatory cases
Scott & Chen (1946)	As for morphine	30	5 oral	80 %	3–4		Nausea, vomiting Headache Dry mouth Lightheadedness	9 cases 4 cases 2 cases 1 case
Bryan & Smyth (1947)	Pain in malignant diseases	72	2.5–17.5 s.c.	most	4			
"	Pain in malignant diseases	21	2.5–10 oral				Anorexia, nausea, vomiting, diarrhoea, dizziness, diaphoresis	In ¾ of oral administrations
Isbell et al. (1947)	Mainly cancer (terminal)	500	5–10 s.c.					
Ishmael & Stacy (1947)	Orthopaedic and arthritic diseases	106	2.5 oral	most	4–8		< morphine	< morphine
Kohlstaedt et al. (1947)	Chronic pain, post-operative	>300	2.5–15 s.c., oral	79 %			Nausea, vomiting, lightheadedness, sweating, confusion	Occasionally; more often in ambulatory cases
Scott, Kohlstaedt & Chen (1947)	Pain of various origins	210	2.5–15 i.m.	73 %		5	Nausea, vomiting, dizziness	
Scott et al. (1947)	Pre-anaesthetic use	58	2.5–15 i.v., i.m.	majority			< morphine	< morphine
"	Post-operative pain	47	2.5–10 i.m.	80 %	3–4			
"	Renal colic	7	2.5–10 i.m.	80 %				

TABLE VI. CLINICAL ANALGESIC DOSAGE OF METHADONE AND ITS SIDE-EFFECTS (continued)

Author	Indication	Number of cases	Dosage				Side-effects	
			effective single dose (mg)	effective in percentage of cases	duration of analgesia (hours)	dose (mg) equivalent to 10 mg morphine	nature	frequency
Batterman & Oshlag (1948, 1949)	Arthritic pain	30	2.5–5 oral	40 %	4		Dizziness, nausea, vomiting, weakness, drowsiness	Most in ambulatory cases; twice as great after oral as after parenteral administration
	Pain of various origins	150	10 s.c.	88 %		10		
Bercel (1948)	Severe protracted pain of various origins	25	5–15 oral, s.c.		3 and more	10	Dizziness	More after oral and ambulatory administration
							Nausea, vomiting	10 cases
							Circulatory depression	2 cases
							Tinnitus	1 case
							Skin reaction	1 case
Bieter & Hirsh (1948)	Pain in internal medicine	34	5–10 oral	70 %			Nausea, vomiting, dizziness Itching	More frequent with oral administration
		81	5 s.c.	73 %				
		39	7.5 s.c.	87 %				
		34	10 s.c.	88 %				
Christensen & Gross (1948)	Pre-anaesthetic use	69	5 i.v. together with 0.3–0.4 scopolamine					
,,	Severe pain	11	2.5–5 i.m., oral	~50 %	3–4	~4	Minimal	
Houde, Rasmussen & LaDue (1948)	Cancer	50	2.5–20 s.c., oral	66 %		(<) 7.5	Nausea, vomiting, dizziness	6 cases
Jacoby, Woolf & Livingstone (1948)	Pre-anaesthetic use	73	5–7.5 s.c., i.v.	70 %			Respiratory depression (10 mg)	4 cases

TABLE VI. CLINICAL ANALGESIC DOSAGE OF METHADONE AND ITS SIDE-EFFECTS (continued)

Author	Indication	Number of cases	Dosage				Side-effects	
			effective single dose (mg)	effective in percentage of cases	duration of analgesia (hours)	dose (mg) equivalent to 10 mg morphine	nature	frequency
Jacoby, Woolf & Livingstone (1948)	Post-operative pain	240	(5), 10, (15)	most	3–4	10	Dizziness, light-headedness (no nausea, vomiting, or constipation) <morphine	50 % < morphine
Kaae (1948)	Incurable cancer	20	5 oral to 25 s.c.	95 %		<10	Nausea	3 cases
Kirchhof & David (1948)	Post-operative pain	149	10–15 s.c.	85 %			Nausea Sweating Dizziness	13 cases 5 cases 2 cases
Popkin (1948)	Ischaemic pain	28	5–15 oral				Nausea, lightheadedness Vomiting Urticaria	8 cases } mostly ambulatory 2 cases } mostly ambulatory 1 case
Rovenstine (1948)	Severe post-operative pain		10 s.c., 5 oral	most	3-4		Minimal	
Troxil (1948)	All types of pain	400	2.5–10 s.c. (i.v., oral)	80 %	3–4 (sometimes 8–12)	6.7	Nausea, vomiting Sedation Dizziness Itching Dry mouth Headache	21 cases 21 cases 10 cases 4 cases 2 cases 1 case
Becker & Wulff (1949)	Carcinoma	130	5 oral, 10 s.c.		6–10		Nausea, vomiting Somnolence	5 %
Costello & McDonald (1949)	Pre- and post-operative; malignancies	137	10 mostly s.c.	94 %	4		Nausea, vomiting Dizziness, drowsiness Dry mouth Respiratory depression Anorexia Blurring of vision Skin rash	32 cases 8 cases 4 cases 2 cases 2 cases 1 case 1 case

TABLE VI. CLINICAL ANALGESIC DOSAGE OF METHADONE AND ITS SIDE-EFFECTS (concluded)

Author	Indication	Number of cases	Dosage				Side-effects	
			effective single dose (mg)	effective in percentage of cases	duration of analgesia (hours)	dose (mg) equivalent to 10 mg morphine	nature	frequency
Denton & Beecher (1949a)	Post-operative pain	112	5 s.c. to 15 s.c.	83 % 98 %		10		
Magaldi & Brandao (1949)	Pain of various origins	18	5 oral, 10 s.c.	100 %	3-8 8-24		Nausea, vomiting	Low
Robbins (1949)	Pre-anaesthetic use		5; 7.5 s.c.	100 %			Nausea	< morphine
"	Post-operative pain		5-20 s.c.	90 %		7.5		
Schwaiger & Bach (1949)	Surgical	250	6-15 oral, s.c.				Nausea, dizziness, respiratory depression	
Baumhoff & Schürmeyer (1950)	Colic and ischaemic pain, pleurilis, migraine		5 oral, 10 s.c.		12 8-10	sometimes > 10 mg	Nausea, vomiting, dizziness, headache	Mostly in ambulatory cases
							Urticaria	1 case
Stamm (1950)	Gynaecological	100	5 oral, 10 s.c.		2-8	10	Nausea, vomiting, sweating	13 %, mostly in ambulatory cases
Schaefer (1951)	Dentistry		5 oral				Nausea, dizziness, collapse	> 10 %
Nathan (1952)	Severe chronic pain of various origins, including cancer		15–30			8	Same as with morphine	
Schmitz-Helff (1953)	Pain of various origins		5[a]–10[b]		6–8	5 10	Nausea, vomiting, dizziness	Prevailing after oral administration

[a] Together with diphenylpiperidinoethylacetamide hydrochloride 0.25 mg
[b] Together with diphenylpiperidinoethylacetamide hydrochloride 0.5 mg

a reversed central action by methadone, i.e., restlessness and other symptoms of cerebral excitation 2-5 hours after administration of 5 mg of methadone, usually not accompanied by analgesia.

Presence or absence of sedation is essential for the usefulness of an analgesic as a pre-anaesthetic agent. Scott et al. (1947), Jacoby, Woolf & Livingstone (1948) and Goeck (1950) judged that analgesic doses of methadone did not provide for sufficient sedation and in particular did not satisfactorily alleviate pre-operative apprehension. Rovenstine (1948) found it, for the same reasons, less useful as a pre-anaesthetic agent than, for example, pethidine. Christensen & Gross (1948) and Pratt & Welch (1955) considered methadone in this respect somewhat inferior to morphine. Robbins (1949), on the other hand, found that 7.5 mg of methadone were sufficient for pre-operative medication. Schwaiger & Bach (1949) observed sedation with 6-15 mg of methadone in all of 250 surgical cases, and Beecher et al. (1951), concluding from controlled trials, objected to the general opinion that methadone had less hypnotic effect than morphine. According to Isbell et al. (1947c) no sedative action could be detected in former morphine addicts after single doses of 5 mg, but definitely appeared after the third or fourth dose, whereupon tolerance to the sedative effect developed within several days. 30 mg of methadone always produced sedation in former morphine addicts (Isbell et al., 1948b). The explanation for the partly contradictory findings as quoted above may be found in the fact that, according to Vogel, Isbell & Chapman (1948) methadone as a slowly acting drug provides little sedation in a single dose, but has a powerful cumulative sedative effect when repeatedly administered.

Antitussive action

As a morphine-like analgesic, methadone was supposed to act, like morphine, as a depressant of cough, and this was confirmed by early clinical observations, for example, by Bryan & Smyth (1947), who found oral doses of 2.5-5 mg most satisfactory in 21 patients. Doses of 1.5-2 mg every 4 hours controlled cough in 32 hospitalized tuberculosis patients without evidence of tolerance to the antitussive effect after prolonged medication over 6-8 weeks (Scott, Kohlstaedt & Chen, 1947). Kohlstaedt et al. (1947) confirmed this in another report on 48 tuberculosis patients, pointing out that 1.5-2 mg of methadone orally acted as well as or better than codeine. Baumhoff & Schürmeyer (1950) reported on cases of irritative cough who had been medicated before with codeine, hydrocodone and thebacon and in whom methadone in oral doses of 2.5 mg proved very effective and equivalent, sometimes even superior, to the aforementioned antitussives. Herold (1953) used in tuberculosis oral or parenteral doses of 2.5 mg up to 10 mg as a maximum, which corresponded to the effective analgesic doses; in 22 of his patients accustomed to thebacon or hydrocodone, methadone replaced the former effectively; in 17 cases of pleurisy,

methadone suppressed cough completely; 36 patients previously disturbed by cough regained sleep. As a practitioner, Wand (1952) had found "methadone to be the most effective drug for the relief of cough in pulmonary tuberculosis".

Experimentally the central suppression of cough by methadone was demonstrated by Hillis (1952) in a single human subject able to tolerate the tube of a sprayer in the pharynx for hours. Subcutaneous doses of morphine and methadone (15 mg each) and heroin (10 mg) were equally effective in suppressing the cough reaction provoked by a spray of peppermint water or ether. The accompanying drowsiness was of the same degree in the case of morphine and methadone but much more marked with heroin.

The clinical experience with regard to the antitussive action of methadone is in line with the results of animal experiments (Friebel, 1955; Friebel & Reichle, 1956; Green & Ward, 1955; Haas, 1955; Winder & Rosiere, 1955). Yet the theoretical and practical interest in methadone as a cough-depressing agent decreased after introduction of dextromethorphan as an antitussive without addiction liability.

Obstetric analgesia

When methadone was introduced into obstetric analgesia, it soon became evident that over and above a certain dose-level it had a marked depressing effect on the newborn's respiration. Kirchhof & David (1947b) did not observe this effect in 9 cases to whom doses of 5-7.5 mg were administered. Lund (1948) saw one asphyxiated baby after administration of 15 mg of methadone to the mother, whereas in the remaining cases of the series receiving 5-15 mg (usually 7.5 mg) no depressing influence on the infant was observed nor any effect of the drug on the frequency, duration or intensity of the contractions. Later on, the same author (1951) stated that methadone had been found unsatisfactory as an obstetric analgesic because the analgesia was irregular and foetal respiratory depression often distressing. Smith & Nagyfy (1949) found doses of 5 mg or 10 mg of methadone followed by 5 mg every 3-4 hours not sufficiently analgesic; after increasing the initial dosage to 10 mg followed by 10 mg every 1-2 hours, the respiratory depression of the newborn increased so greatly that they had to discontinue the series. Davis and his associates (1952), in an analysis of 100 obstetric cases receiving 10 mg of methadone together with 0.4-0.5 mg of scopolamine, reported satisfactory results as to analgesia in 47% of all patients and absence of significant effects on duration of labour and on the infant. In 100 patients treated with single intramuscular doses of 10 mg of methadone, Szirmai, Bajusz & Nyiri (1954) found acceleration of labour in 83%, reduction of pain in 55% and asphyxia of the baby in 3%.

The authors using higher doses of methadone agreed on a relatively high incidence of severe respiratory depression in the infant. Prescott & Ransom (1947) compared a group of 30 patients receiving two intramuscular doses of 100 mg of pethidine one hour apart to another group of 48 patients given two injections of 10 mg of methadone in the same fashion; data for duration of labour, relief of pain and amnesia were very similar in both groups, but there were 10 babies with depressed respiration in the methadone group as compared with 5 slightly blue babies in the pethidine group. In a second series of trials with 55 patients receiving 150 mg of pethidine followed by 100 mg after 1 hour and 14 patients receiving 15 mg and after 1 hour 10 mg of methadone, they observed seven depressed babies in the latter group as compared with 11 blue babies in the pethidine group. Four of the 11 babies were possibly in this state for other reasons than administration of the analgesic. Steel & Gunderson (1947) believed methadone not to be indicated for obstetric analgesia because, in 43 cases with initial administration to the mother of 10 mg or 20 mg of methadone sometimes followed by one or two consecutive doses of 10 mg, 6 babies were limp and the respiration of another 6 was markedly depressed. Barnes, Hapke & Holzaepfel (1947) reported that 15 mg of methadone caused a significant delay in first respiration and first cry in 25 cases when given 2 hours or less before delivery, but little depressant effect if the time interval was greater than 2 hours; 10 mg of methadone administered at whatever time before delivery had no significant effect on the respiration of the newborn. Käser, König & Etterich (1951), Papper (1950), and Stephen, Novill & Martin (1952) concurred in the opinion that methadone was not safe in obstetric analgesia because of the depression of foetal respiration.

From the above reports it can be concluded that single doses up to 10 mg of methadone, which often do not provide for sufficient obstetric analgesia, generally do not influence the foetal respiratory centre, but that repetition or increase of that dose involves the risk of infantile respiratory depression.

Special therapeutic uses

Special therapeutic uses other than those described above have been explored, but not adopted in medical practice to an appreciable extent, perhaps with the exception of the application of methadone as a spasmolytic agent, in particular in the urinary organs. Scott et al. (1947) found intramuscular doses of 2.5-10 mg of methadone effective against bladder spasms and renal colic. Baumhoff & Schürmeyer (1950) confirmed the effectiveness of 10 mg of methadone in a few cases of kidney colic. They also had satisfactory results with subcutaneous administration of 10 mg of methadone in 7 out of 8 cases of gall-bladder spasms, although this could

not be expected from Gaensler & McGowan's experiments (1950) as reported below, which demonstrated that methadone raised the intrabiliary pressure like morphine.

In treating three cases of tetanus, the frequency and intensity of convulsions were diminished by 15 mg of methadone subcutaneously twice a day (Schwaiger & Bach, 1949). Similarly Stephan (1953) said that the convulsions of two tetanus patients were controlled by 50-60 mg of methadone a day. In these cases the site of action of methadone is not known, nor is it known in the case of 33 patients suffering from extrapyramidal diseases in whom Müller (1952) observed the diminution of spastic symptoms by oral doses of 5-10 mg of methadone. It is not known either whether there is any connexion between the preference given by Hammes (1952) to methadone as the drug of choice in brain injuries where pain was not controlled by codeine and the findings of Abreu et al. (1950) that the cerebral blood flow (in voluntary psychiatric patients) showed a rising trend after intramuscular injection of pethidine (100 mg) or morphine (10 mg), a decrease after codeine (65 mg) and was not significantly changed by 5 mg of methadone.

Side-effects

Most of the publications on the therapeutic use of methadone paid attention to its undesired side-effects. Since not all these reports can be dealt with individually in this review, observations regarding side-effects have been inserted in the last column of Table VI. The side-actions of methadone are largely of the same character as those of morphine, as can be seen from Table VI, and as was stated in various reviewing papers, for example, by Isbell (1948), Vogel, Isbell & Chapman (1948) and Seevers (1949).

Dizziness, nausea, vomiting, and sweating occur in many patients with an incidence between a few and 50%. Nearly all the reports concerned agree that side-effects, in particular the aforementioned of a vagomimetic character, were more pronounced and more frequent when the drug was taken orally (Bryan & Smyth, 1947; Batterman & Oshlag, 1948, 1949; Bercel, 1948; Bieter & Hirsh, 1948; Schmitz-Helff, 1953) and also when the patients were ambulatory (Gentling & Lundy, 1946; Kohlstaedt et al., 1947; Batterman & Oshlag, 1948, 1949; Bercel, 1948; Popkin, 1948; Baumhoff & Schürmeyer, 1950; Stamm, 1950). The observation that these side-actions tended to diminish or disappear when the patient rested horizontally, as has often been stated (see also Ehrhart & Schaumann, 1949), and the common correlation of ambulatory treatment and oral application offer perhaps an explanation for the high incidence of side-effects connected with the oral route of administration.

Some authors believed the side-effects caused by methadone to be less than those by morphine (Rovenstine, 1948; Ishmael & Stacy, 1947; Pratt

& Welch, 1955; Scott et al., 1947; Papper, 1950; Robbins, 1949). However, these findings may partly be due to low dosage (Ishmael & Stacy) and to the combination of methadone with parasympathicolytic agents (Pratt & Welch, Robbins) or barbiturates (Scott et al.).

The clinical experiences regarding the side-actions of methadone have been substantiated by observations in normal subjects under experimental conditions. In 13 trials using 5 mg of methadone in non-addicted persons, Isbell et al. (1948b) noticed nausea three times, lightheadedness and pallor twice, and vomiting once; however, nausea was not produced by the same dose in 65 trials on former morphine addicts and occurred only once in 17 trials with 10-mg doses. This may be interpreted as cross-tolerance in respect of the side-effects of morphine and methadone. In eight normal students the intramuscular injection of 10 mg of methadone was followed by vomiting in four cases; in these experiments, the same dose of morphine produced vomiting in two cases (Prescott et al., 1949). In pain threshold studies on 11 normal subjects only minimal side-effects were produced by subcutaneous doses up to 5 mg (Christensen & Gross, 1948). Hewer & Keele (1947) said that, in repeated experiments on four normal men, lightheadedness, giddiness, and disturbances of vision appeared at the same time as the relief of pain and were proportional to the dose of methadone, but less than with morphine. In Keele's experiments (1952) with eight normal volunteers, 10 mg of methadone orally caused nausea in three and vomiting in one whereas oral doses of 5 mg did not have such effects. Wilson et al. (1950) reported that, in studying the influence of various analgesics on ischaemic pain in five normal subjects, dizziness, nausea, and vomiting occurred less frequently with 100 mg and 150 mg of pethidine than with 15 mg of morphine or 15 mg of methadone. From this it might be permissible to conclude that the side-effects were similar after 15 mg each of methadone and morphine. The authors furthermore stated that these effects were particularly apt to begin when the subject assumed an upright position. The connexion between a person's position and the appearance of such side-effects as dizziness, nausea, etc. was the object of an investigation by Gutner, Gould & Batterman (1951, 1952): the labyrinthine sensitivity was increased by morphine and methadone (10 mg of each, subcutaneously, 5 normal persons per drug) as demonstrated by the prolongation of a nystagmus produced by means of the cold microcaloric test, by the increase of the ratio of onset of this nystagmus to its duration, and by the decrease of the milliamperage required to produce tilting of the head by electrical stimulation of the mastoid area. The authors believed that the increase of labyrinthine sensitivity might be involved in the production of side-effects.

Particular attention has been devoted to more serious side-actions such as central depression of circulatory and respiratory functions (for the latter see also under obstetric analgesia). Costello & McDonald (1949), Jacoby,

Woolf & Livingstone (1948), and Schwaiger & Bach (1949) saw respiratory depression occurring in patients after single subcutaneous doses of 10 mg of methadone. Goeck (1950) described a case of respiratory arrest a few minutes after subcutaneous injection of 5 mg. Mushin (1951) said that morphine, heroin, and methadone produced more respiratory depression than pethidine when similarly administered, whereas Van Dyke (1949) judged that analgesic doses of pethidine or methadone caused little or no respiratory depression. Two adults intoxicated with approximately 85 mg and 150 mg of methadone respectively survived the respiratory arrest (Osterwald, 1952); their blood pressure was not decreased (possibly because of the existing asphyxia ?).

Circulatory depression and collapse are apparently less frequently caused by therapeutic doses of methadone than respiratory depression (see also Table VI). The collapses after 5 mg of methadone orally as reported by Schaefer (1951) could possibly have been due to other therapeutic measures. Bieter & Hirsh (1948) described a case of fatal collapse after an obvious overdose of methadone (10, 20, 20 mg subcutaneously within 8 hours). Stamm (1950) saw collapses after intravenous administration of 10 mg. Scott et al. (1947) had seen no depression of respiration or blood pressure in 58 patients premedicated with 2.5-15 mg of methadone by intramuscular or intravenous route.

An accurate appraisal of the side-effects of morphine-like drugs in post-operative patients was considered impossible by Denton & Beecher (1949a), even by means of the double-blind technique including placebos. Using these methods in two groups of 28 and 29 healthy males, they (1949b) found that in comparable subcutaneous analgesic doses methadone was as toxic as morphine with respect to production and duration of symptoms. The two drugs slowed the pulse and respiratory rates to essentially the same degree, but did not alter the blood pressure. In former morphine addicts, doses up to 10 mg of methadone subcutaneously did not affect respiration, blood pressure and pulse rate; 60 minutes after 15-mg doses the respiratory rate decreased moderately for several hours; doses of 10-30 mg slowed the pulse rate 4-10 beats per minute and reduced the systolic blood pressure by 10 mm Hg (Isbell et al., 1948b). Prescott et al. (1949) observed in eight normal students breathing 5% CO_2 that the reduction of the respiratory minute volume was one-and-a-half to two times as great after 10 mg of methadone intramuscularly as after the same quantity of morphine. Under similar conditions in 10 normal men, the stimulating effect of carbon dioxide on the respiration was significantly reduced (seemingly to a similar degree) by 10 mg of morphine, 10 mg of methadone, and 100 mg of pethidine (Remy, 1950).

In reviewing the data given for obstetric analgesia and the above examples of respiratory depression under clinical as well as experimental conditions, it can be said that depression of the respiratory function must be taken into

account for doses of 10 mg and more of methadone. Such doses represent a risk, particularly for the foetal respiratory centre. In the range of analgesic dosages of methadone, circulatory disturbances appear to be of lesser importance.

Another group of side-effects characteristic of morphine-like drugs concerns the intestinal functions. Constipation, a frequently observed side-action (and a still-used therapeutic effect) of morphine, is rarely reported to occur with methadone. Troxil (1948) said that during prolonged (up to 12 months') administration of methadone, constipation or changes in bowel habits did not occur. Müller (1952) saw it in 10 of 33 patients with extrapyramidal diseases treated with high doses of methadone. Nathan (1952) reported on constipation in patients who received large doses of methadone (15-30 mg) for severe chronic pain. According to the observations of Jacoby, Woolf & Livingstone (1948) (in more than 300 patients) and Van Dyke (1949) constipation was not produced by analgesic doses of methadone, which is in agreement with experiments by Kewitz, Remmer & Engelhardt (1951). In a case of fistula of the caecum, they could prove by means of direct registration that 10 mg of morphine intravenously increased the tonus of the small intestine but the same dose of methadone failed to do so. Vesical spasms, a well-known side-action of morphine, have not been reported to occur with methadone. Nathan (1952), for example, explicitly mentioned the absence of vesical spasms after doses of 15-30 mg. Scott et al. (1947) even found marked relief of bladder spasms in 10 post-operative patients given 2.5-10 mg of methadone intramuscularly every 3-4 hours for 2-3 days. By the same dosage, renal colic was promptly relieved in 6 out of 7 of their patients. In the biliary tract, however, methadone exerted spasmogenic effects, according to Gaensler & McGowan (1950). In 17 patients having undergone choledochostomy, they measured the intrabiliary pressures manometrically by means of a T-tube inserted in the common bile duct; in each instance, 7.5 mg of methadone subcutaneously raised the intrabiliary pressure to the mean peak of 120 mm water, which was approximately as high as that produced by 10 mg of morphine and definitely higher than that after 100 mg of pethidine (82 mm) or 60 mg of codeine (56 mm). Intubation studies of these authors showed that the spasmogenic effect of methadone extended to the jejunum and ileum as well.

Skin reactions are not seldom produced by opiates. They were also reported for methadone in the forms of itching and urticaria, their incidence being of the order of at least 1 % of all the cases treated, as far as this can be concluded from relatively few reports. It may also be noteworthy that, out of 29 authors entered in Table VI, six mentioned skin reactions as side-effects. Severe induration and inflammation of the skin were seen when large doses up to 150 mg were injected subcutaneously (Isbell et al., 1947c). Frequent intravenous injections caused extensive phlebo-thrombosis (Isbell & White, 1953).

Of rather a low incidence appear to be other side-effects of methadone, such as tinnitus (Bercel, 1948); blurring of vision (Costello & McDonald, 1949); mental confusion (referred to below in the section on " subjective and psychomotor responses ").

Tolerance

The development of tolerance to the analgesic effect of methadone was not observed by Schwaiger & Bach (1949) in 250 patients receiving single doses of 6-15 mg of methadone orally and parenterally, nor by Müller (1952) in 33 patients. More detailed data on the absence of tolerance were given by Kohlstaedt et al. (1947) (10 patients treated regularly for 6 months with 2.5-15 mg subcutaneously or orally), Popkin (1948) (4 cases receiving total amounts of 2, 4, 1, and 1 g of methadone, mostly by the oral route), Robbins (1949) (2 patients receiving daily 3-6 subcutaneous doses of 5-7.5 mg each up to a total of 126 and 215 doses), and Stamm (1950) (10-20 mg every 2-4 hours for 2 months). Scott, Kohlstaedt & Chen (1947) had no evidence of tolerance to the antitussive effect of methadone when administering 1.5-2 mg orally every 1-4 hours in 15 cases for 8 weeks and in 12 cases for 6 weeks respectively.

On the other hand, a number of reports leave no doubt that tolerance to the analgesic action of methadone does occur. Thus, Troxil (1948) concluded from her experiences with 400 patients that tolerance may develop. Houde, Rasmussen & LaDue (1948) noted tolerance in 2 of 10 cancer patients medicated with doses of between 2.5 mg and 20 mg of methadone. A case requiring doubling of the dose after 2 months' administration was communicated by Lenfield (1949). Several authors (Becker & Wulff, 1949; Baumhoff & Schürmeyer, 1950) reported that the duration of the analgesic effect of oral as well as of subcutaneous doses was halved after 2 weeks' regular administration, which can be interpreted as the result of tolerance.

In extensive studies on 15 former morphine addicts, Isbell et al. (1947a, 1947c) investigated the development of tolerance to various therapeutic effects and side-effects of methadone. Then patients showed complete tolerance to the analgesic effect (as measured by the radiant heat method) of 5 mg after regular administration of this dose 4 times daily for one week. After increasing the dose, analgesia reappeared, but tolerance as well. After 56 days, 7 of the 10 subjects were almost completely tolerant to the analgesic action of single doses of 45 mg. In these experiments, tolerance to the sedative effect developed similarly, but, after 56 days, the men receiving 45-mg doses were not completely tolerant, i.e., tolerance to the sedative action of methadone seemed to develop more slowly than to that of morphine. In contrast to morphine, the tolerance to the miotic effect of methadone was complete within 2 weeks. Partial tolerance to the emetic and to the respiratory and circulatory depressant actions was also observed.

Subjective and psychomotor responses

The question of euphoria by methadone will be dealt with later, in connexion with addiction liability.

A number of psychic functions were investigated by Isbell et al. (1948a) in former morphine addicts who volunteered to take part in experiments with addiction to methadone. The intelligence quotient as measured by the Otis test was 6.8 points lower after several weeks' addiction than before the administration of methadone. When the individual was fully addicted the arithmetic test was performed with the same speed, the visual-motor co-ordination and perseverance tests with a somewhat higher speed, but with more errors in all tests, than was the case before addiction. Decrease in certain psychic functions was also noticed by Nathan (1952), who found that reliable analgesic effects of methadone were accompanied by a decrease of the patients' alertness.

Mental confusion was occasionally seen by Kohlstaedt et al. (1947) and by Batterman & Oshlag (1948, 1949). The latter reported also on toxic psychoses in 5% of the cases treated, occurring most commonly after repeated oral administration of methadone for several days, especially in persons over 50 years of age. Riebeling (1950) described four cases of unusual restlessness and other symptoms of cerebral excitation appearing 2-5 hours after small doses (mostly 5 mg), which usually did not afford analgesia. In the electroencephalogram of a normal subject, 5-10 mg of methadone produced a general decrease of voltage, which is also characteristic of brain injuries (Müller-Limroth & Massmann, 1952); the authors believed this finding noteworthy in view of these patients' known predilection for methadone as an analgesic drug. In the electroencephalogram of highly addicted individuals, Isbell et al. (1948a) observed a shift to the slow side of the frequency spectrum.

Addiction incidence and tests of addiction liability

Early reports on clinical experience with methadone did not mention addiction to it or even explicitly noted absence of euphoria and addiction. Scott et al. (1947), for example, had not seen euphoria in 112 patients given single doses of up to 10 mg of methadone for post-operative pain every 3-4 hours for 2-3 days. Euphoria was not noted in 36 patients receiving 1-3 single doses of 10 mg for obstetric analgesia (Steel & Gunderson, 1947) and only once in 400 patients given 2.5-10 mg, mostly hypodermically (Troxil, 1948). The latter had not encountered withdrawal symptoms after abrupt discontinuation of the drug in 20 patients receiving it regularly for 2-3 months. Out of 200 patients treated with a total of 1438 parenteral doses of 5-20 mg of methadone, mostly for post-operative pain, only one patient experienced euphoria (Kirchhof & David, 1948). These authors

saw no evidence of abstinence phenomena. Out of 154 patients given single subcutaneous doses of 5-10 mg, only one was euphoric after 5 mg (Bieter & Hirsh, 1948). Kaae (1948) reported on the absence of euphoria in 20 cancer patients receiving daily doses of between 20 mg orally and 180 mg subcutaneously; after total administration of 10 g of methadone within 6 months (final daily dose, 180 mg), withdrawal was not followed by abstinence symptoms. From experience with 240 patients post-operatively treated with 5-15 mg of methadone, Jacoby, Woolf & Livingstone (1948) concluded that euphoria was not as marked with methadone as with morphine, as was also noted by Rovenstine (1948) in similar cases with similar doses. They had not noted addiction or habituation. Becker & Wulff (1949) had no evidence of physical dependence when giving daily doses of between 8 mg and 20 mg of methadone by the subcutaneous or oral routes to 130 cancer patients. In 250 surgical patients, Schwaiger & Bach (1949) could not observe euphoria or addiction; there were no withdrawal symptoms after abrupt cessation of administration of 3×15 mg daily.

In 1949, Ehrhart & Schaumann summarized that euphoria had been infrequent and there had been no evidence of addiction to methadone.

A statement of Tainter & Buchanan in 1949 said that clinicians who had used methadone in non-addicted patients had been impressed by the relative freedom from abstinence symptoms after withdrawal, and according to Seevers (1949) primary addiction due to methadone alone had not been described before 1949. It seems noteworthy that reports referring to the absence of addiction liability of methadone were published before 1949. It would, however, appear that since 1949 the possibility of addiction to methadone has been a generally accepted fact which has been more or less emphasized in many case reports and reviews, a number of which are referred to below.

The majority of the early reports on addiction to methadone refer to so-called secondary addicts, i.e., persons who were previously addicted to some other drug which, for various reasons and with or without temporary interruption, was replaced by methadone. Amongst the first reports is a personal communication (1948) from H. J. Anslinger on a morphine-addicted woman who, after a morphine withdrawal in April 1947, 6 months later was given methadone tablets by a physician for relief of headaches and when continuing to take 50-60 mg a day became readily addicted, as severely as to morphine and with the same withdrawal symptoms. Whereas Van Dyke (1949) believed that the addiction liability of methadone was lower than that of morphine, a number of reports between 1950 and 1952 agree on the close similarity between addiction to methadone and that to morphine: one case of secondary addiction to methadone following established addiction to morphine (Beese, 1950); one case of primary addiction with daily injection of 200-300 mg of methadone, nearly without withdrawal symptoms after cessation (Maier, 1950); three cases of secondary

(after morphine) and one case of primary addiction to methadone (Pieck, 1950). Having been successfully withdrawn from 200 mg of oxycodone daily, a patient, on a physician's advice, began to take methadone for relief of severe pain and soon became addicted, taking 100 mg of methadone a day (Riess, 1950). After daily self-administration of 10×4 ampoules of pethidine, a man switched to 50 mg of methadone, which was not yet under restriction, and exhibited abstinence symptoms when without methadone (Smoler, 1950). A similar case, taking 50 mg of methadone after being addicted to oxycodone, phanodorm and pethidine, but without distinct symptoms after withdrawal of methadone, was reported by Tewes & Rupprecht (1950); two physicians addicted to methadone (250 mg and 75 mg a day respectively) had thought it was not dangerous and found it more sedating and less euphorizing than morphine (Kraemer, 1952). Two physicians became addicted to methadone plus phenobarbital and phanodorm respectively after having been addicted to morphine plus phanodorm (Sattes, 1950). Five morphine addicts successfully substituted methadone (up to 200 mg subcutaneously a day) for morphine and after withdrawal of methadone had severe abstinence symptoms; two of these five had not experienced euphoria by methadone (Becker, 1951). Before 1952 Zech (1952a) observed 12 cases of addiction to methadone. Persch (1954) reported eight cases of secondary addiction to methadone implanted on previous addiction to opiates; Salm (1953) reported nine cases secondary to morphine, oxycodone, hydrocodone or hydromorphone, some of whom had tried to cure themselves by means of the " non-addictive " methadone. Between 1949 and 951, 24 cases of (mostly secondary) addiction to methadone in Berlin were reported by Mühlau (1952) (13 physicians, 2 nurses, 2 students of medicine, 7 of other professions). Among 381 cases of addiction in Berlin as reported by Linz (1953) the drug of addiction was morphine in 61, pethidine in 23, oxycodone in 10, methadone in 9, and hydromorphone in 2 cases; when the aforementioned drugs were taken together with other addicting drugs, the corresponding figures were for morphine 168, pethidine 92, oxycodone 96, methadone 66, and hydromorphone 59. In 1955 the percentages of addicts in the Federal Republic of Germany (Gewehr, 1956) taking a single drug were for morphine 19.4%, methadone 17.1%, pethidine 14.2%, oxycodone 10.6% and hydromorphone 6.1%. In Finland (Huhtala, 1955) a shift was observed in the preference for addicting drugs; many addicts began with heroin, switched to morphine and ended with methadone; in 1955 the latter had almost completely replaced both heroin and morphine; except for one morphine addict, all of more than 50 addicts examined since 1953 took methadone. From the above quotations it is revealed that the addiction liability of methadone and the incidence of addiction to it are of the same order as for morphine and that addicts can tolerate doses of methadone, for example 400 mg a day (Zech, 1952b), which are many times greater than doses toxic for normal subjects.

Isbell and his associates studied the addiction liability of methadone in patients with a view to its quantitative evaluation. When they administered methadone in daily doses of between 5 mg and about 100 mg to more than 500 patients for relief of pain, they never observed a euphoric reaction (1947c); nor did they observe it in 19 cases of terminal cancer who had been given increasing doses of up to 140 mg a day for from 3 weeks to 5 months. In 15 of these patients methadone was temporarily withdrawn for 24-48 hours after a month or more of medication, but only two of them showed signs of abstinence after abrupt withdrawal.

The assessment of the addiction liability of methadone under experimental conditions was also carried out by Isbell et al. (1947c, 1948a). In 10 morphine addicts, who had been stabilized on 75-90 mg of morphine subcutaneously 4 times daily for 3 weeks, morphine was abruptly withdrawn. After evaluation of the subsequent withdrawal syndrome, methadone was administered in order to relieve the symptoms of withdrawal. The reduction in the intensity of abstinence symptoms after injection of methadone was as good as that seen after the administration of 30 mg of morphine to four of the same subjects under similar conditions. With methadone, relief was attained more slowly than with morphine, but persisted longer. On an average, 1 mg of methadone given for each 4 mg of the stabilization dose of morphine reduced the abstinence symptoms to below 20 points as measured by the Himmelsbach point-scoring system (Kolb & Himmelsbach, 1938; Himmelsbach, 1939). In experiments with substitution of methadone for morphine in 12 addicts, whose stabilization dose was between 60 mg and 80 mg of morphine 4 times daily, no signs of abstinence appeared and the patients did not notice the change when 1 mg of methadone was substituted for each 4 mg of morphine. To 15 individuals formerly addicted to morphine, but abstinent for at least 3 months prior to the trial, methadone was administered by the subcutaneous route 4 times a day. The daily dose was initially 20 mg and after maintenance for a week was raised as rapidly as tolerance permitted. Thus, the daily dose-levels reached were: 240 mg in 3 cases receiving methadone for 28 days, 180 mg in 7 cases receiving it for 56 days, and 200-400 mg in 5 cases receiving the drug for 142-182 days. Daily doses of 20 mg did not affect the general behaviour. After increasing the dosage to 40-60 mg daily, sedation appeared after the third or fourth injection and the behaviour became very similar to that observed during addiction to morphine. After a given dose-level had been maintained for two weeks or longer, tolerance to the sedative effects became evident, whereupon the individual usually requested an increase in the dosage. Euphoria, which could not be observed in 500 non-addicts treated for pain with doses of up to 100 mg of methadone (see above) and was observed rarely by other authors under the same circumstances, was definitely produced in former morphine addicts by 10 mg and more of methadone. Most of the subjects said that the effects of methadone

were very similar to those obtained from morphine, heroin or hydromorphone, but developed more slowly and that methadone produced the highest degree of satisfaction when administered intravenously. Somnolence and lack of activity were greater during addiction to methadone than during that to morphine. Following abrupt withdrawal of methadone from the 15 subjects stabilized on large doses for 28 to 186 days as well as from the 12 subjects in whom methadone had been substituted for morphine, the abstinence syndrome developed more slowly and was less intense, but lasted longer than that seen after withdrawal of morphine. Nevertheless, all the subjects agreed that the abstinence symptoms, although much milder than those after withdrawal of morphine, were " sufficiently intense to cause them to return to the use of morphine or methadone if either drug had been obtainable ".

Isbell and his associates (1948a) concluded that the average Himmelsbach point-score, which rose slowly and reached a maximum of 25 points only on the sixth day after withdrawal from methadone " is indicative of a degree of abstinence syndrome which should in ordinary practice require little treatment with morphine or morphine-like drugs ". This was the concept of the methadone substitution technique in the withdrawal of patients addicted to opium, opiates or morphine-like synthetic drugs, which is now being widely practised (Isbell et al., 1947b; Vogel, Isbell & Chapman, 1948; Bercel, 1948; Robbins, 1949; Schwaiger & Bach, 1949; Schader, 1950).

The experimental evaluation of the addiction liability of methadone, which was completed in 1947-48, was later on confirmed by the evidence of a high incidence of addiction to methadone (see above)—an example of the validity of trials in former addicts with regard to the prediction of incidence in the general population.

Optical isomers of methadone

The carbon atom 6 of 4,4-diphenyl-6-dimethylamino-3-heptanone being asymmetric, methadone exists in two optically isomeric forms and as a racemate. The preceding discussion refers to the racemic form (*dl*-methadone) only. The dextro-isomer had little analgesic effect in animals and the levo-isomer was twice as effective as the racemic mixture (Leimbach & Eddy, 1954; Thorp, 1949). Thus, Bieter & Hirsh (1948) could not find a " striking difference " between the analgesic effects of various doses of methadone and levo-methadone in 16 and 26 patients respectively; nor was there a difference in the sedative action and the incidence of nausea and vomiting. In a trial conducted by Denton & Beecher (1949a) with all precautions (placebo, double-blind technique, randomization of standard, impartial observer) the effects of 7-9 mg of methadone in 33 post-operative patients were not distinguishable from those of 4-6 mg of *l*-methadone in 25 patients

of the same category. Robbins (1949) administered methadone and *l*-methadone pre- and post-operatively in a dose ratio of two to one with the same analgesic effects and noticed no difference in the side-effects which occurred with these doses. In experiments with the radiant heat method (Wolff, Hardy & Goodell, 1940) in six trained normal subjects, Slomka & Sleeth (1953) too found the dextro-isomer devoid of analgesic effect. Their results as expressed in percentage of increase of the pain threshold indicated the possibility of an antagonistic behaviour of the dextro- and levo-isomers since the racemic mixture had less than half the effect of the levo-isomer. In these experiments, 5 mg of *l*-methadone subcutaneously caused nausea and dizziness in three of the six subjects and emesis in one. From observations on about 100 hospitalized patients suffering from various painful diseases, Manziori, Bianchi & Camera (1951) concluded that *l*-methadone was, as an analgesic, superior to morphine; it had similar side-effects to morphine except for constipation. When studying side-effects in normal healthy men, Denton & Beecher (1949b) found that comparable analgesic doses of *dl*-methadone and *l*-methadone were as toxic as morphine with respect to symptoms and to their incidence and duration. The antitussive effect of *d*-methadone was superior to that of codeine in experimentally induced cough and marked in pathological cough (Rasch, 1957).

Isbell & Eisenman (1948) found that *l*-methadone produced euphoria in former morphine addicts; in cases strongly addicted to morphine it relieved the abstinence symptoms after withdrawal from morphine and suppressed signs of physical dependence when substituted for morphine. The abstinence syndrome as observed after withdrawal of *l*-methadone was identical with that after withdrawal of *dl*-methadone (see above). When intravenously administered *l*-methadone could not be distinguished from heroin or hydromorphone by addicted patients. The dextro-isomer of methadone, although it did not produce euphoria in former morphine addicts, partially relieved abstinence from morphine.

SUMMARY

The analgesic potency of methadone is a little superior, irrespective of the route of administration, whereas its sedative effect appears to be somewhat inferior to that of morphine. Both the analgesic and sedative effects develop more slowly than with morphine and have a tendency towards cumulation. The duration of the analgesic effect of methadone is at least as long as that of morphine. Methadone is a powerful antitussive. It is satisfactorily spasmolytic, in particular in the urinary tract.

The side-effects of methadone are in nature, degree, and incidence similar to those of morphine and occur more often after oral than after parenteral administration. Constipation is produced less by methadone. Its use as a pre-anaesthetic agent is impaired by its low sedative action, as

is its use as an obstetric analgesic by its relatively high respiratory depressive action. After repeated administration of methadone, tolerance develops to its therapeutic action as well as to its side-effects.

Whereas methadone rarely produces euphoria in normal subjects, it definitely does so in addicts. Methadone has marked addiction-sustaining potency. It will substitute for morphine in one-quarter the amount of the latter and its effect lasts much longer. The incidence of addiction to methadone is in some countries of the same order as that to morphine. The slow onset and relatively low degree of the abstinence syndrome after withdrawal of methadone enable it to be used therapeutically for the withdrawal of patients from morphine and morphine-like addicting drugs.

Analgesic action as well as side-effects and addiction liability are possessed by levo-rotatory methadone, the dextro-isomer being relatively less effective.

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9. Methadone derivatives

(*a*) Acetylmethadols [a] (4,4-diphenyl-6-dimethylamino-3-acetoxyheptane)

Reduction of methadone or of one of its optical isomers results in the appearance in the molecule of a new asymmetric carbon and hence makes possible additional isomeric forms. The production of all of these and their acetylated derivatives and the results of their laboratory examination were described by Eddy, May & Mosettig (1952) and by Leimbach & Eddy (1954). The predominant products of one reduction procedure were arbitrarily given the prefix *alpha* and the isomeric forms resulting from the other reduction procedure the prefix *beta*. Only the α-acetylmethadols have been tested in man, but this testing has included in some measure the alpha-racemate and the α-*l*- and the α-*d*- forms. The *l*- and *d*- in each case refer to the observed optical activity, whereas in fact the α-*l*-isomer is derived by reduction and acetylation of *d*-methadone and the α-*d*-isomer by similar treatment of *l*-methadone.

[a] International non-proprietary names: acetylmethadol, alphacetylmethadol, betacetylmethadol.

The laboratory results indicated that the α-acetylmethadols were at least as effective analgesic agents as the ketones from which they were derived, that their relative toxicity was not increased but rather slightly decreased, that their duration of action was increased and that they had a comparatively high effectiveness by oral administration. With this background Keats & Beecher (1952) tried α-*l*-acetylmethadol and α-*d*-acetylmethadol in patients with post-operative pain. The method was that employed by Denton & Beecher (1949): double-blind technique, administration subcutaneously of doses of experimental drug alternating with morphine or a placebo, and observation of degree of pain relief by trained disinterested observers. Not more than two doses of the acetylmethadol were given to the same patient.

The doses of α-*l*-acetylmethadol were 5 mg, 20 mg and 40 mg and the results in percentage of doses affording pain relief compared with the effect of morphine in the same patients were as follows:

Number of patients	*Morphine*			*α-l-Acetylmethadol*		
	dose (mg)	*no. of doses*	*percentage relief*	*dose (mg)*	*no. of doses*	*percentage relief*
36	10	48	75.0	5	48	47.9
25	10	32	68.8	20	32	56.3
20	10	27	66.7	40	27	59.3

20 mg were less effective and 40 mg not quite as effective as 10 mg of morphine. By extrapolation of a dose-effect curve based on the results shown, Keats & Beecher estimated 50 mg of α-*l*-acetylmethadol to be approximately equivalent to 10 mg of morphine, a much poorer range of effectiveness than had been shown in laboratory experiments.

Four patients receiving acetylmethadol exhibited a type of coma such as might result from over-sedation, somewhat like morphine-poisoning. The doses associated with these comas were:

α-*l*-Acetylmethadol 16 mg twice in 30 hrs+morphine 8 mg twice in the same period.

α-*l*-Acetylmethadol 32 mg twice in 25 hrs+morphine 8 mg three times in the same period.

α-*l*-Acetylmethadol 40 mg twice in 34 hrs+morphine 10 mg once in the same period.

α-*l*-Acetylmethadol 26 mg twice in 30 hrs+morphine 6 mg once in the same period.

The onset of coma was 12-24 hours (average 20 hours) after the last dose of acetylmethadol. Deep apathy, even a comatose state, is not uncommon in seriously ill post-operative patients, but there was at least a reasonable supposition that the acetylmethadol was a factor in the present series.

Keats & Beecher (1952) made only a few observations on the effect of α-*d*-acetylmethadol. It was given 33 times to 22 patients at a dose of 2.5 mg

subcutaneously, alternating with 10 mg of morphine. The result was 54.5% of doses affording relief compared with 84.8% relief with morphine in the same patients. There was no evidence of delayed or unusually prolonged analgesic action with either of the acetylmethadol isomers.

David and his associates (1952, 1955, 1956) have studied over a number of years the analgesic effectiveness of racemic α-acetylmethadol. In their first series (1952), 5-mg doses were given orally or subcutaneously, with a total daily dose of 20-30 mg. They noted at first some cumulative action because they said that in patients treated longer than three days the daily amount required could be reduced by a third or the drug could be omitted for a day. If administration continued for 60 days or more, however, some tolerance to the analgesic action was seen. There was in no case evidence of respiratory depression or apathy. In the second series of cases (1955), oral doses only were given for chronic pain, usually 5 mg, but occasionally 10 mg, 3-5 times a day and satisfactory relief was obtained over long periods.

In their last series of 76 patients, 49 of whom had metastatic carcinoma, David, Semler & Burgner (1956) again reported on the use of oral and subcutaneous doses. If the patient had been getting other narcotics these were not always stopped but the dose and frequency of administration was decreased. The dose of acetylmethadol varied from 5 mg 2 or 3 times a day to 10 mg 4 or 5 times a day and in two patients only to repeated doses of 15 mg. Twenty-six patients were treated for 10 days or less, 19 were treated for 10-30 days and 31 for more than 30 days. Thirty-six of the patients were presumed to be already addicted because of the large doses of narcotics which they required. Only 13 patients received acetylmethadol by injection. With respect to the patients as a whole the authors said the analgesic effect was excellent in 14, satisfactory in 44 and fair in 16. In only two was it poor or uncertain. Also, for the whole group side-effects were reported (in numbers of patients) as follows:

	Period of treatment			
	2-10 days	*10-30 days*	*over 30 days*	*total*
Constipation	—	—	10	10
Nausea	2	1	5	8
Vomiting	4	4	9	17
Lethargy	3	3	7	13
Cumulation	3	3	3	9
Dizziness	2	1	3	6
Confusion	—	4	1	5
Hallucinations	—	2	1	3
Severe depression	2	—	—	2
No side-effects	13	2	7	22

It should be pointed out that 25 patients of the third group, receiving acetylmethadol for more than 30 days and in whom side-effects were most frequent, also received other narcotics and 19 of the group were believed to be addicted at the start of treatment. Also, since two-thirds of the whole

group had metastatic cancer, some of the side-effects, especially nausea and vomiting, might have been due to the disease. The authors' general conclusion was that doses of 5-10 mg of racemic α-acetylmethadol given orally 3 or 4 times a day were well tolerated, safe and highly effective on continued use. They believed that slow cumulation of the drug accounted for the continued analgesic effectiveness and prolonged action of the drug, but they admitted that cumulation leading to severe toxic effects might occur if too large doses were used.

Addiction liability

Fraser & Isbell (1951, 1952) studied racemic α-acetylmethadol and its *l*- and *d*- isomers in post-addicts for the appearance of morphine-like effects and in addicted individuals for suppression of morphine abstinence and for ability to substitute for morphine. 15-40 mg of the racemate or 5-20 mg of the *d*-form injected subcutaneously in post-addicts produced morphine-like effects pleasing to the individuals within 15-30 minutes. The racemate caused burning, aching pain at the site of injection. 10-30 mg of the *l*-isomer on subcutaneous or intravenous injection had no apparent effect for 4-6 hours after injection. Thereafter an effect like that of morphine or methadone developed slowly and was very persistent, sometimes lasting 48-72 hours. The *d*-isomer was less effective orally than subcutaneously. On the other hand, when the *l*-isomer was given orally, morphine-like effects appeared within an hour and a half, much more quickly than when the drug was given to the same subjects parenterally, but were as intense as when given by the parenteral route and were again very persistent, 24-72 hours. This greater effectiveness of *l*-acetylmethadol by oral administration was very striking and is in part borne out by the contrast between the results obtained by David et al. with oral doses and those seen by Keats & Beecher after subcutaneous administration.

The subjective changes observed with the optical isomers and particularly the difference between the effects of oral and subcutaneous doses of the *l*-isomer were paralleled by the time of appearance, intensity and persistence of pupillary constriction. The effect of the *d*-isomer on the pupil paralleled that of morphine when each was given in a dose of 30 mg subcutaneously. 30 mg of the *l*-isomer subcutaneously produced constriction of the pupil only after a delay of about 4 hours, but the constriction was still apparent 72 hours later. The same dose orally produced a greater constriction of the pupil promptly, reaching its maximum within 2 hours. The pupils were nearly normal again in 24 hours and completely normal in 48 hours.

In addicts who had been stabilized on morphine, two doses of 15-50 mg of α-*dl*-acetylmethadol subcutaneously at the 28th and 34th hour of abstinence completely suppressed the morphine abstinence syndrome. A nearly comparable suppression of abstinence was obtained with two doses of 30-40 mg of α-*d*-acetylmethadol subcutaneously but similar doses of the

l-isomer also subcutaneously had only a small and inconsistent effect. If, however, the *l*-isomer was given orally abstinence was suppressed strikingly and for a long time.

When substitution for morphine in addicted individuals was attempted, 60 mg of the *d*-isomer subcutaneously 4 times a day were required and these doses also produced signs of toxicity, sedation, dizziness and ataxia. On the other hand, a single oral dose of 60 mg of the *l*-isomer as infrequently as once in 72 hours completely prevented the appearance of signs of morphine abstinence. When the *l*-isomer had been substituted for morphine and then was stopped abruptly, an abstinence syndrome developed very like that after withdrawal of methadone, slow in onset and prolonged, and less intense than after morphine withdrawal.

Finally, Fraser & Isbell (quoted by Eddy, Halbach & Braenden, 1956) estimated the doses of the acetylmethadols equivalent to 50 mg of morphine in addiction-sustaining power as >15-<50 mg for α-*dl*-acetylmethadol, 33 mg for α-*l*-acetylmethadol, and 16 mg for α-*d*-acetylmethadol.

SUMMARY

α-*l*-Acetylmethadol administered subcutaneously had an analgesic effectiveness against post-operative pain equivalent to that of 10 mg of morphine only when doses greater than 40 mg were given; the equivalence was estimated at 50 mg. The drug, however, sometimes produced a dangerous comatose state something like that of morphine-poisoning. On the other hand, α-*dl*-acetylmethadol administered orally was effective against chronic pain at a dose of only 5 mg or 10 mg 3-5 times a day. Such doses were not infrequently accompanied by morphine-like side-effects. Their duration of effect is at least equal to that of morphine and some cumulation is possible. The α-acetylmethadol racemate and both of its optical isomers are addicting. The *l*-isomer only is more effective and more rapid in the production of morphine-like effects when given orally than when injected subcutaneously or intravenously. As little as 60 mg of the *l*-isomer orally as infrequently as once in 72 hours completely prevents the appearance of morphine abstinence symptoms in persons addicted to the latter drug.

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9. Methadone derivatives

(*b*) Dipipanone [a] (4,4-diphenyl-6-piperidino-3-heptanone)

Dipipanone, like methadone, is prepared as a racemate and all the observations reviewed were carried out with the racemate. The analgesic effect of the compound has been tested clinically against chronic pain by essentially the same technique in three institutions, and against post-operative or other types of pain by different methods of evaluation. All have used a double-blind technique and an impartial observer to record the degree of pain relief. In the chronic pain study (R. W. Houde, J. C. Seed & J. Cochin[b]), two doses of a standard, 8 mg and 12 mg of morphine, a placebo, and two doses of dipipanone differing from each other in the same ratio as the two doses of standard, were given in random order to the same patient, one dose per day on successive days. Throughout the remainder of the 24 hours the patient received other medication for his pain as necessary (morphine, levorphanol, pethidine or methadone). The daily dose of the unknown was given by the observer when the patient's pain was judged of such severity as to warrant the use of an opiate, and the observer inquired, at half-hour or hourly intervals up to 4 hours, if pain had not returned to the original level before then, as to the degree of pain present. The categories of pain were given numerical values—severe pain 4, moderate pain 3, slight pain 2, and no pain 1— and the degree of relief or the pain score was the sum of the differences between the original level of pain and that present at each observation for the 4-hour period. No patient was included in the final calculations unless he had received all five of the medications, called a quintet, and an effort was made to give two complete rounds of a particular quintet to a patient. In successive quintets the doses of standard remained the same but the doses of dipipanone were varied to facilitate determination of equivalence of potency to that of the standard, always retaining, however, the same ratio between the two doses. Four different quintets were employed in which the doses of morphine were always 8 mg and 12 mg and the doses of dipipanone were 12 mg and 18 mg, 18 mg and 27 mg, 27 mg and 40.5 mg, and 40.5 mg and 60.7 mg. Two hundred and twenty rounds in the various quintets were completed. Regression slopes, dose-effect relationship curves, and the equivalence of dipipanone to each milligram of morphine were calculated for each institution and for the combined data. There was very good agreement in the results at two institutions and a higher potency for dipipanone was shown in the third instance. The milligrams of dipipanone equivalent to 10 mg of morphine were 21.9, 20.5 and 11.3 mg for the three hospitals, respectively, and

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[a] International non-proprietary name for the racemic form; for other designations, see *Estimated World Requirements of Narcotic Drugs in 1958* (UN document E/DSB/15).

[b] Personal communication, 1957

18.8 mg for the combined data. In each of these studies side-effects were minimal.

In a trial against post-operative pain (H. K. Beecher,[a] Gravenstein, 1957) each patient got alternately 10 mg of morphine per 70 kg of body-weight or 15, 25 or 35 mg of dipipanone per 70 kg of body-weight subcutaneously. At 45 and 90 minutes and hourly thereafter the patients were queried as to their pain and scores were assigned according to the degree of relief—0 for no relief and 1, 2 and 3 for poor, good and complete relief, respectively. Also, the patients and their responses were grouped according to whether the pain was severe or moderate at the time of drug administration. The relief scores (first figure in each column) and the number of patients on which they were obtained (second figure in each column) were as follows:

	Severe pain time after medication (minutes)			*Moderate pain* time after medication (minutes)		
	45	*90*	*150*	*45*	*90*	*150*
Morphine, 10 mg.	15/9	15/9	12/9	22/10	24/10	24/10
Dipipanone, 15 mg	9/9	12/9	7/9	16/10	19/10	17/10
Morphine, 10 mg.	28/16	33/16	20/16	54/27	63/27	61/27
Dipipanone, 25 mg	22/16	24/16	20/16	57/27	63/27	58/27
Morphine, 10 mg.	22/13	27/13	25/13	44/18	44/18	39/18
Dipipanone, 35 mg	21/13	25/13	21/13	37/18	42/18	42/18

Dipipanone at a dose of 15 mg was inferior to 10 mg of morphine whether the pain was moderate or severe. At a dose of 25 mg it was equal to 10 mg of morphine against moderate pain only, and 35 mg of dipipanone were required to equal the effect of 10 mg of morphine against severe pain. The duration of action of morphine was slightly longer throughout.

Gillhespy et al. (1956) tested dipipanone in medical and surgical patients whose pain was so severe that an opiate would have been ordered. In 100 consecutive medical cases the dose was 20 mg; in 100 consecutive surgical patients with pain after gynaecological operations, the dose was 25 mg. All doses were given subcutaneously. Observations for pain relief and side-effects were made by the nurse in charge. The effectiveness of the medication was recorded as follows:

	Medical cases (803 doses)	*Surgical cases (800 doses)*
Complete relief	67	95
Moderate relief	27	4
Slight relief	3	1
No relief	3	0

Onset of effect was rapid in all cases and duration about 5 hours.

The incidence of side-effects varied from 4% to 5%; in only one medical patient were they severe enough to cause discontinuance of the drug. However, it was shown in preliminary trials on medical patients that side-effects

[a] Personal communication, 1957

were more frequent and more severe if the dose was 25 mg. The kind and incidence of side-effects in the two groups of patients were as follows:

	Medical cases (dose 20 mg.)	*Surgical cases (dose 25 mg)*
Sweating	8	21
Giddiness	5	10
Nausea	7	4
Vomiting	9	4
Headache	5	1
Blurring of vision	1	0

There was no complaint of anorexia or constipation, no obvious respiratory depression and little hypnotic effect. There was no local reaction or pain at the site of injection. The authors judged 25 mg of dipipanone to be more effective than 11 mg of morphine or 100 mg of pethidine.

Cahal (1957) sought to determine a dose-effect relationship curve for dipipanone by giving a series of doses on a logarithmic scale (from 4.4 mg to 33.75 mg) subcutaneously to each of 26 normal subjects. Doses were given in random order not more frequently than at 48-hour intervals with 0.5 ml N-saline as the control. The technique was double-blind. The procedure was a modification of Keele's method for ischaemic pain. The blood supply to the arm was cut off by a sphygmomanometer cuff about the upper arm and pain was elicited by rhythmical closing of the hand on a rubber bulb. The criterion of effect was the increase in number of contractions required to elicit pain after medication.

Two subjects were hypersensitive to the drug and their results were excluded. One was unable to reach pain threshold after any dose above 6.7 mg and experienced generalized pruritus on all doses with severe nausea and vomiting on the two highest doses. The other became very euphoric and garrulous even on the lowest dose; with the two highest doses he suffered severe nausea and vomiting and with the highest dose was disoriented and ataxic. The mean responses (difference in the number of contractions to produce pain before and after injection) for all subjects were as follows:

Dose	*Response at (hours):*				
	1	*2*	*3*	*4*	*5*
0.5 ml N-saline	11	10	8	7	5
4.4 mg dipipanone	12	12	10	8	7
6.7 mg dipipanone	11	13	12	9	7
10.0 mg dipipanone	13	13	13	11	11
15.0 mg dipipanone	14	16	14	12	11
22.5 mg dipipanone	19	24	21	21	17
33.75 mg dipipanone	24	24	23	18	15

The dose-effect relationship appeared to be linear, 10 mg being the lowest dose with a significant effect and 20 mg the optimal dose. Side-effects increased with dose but were greater than for saline at all doses. Table VII gives the incidence of side-effects.

TABLE VII. SIDE-EFFECTS FOLLOWING SUBCUTANEOUS ADMINISTRATION OF DIPIPANONE OR SALINE (26 NORMAL SUBJECTS)

Side-effects	Saline	Dipinanone dose (mg)					
		4.4	6.7	10.0	15.0	22.5	33.75
Drowsiness	1	3	2	7	8	14	16
Nausea	2	3	2	5	5	14	17
Dizziness	0	0	2	4	5	10	18
Euphoria	0	2	0	4	5	4	10
Muzziness	0	0	0	2	3	6	6
Vomiting	0	0	0	0	0	2	8
Headache	1	2	3	2	3	5	4
Dry mouth	0	0	2	0	1	5	6
Ataxia	0	0	1	0	1	5	6
Epigastric discomfort	0	1	1	3	2	0	1
Detachment	0	0	0	1	1	2	4
Pruritus	0	1	0	0	2	1	4
Tremor	0	0	0	0	0	2	5
Constriction of throat	0	0	0	1	1	1	4
Anorexia	0	0	0	0	0	3	1
Irritability	0	0	0	0	0	1	1
Deafness	0	0	0	0	0	1	1
Sleep	0	0	0	0	0	0	1
Total	4	12	13	29	37	76	113

The itching of which some subjects complained was rather distressing and persisted for many hours. All the injections were painful and often the pain was very persistent. Many subjects had tenderness and induration at the sites of injection for many weeks. The analgesic effect of dipipanone passed its peak within 4 hours and was nearly gone in 5 hours.

Fraser & Isbell (1956) gave doses of 5-30 mg of dipipanone subcutaneously to 22 former addicts. Typical morphine-like effects were observed after doses of 10-30 mg. If 30 mg were given, followed in two hours by a second dose of 30 mg, the effects persisted for about 24 hours. Four patients who had been stabilized on 260 mg of morphine per day were each given 50 mg of dipipanone subcutaneously at 0, 4, 8, 14, 18 and 22 hours after discontinuation of morphine, and the intensity of abstinence was followed

hourly from the 14th to the 24th hour. The observations were controlled by the administration of a placebo or the man's accustomed dose of morphine (45 mg) at corresponding hours during two other withdrawals in the same subjects. Dipipanone suppressed morphine abstinence as well as morphine. Isbell (quoted by Eddy, Halbach & Braenden, 1956) concluded that the addiction liability of dipipanone was approximately equivalent to that of morphine; i.e., 50 mg of one were equivalent to 50 mg of the other in physical dependence potency.

SUMMARY

Dipipanone appears to be more effective against moderate than against severe pain. Its optimal analgesic dose is 20-25 mg for chronic pain or acute moderate pain and its duration of effect about the same as that of morphine. Only minimal side-effects have been observed with doses of this order but side-effects increase materially with increase in dosage. The addiction liability of dipipanone is approximately equivalent to that of morphine.

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9. Methadone derivatives

(*c*) Normethadone[a] (4,4-diphenyl-6-dimethylamino-3-hexanone)

Normethadone differs from methadone or isomethadone by the absence of one methyl group. Experimentally (Eddy, Touchberry & Lieberman, 1950), it has an analgesic effect approximately like that of isomethadone, significantly less than that of methadone. Kirchhof (1948) found that 50 mg were required for analgesia in man, but at that dose side-effects were too frequent.

About six years ago normethadone was introduced in Germany as one of the constituents of an antitussive preparation, known as Ticarda. This preparation in liquid form contained 1% of normethadone and 2% of

[a] International non-proprietary name for the racemic form: for other designations, see *Estimated World Requirements of Narcotic Drugs in 1958* (United Nations document E/DSB/15).

p-oxyphenylmethylaminopropanol (Suprifen), both as hydrochlorides. Solid preparations, tablets, contained 7.5 mg of normethadone and 10 mg of Suprifen. Normethadone was expected to be antitussive because of the demonstration of a respiratory depressant effect in animals. Suprifen has sympathomimetic effects, blanching of mucous membranes and a bronchodilator action, which might be helpful at least in some varieties of cough. It also has central stimulant effects, and it was argued that these would prevent abuse of the mixture because tolerance to the central effect would not be expected. Hence the stimulant effects would limit attempts to increase the dose.

Ten reports on the use of Ticarda as an antitussive are summarized briefly in Table VIII. The statements were for the most part qualitative, based on impressions of patients and attendants. No quantitative comparison by a double-blind technique with control observations with a placebo and a standard such as codeine and with quantitative measurement of the incidence of coughing has been reported. Nevertheless, the reports indicate satisfactory relief of cough in most cases, appearing promptly, as a rule, and lasting from 3 to 12 hours. They are so uniform that a quantitative comparison of the preparation would be justified. Most authors have preferred the liquid preparation and the dose for adults has varied from 10 to 20 drops, once or more times a day. Fifteen drops were said to equal 7.5 mg of normethadone. The reports have been uniformly negative with respect to side-effects and, when they were mentioned at all, tolerance and dependence were said not to occur. This is the usual statement with new narcotic preparations without adequate control or details being given about duration of administration.

Vieten (1951) has described the use of Ticarda orally with 0.25-0.5 mg of atropine one half-hour before bronchography. It decreased the tendency to cough and decreased secretion.

Isbell & Fraser (1955) tested normethadone for morphine-like effect and addiction liability by the usual techniques employed at Lexington, Ky. With doses of 45 mg or more, orally or subcutaneously, definite morphine-like effects were seen in post-addicts, appearing within an hour and lasting 3 or 4 hours. Single doses of 60 mg subcutaneously were required for a definite effect on the morphine abstinence syndrome. These doses were given 30 hours after abrupt withdrawal of morphine from addicts stabilized on 240-480 mg per day. 60 mg of normethadone subcutaneously every 6 hours substituted for morphine in stabilized addicts with almost complete suppression of any signs of morphine abstinence. The authors concluded that normethadone had addiction liability which exceeded that of codeine but was probably less than that of methadone. Reviewing the work at Lexington, Isbell (quoted by Eddy, Halbach & Braenden, 1956) estimated that 50 mg of normethadone were equivalent to 50 mg of morphine in addiction-sustaining power.

TABLE VIII. ANTITUSSIVE EFFECT OF TICARDA

Author	Number and type of cases	Dosage [a]	Relief	Duration of effect	Side-effects	Remarks
Buchheim & Angermann (1951)	30 tubercular	1 or 2 × 8–12 drops per day	Satisfactory in most cases	About 8 hours	No euphoria	In 5 of 6 patients with 100 ml sputum per day, the amount decreased; others were usually not affected.
Reiman (1951)	53 tubercular	20 drops per dose up to 5 times per day	Better than dionin in 10 %; ineffective in 5 %	Longer than dionin in 10 % of cases	No euphoria or other side-effects	
Berger (1951)	Tubercular patients	1 or 2 × 15 drops per day	Satisfactory	Usually 5–6 hours	None	Prompt action, 10–15 minutes.
Morawetz (1951)	80 tubercular, 30 others with cough of various origins	15–20 drops	Satisfactory		None	
Riess (1951)	50, various types of cough		Satisfactory	10–12 hours		Prompt action, 15–20 minutes; no interference with secretion.
Riess & Tonjes (1951)	All types of cough	10–12 drops for children of 10 years or more and adults	Satisfactory			Promotes sleep by relief of night coughing.
Heimendinger (1952)	32, persistent cough of various types	20 drops for adults; 8 drops or more for children	Satisfactory in all but 3 cases	3–8 hours	Somnolence without other ill effect in child accidentally given adult dose.	No evidence of tolerance or dependence.
Giammarinaro & Agnoletto (1952)			Satisfactory			
Kelling (1952)	Children with acute or chronic cough					Satisfactory substitute for morphine derivatives.
De Beule (1953)						Satisfactory substitute for codeine in chronic cough.

[a] **Solution contains 1 % of normethadone and 2 % of Suprifen ; 15 drops are said to equal 7.5 mg of normethadone.**

The Lexington group did not employ the mixture known as Ticarda in their tests, because, at the doses required to produce morphine-like effects with normethadone alone, definite and perhaps serious signs of toxicity would be produced by the Suprifen component whether it was present in the 2:1 ratio of the liquid preparation or the 10:7.5 ratio of the tablets. Nor did they undertake to determine the effect of repeated administration of the mixture at therapeutic dose-levels. It has been clearly demonstrated in clinical practice, in spite of the early statements to the contrary, that such administration can produce or sustain addiction. W. van Lessen[a] appears to have encountered the first case of Ticarda addiction. The patient had taken hydrocodone and pantopon previously but it was not clear from the history whether or not he was addicted to either. He purchased Ticarda for cough and rapidly increased the dose because he felt stimulated. When the use of the preparation was interrupted he complained of sleeplessness, headache, trembling and inability to concentrate. Eventually he was taking 30-37.5 ml of the solution, up to 375 mg of normethadone, per day. Ebermann (1954) described another case, a young woman who was taking between 45 ml and 75 ml a day, 30-50 times the normal dose. This was quite probably a secondary addiction; she had taken pethidine, morphine and a barbiturate previously. Schmid (1954) reported six cases, four of them certainly secondary. One person took dihydrocodeine and Ticarda simultaneously, and the details of the sixth case were not given. Cieslak (1955) observed two cases of addiction to Ticarda, secondary to opiates and methadone; the daily oral doses corresponded to 120 mg and 450 mg of normethadone respectively. Haibach (1955) described the case of a soldier who had taken various narcotics for war injuries and who turned to Ticarda, increasing to 20 tablets, 150 mg of normethadone, a day; and Burkhardt & Orzechowski (1954) gave the details of still another case of secondary addiction.

Bühler in 1954 described a case of addiction where Ticarda was the only drug taken. The man, without medical advice, purchased the preparation for an irritating cough. With each coughing spell he took 30-40 drops, taking a total of more than 50 ml within a week. At that time, 12 hours after a dose, he broke into a sweat and complained of pain in his legs and back, pressure in his stomach and hot and cold flashes. Forty to fifty drops of the preparation caused all symptoms to disappear, but they reappeared whenever the use of the drug was interrupted. He increased his daily dose to about 37.5 ml. The man was eventually withdrawn under strong sedation followed by psychotherapy.

O. Schaumann[b] has attempted to gather the records of all cases of misuse of Ticarda and concludes from this search that the abuse of the

[a] Personal communication, 1953
[b] Personal communication, 1957

preparation is similar to abuse of codeine, and that, in relation to total use, incidence of addiction to Ticarda, either secondary or primary, is not greater than for codeine.

SUMMARY

Normethadone has been used clinically only as an antitussive and only in the form of a mixture with Suprifen, a sympathomimetic, added in part at least to bring about bronchodilation. The usual dose is the equivalent of 7.5 mg of normethadone orally in solution. Qualitatively the result has been mainly satisfactory in cough of various origins and the occurrence of side-effects has been denied. Normethadone has addiction liability, the addiction-sustaining dose equalling that of morphine. Instances have been described of the use of the mixture by addicts in place of other drugs of addiction, maintaining their addiction, and there has been recorded at least one case of primary addiction. Therefore the addition of the centrally stimulating agent, Suprifen, to normethadone in an antitussive mixture has not mitigated the addiction liability of the latter.

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9. Methadone derivatives

(*d*) Phenadoxone [a] (4,4-diphenyl-6-morpholino-3-heptanone)

The pharmacological examination of phenadoxone was reported in detail by Basil, Edge & Somers (1950) and its analgesic effect in man was measured in normal individuals by Hewer & Keele (1948) and Wilson & Hunter (1948), and in individuals with pain of pathological origin by Wilson & Hunter (1948), Hewer et al. (1949), Nathan (1952) and Keats & Beecher (1950, 1952). Hewer & Keele used only three subjects and produced ischaemic pain by having the individual close and open the hand rhythmically with the blood supply to the arm cut off. The drug was given intravenously and the smallest dose which definitely affected the rising pain intensity was determined. This threshold dose varied from subject to subject and the interrelationship between drugs varied from subject to subject, yet the authors thought the procedure advantageous because it avoided irregularity of absorption and applied the drug when pain was already present, as in clinical experience. The results, however, do not seem to be applicable to clinical experience. The threshold doses for the three subjects for several analgesics including phenadoxone were:

	Threshold doses (mg)		
Morphine . . .	0.002	0.1	0.35
Pethidine	7.5	1.0	7.5
Methadone . . .	0.25	0.1	0.3
Phenadoxone . .	0.25	0.01	0.4

Wilson & Hunter used the same method to produce ischaemic pain and injected the drugs intravenously, but their criterion of effect was a greater reduction in pain intensity. They rated pain intensity at the end of five minutes of ischaemia as 100%, an appreciable reduction in intensity as 50% reduction and decrease in the pain to a barely perceptible level as reduction to 20%. In these terms their results in 10 subjects, all receiving each agent, were:

	Pethidine 50 mg	*Methadone 5 mg*	*Phenadoxone 5 mg*
Pain reduction to 20% . . .	—	3	8
Pain reduction to 50% . . .	—	3	1
No pain reduction	10	4	1

Phenadoxone produced transient dizziness. In both tests on normal subjects phenadoxone would have to be rated as not materially different from methadone.

Wilson & Hunter (1948) gave phenadoxone in doses of 10-50 mg to 18 subjects with clinical pain, obtaining complete relief in 12, some relief in 4 and none in 2. The route of administration was oral, intramuscular

[a] International non-proprietary name for the racemic form; for other designations see *Estimated World Requirements of Narcotic Drugs in 1958* (UN document E/DSB/15).

or intravenous. The oral dose was 20 mg if the pain was not too severe, 30-50 mg for severe pain, with a duration of effect of 3-4 hours. The intramuscular dose was 10 mg or 20 mg, the effect lasting 2 or 3 hours. Giddiness and vomiting occurred if the patients were ambulatory. The intravenous dose also was 10 mg or 20 mg, but relief was of only 1-2 hours' duration. In their experience phenadoxone was shorter-acting than methadone. Spies (1955) used subcutaneous and intramuscular doses of 10 mg in patients with chronic and acute pain; the duration of effect was from 7 to 10 hours; of side-effects nausea was noticed, but no vomiting.

Hewer et al. (1949) were concerned with the development of a method in which the patient recorded the severity of his pain at hourly or shorter intervals and his estimations were given numerical values from 0 for no pain to 4 for severe pain, so that a pain score for statistical comparison could be calculated or pain charts representing onset and duration of effect could be constructed. They illustrated the method with charts of the effect of pethidine and methadone and reproduced the result of only a single administration of phenadoxone. A dose of 10 mg was given intramuscularly and the patient recorded his pain at 5-minute intervals. He obtained complete relief within 10 minutes but pain of slight severity reappeared in another 10 minutes. It remained slight for about 30 minutes and then returned to its initial severity at just under an hour from the time of administration.

Nathan (1952) attempted to establish equal analgesic potency by giving two drugs to the same patient with chronic pain. The usual procedure was to give one drug for 3 days, another drug for 2 days and the first drug again for one day. A minimum of 10 administrations of a dose were required for a comparison, often there were 40 or 50. Nathan considered 16 mg of morphine equivalent to 12 mg of methadone, to 125 mg of pethidine or to 10 mg of phenadoxone, each administered subcutaneously. The margin of safety with phenadoxone subcutaneously was narrow; 20 mg might produce dangerous respiratory depression. Orally the smallest dose which would produce significant analgesia was 30 mg; the dose which produced intolerable side-effects was 70 mg. The kinds of side-effects with phenadoxone were like those with morphine and methadone and there was always some depression of the individual's alertness if relief of pain was obtained.

Keats & Beecher (1950, 1952) evaluated phenadoxone in the treatment of post-operative pain, alternating administration of it and morphine in the same patient. The dose of morphine was always 10 mg per 150 pounds of weight, that of phenadoxone varied until a dose was used which gave relief with the same percentage of trials as with morphine. The technique was double-blind and effects were determined by trained observers, questioning the patients 45 and 90 minutes after drug administration. Satisfactory relief was scored only if the patient judged his pain reduced by at least 50% at both times of questioning. Keats & Beecher said that 60 mg

of phenadoxone were equivalent to 10 mg of morphine in analgesic potency. These are the only observations in which phenadoxone was rated as materially less effective than morphine. The data upon which their conclusion was based were as follows:

	Phenadoxone			*Morphine*		
Number of patients	*dose (mg)*	*no. of doses*	*percentage relief*	*dose (mg)*	*no. of doses*	*percentage relief*
42	6, 8, 10	66	54.5	10	66	83.3
72	12, 14	117	55.6	10	117	70.9
56	16, 20	83	53.0	10	83	77.1
22	30	33	63.6	10	33	75.8
38	40	58	51.7	10	58	70.7
40	50	60	71.7	10	60	71.7
36	60	55	69.1	10	55	72.7
12	70	19	89.5	10	19	84.2

The incidence and kind of side-effects after phenadoxone, morphine and a placebo were determined by Keats & Beecher (1951, 1952) in normal subjects, each of whom received each of the three agents on a double-blind basis in random order. The observations on normal subjects included also pulse rate, oral temperature, respiratory rate and minute volume, respiratory response to carbon dioxide and oxygen consumption. With respect to every symptom in the tabulation of side-effects (see Table IX) phenadoxone ranked above morphine in percentage incidence. Also side-effects persisted for more than 5 hours in 38% of the subjects after phenadoxone, in 27% after morphine.

The pulse rate was slowed about 10% by phenadoxone and by morphine. The oral temperature declined a little more (0.6°F) with phenadoxone than with morphine (0.4°F). The effect on respiratory rate, on respiratory minute volume and respiratory response to carbon dioxide and on oxygen consumption was practically the same for both drugs. Respiratory minute volume decreased on the average to about 80% of normal; oxygen consumption was reduced 5%-10%.

Hill (1951) employed phenadoxone in 50 obstetrical cases, in 40 of whom it was the only analgesic drug given, and compared the results with those of pethidine and of pethidine plus hyoscine. The results with respect to analgesia in numbers of cases were as follows:

Analgesic effect	*Phenadoxone : 10 mg i.m.*	*Pethidine : 100 mg i.m.*	*Pethidine : 50 mg+hyoscine 1/300 i.m.*
Good	29	35	32
Fair	5	3	7
Unsatisfactory . . .	6	2	1

In spite of these figures Hill said the general impression was that phenadoxone was more effective in relieving pain than 100 mg of pethidine. Perhaps he meant that when the result was good, pain was more completely relieved. Ten of the patients slept after phenadoxone and six others were

TABLE IX. PERCENTAGE INCIDENCE OF SIDE-EFFECTS IN NORMAL SUBJECTS OF PHENADOXONE, MORPHINE, AND PLACEBO

Side-effects	Placebo (72 subjects)	Morphine 10 mg (33 subjects)	Phenadoxone, 60 mg (45 subjects)
Drowsiness	36	91	96
Sleep	7	24	64
Difficulty in concentrating	10	43	62
Dizziness	1	41	73
Difficulty in focusing eyes	3	14	62
Thick speech	3	2	22
Ataxia, objective	3	31	56
Uneasy stomach	2.7	10	27
Nausea	6	34	58
Vomiting	0	7	31
Warm glow	6	29	29
Drunkenness	2.3	0 [c]	16
Headache	16	21	18
Pallor	-	16	56
Sweating	1	7	27
Hiccups	0	10	22
Itching	0	12	56
Constricted pupils	7 [b]	40 [c]	67
Generalized numbness	0 [b]	3 [c]	29

[a] Data on 44 subjects
[b] Data on 15 subjects
[c] Data on 30 subjects

drowsy. Labour seemed to be shortened slightly. The three drug regimens had a similar effect, or lack of it, on the babies. All but two of those whose mothers received phenadoxone breathed and cried immediately. One of the other two was born macerated, obviously not the effect of the drug.

Mushin (1951), who was one of those advocating pethidine as a supplement to nitrous oxide/oxygen anaesthesia, tried phenadoxone in a few cases, but found that it produced too much respiratory depression.

Addiction liability

Arnold, Hift & Solms in 1952 reported two cases of phenadoxone addiction and Carratala in 1953 reported two others. The Lexington Addiction Research Center [a] found that 30 mg of phenadoxone subcuta-

[a] H. Isbell, personal communication, 1949

neously produced definite signs of morphine-like "euphoria" (talkativeness, increased psychomotor activity, scratching, expressions of satisfaction with the drug, etc.) in six of eight post-addicts, but the effect lasted only 1-2 hours. Three of the patients complained of weakness, nausea and dizziness about 40 minutes after the drug was given. Doses of 10-30 mg intravenously produced a very intense morphine-like reaction very quickly, which the subjects described as very pleasurable despite the development of rather alarming cardiovascular symptoms, collapse-like in nature. The man who received the larger dose fainted; two others became very pale and dizzy and one vomited. Individuals who had been stabilized on morphine were given 30-60 mg of phenadoxone subcutaneously or 15 mg intravenously when the morphine abstinence syndrome was well developed at the 30th to 34th hour of abrupt withdrawal. All doses produced a striking alleviation of the abstinence symptoms, which was, however, very short-lived, persisting only 1-2 hours. Five subjects were experimentally addicted to phenadoxone. The dose was shortly increased to 35 mg every 3 hours subcutaneously and maintained at that level for 30 days because there was very little evidence of tolerance to the drug's sedative action. On one occasion, when the regular dose was accidentally injected intravenously, severe respiratory depression to complete apnoea followed. The patient responded to analeptics and artificial respiration. The total period of administration in these five patients was 52 days. Following withdrawal definite signs of abstinence were observed in only one of the five. Troublesome induration and inflammation at the injection sites developed in these men subjected to repeated administrations. Isbell (quoted by Eddy, Halbach & Braenden, 1956) estimated the dose of phenadoxone equivalent to 50 mg of morphine in addiction-sustaining power as less than 60 mg but commented on the unsatisfactoriness of this estimate because of the relatively short action of the drug.

SUMMARY

The analgesic effect of phenadoxone has been estimated in one instance as 10 mg equivalent to 16 mg of morphine, in another as 60 mg equivalent to 10 mg of morphine. In the first case chronic pain was treated, in the second post-operative pain; in both, administration was subcutaneous. Such a wide divergence in observations on analgesic action is very unusual. The duration of effect of phenadoxone is shorter than that of morphine. Side-effects in normal subjects given the larger dose (60 mg) of phenadoxone were more frequent than with morphine. Phenadoxone can produce severe respiratory depression, apparently also circulatory disturbances, and the margin between safe and toxic doses seems to be very narrow. Phenadoxone has addiction liability, based on its morphine-like effects and its ability to suppress the morphine abstinence syndrome, but probably less than that of morphine.

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10. Metopon [a] (Methyldihydromorphinone)

The first report on the clinical use of metopon appeared in 1941 (Lee, 1941) and in more complete form (Lee, 1942) a year later. There had been some trial of the compound in hospital practice under the direction of the Drug Addiction Committee of the National Research Council, USA, prior to this, but the results were not published. Lee (1941) administered metopon subcutaneously and later orally for the relief of severe pain in cancer patients who had had little or no previous narcotic experience. At the same time other similar cases were given morphine. Nurses and patients knew only that the medication was for pain relief. Results were determined from the nurses' and physician's notes; the latter were the outcome of periodic questioning of the patient. In a specific case administration of either drug began with a dose below that expected to give good relief; the dose was increased until satisfactory relief for that patient was obtained and then continued at that level and at an interval to maintain adequate relief. Further increase in the dose did not occur until the effect waned as the result of the development of tolerance. In the first study of subcutaneous administration 25 patients received metopon, 20 others morphine. Equivalent dosages for pain relief were 5 mg of metopon and 10 mg of morphine. The onset of relief was a little faster and the duration of effect a little shorter with metopon. The amount of sleep per dose and of mental sluggishness was less with metopon. Also nausea and vomiting were less frequent after metopon; the difference was greater with respect to vomiting. After 10 247 subcutaneous doses of metopon given to 25 patients nausea was noted 274 times (2.67%) and vomiting only 107 times; after 4233 subcutaneous doses of morphine given to 19 patients nausea occurred 125 times (2.95%) and vomiting 134 times. Three additional patients were given metopon

[a] International non-proprietary name

orally and three others oral doses of morphine. The effective oral dose of metopon was the same as the subcutaneous dose and in this small group of cases the ratio of its oral effectiveness to that of morphine was 2 : 1.

Lee (1942) carried out a second study of the relative effectiveness of metopon on a large number of medical and surgical patients chosen only on the basis of their need for narcotic for pain or tranquillity, and representing a fair cross-section of hospital admissions to the emergency department and to the medical and surgical wards. Comparison again was with morphine, but the two drugs were not given to the same patient. As in the previous study nurses and patients did not know the nature of the medication. The number of patients receiving morphine was 776, the number receiving metopon 135. The average individual dose of morphine was 9.6 mg and 96.8% of morphine doses afforded adequate relief. The average individual dose of metopon was 5.1 mg and all but 10 of the metopon doses gave adequate relief. Sleep followed 80.5% of the morphine doses, 65.1% of the metopon doses. The incidence of nausea and vomiting was 3.5% and 2.3% respectively with morphine, 2.1% and 0.5% with metopon. In one respect, namely as pre-anaesthetic medication, metopon was inferior to morphine and in some cases was a real hazard. Both drugs were administered as unknowns and the anaesthetist's judgement of the effects was the basis of comparison. Morphine was used as pre-medication in 550 cases, metopon in 114; both were used alone and in combination with other substances. The anaesthesias were nitrous oxide/oxygen/ether (58%), spinal, local and intravenous, and it was only in the first group that any difficulty was encountered. In 16 of the nitrous oxide/oxygen/ether cases, when metopon was used, respiratory depression was so marked as to cause the anaesthetist concern for his patient. The breathing became slow and shallow, required stimulation, and sometimes even artificial respiration. The less marked hypnotic action of metopon was a disadvantage for pre-medication, but led to repetition of the dose to provide the patient with greater mental depression in only two of the patients who suffered severe respiratory depression.

The Drug Addiction Committee of the National Research Council in the USA sponsored a country-wide trial of metopon for a period of a year (Eddy, 1949). Use was restricted to cancer patients and administration was oral only. Physicians were required to report to the Committee details of the patients treated and the results obtained; they reported on 3672 cases. The dose of metopon was 3 mg in 30.4%, 6 mg in 32.8%, 9 mg in 19.5%, more than 9 mg in 1.8%, and unreported in 15.4% of the cases. Pain relief was fair or better in 56.7%, poor in 27.4% and none in 15.8% of the cases. Sleep followed administration in only 27.4%, and mental clarity was retained in 73% of the patients. A euphoric effect was reported only 13 times. Nausea attributable to the drug occurred in only 4.0%. Nausea and/or vomiting was reported to have occurred in 490 patients with previous

medication; of these only 40 were nauseated after the shift to metopon. Many of the patients had received considerable narcotic medication before metopon was tried. In those for whom metopon was the first morphine-like drug employed, results were much better than in the group as a whole; there was a very definite shift from poor to complete relief of pain. The following figures show the percentage of pain relief obtained:

	3-mg doses				*6-mg doses*			
	complete	*fair*	*poor*	*none*	*complete*	*fair*	*poor*	*none*
All patients	24.2	36.4	24.0	15.2	28.3	35.1	23.2	13.4
Patients receiving metopon as first narcotic	47.3	36.4	10.8	5.4	58.4	33.9	3.7	3.7

Monroe (1949) reported on a small group (18 cases) of malignancies, who received oral doses of metopon up to 9 mg. Again the results were better if the patients had received no narcotic previously. Only four persons thought they experienced slight pleasurable sensations apart from their pain relief.

Wolff, Hardy & Goodell (1940), using themselves as highly trained subjects, injected 6.6 mg of metopon subcutaneously and found that it raised the threshold to pain evoked by radiant heat by 95%. The peak effect occurred in about 1½ hours; the threshold returned to normal in 6½ hours. This was approximately the effect obtained with 30 mg of morphine, except that with the latter the peak occurred about an hour later and the effect lasted about an hour longer.

Keats & Beecher (1952) compared the effectiveness of metopon and morphine for the relief of post-operative pain, using a double-blind technique and alternating subcutaneous administration of the drugs in the same patients. They found 3.5 mg of metopon equivalent in analgesic potency to 10 mg of morphine. They also compared the two drugs at these dose-levels in 15 normal men for incidence of side-effects and degree of respiratory depression. The two drugs were similar in both respects (Keats & Beecher, 1951). R. W. Houde & S. L. Wallenstein [a] have also compared metopon and morphine. They too gave the drugs subcutaneously and measured their effect on chronic pain. The dose of metopon calculated to be equivalent to 10 mg of morphine was 2.75 mg.

M. T. Pennell (1949), in a thesis presented at the St. Louis, Mo., University School of Medicine, reported on the use of metopon as an obstetric analgesic in 120 cases. The results are shown in Table X.

There was no apparent effect on the infant after oral or rectal doses, and the results with the latter were promising except for the incidence of nausea, which may not have been due entirely to the drug. When metopon was given intramuscularly, however, although the analgesic effect was very

[a] Personal communication, 1956

TABLE X. RESULTS OBTAINED WITH METOPON AS AN OBSTETRIC ANALGESIC IN 120 CASES

Number of Cases	Route of administration	Dose (mg)	Average total dose per patient (mg)	Effect (%)		
				good analgesia	drowsiness	nausea and/or vomiting
46	Oral	3–12	20.7	48.0	48.0	10.8
14	Rectal	12–18	27.0	78.5	85.7	21.4
60	Intramuscular	5–15	16.6	93.0	90.0	11.6

good, there was considerable depression of the infant. Only 68.3% of the babies breathed immediately; 6.7% breathed spontaneously after a minimal delay, and 25% required some degree of resuscitation.

Gaensler & McGowan (1950) found that metopon, like morphine, produced spasm about the opening of the common bile duct into the intestine. They placed a T-tube in the common bile duct of cholecystectomized patients, connected it with a manometer, and recorded the pressure in millimetres of water. The pressure rose 121 mm (average for 40 subjects) after 10 mg of morphine, and 112 mm (average for 16 patients) after 7.5 mg of metopon. Both drugs were given subcutaneously. In another series of tests (Gaensler, 1951) on some of the same patients a pressure system was connected with the T-tube in the common bile duct and the pressure required to evoke pain was measured. This threshold was raised 56.4% by the 10-mg dose of morphine and 46.4% by the 7.5-mg dose of metopon. The drugs were practically identical in their effect on this visceral pain threshold as well as in their spasmogenic effect on the biliary tract.

Addiction liability

Himmelsbach (1939) substituted metopon for morphine in 10 stabilized morphine addicts. Eight doses of metopon were given subcutaneously per day and 7 mg of the substitute were approximately equivalent to each 50 mg of the morphine stabilization dose. During the 7 days of substitution satisfaction of the addict was not quite complete and neither slightly larger doses nor shorter intervals of administration improved the situation. On abrupt withdrawal of the metopon an abstinence syndrome developed which was more abrupt in onset and less intense than after abrupt withdrawal of morphine.

In his studies on cancer patients, Lee (1942) found that tolerance to the analgesic effect of metopon developed, but a little more slowly than tolerance to morphine. With both drugs the intensity of the analgesic effect per dose decreased less than the duration of action; in other words, during prolonged administration the dose per day had to be increased more than

the individual dose. Also the quieting effect of both drugs showed a greater diminution in the chronic study than did the analgesic effect. With metopon the amount of sleep per dose averaged 157 minutes and the duration of analgesic effect 238 minutes when single doses were given, whereas the sleep per dose was only 85 minutes and the duration of analgesic effect 153 minutes on the average when many doses were given to the same patients. Most striking, however, was the rapid loss of tolerance to metopon even during a brief period of interruption of administration. In the chronic study the attempt was made to reduce the dose of analgesic at the beginning of re-administration after brief periods of withdrawal, up to 22 hours. This was never possible with morphine, but with metopon, when some tolerance had occurred, it was frequently possible after a brief withdrawal to reduce the dose to that at the very beginning of the injections in that patient and produce the same degree of comfort as before the interruption of administration.

Physical dependence (addiction) developed with metopon and with morphine in Lee's studies on cancer patients (1942), as evidenced by the appearance of abstinence phenomena during brief periods of withdrawal. These short withdrawals of 6-22 hours' duration were carried out at about 2-week intervals during the chronic administration of morphine and metopon. The intensity of abstinence was definitely less with metopon whether one compared the composite of all withdrawals after 21 days or more of administration or the withdrawal periods after the same duration of administration of each drug.

In the large series of cancer cases reported by Eddy (1949), the existence of addiction to the previous narcotic was mentioned specifically in 154 physicians' reports and was indicated clearly in the histories of many more cases. Metopon failed in some of these, presumably because of cross-tolerance; yet it relieved many more; that is, it substituted more or less completely for the previous narcotic. In at least 50 cases in which mild abstinence symptoms appeared at the beginning of metopon administration these disappeared during continued administration of the drug. The use of metopon for 4 weeks or more was reported for 500 cases; in 381, or 76%, no apparent tolerance occurred.

SUMMARY

About 3 mg to 5 mg of metopon were equivalent to 10 mg of morphine when administered subcutaneously for relief of acute or chronic pain. The duration of analgesic effect was slightly less for metopon than for morphine. Under conditions of chronic administration, metopon produced fewer side-effects, especially nausea and vomiting, and less sleep per dose. Mental clarity was better retained with metopon. The dose of metopon for an analgesic effect in chronic pain was the same for oral and subcutaneous

administration; it was nearly the same for oral and rectal as for intramuscular administration for obstetric analgesia. Effective analgesic doses injected intramuscularly in obstetrics produced significant depression of the infant. When metopon was given subcutaneously as premedication for nitrous oxide/oxygen/ether anaesthesia, severe respiratory depression sometimes developed. Tolerance and physical dependence occurred with prolonged administration of metopon, but they developed less rapidly and were less marked and tolerance disappeared more quickly with metopon than with morphine.

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11. Morphinan derivatives

(*a*) Racemorphan [a] (*dl*-3-hydroxy-N-methylmorphinan)

Substances of the morphinan group were the first and still are the only analgesics which have essentially the same chemical structure as morphine and the complete synthesis of which (see Braenden & Wolff, 1954) is being carried out starting from raw material having no connexion with opium alkaloids. The first morphinan derivative widely used as an analgesic was the racemic form of 3-hydroxy-N-methylmorphinan.

Analgesic effectiveness

Table XI shows the clinical experience of 18 authors with more than 4000 patients. Single doses of racemorphan of between 2 mg and 5 mg parenterally as well as orally were reported to be very effective against severe, acute and chronic pain, particularly in post-operative patients and those suffering from intractable cancer. The majority of authors used the parenteral routes, mostly the subcutaneous, but oral administration, even of small doses such as 1.5 mg (Hagemeyer, 1951) or 2 mg (Smith, 1950; Griesser & Henftling, 1953; and Mayer, 1955), was also satisfactory. Houde

[a] International non-proprietary name; for other designations, see *Estimated World Requirements o Narcotic Drugs in 1958* (United Nations document E/DSB/15).

TABLE XI. CLINICAL ANALGESIC DOSAGE AND SIDE-EFFECTS OF RACEMORPHAN

Author	Indication	Number of cases	Dosage				Side-effects	
			effective single dose (mg)	effective in percentage of cases	duration of analgesia (hours)	dose (mg) equivalent to 10 mg morphine	nature	frequency
Junkerman, Heen & Pohle (1949)	Cancer Pain of various origins	11 24	5	80 %		≃ 3.3	Nausea, vertigo	< Morphine
Tidrick et al. (1949)	Post operative pain [a]	270	5		same as morphine	5	Same as morphine	Same as morphine
Zager et al. (1949)	Surgical pain	58	4.5 6 s.c.	highly	probably > morphine			
Curreri, Gale & Dickie (1950)	Pain after thoracic surgery	28	5 s.c.	90 %	5		Nausea, vomiting Mental confusion	2 1
Jaggard, Zager & Wilkins (1950)	Post-operative pain	304	5 i.v.	88 %		5	Nausea, vomiting Oversedation Restlessness Sweating Respiratory depression teching	15 8 1 1 2 5
Smith (1950)	Cancer Persistent pain	8 4	2 oral 5 s.c.				Numb feeling Mild delirium	2 2
Theye, Stoelting & Graf (1950)	Pre-operative medication	314	3.7 s.c. (average)	majority			Minimal (atropine or scopolamine given where necessary)	Minimal
Crescente (1951)	Post-operative pain	75	2–5 s.c.	97 %	6–12 > morphine		Nausea, vomiting[b] Dizziness	5 1
Hagemeyer (1951)	Acute, chronic and post-operative pain		1.5 oral 2 s.c.	100 %	6–8 12		Dizziness, nausea weakness, sweating	Mostly in ambulatory patients
Junkerman, Heen & Pohle (1951)	Pain of various origins	39	5 s.c.		5–10	5	Nausea Vomiting Dizziness Lethargy	2 1 1 1

[a] **Double-blind technique ; racemorphan and morphine to same patient.**

[b] **Probably attributable to anaesthetic**

TABLE XI. CLINICAL ANALGESIC DOSAGE AND SIDE-EFFECTS OF RACEMORPHAN (concluded)

Author	Indication	Number of cases	Dosage				Side-effects	
			effective single dose (mg)	effective in percentage of cases	duration of analgesia (hours)	dose (mg) equivalent to 10 mg morphine	nature	frequency
Keutmann & Foldes (1951)	Post-operative pain	311	5 s.c.	92 %	6 (average) probably > morphine	< 5	Weak, drowsy, groggy Dizziness Nausea Vomiting Sweating Dry mouth Confusion Itching	39 6 26 11 66 15 3 3
Stange (1951)	Pre-operative medication Post-operative pain Obstetric pain Cancer (terminal)	62 200 47 48	3 s.c. 3–6 s.c. 2 s.c. 10–30 oral, i.d.	100 %	6 10		Vomiting	4
Stoelting, Theye & Graf (1951)	Pre-anaesthetic medication	1500	3–5 s.c.	93 %			None	
Wegerhoff (1951)	Cancer	several hundred	2 oral 3 s.c., rectal	almost 100 %	3–12 (average 4–6)		Vomiting, headache	Very low, except in ambulatory patients
Griesser & Henftling (1953)	Post-operative pain	200	2 oral, s.c., i.m., i.v.	97 %	3–7		None	
Houde & Wallenstein (1954)	Cancer	21	5 oral 5 i.m.					
Peukert (1954)	Pain of various origins	105	2.5–5 i.m.	94 %			Nausea Vomiting Dizziness	1 2 2
Strake (1954)	Post-operative pain Cancer Obstetrical	53 18	2.5 s.c. 5 s.c. 2.5 rectal		4–6			
Mayor (1955)	Surgical pain	330	2 oral 2.5 s.c., rectal		4–6		None None	

& Wallenstein (1954) varying the route of administration in blind experiments in the same patients, judged that 5 mg of racemorphan were significantly more analgesic by the intramuscular than by the oral route. 5 mg of racemorphan were found to be equivalent to 10 mg of morphine by several authors (Junkerman, Heen & Pohle, 1951; Tidrick et al., 1949; Jaggard, Zager & Wilkins, 1950; Keutmann & Foldes, 1951), the last three of whom based their statement on controlled trials with large numbers of patients. Tidrick et al. (1949) gave 5 mg of racemorphan and 10 mg of morphine to 270 post-operative patients under the precautions of the double-blind method and found these doses equally effective in respect of both the duration of effect and the side-effects produced. 642 surgical patients were given alternately 10 mg of morphine and 5 mg of racemorphan intravenously for post-operative pain by Jaggard, Zager & Wilkins (1950); 10% of the morphine group (338 patients) and 12% of the racemorphan group (304 patients) had no relief. Both drugs were equally effective in various groups of painful disorders except that after laminectomies significantly more racemorphan and after renal operations more morphine was required. Under similar conditions and precautions, Keutmann & Foldes (1951) administered subcutaneously 1336 doses of 5 mg of racemorphan to 311 patients and 1097 doses of 10 mg of morphine to 312 patients. Complete relief for 3 hours or less were obtained by racemorphan in 92% of all doses and by morphine in 85%; for complete analgesia lasting 3 hours and longer the corresponding figures were 75% for racemorphan and 55% for morphine.

It is noteworthy that children require relatively high doses of racemorphan. Theye, Stoelting & Graf (1950) reported that, for pre-operative medication, children with an average age of 13 years needed on an average 3.2 mg as compared with the average dose of 3.7 mg for adults. Later on, the same authors (Stoelting, Theye & Graf, 1951) said that for induction of anaesthesia children require and stand larger doses than adults.

Experimentally, the analgesic potency of racemorphan was evaluated by Zager et al. (1949) who used the radiant heat method (Wolff, Hardy & Goodell, 1940) in six normal subjects. The peak rise of the pain threshold by 3 mg of racemorphan was 25% in comparison to 21% and 27% by 10 mg and 15 mg of morphine respectively. Stange (1951) found in experiments with 12 healthy males that 3 mg of racemorphan had the same relieving effect on mechanically induced pain as 15 mg of morphine in the same subjects. Lee & Pfeiffer (1951) compared in 10 normal subjects the effects of subcutaneous injections of morphine, racemorphan and a placebo on pain using the warm wire algesimeter and the tooth pulp method. In both types of experiment the rise of the pain threshold by 3 mg of racemorphan was not significantly different from that by 20 mg of morphine. The double-blind experiments of Slomka & Gross (1952) with application of the radiant heat method to 5 trained volunteers gave similar figures for the ratio of

effectiveness in raising the threshold of pain, namely 1 mg of racemorphan to 5 mg of morphine. Thus, the ratio of analgesic effectiveness of morphine and racemorphan, as evaluated experimentally in normal men, was generally one to five (all authors in fairly good agreement with each other) whereas the evaluation under clinical conditions (again most authors in fairly good agreement) showed this ratio to be one to two.

Onset and duration of analgesia

After subcutaneous injection of from 2 mg to 5 mg of racemorphan, its analgesic effect began to appear within the usual (physiological) delay as was the case with morphine (Griesser & Henftling, 1953; Hagemeyer, 1951; Keutmann & Foldes, 1951; Peukert, 1954; Stange, 1951; Strake, 1954; Wegerhoff, 1951). As Table XI shows, the analgesic effect of parenteral doses of between 2 mg and 6 mg of racemorphan lasted from 3 to 12 hours, the average of which would seem to be somewhat longer than the duration of analgesically equivalent doses of morphine, as was explicitly stated by several authors (Crescente, 1951; Keutmann & Foldes, 1951; Zager et al., 1949). When administered intravenously as a supplement to nitrous oxide anaesthesia, racemorphan relieved pain for about 18 hours from the end of anaesthesia, as did morphine when given in an amount three and a half times that of racemorphan (Brotman, Cullen & Wilkins, 1950). Under experimental conditions with normal subjects, Zager et al. (1949) confirmed the somewhat longer duration of the analgesic effect of racemorphan as compared with that of morphine when the drugs were administered in a dose ratio of one to five.

Sedative action

A few authors considered racemorphan sufficiently sedative to be used for pre-operative medication. Thus, Wegerhoff (1951) noted some sedation after subcutaneous doses of 3 mg, but not after oral ones of 2-4 mg; Stange (1951) observed satisfactory sedation by 3 mg of racemorphan in 62 cases and Stoelting, Theye & Graf (1951) by doses of between 1 mg and 6 mg in 1500 cases before induction of anaesthesia. The latter said that the patients appeared droswy, but responded readily to questions, and that children needed larger doses than adults. Among 304 patients receiving 5 mg of racemorphan intravenously post-operatively, two were oversedated (Jaggard, Zager & Wilkins, 1950). Normal subjects were slightly sedated by 1 mg and definitely so by 3 mg of racemorphan subcutaneously (Zager et al., 1949). Several authors judged the sedative action of racemorphan to be nil or considerably inferior to that of morphine. Crescente's (1951) 75 post-operative patients, for example, were in general mentally alert after 2.5-3.75 mg of racemorphan subcutaneously, as were Mayer's (1955) 320 patients after subcutaneous or rectal administration of 2.5 mg. Poor or no

sedative effect was observed by Hagemeyer (1951) and Griesser & Henftling (1953) after subcutaneous doses of 2 mg and by Peukert (1954) after 2.5-5 mg parenterally. Junkerman, Heen & Pohle (1951) said that the sedation obtained by 5 mg of racemorphan subcutaneously was less than that with the equivalent analgesic dose of 10 mg of morphine. Racemorphan, therefore, is generally not considered useful for pre-operative medication.

Special therapeutic uses

For supplementation of nitrous oxide anaesthesia, racemorphan was used by Brotman, Cullen & Wilkins (1950) in 50 cases and its effects were compared with those of morphine in another group of 50; the depth and length of analgesia produced by the administration of a total of 9.7 mg of racemorphan were similar to those produced by 33.4 mg of morphine (which would seem to be in line with the ratio figures for analgesic effectiveness as given in Table XI; side-effects of racemorphan did not significantly differ from those of morphine (see above). The authors said that comparable anaesthetic results could be obtained with the two drugs as well as with pethidine and that these drugs had the advantage of wide applicability, smooth rapid recovery, prolonged (less for pethidine) post-operative analgesia and flexibility with careful dosage.

For obstetric analgesia, racemorphan was tried by Stange (1951). In 47 patients he found 1 mg insufficient, but 2 mg always satisfactory except that with the latter dosage three babies showed decrease of the heart's action. Strake (1954) stated (without details) that 2.5 mg suppositories of racemorphan eased labour without causing asphyxia in the infant. Racemorphan was not generally introduced into obstetrics, nor did it prove to have spasmolytic properties. For example, Griesser & Henftling (1953) found it relatively short-acting in cases of renal colic. Suppression of severe cough by 2-4 mg was seen by the same authors. In view of the relatively low sedative and respiratory depressive effects of racemorphan (see below), this would not seem to happen in general and the drug was not introduced as an antitussive.

Side-effects

Reports on side-effects will be discussed below in four groups: observations in normal human subjects (group 1); authors who considered the side-effects of therapeutic doses of racemorphan in patients either negligible or less than those produced by comparable doses of morphine (group 2), or of the same order as morphine (group 3), or definitely greater than those of morphine (group 4).

Group 1. In six normal subjects, doses of 0.5-1 mg of racemorphan were followed by awareness of vague gastro-intestinal distress, whereas 3 mg produced nausea in all and vomiting in two subjects (Zager et al., 1949).

Lee & Hasegawa (1950) saw in 12 healthy volunteers nausea, vomiting, and itching less frequently after 3 mg of racemorphan than after 20 mg of morphine, both drugs given subcutaneously. In 12 normal men, 2 mg of racemorphan subcutaneously caused nausea and vomiting in two cases, but no noteworthy changes in respiratory and circulatory functions, whereas 3 mg produced vomiting in three and a definite respiratory depression in all cases (Stange, 1951). In the experiments of Slomka, Keasling & Gross (1951) with seven normal male adults, 6 mg of racemorphan orally caused severe and prolonged nausea, dizziness, and sweating in all subjects; 3 mg produced less severe and less frequent side-effects such as drowsiness, sweating, nausea, dizziness, and general weakness.

Group 2. The majority of authors reporting on clinical experiences with racemorphan said that the side-effects of clinical doses were nil or less than those caused by equivalent doses of morphine, as can be seen from Table XI (Junkerman, Heen & Pohle, 1949; Curreri, Gale & Dickie, 1950; Theye, Stoelting & Graf, 1950; Stoelting, Theye & Graf, 1951; Griesser & Henftling, 1953; Peukert, 1954; and Mayer, 1955). Hagemeyer (1951) noticed dizziness, nausea, weakness and sweating, mostly in ambulatory patients. 2-4 mg of racemorphan parenterally did not influence the respiratory nor the circulatory functions (Griesser & Henftling, 1953; Peukert, 1954). To three groups of 50 patients each morphine, pethidine, and racemorphan were administered in equally effective amounts, usually together with pentobarbital for induction of nitrous oxide anaesthesia; the respiratory rate fell below 16 per minute in 25 patients with morphine, in 24 with pethidine, and in 32 patients with racemorphan (Brotman, Cullen & Wilkins, 1950), which does not demonstrate a significant difference between the drugs in this respect. Constipation and abdominal distension were caused less by racemorphan (2 mg) than by morphine (Hagemeyer, 1951; Griesser & Henftling, 1953) and were reported as absent (after 2.5-3.75 mg of racemorphan) by Wegerhoff (1951) as well as by Crescente (1951) and Peukert (1954). Experiments with unanaesthetized dogs and observations in a human patient with a Maydl jejunostomy led Gross & Featherstone (1950) to believe that racemorphan might produce constipation; however, this was not a noticeable feature of the drug's action as observed in 300 post-operative hospitalized cases. Their experiments in dogs did not demonstrate any significant effect of racemorphan upon the tone of the bladder or upon urethral resistance to the outflow of urine. Correspondingly, vesical spasms were not mentioned in the clinical reports reviewed in the present study and were explicitly reported not to occur with 200 patients receiving 2-4 mg of racemorphan by parenteral routes (Griesser & Henftling, 1953). They were not seen in several hundred patients after 2-3 mg, often several times daily by all routes (Wegerhoff, 1951), nor in 39 cases treated with 3 mg and more often with 5 mg (Junkerman, Heen & Pohle, 1951). Oliguria

was, however, reported by Brotman, Cullen & Wilkins (1950) in two cases out of 50 who had been given an average of 9.7 mg of racemorphan before and during nitrous oxide anaesthesia.

Group 3. The number and incidence of side-effects as seen in 270 post-operative patients receiving 2.5 mg or 5 mg of racemorphan every 3 hours were considered by Tidrick et al. (1949) as being the same as those caused by 5 mg or 10 mg of morphine. Keutmann & Foldes (1951), when comparing the effects of 5 mg of racemorphan with those of 10 mg of morphine in two groups of about 300 surgical patients, said that diaphoresis and drowsiness were more frequent and nausea and vomiting less frequent with racemorphan than with morphine; with regard to other side-effects, the difference between the two drugs was not significant. In normal men, pruritus was caused less frequently by 3 mg of racemorphan than by 20 mg of morphine subcutaneously (Lee & Hasegawa, 1950). Of 311 patients receiving 5 mg of racemorphan, itching occurred in 3, whereas 10 mg of morphine given (also subcutaneously) to a similarly composed group of 312 patients produced itching in 6 cases (Keutmann & Foldes, 1951). In two groups of post-operative patients (one group, of 338 patients, receiving 10 mg of morphine and the other group, consisting of 304 patients, treated with 5 mg of racemorphan), both drugs being given intravenously every 3 hours for several days, itching was observed in one case of the morphine group and in five of the racemorphan group (Jaggard, Zager & Wilkins, 1950). Hence, the incidence of skin reactions to racemorphan would not seem to differ essentially from that to morphine, as was confirmed by observations in former morphine addicts (Fraser & Isbell, 1950).

Group 4. Observations in the two groups of post-operative patients referred to above, i.e., 338 receiving 10 mg of morphine and 304 receiving 5 mg of racemorphan intravenously (or half these dosages for young and debilitated patients), led Jaggard, Zager & Wilkins (1950) to conclude that the over-all incidence of side-effects was significantly greater with racemorphan than with morphine.

On the whole, it would appear that the average dosage used by authors reporting little or no side-effects was below 5 mg, whereas a higher degree and incidence of side-effects of racemorphan comparable or even superior to those caused by morphine were generally seen with the higher dosage of 5 mg of racemorphan.

Tolerance

The following authors did not observe tolerance to the analgesic effect of racemorphan when administered over periods of between 12 days and 6 weeks:

Zager et al. (1949): 6 cases, 3-6 mg subcutaneously, daily, up to 6 weeks;

Stange (1951): 1 case, ~20 mg subcutaneously, daily for 33 days;

Wegerhoff (1951): several cases, 2-8 mg oral or subcutaneously, daily for several weeks;

Griesser & Henftling (1953): starting single dose (2 mg parenterally) remained effective up to 24 days.

However, development of tolerance during prolonged administration of racemorphan had been observed by Junkerman, Heen & Pohle (1949, 1951).

Addiction incidence and tests of addiction liability

Only a few of the authors reporting on clinical experience with racemorphan communicated observations relating to its capability of causing euphoria or addiction. Euphoria was not observed by Smith (1950) in 12 patients receiving from 2 mg orally to 5 mg subcutaneously for chronic pain; nor was it evident in 1500 patients premedicated with subcutaneous or intravenous doses of between 1 mg and 6 mg for induction of anaesthesia (Stoelting, Theye & Graf (1951), nor in Griesser & Henftling's (1953) 200 post-operative patients after parenteral single doses of 2 mg. Three mg of racemorphan did not produce euphoria (Zager et al. 1949) in six normal subjects not suffering from pain, but did so in one of 12 healthy volunteers (Stange, 1951). In a group of 304 post-operative patients, intravenous administration of 2.5 mg or 5 mg of racemorphan was followed by euphoria only once. Doses of up to 20 mg produced euphoria in 4 of 35 patients (Junkerman, Heen & Pohle, 1949) and up to 5 mg led to euphoria, but not to physical dependence within 13 weeks' administration, in a group of 105 cases as reported by Peukert (1954). Abstinence symptoms as signs of physical dependence on the drug were not seen by Zager et al. (1949) when, in 11 patients, the administration of racemorphan was abruptly stopped after subcutaneous injection of a total of between 30 mg and 590 mg over periods of between 3 and 52 days. No signs of physical dependence were observed after withdrawal of patients who had received 5 mg of racemorphan daily for 4-8 weeks (Curreri, Gale & Dickie, 1950) or 2-10 mg a day for several weeks (Wegerhoff, 1951). Junkerman, Heen & Pohle (1951), however, had evidence of dependence in two cases after daily injection of 5 mg for 25 and 28 days.

The evaluation of the addiction-producing potency of racemorphan carried out by Fraser & Isbell (1950) in former morphine addicts comprised the following tests.

When administered subcutaneously to 10 former morphine addicts, single doses of 7.5 mg of racemorphan induced euphoria (characterized as usual by loquaciousness, increased psychomotor activity, slurring of speech and requests for more of the drug) to an extent approximately equivalent to that produced by 30 mg of morphine. The euphoria was more intense after intravenous injection, its onset in the case of racemorphan being slightly delayed as compared with morphine.

Five healthy adult males, former morphine addicts who had been abstinent from morphine for at least six months, received racemorphan subcutaneously; the initial daily dose of 6 mg was increased as quickly as tolerance permitted, i.e., within 17 days, to 60 mg a day (divided into 4 equal doses), this being continued for another 3 weeks. Pulse, respiration and systolic blood pressure were slightly depressed; miosis was less than during morphine addiction. All patients liked the drug, which satisfied them in the same way as morphine. During addiction to racemorphan the pattern of the electroencephalogram was similar to that observed in addiction to morphine or methadone (see page 635). The abstinence symptoms produced by abrupt withdrawal of racemorphan were in nature, onset, intensity, and duration not different from those after withdrawal of morphine. The authors considered the total addiction liability of racemorphan therefore as approximately equal to that of morphine. Furthermore, Isbell & Fraser (1951) found that racemorphan relieved signs of abstinence from morphine.

SUMMARY

Racemorphan is a strongly analgesic drug with the same therapeutic indications as morphine (except perhaps for pre-anaesthetic medication). Its analgesic potency in patients is about twice that of morphine and five times greater than that of morphine when tested in normal healthy men. Its effectiveness by the oral route equals that by the subcutaneous route. The usual analgesic single dose is 5 mg. The onset of the analgesic effect of racemorphan is within normal limits; its duration is somewhat longer than that of morphine.

Racemorphan provides less sedation than equally analgesic doses of morphine. Like pethidine, it can be used as an adjunct to nitrous oxide/oxygen anaesthesia.

The side-effects of analgesic doses of racemorphan resemble in general those produced by morphine, but are perhaps somewhat less frequent. Constipation, abdominal distension, and vesical spasm occur less frequently than with morphine.

The development of tolerance to the analgesic effect of racemorphan is possible. Euphoria and addiction have been reported in clinical practice. The addiction liability of racemorphan as assessed in *ad hoc* experiments is approximately equal to that of morphine.

Analgesic as well as addiction-producing properties of racemorphan are possessed by its levorotatory component only and not by the dextrorotatory (see monograph on levorphanol, page 677).

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11. Morphinan derivatives

(*b*) Levorphanol [a] (*l*-3-hydroxy-N-methylmorphinan)

Analgesic effectiveness

Soon after the introduction of racemorphan into clinical use, it became evident from animal experiments (Benson, Stefko & Randall, 1953; Fromherz, 1951; Randall & Lehmann, 1950) that only its levorotatory isomer was an analgesic agent and that the dextrorotatory form (dextrorphan [b]) was devoid of such a property. This was confirmed by Slomka & Gross (1952) in experiments with five trained volunteers by means of the Wolff-Hardy-Goodell (1940) method and under the precautions of double-blind procedures, application of placebos, and randomization of the drugs administered subcutaneously. In these experiments 0.5 mg of levorphanol raised the pain threshold by 10.9% whereas the rise produced by the same quantity of dextrorphan was 0.8%. The combination of 0.5 mg each of the levo- and dextro-isomers raised the pain threshold by only 7.7%, which was interpreted by the authors as the result of an antagonistic action of the dextro-isomer since it diminished the analgesic effect of the levo-isomer.

[a] International non-proprietary name: for other designations, see *Estimated World Requirements o Narcotic Drugs in 1958* (United Nations document E DSB.15).

[b] International non-proprietary name

Later on this difference between the optical isomers of racemorphan was confirmed by another series of experiments in six trained normal subjects (Slomka & Sleeth, 1953), with administration of higher doses demonstrating even more clearly the lack of analgesic action as well as the antagonistic behaviour of the dextro-isomer.

The clinical experiences of 13 authors regarding the analgesic action of levorphanol in about 2600 patients are summarized in Table XII. Six authors administered it orally and parenterally, seven authors by subcutaneous injection only. The single-dose ranges were 1-2 mg for oral and 1-4 mg for parenteral application. The majority found 2 mg subcutaneously very effective in nearly all cases treated. Two authors found it necessary to increase the single dose to 4 mg and 6 mg respectively in exceptional cases of most severe pain. Becker & Bundschuh (1952) found no difference between oral, rectal, and parenteral application in regard to the analgesic effectiveness. Some patients found the oral administration more effective than the injection (Glazebrook, 1952). Von Rechenberg & Zeerleder (1951) stressed the high effectiveness of oral administration and Harnasch (1952) that of both oral and rectal application. Cullen & Santos (1954) evaluated different doses of levorphanol in patients with chronic pain; the analgesic effect of 4 mg was significantly greater than that of 2 mg, but with 5 mg no further increase of effect could be obtained.

The estimates for the dose of levorphanol which produced an analgesic effect equal to that produced by 10 mg of morphine were between 1 mg and 3 mg (Bitter, 1953; Glazebrook, 1952; von Rechenberg & Zeerleder, 1951). From Hunt & Foldes' (1953) trials in two groups of 311 and 312 post-operative patients it can be concluded that a little less than 3 mg of levorphanol were equally analgesic as 10 mg of morphine. Furthermore, comparison of the levorphanol group with another group of 311 patients receiving racemorphan in a dose which contained the same quantity of the levo-isomer as the levorphanol group showed that the admixture of the non-analgesic dextro-isomer decreased the analgesic potency of the levo-isomer. These findings were in line with those of Slomka & Gross (see above), demonstrating an inhibitory effect of the dextro-isomer on the analgesia of the levo-isomer. Crehan (1954) believed that 1 mg of levorphanol was equivalent in analgesic respect to 50 mg of pethidine, 5 mg of methadone or 2 mg of phenadoxone, from which figures a ratio of approximately 2 : 10 for equi-analgesic doses of levorphanol and morphine can be deduced. The aforementioned findings are in line with the ratio of 1 : 2 valid for equi-analgesic doses of racemorphan and morphine on the one hand and for equi-analgesic doses of levorphanol and racemorphan on the other. For the latter two substances, the same ratio was confirmed in patients by Harnasch (1952). Of 90 of Glazebrook's (1952) patients who had received morphine and levorphanol for pain, 84% preferred levorphanol, 8% preferred morphine and 8% had no preference.

TABLE XII. CLINICAL ANALGESIC DOSAGE AND SIDE-EFFECTS OF LEVORPHANOL

Author	Indication	Number of cases	Dosage				Side-effects	
			effective single dose (mg)	effective in percentage of cases	duration of analgesia (hours)	dose (mg) equivalent to 10 mg morphine	nature	frequency
Von Rechenberg & Zeerleder (1951)	Pain of various origins, cardiac insufficiency, angina pectoris	250	1.5 oral 2 s.c.	90%	4–6	2–3	Vomiting Nausea Dizziness Confusion Pruritus Respiratory depression	6% 4% 3% 3% 1 case <morphine
Becker & Bundschuh (1952)	Mostly terminal cancer	200	1-2 s.c., i.m. 2 oral, rectal		7–12		Decreased pulse rate Decreased respiratory rate	
Glazebrook (1952)	Malignant diseases, chronic bone and joint diseases, occlusion, vascular diseases, nervous diseases	200	1.5–2(–4) oral, parenteral	92%	8–10	≈2	Lightheadedness, dizziness, numbness Nausea Vomiting Headache Confusion Respiratory depression	39%, after 2.6 mg, disappeared with 2nd or 3rd dose 9% 2% 2% 1% 5% (33% after 4 mg)
Harnasch (1952)	Mostly cancer	76	2 [a] oral 4–6 [b] oral, rectal, parenteral	95%	8–10 [a] 3–6 [b]		Nausea, dizziness, palpitation Vomiting	13% higher in upright position 5%
Bitter (1953)	Sciatica		1 oral, s.c.			1		
Crawford & Binning (1953)	Pre-anaesthetic medication	400	2–5 s.c.					

[a] Moderate pain [b] Severe pain

TABLE XII. CLINICAL ANALGESIC DOSAGE AND SIDE-EFFECTS OF LEVORPHANOL (concluded)

Author	Indication	Number of cases	Dosage				Side-effects	
			effective single dose (mg)	effective in percentage of cases	duration of analgesia (hours)	dose (mg) equivalent to 10 mg morphine	nature	frequency
Hunt & Folden (1953)	Post-operative pain	311	3 s.c.	95%	5½ (average)	<3	Sweating Drowsiness, grogginess Nausea Vomiting Dry mouth Headache Pruritus	11% 10% 9% 5% 5% 1% 1%
Senne (1953)	Post-operative pain	>80	1.5 oral 2 s.c.		6–10		Not significant	
Bozza (1954)	Post-operative pain	∿80	2 s.c. (average)		8–15 (average)		Retention of urine Vomiting Circulatory collapse	15 cases 9 cases 2 cases
Brown (1954)	Pre-anaesthetic medication	100	2 s.c.	66%	7		Drowsiness Nausea Respiratory depression (mild)	≈20% ≈ 6% ≈ 5%
Quaglia & Franco (1954)	Cancer	52	2 s.c.	85%	4–8		Nausea Diminished intestinal peristalsis Vomiting Urticaria	4 cases 3 cases 1 case 1 case
Starke (1954)	Pre-operative (rhino-laryngology)	800	2 s.c.	Mostly			Dizziness, nausea, vomiting	<morphine
Emmons et al. (1955)	Post-operative pain	110	2 s.c. 3 oral	96% 74%			Drowsiness Nausea, vomiting Hypotension Vertigo Headache Pruritus, skin reaction	15 cases 8 cases 4 cases 2 cases 2 cases 2 cases
Gaard (1955a)	Post-operative pain	51	1–2 s.c.	Mostly satisfactory				

Onset and duration of analgesia

The time lapse between ingestion or injection of levorphanol and onset of the analgesic action was reported to be 20-60 minutes (Harnasch, 1952; von Rechenberg & Zeerleder, 1951) and 10-20 minutes, respectively (Becker & Bundschuh, 1952; Brown, 1954; Quaglia & Franco, 1954; von Rechenberg & Zeerleder, 1951; Senne, 1953; Starke, 1954). Brown (1954) observed the peak analgesic effect 90 minutes after subcutaneous administration. The analgesic effect of therapeutic doses (1-4 mg, mostly 2 mg) of levorphanol lasted between 4 and 15 hours, depending also on the degree of pain (see Table XII). Thus the duration of equally effective doses of racemorphan and levorphanol is practically the same, as could be expected. In Hunt & Foldes' (1953) trial with a large number of post-operative patients, the analgesia produced by 3 mg of levorphanol lasted on an average 5.5 hours, as compared with 5.8 hours after 10 mg of morphine. Glazebrook (1952) and Quaglia & Franco (1954) considered levorphanol superior to morphine in regard to the duration of action.

Sedative action

Of eight authors in whose reports on levorphanol mention was made of its sedative action, all but one agreed that analgesic doses of levorphanol produced some sedation which, although less pronounced than with morphine, was therapeutically useful. Harnasch (1952) had not noticed sedation with doses of 2-6 mg of levorphanol. Von Rechenberg & Zeerleder (1951) and Quaglia & Franco (1954) said that its sedative effect was less than that of morphine. Glazebrook (1952) considered levorphanol not as soporific as morphine yet able to relieve anxiety; according to Becker & Bundschuh (1952) it was sedative, but not hypnotic. Brown (1954) found its sedative action sufficient for pre-anaesthetic purposes in about two-thirds of cases.

Supplementation of anaesthesia

Brotman, Cullen & Wilkins (1950) had used racemorphan intravenously in total doses up to 9.7 mg (which contain half that amount of levorphanol) for supplementation of nitrous oxide anaesthesia. From comparison of recovery time and post-operative analgesia with those of two other series using morphine and pethidine as supplements, they concluded that the three drugs were equally useful for this purpose when administered in equivalent doses. Further reports on the subject as summarized in Table XIII lend themselves fairly well to a comparison with each other since, in all but one series, opium alkaloids together with scopolamine or atropine were administered pre-anaesthetically and barbiturates were used for induction of anaesthesia. The initial intravenous dose of levorphanol was usually about 1 mg and the total amount used generally two to three

TABLE XIII. USE OF LEVORPHANOL AS SUPPLEMENT TO NITROUS OXIDE/OXYGEN ANAESTHESIA

Author	Number of cases	Induction of anaesthesia	Premedication other than levorphanol	Levorphanol		Side-effects
				initial dose (mg)	total dose (mg)	
Brown (1952)	100	Thiopentone 0.5 g	Omnopon-scopolamine (morphine in patients > 60)	0.5 after wearing off of thiopentone effect	1.5 (2.0)	Some respiratory depression in poor risk cases, less than with pethidine
Bozza (1954)	80	Pentothal	Pantopon-scopolamine or Pantopon-atropine	0.5–2	up to 3	Post-operative Vomiting 9 cases Retention of urine 15 cases Collapse 2 cases Respiratory depress. 1 case
Cavaciuti & Rolandi (1954)	150	"Tiobarbiturato" 0.5–0.8 g	Pantopon-scopolamine or Pantopon-atropine		1–4 (average 1.5)	Less vomiting and more sedation than with pethidine
Crehan (1954)	252	Thiopentone 0.5 g	Omnopon-scopolamine (morphine-atropine in patients > 60)	1	3.5 (max.) (¼ of cases 2.5; ¼ of cases 1.5–2)	Post-operative; vomiting in 20 % of cases
Franks (1954)	Intra-nasal & intra-oral operations	Thiopentone 0.15–0.3 g	Papaveretum-scopolamine or morphine-atropine	1	repetition: 0.5–1 when cough reflex recurred	
Hamilton & Cullen (1955)	10	Pentothal	Morphine-scopolamine (sometimes barbital oral)	5–14		Respiratory depression antagonized by levallorphan (in $^1/_{10}$ the dose of levorphanol)
Radnay & Hechter (1955)	23		Atropine	1–3 (average 2.2) (15 min. before operation). For induction of anaesthia: i.v. drip or intermittently (average 3.8)		As above

times greater. Brown (1952) compared the results of the series of 100 cases as shown in Table XIII with another group of 100 receiving in a similar fashion 25 mg of pethidine as the first dose, which was repeated as necessary. In both groups the percentage of satisfactory results was the same and the incidence of post-operative complications, such as vomiting and minor respiratory depression, was similar. Later on, the same author (1954) reported on the administration of levorphanol by continuous drip in 25 cases of supplementation to nitrous oxide anaesthesia; since the rate of the drip had to be increased to an extent which led to a significant increase of the respiratory depression during and after the operation, he believed this procedure contra-indicated. However, when levallorphan as a specific antagonist against opiate-induced respiratory depression became available, it was possible to increase considerably the dose of levorphanol as well as to administer it by continuous drip, the resulting respiratory depression being antagonized by levallorphan in a dose ratio of approximately one-tenth that of levorphanol (Cullen & Santos, 1955; Hamilton & Cullen, 1955; Gaard, 1955b; Radnay & Hechter, 1955; Radnay, 1956).

Side-effects

The comparison of Table XII with the table given for analgesic doses and side-effects of racemorphan (Table XI) shows a close similarity between the nature and incidence of side-effects produced by racemorphan and levorphanol in equally analgesic dosage. From this it could be inferred that the side-effects of racemorphan are due to its levorotatory component only, which was confirmed by Isbell & Fraser (1953) with respect to the respiratory depressive and miotic effects. These relations as well as the parallelism regarding character and frequency of side-effects between equi-analgesic doses of the racemic and levorotatory forms of 3-hydroxy-N-methylmorphinan on the one hand and morphine on the other are illustrated by a survey of Hunt & Foldes (1953) of three groups comprising each about 300 post-operative patients treated under the same conditions with nearly equally analgesic doses of morphine, racemorphan and levorphanol, respectively, as partially reproduced in Table XIV.

Experiments in guinea-pigs had shown that in a dose comparable with the analgesic dose in man (on the basis of mg per kg of guinea-pig and man respectively), morphine decreased the tonus of the small intestine (Straub & Ozaki, 1933), whereas levorphanol did not do so in the same dose ratio, but only in doses corresponding to about five times the analgesic dose in man (Hildebrandt & Matthäy, 1953). In 10 normal subjects, 3 mg of levorphanol and 16 mg of morphine, both by injection, were strongly spasmogenic to the small gut as demonstrated by means of an intrajejunal balloon (Glazebrook, 1952), but the morphine-induced spasms were uncomfortable in these cases and painful in one case, whereas those induced by levorphanol were not noticed by the subjects themselves. In clinical practice,

TABLE XIV. EFFECTS OF APPROXIMATELY EQUI-ANALGESIC DOSES OF LEVORPHANOL, RACEMORPHAN AND MORPHINE SULFATE

	Levorphanol 3 mg	Racemorphan 5 mg	Morphine sulfate 10 mg
Number of patients	311	311	312
Number of doses	1067	1336	1097
Relief, 1st dose (%):			
Complete	77.2	66.5	46.2
Moderate	19.3	20.9	32.0
Slight	2.6	10.0	16.0
None	1.0	2.6	5.8
Relief, all doses (%):			
Complete	77.5	75.0	54.7
Moderate	17.2	17.4	30.3
Slight	3.4	6.0	11.7
None	1.9	1.6	3.3
Side-effects, 1st dose (%):			
Sweating	10.9	21.2	17.0
Dryness of mouth	4.8	4.8	1.8
Anorexia	—	0.3	—
Pruritus	1.0	1.0	2.0
Weakness	—	2.6	—
Headache	1.3	0.6	1.8
Drowsiness	8.0	7.7	5.5
Grogginess	1.9	2.2	0.3
Confusion	0.3	1.0	0.6
Visual disturbance	—	0.6	0.3
Tachycardia	—	—	0.6
Chills	—	—	0.3
Dizziness	0.6	1.6	1.6
Nausea	9.0	8.4	12.2
Vomiting	5.1	3.5	8.0

no constipation was seen after 2-6 mg of levorphanol (Harnasch, 1952) or after daily doses up to 8 mg (von Rechenberg & Zeerleder, 1951). Starke (1954) said that 2 mg sometimes caused slight constipation. Quaglia & Franco (1954) observed a decrease in intestinal peristalsis in three of 52 patients treated with daily doses of 2-6 mg. No abdominal distension was seen in 150 patients premedicated before nitrous oxide/oxygen anaesthe-

sia with 1-4 mg of levorphanol. Thus, constipation and abdominal distension appeared to occur less with levorphanol than with morphine, as was also reported for racemorphan. Retention of urine was reported by Bozza (1954) in 15 of 80 patients after average doses of 2 mg administered as supplement to nitrous oxide/oxygen anaesthesia. Changes in vesical functions were, however, not seen by other authors (Quaglia & Franco, 1954; Randall & Lehmann, 1950) after daily doses of 8 mg and 6 mg respectively.

Pruritus was sometimes caused by levorphanol, the incidence being reported as 1 in 250 (von Rechenberg & Zeerleder, 1951), 1 in 52 (Quaglia & Franco, 1954), 3 in 311 (Hunt & Foldes, 1953), and 1 (skin rash) in 7 cases (Slomka & Sleeth, 1953), and was thus approximately of the same order as with racemorphan and morphine. A rarely reported side-effect—increased tone of striated muscles—was frequently observed by Hamilton & Cullen (1955) after administration of pethidine and levorphanol to 40 patients for supplementation of nitrous oxide anaesthesia and also in some of 23 patients given levorphanol for the same purpose (Radnay & Hechter, 1955). In both series the muscular rigidity was relieved by levallorphan.

Whereas circulatory depression is one of the least frequently reported side-effects of levorphanol, careful attention was paid to the drug's depressing action on the respiration by all investigators and it was even therapeutically exploited, for example, when levorphanol was used as an analgesic in cases of cardiac dyspnoea or myocardial infarction (von Rechenberg & Zeerleder, 1951). As can be seen in Table XII, respiratory depression with therapeutic doses was generally less frequently observed than were, for instance, certain side-effects of a vagomimetic character such as dizziness, nausea and vomiting. Hunt & Foldes (1953) did not register respiratory depression among the side-effects caused by 3 mg of levorphanol in 311 post-operative cases. A short review of these data shows that respiratory depression was significant above a certain dosage level of about 2-3 mg of levorphanol. No effect on respiration was seen by Gaard (1955a) in 100 cases receiving 1-2 mg post-operatively nor by Crehan (1954) when administering intravenous doses of between 0.5 mg and 1 mg to 252 patients as a supplement to thiopentone/nitrous oxide anaesthesia, but one case of apnoea lasting 30 minutes after a single dose of 2 mg was seen by the latter. Similarly, Meyer & Oehmig (1956) saw a decrease of respiratory rate and volume to half the normal values after intravenous injection of 2 mg during anaesthesia. Of 100 cases given 2 mg levorphanol subcutaneously together with atropine or scopolamine as pre-anaesthetic medication, mild respiratory depression occurred in five (Brown, 1954). One-third of 69 patients were depressed by 4 mg as opposed to only 5% of 180 patients by single doses of 2.6 mg (Glazebrook, 1952). A critical dose-level (of about 3 mg) regarding the respiratory depression caused by levorphanol was also observed in experiments on normal subjects. For example, 3 mg of levorphanol and 16 mg of morphine had similar depressant effects on the respiration

of 10 normal men (Glazebrook). In nine healthy volunteers, levorphanol intravenously in a dosage of 0.0054 mg per kg of body-weight reduced the ventilation for 3 hours to 65% of normal when breathing room-air and to 45% of control when breathing 5% carbon dioxide (Thomas & Tenney, 1955). Among 10 patients apnoea was produced in one by 10 mg of levorphanol and the respiratory rate was diminished considerably (to between 4 and 14 per minute) by doses of 5-10 mg (Gross & Hamilton, 1954). These trials, as well as the administration of even greater doses of levorphanol for supplementation of nitrous oxide anaesthesia (see above), were, of course, possible only after effective antagonists (for example, levallorphan) against the opiate-induced respiratory depression had become available.

A drug having a depressing effect on the respiratory centre might be expected to have antitussive properties. However, only a few authors mentioned this subject. Von Rechenberg & Zeerleder (1951) said that patients with irritating cough regained sleep after one tablet (1.5 mg of levorphanol). Glazebrook (1952) believed that levorphanol did not suppress cough as well as codeine or methadone. As a supplement to nitrous oxide anaesthesia in nasal or oral surgery, intravenous injection of levorphanol (like pethidine) was repeated whenever the cough reflex threatened to recur (Franks, 1954). Bozza (1954) mentioned that the influence of levorphanol on the cough reflex was minimal when she used it as an adjuvant to nitrous oxide/oxygen/pentothal anaesthesia. Thus, the experience that racemorphan is not particularly useful as an antitussive was generally confirmed by further observations on its levorotatory isomer.

Tolerance

In the opinion of von Rechenberg & Zeerleder (1951), the analgesia obtained from regular administration of levorphanol during several weeks and even months was remarkably constant. Glazebrook (1952) believed that slight tolerance to the analgesic effect occurred when the drug was continued for more than two weeks. Reports saying that doses had to be increased when given for weeks and months (Becker & Bundschuh, 1952) or up to 40 days (Quaglia & Franco, 1954) are possibly indicative of the development of tolerance. There were also some indications of the development of tolerance to the less severe side-effects of levorphanol (von Rechenberg & Zeerleder, 1951), and 39% of 180 patients experiencing lightheadedness, dizziness or numbness following 2.6 mg of levorphanol did not complain of these effects after the second or third dose (Glazebrook, 1952).

Addiction incidence and tests of addiction liability

Euphoria due to therapeutic doses of levorphanol was not observed by Senne (1953) (80 cases, 1.5 mg orally up to 4 times a day), nor did he have evidence of addiction (during only 2 weeks' observation). Glazebrook

(1952) believed that the uplifting effect in mood of analgesic doses was not true euphoria since it was not seen in normal subjects or in patients with minor pain. 2 mg up to three times a day caused euphoria in all of 52 cancer patients (Quaglia & Franco, 1954), but the drug could be suspended without signs of abstinence when pain waned. After administration of daily doses of 2-4 mg during 2-3 months, levorphanol could be withdrawn without abstinence symptoms except in one case, who received 16 mg a day (von Rechenberg & Zeerleder, 1951). These authors had seen euphoria in 4% of their cases. Becker & Bundschuh (1952) did not believe addiction to levorphanol impossible, although some of their cancer patients could be withdrawn without difficulty after more than a year's medication. In the Federal Republic of Germany (Gewehr, 1956), the percentages of addicts (total of addicts=100%) taking morphine and levorphanol as the only drug of addiction were:

	1952	*1953*	*1954*	*1955*
Morphine	19.5	15	21.4	19.4%
Levorphanol . . .	0.7[a]	3.3[b]	2.8	2.6%

[a] Not under narcotics control at the time
[b] Put under narcotics control on 16 June 1953

In two types of experiment Isbell & Fraser (1953) assessed the addiction liability of levorphanol. The effect of single doses was studied in 15 non-tolerant former morphine addicts and the effects produced by 3-4 mg of levorphanol subcutaneously or orally were roughly equivalent to those produced by 30 mg of morphine subcutaneously and included increased psycho-motor activity, loquaciousness and requests for more of the drug. These effects were less pronounced after oral than after subcutaneous administration of levorphanol. 10-100 mg of the dextrorotatory 3-hydroxy-N-methylmorphinan subcutaneously or orally did not cause such changes of behaviour. In six patients addicted to morphine and stabilized on daily doses (120-300 mg) which just prevented the appearance of signs of abstinence, morphine was abruptly withdrawn and, at the 28th to 32nd hour of abstinence, single doses of levorphanol (orally as well as subcutaneously) relieved the symptoms of abstinence from morphine very effectively. The dextrorotatory form had no significant effect on abstinence from morphine. Levorphanol, therefore, was considered to have a high degree of addiction liability, whereas dextrorphan was considered to be devoid of addiction liability.

SUMMARY

Levorphanol is the levorotatory component of racemorphan and represents the total of the latter's analgesic and addiction-producing properties since the dextrorotatory component is devoid of both. Accordingly, the analgesic effectiveness of levorphanol is twice that of racemorphan. The

average analgesic single dose of levorphanol is 2 mg, which is considered to be equivalent to 10 mg of morphine. Because of its high effectiveness if taken by mouth, the usual oral dose of levorphanol is between 1 mg and 2 mg. Its analgesic action appears within the normal delay after administration by all routes and lasts somewhat longer than that of morphine.

Levorphanol has some sedative effect (but less than morphine) and is used by means of intravenous drip or repeated injections as a supplement to general anaesthesia with nitrous oxide/oxygen.

The side-effects of levorphanol are generally qualitatively and quantitatively similar to those produced by morphine except that decrease of intestinal peristalsis, constipation and vesical spasms occur less frequently.

Tolerance to the analgesic action and to some side-effects of levorphanol can develop. The addiction liability of levorphanol is at least as great as and probably greater than that of morphine. Cases of addiction to levorphanol are reported.

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11. Morphinan derivatives

(c) Dextromethorphan [a] (*d*-3-methoxy-N-methylmorphinan)

3-Hydroxy-N-methylmorphinan and 3-methoxy-N-methylmorphinan were prepared in the laboratory as racemates. They bear the same relation one to another as morphine to codeine. When these racemates were resolved into their optically active antipodes, it was shown (Benson, Stefko & Randall 1952) that analgesic, sedative and morphine-like effects in general were exhibited by the levo-isomers only (levorphanol and levomethorphan). Yet the dextro-isomer (dextromethorphan) in experimental animals had distinct antitussive action. Proof that addiction liability too was exhibited by the *l*- and not by the *d*-isomer (Fraser & Isbell, 1952; Isbell & Fraser, 1953) led naturally to the trial of the latter for antitussive action in man.

The first studies of the antitussive action of dextromethorphan were by Cass & Frederik (1953) and Cass, Frederik & Andosca (1954) in America and by Capello & Di Pasquale (1955) in Europe. Cass & Frederik initially (1953) gave codeine 17 mg, dextromethorphan 4 mg and a placebo, each under three code designations in identical capsules, 4 times daily to 65 patients with chronic cough. A coded medication was given for 5 consecutive days. An impartial observer, the patient and the physician reported on the severity of the cough 4 times daily—reports that generally agreed very well. The physician's estimate was used in the analyses. The cough was given a numerical rating—0 for no cough, 1 for occasional barely troublesome cough, 2 for moderately troublesome cough, 3 for markedly troublesome cough and 4 for incessant coughing. This permitted calculation of a mean score for cough with each medication and ranking of the medications according to their antitussive effect. Coughing was significantly less with both dextromethorphan and codeine than with the placebo, but at the doses used codeine had the greater effect. The patients were observed and questioned for side-effects, particularly nausea, constipation and drowsiness. The incidence of side-effects was not different with dextromethorphan and placebo, but was significantly greater with codeine.

Since dextromethorphan appeared to have some antitussive action, Cass, Frederik & Andosca (1954) carried out a second series of observations

[a] International non-proprietary name

by a similar technique. In this series there were 69 patients and five medications—dextromethorphan 6 mg, 12 mg and 18 mg, codeine 15 mg, and a placebo. Each medication was given to each patient three times a day for seven days. As in the previous series, cough intensity at each observation was given a numerical rating and a mean value was calculated for all observations with each medication, as follows:

Medication and dose	*Mean intensity of cough*
Placebo	1.4887
Dextromethorphan, 6 mg	1.3655
Dextromethorphan, 12 mg	1.2833
Codeine, 15 mg	1.2629
Dextromethorphan, 18 mg	1.2527

Thus a good dose-effect relationship was shown for the antitussive action of the three doses of dextromethorphan and it was calculated that 15 mg were equivalent in effectiveness to 15 mg of codeine. Again the side-effects of dextromethorphan were hardly different from those of the placebo whereas their incidence with codeine was greater than with any other medication.

Capello & Di Pasquale (1955) treated 23 tubercular patients with refractory cough with dextromethorphan, 30 mg daily, either orally or by injection. There was a marked decrease in coughing and expectoration was facilitated. The authors said that respiratory function, by a variety of tests, was usually improved.

In a third study on 63 patients with chronic cough Cass & Frederik (1956) compared dextromethorphan at doses of 10 mg and 20 mg with codeine 15 mg, carmiphen ethanedisulfonate 10 mg and a placebo. All medications were given under code designations 4 times a day for 10 days each. Each such period of drug administration was followed by three days on which the patients received known placebo medication 4 times a day before the next medication was given. The coded medications were given to each patient in random order and severity of cough was determined by a single observer 3 times a day. Cough severity was recorded as a numerical value for statistical analysis as in the previous studies.

Dextromethorphan at both dose-levels, codeine and carmiphen ethanedisulfonate were all significantly more effective than placebo. While dextromethorphan at both dose-levels and codeine had significantly greater activity than carmiphen ethanedisulfonate, a statistically significant difference among the first three was not demonstrable. The authors again said that for practical purposes dextromethorphan and codeine may be considered of equal antitussive effectiveness on a weight basis.

In contrast to Cass & Frederik, Beecher, Gravenstein & Devloo (1954) and Gravenstein, Devloo & Beecher (1954) could not detect a positively significant reduction in the number of coughs either experimentally produced in normal subjects or of pathological origin with dextromethorphan

at a dose of 10 mg. The patients could not distinguish between dextromethorphan and a placebo. They could distinguish the effect of codeine and with it there was a downward trend but not a statistically significant difference in the number of coughs.

Ralph (1954) gave doses of 4 mg and 15 mg of dextromethorphan for cough, usually 4 doses a day for periods of 3 days to 6 months. Relief was recorded as slight, moderate or marked as follows:

Degree of relief	*Patients given 4 mg*		*Patients given 15 mg*	
	number	*%*	*number*	*%*
Slight	13	28.2	10	10.2
Moderate . .	23	50.0	44	44.8
Marked . . .	10	21.7	44	44.8

It was the author's impression, not based on statistical comparison, that in patients who had received both drugs 15 mg of dextromethorphan gave as good relief as 30 mg of codeine. Side-effects, temporary nausea or dizziness, were seen in only 7 of 183 patients and in 5 of these the author believed the drug was not responsible.

Hottinger (1954) reported on the use of dextromethorphan in 453 patients, mostly children with acute or chronic cough. He said that it was at least as effective as hydrocodone, thebacon or codeine, basing his conclusion on administration of dextromethorphan for two days followed by one of the other drugs for two days or administration of the two drugs in the reverse order in the same patients. The usual dose for infants was 2-5 mg of dextromethorphan, for adolescents and adults 5-20 mg. Hottinger said the dose could be increased safely to 10 mg in infants or 30 mg in adults. Even with such dose increases no side-effects were observed.

Tünnerhoff & Schwabe (1955) also said that dextromethorphan at a 10-mg dose was as good an antitussive as 20 mg of codeine, 15 mg of dionin, 5 mg of thebacon or 15 mg of hydrocodone, based on paired administrations to the same patients. They administered 7.5-15 mg of dextromethorphan per dose, with an average daily dose of 12.9 mg, to 120 patients and 20-30 mg per dose, with an average daily dose of 28.8 mg, to 73 patients. Relief was obtained as a rule in 20 to 30 minutes and lasted on the average 3 hours with the smaller doses and 3¼ hours with the larger. The effect sometimes persisted for 6 or 7 hours. The degree of cough suppression observed was as follows:

Degree of relief	*Patients given 7.5-15 mg*		*Patients given 20-30 mg*	
	number	*%*	*number*	*%*
Cough suppressed . . .	49	40.8	23	31.5
Cough lessened	16	13.3	27	37.0
Cough unchanged but expectoration easier .	28	23.3	14	19.1
No effect	27	22.5	9	12.3

Kummer (1955), Steiger (1955) and Zettel (1955) have reported a satisfactory antitussive effect with dextromethorphan. Kummer reported a series of 120 cases of irritative cough, given doses of 10 mg 3 or 4 times in 24 hours. He said the effect was slower and less lasting but just as intense as that of opiate antitussives. Steiger treated more than 100 tubercular patients and found the effect as good as that of codeine. 10-20 mg of dextromethorphan were given usually in syrup 2 or 3 times a day. Secretion was not affected and expectoration was easier. No nausea or constipation was observed. The only side-effect was a burning sensation in the stomach in one patient taking 3 doses of 15 mg per day.

Bickermann et al. (1957) have developed a quantitative method for evaluation of experimentally produced cough and by means of this method have compared the antitussive effect of codeine, dextromethorphan, propoxyphene, and noscapine at different dose-levels with a placebo on a double-blind basis. Nineteen healthy individuals were used in the study. Each was required to inhale citric acid aerosols of varying concentration to determine the threshold stimulus—that concentration which evoked not less than 4 coughs when inhaled 5 times. Immediately after a control run (five inhalations of the threshold concentration at 1- or 2-minute intervals), a drug to be tested was administered orally and repeat studies were performed at hourly intervals for a period of 4 hours. The number of cough responses and the mean flow rate of exhaled air were recorded. The drugs, doses, number of subjects per dose and percentage change in number of coughs at each hour are shown in Table XV. There was no statistical difference in the antitussive activity of dextromethorphan 10 mg, noscapine 15 mg, and propoxyphene 130 mg when compared with codeine 15 mg. At the highest dose of each drug, except propoxyphene, the effect lasted throughout the 4-hour period of observation. Side-effects, slight in character, were reported by only 8 of the 19 subjects and were most frequent when codeine was the drug given.

Fraser & Isbell (1952) and Isbell & Fraser (1953) tested dextromethorphan for morphine-like effect and addiction liability by their usual techniques. In doses up to 100 mg subcutaneously or orally in former addicts it produced no perceptible morphine-like effect, no constriction of the pupil and no respiratory depression. In similar doses it had no effect on the morphine abstinence syndrome. They judged dextromethorphan to have no addiction liability.

SUMMARY

Dextromethorphan appears to be an effective antitussive; its effect at its optimal dose of 10-15 mg equals that of codeine. It has no detectable analgesic or sedative action and is practically devoid of side-effects. Dextromethorphan has no addiction liability.

TABLE XV. ANTITUSSIVE EFFECT OF CODEINE, DEXTROMETHORPHAN, PROPOXYPHENE AND NOSCAPINE

Agent	Number of subjects	Dose (mg)	Percentage decrease in coughs at hours:			
			1	2	3	4
Placebo	8	—	— 7.5	+ 2.5	+ 5.0	+25.0
Placebo	8	—	+10.6	— 4.3	— 4.3	+12.8
Placebo	8	—	— 8.0	—12.0	—12.0	+ 2.0
Codeine	7	5	—17.2	—22.4 *	—22.4 *	—17.2
Codeine	6	15	—32.5 *	—32.5 *	—27.5 *	—10.0
Codeine	6	30	—32.8 *	—43.1 *	—34.5 *	—22.4 *
Dextromethorphan	6	5	—33.5 *	—30.6 *	—18.1 *	—12.7
Dextromethorphan	8	10	—29.8 *	—24.6 *	—24.6 *	—26.3 *
Dextromethorphan	7	20	—23.9 *	—25.4 *	—33.3 *	—25.4 *
Propoxyphene	8	65	— 6.0	— 8.0	—26.0 *	—12.0
Propoxyphene	8	130	—21.7 *	—29.0 *	—15.9 *	— 7.2
Noscapine	6	5	—31.9 *	—19.1	—19.1	— 6.4
Noscapine	7	15	—30.0 *	—16.7 *	—23.3 *	—20.0 *
Noscapine	10	30	—35.5 *	—39.5 *	—31.4 *	—26.7 *

* Statistically significant difference

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12. Myrophine [a] (myristyl ester of benzylmorphine)

In mice, the toxicity of myrophine was found to be very low (LD_{50}:800 mg orally/kg body-weight) (R. Digo [b], J. J. Pocidalo [b]) and 31 times less than that of benzylmorphine when administered intraperitoneally (J. J. Pocidalo [b]). Since the ester of benzylmorphine with myristic acid is not soluble in water, an oily solution was prepared for parenteral and oral administration. C. Brun & H. Legger[b] treated 49 cases of sciatica, neuralgia, lumbago, and periarthritis with doses of between 20 mg and 100 mg, which were particularly effective when injected intramuscularly or around the nerves concerned. For this reason, the authors believed that the analgesic effect was mainly of a local character. In five cases of gastric or duodenal ulcer, only the oral administration of the oily solution of myrophine gave relief. R. Digo[c] judged that pain of neuralgic origin and painful gastric symptoms, as well as colitis, were particularly liable to be relieved by myrophine. He said that the analgesic action had a rapid onset and found that it lasted longer when myrophine was injected at the site of the pain. He also noticed a sedative action in certain cases of anxiety and depression. The analgesic effect of a 40-mg injection lasted 12-24 hours and that of a 40-mg suppository 4 hours and longer. In some cases, where myrophine suppositories had no effect, about half the amount of morphine given by the same route was successful. In almost all of 42 poliomyelitis patients, the muscular pains were relieved by one intramuscular injection of 40 mg of myrophine (J. J. Pocidalo [b]). In 80% of these, the effect lasted about 12 hours, in the remaining cases, 1-4 hours. Three cases failed to obtain relief from myrophine. M. Zara [b] administered 40-mg doses to patients suffering from neuralgia of different origins, periarthritis humeroscapularis, epicondylitis and sciatica. In cases of neuralgia, 3-10 injections were given as closely as possible in the painful region. The results were good; they were less satisfactory in cases of arthrosis and nil in cases of severe cephalalgia. In a number of cases, where the pain could be relieved by morphine only, two daily injections of 40 mg of myrophine gave partial relief. The author concluded from his experiences with a total of 50 cases that myrophine had a pronounced local anaesthetic effect and a much weaker central analgesic effect. In some cases the oral administration of the oily solution (40 mg of myrophine and more) was effective against the gastric sensations produced by cortisone derivatives (M. Zara [c]).

Side-effects

The above-mentioned authors agreed that myrophine was generally well tolerated. C. Brun & H. Legger [b] and R. Digo [b, c] reported on the absence of constipation. M. Zara [c] saw local reactions at the site of injec-

[a] International non-proprietary name
[b] Personal communication, 1955
[c] Personal communication, 1956

tion, as well as urticaria. Of 22 patients given oral doses of between 25 mg and 600 mg of myrophine, four developed an erythematous, intensely itching rash which was of a severe, generalized character in one case receiving 100 mg (Fraser & Isbell, 1955).

Addiction liability

In none of the patients treated with myrophine as reported above were signs of addiction to this substance noticed (C. Brun & H. Legger; [a] R. Digo; [a, b] J. J. Pocidalo; [a] M. Zara [a, b]). R. Digo [a] stated that myrophine did not have any influence on behaviour and that its abrupt cessation was never followed by any disturbances. He reported that, in a case of addiction to morphine administered for stump pain, the pain was completely relieved by three daily injections of 40 mg of myrophine for three days, but the patient could no longer stand the abstinence from morphine. In a similar case of addiction to oxycodone, the pain and then the sensation of the phantom limb disappeared after three days' treatment with 3 daily intramuscular doses of 40 mg of myrophine; cessation of myrophine after 8 days was not followed by abstinence symptoms. Although in this case and in a case of heroin addiction, the withdrawal of the drug of addiction was facilitated by administration of myrophine, Digo did not believe that myrophine could be used as the sole drug of substitution in the course of withdrawal of an addict from morphine. With a view to detecting addiction-producing properties of myrophine, Zara [a] administered it to incurable cancer patients in 2 daily doses of 40 mg regularly over 2 weeks without finding any evidence of an abstinence syndrome after abrupt cessation.

For detection of morphine-like euphoria, 18 former morphine addicts were given single doses of between 25 mg and 600 mg of myrophine (Fraser & Isbell, 1955); the drug had to be given orally because of the impracticability of parenteral administration of the necessarily large doses. No evidence of morphine-like effects was obtained in any one of the subjects at any time. To four patients who had been stabilized on daily doses of 240-320 mg of morphine, 100 mg of myrophine were administered every 4 hours, the first of these doses being given 8 hours before the abrupt discontinuation of morphine. Signs of abstinence were the same, as regards onset and intensity, as those following abrupt withdrawal of morphine without substitution of myrophine. Hence, it was concluded that myrophine possessed no addiction liability (World Health Organization, 1955, 1956; Fraser & Isbell, 1955).

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[a] Personal communication, 1955
[b] Personal communication, 1956

SUMMARY

The analgesic action of myrophine is substantially less but lasts usually longer than that of morphine. A certain local analgesic action appears to be present after injection. With the exception of skin reactions, side-effects have not been observed. Myrophine does not produce addiction.

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13. Nalorphine [a] (N-allylnormorphine)

Three reviews (Huggins & Moyer, 1955; Lasagna, 1954; Woods, 1956) on the general pharmacology and antagonistic action of nalorphine have been published recently, the third being the most comprehensive and containing more than 100 references. Attention here will be focused, therefore, on its analgesic effect in man, whether alone or in combination with morphine, on its side-actions and on the study of the compound for morphine-like effects and addiction liability.

Lasagna & Beecher (1954) and Beecher & Lasagna (1955), using the method of Denton & Beecher (1949) for quantitative evaluation of drug effects on post-operative pain, were interested first of all in determining whether or not nalorphine could be given in combination with morphine without interfering with the analgesic effect of the latter. If it could, the possibility existed that its addition might reduce the side-effects of morphine. Morphine plus nalorphine and nalorphine alone alternately with the standard 10-mg dose of morphine were given subcutaneously to the same patients and their effects compared on the basis of the percentage of doses giving 50% or greater relief of pain 45 and 90 minutes after administration. The results were as follows:

Number of patients		*Percentage relief*		*Percentage relief*
30	Morphine 10 mg + nalorphine 2 mg	63.0	Morphine 10 mg	67.1
19	Nalorphine 5 mg	28.1	Morphine 10 mg	73.0
35	Nalorphine 10 mg	63.5	Morphine 10 mg	73.8
31	Nalorphine 15 mg	58.6	Morphine 10 mg	53.2

The addition of nalorphine in the ratio of 1 : 5 did not materially reduce analgesic effectiveness. While nalorphine alone in a dose of 5 mg had no greater analgesic effect than a placebo, a 10-mg dose had nearly and a 15-mg dose had as much analgesic effect as 10 mg of morphine in the same patients. With the higher doses of nalorphine the incidence of side-effects was

[a] International non-proprietary name

increased. These were unpleasant dreams, dryness of the mouth, queer feelings and restlessness and were so disturbing as to make the practicability of nalorphine analgesia doubtful.

Houde & Wallenstein (1956) investigated initially the analgesic effectiveness of 10 mg of morphine plus 1 mg of nalorphine in 14 hospitalized cancer patients. The mixture was significantly superior to a saline control and, except for the first hour, about as effective as 10 mg of morphine alone. They then carried out studies on morphine-nalorphine mixtures containing 5 mg or 10 mg of morphine and nalorphine in proportions of 8 : 1, 4 : 1, 2 : 1 and 1 : 1. Corresponding doses of 5 mg or 10 mg of morphine alone and a saline placebo were included as standards and control, respectively. Cross-over comparisons were carried out in 38 patients. Pain relief was estimated on the basis of patients' hourly reports of changes in pain intensity for a 6-hour period after intramuscular drug administration. A biphasic slope of analgesic effectiveness of these combinations was obtained. This was interpreted as indicating that nalorphine not only progressively interfered with the analgesic effect of morphine but also exerted an analgesic effect of its own as the amount of nalorphine in the mixture was increased. It was also noted that the incidence of volunteered and observable side-effects increased in direct proportion to the amount of nalorphine in the mixture. A separate limited study of the respiratory effects of the mixtures in normal volunteers indicated that the combinations produced as much respiratory depression as morphine alone or more.

Cappe, Himel & Grossman (1953) also gave mixtures of morphine and nalorphine to paediatric, geriatric and obstetric patients. Doses were 5, 10 or 15 mg of each drug. Sedation and analgesia were intense with slight or no effect on respiration or circulation. In obstetrics the addition of nalorphine to morphine in equal amount neutralized to a variable degree in some patients the analgesic action, but the effect on the respiration of the infant was minimal.

The analgesic effect of nalorphine alone against post-operative pain was evaluated by Keats & Telford (1956a). Nalorphine in doses of 5, 10 and 15 mg and morphine in doses of 5, 10, 15 and 20 mg per 70 kg of body-weight were given alternately with placebo in alternate patients. Nalorphine and morphine were not given to the same patient and premedication was omitted if nalorphine was to be used. Only paired doses were compared and effectiveness was determined by the percentage of doses which were analgesic. The results with morphine and placebo were as follows:

Number of patients	*Number of paired doses*	*Morphine*		*Placebo*
		mg	*percentage analgesic*	*percentage analgesic*
56	109	5	66.1	40.4
38	71	10	69.0	33.8
31	59	15	79.7	42.4
18	40	20	82.5	45.0

With nalorphine and placebo the following results were obtained:

Number of patients	*Number of paired doses*	*Nalorphine*		*Placebo (percentage analgesic)*
		mg	*percentage analgesic*	
26	43	5	54.3	28.3
20	53	10	74.4	23.3
22	52	15	82.7	15.4

The average duration of relief with 147 doses of morphine was 4.61 hours, with 91 doses of nalorphine 4.93 hours. Excessive sedation, sweating, pallor and hypotension were reported in several patients with each drug.

Twenty patients who had no pain at the time were each given 10 mg of nalorphine intramuscularly. None had had morphine or other narcotic. Marked sedation was seen in 14 and when they were roused they were dizzy and groggy. Three had vividly coloured dreams and visual hallucinations. When nalorphine was the sole narcotic its effect was not distinguishable from that of other potent narcotics by casual observers. Its side-effects were not prohibitive when it was the only narcotic given, though their incidence was probably greater than with morphine.

Lasagna & Beecher (1954) gave nalorphine and morphine separately and together to 10 normal subjects and recorded the incidence of side-effects as shown in Table XVI.

5 mg of nalorphine produced approximately the same kind and number of side-effects as 10 mg of morphine, and 2 mg of nalorphine added to 10 mg of morphine did not reduce the number of side-effects. When 5 mg of nalorphine were given with 15 mg of morphine the incidence of side-effects was greater than with 5 mg of nalorphine alone but less than with 15 mg of morphine alone. Certainly nalorphine did not prevent the usual side-effects of morphine. Six additional healthy male volunteers were each given 10 mg of nalorphine subcutaneously and asked to describe their feelings. They described a mixture of morphine-like feelings of relaxation and disinterest and definite dysphoria; the sensations were mainly pleasant.

Keats & Telford (1956b) found that the side-effects of nalorphine were affected by the previous administration of morphine and apparently by the psychological setting in which the drug was administered. Four groups of hospitalized surgical patients were given intramuscular injections of 10 mg of nalorphine and two groups of similar patients were given intramuscular injections of 15 mg of morphine. The characteristics of the groups and time of administration were as follows:

Group A, 50 post-operative patients: nalorphine during afternoon of first post-operative day; no other narcotic since single pre-operative dose of morphine or pethidine, 24-30 hours previously.

Group B, 50 post-operative patients: nalorphine during afternoon of first post-operative day; 40 mg or more of morphine had been given during preceding 24-30 hours, last dose 4-10 hours before nalorphine.

Group C, 50 pre-operative patients : nalorphine during afternoon of day preceding operation.

Group D, 30 pre-operative patients : morphine during afternoon of day preceding operation.

Group E, 46 convalescing patients : nalorphine and morphine on succeeding days, 5-10 days post-operatively; half got nalorphine first, half morphine first; no other narcotic within preceding 48 hours.

TABLE XVI. NUMBER OF SUBJECTS EXPERIENCING SIDE-EFFECTS WITH NALORPHINE, AS SEEN BY LASAGNA & BEECHER (1954)

Side-effects	Placebo	Nalorphine 5 mg	Morphine 10 mg	Morphine 10 mg + nalorphine 2 mg	Morphine 15 mg	Morphine 15 mg + nalorphine 5 mg
Shaky	1	2	4	3	4	3
Heavy-headed	2	5	7	4	3	6
Light-headed	1	5	2	6	4	2
" Feel terrible "	1	5	4	5	8	5
Headache	0	3	3	2	3	1
Nausea	2	4	4	3	6	6
Difficulty in concentrating	1	3	7	7	9	8
Difficulty in focusing eyes	1	2	5	6	6	7
Itching	1	3	4	4	5	6
Apprehensive	2	1	0	1	3	3
Apathetic	1	5	3	3	7	6
Hiccups	1	1	2	1	4	1
Dry mouth	1	6	3	7	9	7
Lethargic	2	7	6	10	9	7
Palpitation	1	2	1	4	3	3
Dizziness	4	8	6	10	8	8
Senses dulled	2	5	8	6	6	6
Heavy limbs	3	5	6	8	8	7
Total	27	77	80	89	103	92

The technique of these administrations was double-blind. Observers used a check-list to record drug effects and wrote in the patients' own words their descriptions of their feelings. They also estimated the general condition of the patient as friendly or unfriendly, sedated or stimulated, etc.,

and the over-all effect of the medications as pleasant, unpleasant or extremely unpleasant. The frequency of subjective effects in percentage for the various groups is shown in Table XVII.

It is apparent that nalorphine could produce the same side-effects as morphine but in addition evoked unpleasant sensations which were more pronounced when morphine had been given previously or when the patient was in an anxious state preceding operation. The kind and incidence of side-effects with nalorphine and morphine were much more nearly the same in the pain-free convalescing patients.

Lasagna & Beecher (1954) also measured in nine normal subjects the respiratory minute volume response to 5% carbon dioxide. 10 mg of morphine and 10 mg of morphine plus 2 mg of nalorphine depressed the minute volume response to about the same extent, i.e., to about 75% of normal. 15 mg of morphine had a slightly greater effect, depression to about 70% of normal; and 15 mg of morphine plus 5 mg of nalorphine had the greatest effect, depression to about 60% of normal. 5 mg of nalorphine depressed the minute volume response practically to 70% of normal, but the effect was briefer than with morphine or the other mixtures. At 3 hours, about the time of peak effect with the latter, minute volume was back to 85% of normal when 5 mg of nalorphine alone had been given. Nalorphine was a respiratory depressant by itself and did not abolish the respiratory effect of therapeutic doses of morphine.

Respiratory depression by nalorphine has been reported also by Tenney & Mithoefer (1953), Salomon et al. (1954), Wendel & Lambertsen (1956) and Fraser, Van Horn & Isbell (1956). Tenney & Mithoefer estimated that nalorphine lowered the sensitivity of the respiratory centre to carbon dioxide approximately 50%. Their observations were on four normal subjects and four patients with pulmonary emphysema. Salomon et al. (1954) gave 10 mg of nalorphine intravenously to each of five normal volunteers. A decrease in respiratory rate, respiratory minute volume and maximal breathing capacity was observed, also miosis and marked sedation. The respiratory changes lasted from 40 to 90 minutes, the sedation from 150 to 240 minutes.

Wendel & Lambertsen studied the separate and combined effects upon respiration of morphine (10 mg per 70 kg) and nalorphine (10 mg per 70 kg) in 15 volunteers. They related respiratory minute volume to corresponding alveolar pCO_2 at various inspired carbon dioxide concentrations. Nalorphine alone was half as potent a respiratory depressant as morphine in terms of moles of pure base injected. When the two drugs were given together sometimes synergism, sometimes antagonism was observed, but on the average the combined effect was not significantly different from that of morphine alone.

Fraser, Van Horn & Isbell gave doses of 3, 6 and 10 mg of nalorphine subcutaneously to former opiate addicts. They said that the effect of nalor-

TABLE XVII. SIDE-EFFECTS WITH NALORPHINE, AS SEEN BY KEATS & TELFORD (1956b)

Side-effects	Day after operation		Day before operation		Convalescent, 5-10 days post-operative	
	nalorphine		nalorphine	morphine	nalorphine	morphine
	Group A	Group B	Group C	Group D	Group E	Group F
Groggy	74	62	76	67	63	46
Feel drunk	16	14	20	27	13	9
Restless	2	16	4	3	2	2
Irritable	2	18	2	3	7	4
Unfriendly	4	12	4	3	7	7
Shaky	2	10	6	10	2	9
Sleepy but cannot sleep	2	10	12	3	4	2
Cheerful	12	12	2	3	7	24
Difficulty in focusing	24	18	32	13	20	9
All unreal	2	20	20	3	11	2
Unreal dreams	8	20	12	0	9	4
Crazy feeling	10	22	14	3	20	2
Upset (crying, frightened)	8	6	18	10	2	2
Shortness of breath	2	8	12	0	0	0
Paraesthesias	14	4	18	7	11	0
Visual hallucinations	2	2	12	0	4	2
Disorientation	2	0	4	0	2	0
Impending death	0	4	4	0	4	0
Sweating	40	30	20	7	28	4
Nausea	10	12	30	40	4	13
Relief of nausea	2	14	0	0	0	0
Return of pain	0	12	0	0	0	0
Desire to move bowels	0	6	0	0	0	2
Marked sedation	46	24	24	17	28	22
Stimulation	6	14	18	20	17	7
Extremely unpleasant	10	34	22	13	7	4
Desire to repeat drug	14	13	8	17	24	22

phine on rectal temperature and on respiratory minute volume was approximately equivalent to that of 30 mg of morphine. They found also that, if the doses of nalorphine were given simultaneously with 30 mg of morphine, the effect on body temperature and respiration was the same as if morphine had been given alone.

According to Beal & Schapiro (1953), intravenous nalorphine inhibited spontaneous motor activity of the stomach, jejunum and sigmoid (one subject only). In two other subjects gastro-intestinal activity, stimulated by prior administration of morphine, was inhibited by intravenous nalorphine. Activity was recorded from an inserted balloon. The inhibitory effect lasted 20-60 minutes. It could be obtained after subcutaneous administration but was less marked.

In seven normal subjects, as reported by Van Liere & Northup (1956), 5 mg of nalorphine subcutaneously 15 minutes before a test meal delayed gastric emptying from 0.58 to 4.34 hours (average 2.67 hours). When 10 mg were given in four subjects practically no food had left the stomach at the end of 4 hours. The authors concluded that the effect of nalorphine on gastric emptying time was at least as great as that of morphine.

Bickerman, Barach & Drimmer (1954) elicited cough in normal subjects and in patients with controlled bronchial asthma by inhalation of citric acid aerosol and determined the effect of codeine and other agents on the number of coughs. Nalorphine at a dose of 30 mg had a suppressive effect like that of codeine at 30 mg.

Wikler (1951) and Wikler, Fraser & Isbell (1953) have described the similarities and differences in the subjective effects of nalorphine and morphine in post-addicts. Doses of 5 mg or 10 mg were given subcutaneously to nine and doses of 15-75 mg to 24 subjects. Many individuals said that the small doses made them feel relaxed and drowsy, that they liked the effect, but that there was no " drive " such as they experienced with morphine. Others said the effect was unpleasant. Although they were drowsy they were unable to sleep because of vivid disturbing daydreams or visual hallucinations. Miosis occurred regularly with 15 mg or more of nalorphine, nausea, giddiness, sweating and feelings of instability on standing occasionally, but vomiting rarely. Itching was lacking, pseudoptosis of the eyelids was seen frequently and occasionally marked diuresis. After doses of 30-75 mg dysphoric effects were pronounced. Those who received the largest doses became very anxious, complained of thoughts racing through the head and demanded relief. The unpleasant experiences were hardly ameliorated by administration of morphine but were promptly relieved by intravenous injection of pentobarbital.

Huggins & Moyer (1955) gave doses of 10-25 mg of nalorphine to 30 patients. Miosis occurred in all, sweating in 22, some degree of sedation in 15 and hallucinations in 23. The patients found the hallucinations produced by nalorphine most unpleasant and, in some cases, terrifying. Occasional complaints were nausea, giddiness, numbness of the limbs and sensations of a " cheap drunk ".

Wikler, Fraser & Isbell (1953) and Wikler (1954) described the effect of nalorphine on the electroencephalogram. This appeared to depend on the control pattern and on the changes produced by the drug on affect and level

of consciousness. Relaxation and euphoria appeared to be associated with increased rhythmicity and slight slowing of alpha frequencies. On the other hand, anxiety was associated with intermittent or continuous reduction in amplitude and decrease in rhythmicity of the electroencephalogram. Marked drowsiness was accompanied by " flattening " of the record and the appearance of irregular low to moderate voltage slow waves.

Bauer & Pearson (1956) tested the effect of nalorphine and morphine and of mixtures of the two on psychomotor performance. The subjects were 96 air force trainees required to make multiple adjustments in response to random movements of instrument pointers in a multidimensional pursuit test. 8 mg of morphine were given alone or in combination with 1, 2 or 4 mg of nalorphine. On other occasions 4 mg of nalorphine alone or a placebo were given. There was no significant difference in the performance scores for morphine alone and the placebo. The worst score was obtained with nalorphine alone and performance declined with the mixtures as the amount of nalorphine increased. Drowsiness was complained of more frequently and subjects were seen to sleep when nalorphine was given alone or in a dose of 2 mg or 4 mg combined with morphine as compared with morphine alone. Also sweating, retching and vomiting occurred more frequently with the mixtures than with morphine alone.

In an attempt to produce addiction with nalorphine, Isbell (1956a) gave six former addicts 10 mg subcutaneously every 6 hours, increasing in 14 days to 25-35 mg every 6 hours. Two patients withdrew from the experiment because of the occurrence of hallucinations. The other four continued but objected to increase in dose beyond 100-130 mg daily. Hallucinations disappeared after two weeks. No definite symptoms were observed after abrupt withdrawal of nalorphine at the end of 28 days. In another group of four former addicts the dose of nalorphine was increased only to 7-12 mg every 4 hours during 25-31 days and one patient received doses increasing to 9 mg every 3 hours in 42 days. Disagreeable side-effects were less with such small doses, but again the patients disliked the medication. No definite symptoms of abstinence occurred following withdrawal of nalorphine.

Isbell [a] also gave mixtures of morphine and nalorphine, at ratios of 10 : 1, 5 : 1 and 3 : 1, to former addicts every 3-4 hours for 28-30 days. The total amount of drug given was pushed upward as rapidly as seemed safe; the total daily dosages attained were 360 mg of morphine with 36 mg of nalorphine, 210 mg of morphine with 42 mg of nalorphine, and 180 mg of morphine with 60 mg of nalorphine. Eight patients were used in the experiment and all disliked the mixtures intensely; they complained that the drug did not " pick them up " and insisted at times that they were being given only water. Despite these complaints the pupils were constricted, the respiratory rate was decreased, all were severely constipated and all showed

[a] Personal communication, 1954

alternate somnolence and wakefulness. All complained of bad dreams and twitching of the arms and legs. After a few days all the patients began to perspire profusely after each dose and complained of hot and cold sensations, a sense of constriction in the chest and severe headache. These symptoms appeared within a few minutes of the injection of a mixture and subsided in about 20 minutes only to reappear after the next dose was given. The symptoms were strongly suggestive of precipitation of mild abstinence. Following abrupt withdrawal of the mixtures, all eight subjects showed definite symptoms which resembled abstinence from morphine, but much milder than following abrupt withdrawal of morphine, administered subsequently without nalorphine in the same amounts for the same length of time as in the first part of the experiment to the same individuals.

Nalorphine administered during addiction to morphine or another opiate, instead of replacing the opiate, precipitated an acute abstinence syndrome (Wikler et al., 1952; Wikler, 1955). The syndrome resembled strikingly that observed after abrupt withdrawal of morphine except that withdrawal signs appeared within 15 minutes, reached peak intensity by 45 minutes and then subsided slowly. Even intravenous injection of morphine had little ameliorating effect on the nalorphine-induced abstinence syndrome. Such an abstinence syndrome could be precipitated by subcutaneous injection of a single dose of 15 mg of nalorphine as early as after one week of administration of 15 mg of morphine or 10 mg of methadone 4 times daily. The intensity of the abstinence syndrome increased and the dose of nalorphine required to precipitate it decreased as the intensity and duration of addiction increased. As pointed out by Keats & Telford (1956a) and Isbell (1956b), nalorphine is the first morphine-like analgesic without addiction liability.

SUMMARY

Nalorphine has been demonstrated to have an analgesic effect in man approximately equivalent to that of morphine. Its subjective side-effects are partly morphine-like but largely dysphoric. Given simultaneously with morphine it may not interfere with the analgesic effect of the latter but it does not decrease, rather increases the incidence of side-effects. It has not been possible to demonstrate any addiction liability of nalorphine and, given during morphine or other opiate addiction, instead of substituting for the opiate it precipitates an acute abstinence syndrome. Nalorphine is the first example of a morphine-like analgesic without addiction liability. Unfortunately its side-effects and dysphoric action preclude its practical applicability.

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14. Oxycodone [a] (dihydrohydroxycodeinone)

Oxycodone has been used in medical practice for about 40 years and again the early reports denied or minimized its addiction-producing properties. Falk's was the first report (1917) on the clinical use of oxycodone (eucodal). In 300 cases he used doses ranging from 5 mg to 30 mg and concluded that it was more rapid in its action than morphine and that it was more narcotic. Other early reports were by Hesse (1917), Siegfried (1918) and Wohlgemuth (1918), and within two years cases of addiction were appearing. König (1919) described two cases; in one the dose reached 300 mg per day, in the other the maximum was 150-200 mg per day. The first case had taken the drug for 2 years, the second for 10 months. Alexander (1920) told of a woman who took only one or two doses a day postoperatively and became dependent on the drug in a matter of 2 weeks. The usual morphine-like side-effects were seen after oxycodone, but they were reported to occur usually somewhat less frequently than with morphine (Keutzer, 1920). Weise (1923) found eucodal useful for quieting the apprehension and restlessness of children submitted to tonsillectomies, etc. He used doses of 2.5-10 mg both orally and subcutaneously. The larger doses sometimes caused vomiting.

Keim (1923) said that the analgesic potency of oxycodone lay between that of codeine and that of morphine. He employed a dose of 10 mg orally or subcutaneously for chronic pain. Pfeiler (1928), on the other

[a] International non-proprietary name: for other designations, see *Estimated World Requirements of Narcotic Drugs in 1958* (United Nations document E/DSB/15).

hand, found the drug more effective than morphine, also in chronic pain, but he used a dose of 20 mg. According to Stern (1926), oxydone, at a dose of 20 mg, was always successful in the treatment of biliary colic. He confirmed the occurrence of addiction.

The Technical Study of the Comparative Effects of Morphine and of Certain Habit-forming Drugs, reported in the *Bulletin of the Health Organisation* of the League of Nations (League of Nations, 1939), concluded that the analgesic effect of eucodal was at least equal to that of morphine, and Chopra and his associates (1942) said that eucodal was more potent. They ranked it above both morphine and heroin in this respect, but below both of these drugs in the production of euphoria. The onset and development of the analgesic effect of oxycodone might often be more rapid than with morphine and it might last as long or longer (Baumm, 1919; Falk, 1917; Mayer, 1927; Wohlgemuth, 1918) or not as long (Pfeiler, 1928). Beck (1919, 1923) said that 5-10 mg of eucodal were usually sufficient for the relief of pain, but occasionally 20 mg had to be given. Falk (1917) found eucodal unsuitable for use in obstetrics because it retarded the progress of labour.

Most recently oxycodone has been used in combination with homatropine and terephthalic acid, as in the case of hydrocodone, with the thought that this would diminish the possibility of abuse. Blank & Boas (1952) compared the analgesic potency of this combination with that of a codeine mixture in 168 surgical and 163 medical cases. The mixtures contained 5 mg of oxycodone and 32 mg of codeine, respectively, and were given orally in each case. The oxycodone preparation gave satisfactory relief of pain in just over 79% of each group of cases; the codeine combination gave satisfactory relief in 76.7% of the surgical and in 73.7% of the medical patients. The duration of effect averaged 4-5 hours with oxycodone, and about 3 hours with codeine. At the doses used the incidence of side-effects was very similar with both drugs, except that constipation and urticaria were noted less than half as frequently after oxycodone.

Piper & Nicklas (1954) also compared the oxycodone and codeine combinations at the same dose-levels, 5 mg and 32 mg of opiate ingredient, again orally, in minor accident cases—that is, in ambulatory patients. The procedure was to dispense the oxycodone mixture during one month (96 cases) and the codeine mixture during the following month (71 cases). The patients were questioned when next seen as to the results. Oxycodone was reported to be more rapid in its action, to give complete relief of pain in 76% and to have an effect lasting 2-3 hours or more in 86% of trials. Codeine gave complete relief in 74%, lasting 2-3 hours or more in 85% of trials. The oxycodone combination was prescribed in an additional 390 traumatic and miscellaneous medical cases, one tablet (5 mg of oxycodone) every 3-6 hours, rarely more than 12 tablets per patient. Pain control was adequate, but nausea was reported 29 times.

Myers & Davidson (1938), in their experiments on gastro-intestinal motility in normal subjects, gave oxycodone on one occasion only, 10 mg subcutaneously. The progress of a barium meal was followed fluoroscopically and by X-ray photographs. Oxycodone caused almost immediate pyloric spasm and some increase in the rate of gastric peristalsis. The effect was transient, however, briefer than with morphine, heroin or dilaudid, because the stomach was empty at the 3-hour examination and the distribution of the barium meal was approximately normal 6 hours after the drug. With each of the other drugs barium was still present in the stomach, in varying amount, 3 hours after the drug, and there was definite delay in the arrival of the head of the barium column at the hepatic flexure.

Miadowski (1949) has described the occurrence of nystagmus after the administration of oxycodone, attributing it to an effect on the vestibular nucleus, which might be used as a diagnostic tool in otoneurology.

The depressant effect of oxycodone on respiration has generally been reported to be as great as that of morphine (Falk, 1917; Hesse, 1917; Leichtweiss, 1921). Chopra and his associates (1942) placed eucodal next to heroin in respiratory depressant action, and heroin was at the top of the list of the drugs which they compared, but they said that eucodal was inferior to both morphine and codeine in antitussive action. Only Mayer (1927) found eucodal to have less effect than morphine on respiration. Baumm (1919), Hesse (1917) and Schroeder (1921), contrary to Chopra (1942), found eucodal to be a good antitussive.

Addiction liability

Some reference to early addiction to oxycodone has already been made. Beck (1923) thought that the development of tolerance to oxycodone was less than for morphine, but he cautioned that its use should be restricted to the lowest adequate dose for the shortest possible time, thus very definitely suspecting the likelihood of addiction. Both Meyer (1924) and Chopra (1942) judged the addiction liability of oxycodone to be at least as great as that of morphine. Among the 280 questionnaires analysed by Wolff (1928), 83 mentioned addiction to eucodal, more than for any other drug. Menninger-Lerchenthal (1930) described 21 cases of " eucodalismus ", 6 from his own experience, and Dansauer & Rieth (1931) found 26 users of eudocal in their review of 238 war-wounded drug addicts. Many other references to eucodal addiction, whether primary or secondary is not always clear, were listed in the extensive bibliography of Krueger, Eddy & Sumwalt (1942) and the Technical Study of the Comparative Effects of Morphine and of Certain Habit-forming Drugs (League of Nations, 1939), referred to above, summed up the situation in these words: " The danger of contracting a habit (addiction) through taking eucodal should not be thought to be a less serious matter than the risk of morphine addiction ".

Himmelsbach (Small et al., 1938) substituted oxycodone for morphine in three stabilized morphine addicts at the Lexington hospital, for a period of 7 days. The substitution dose was one and a half times the morphine stabilization dose; the interval of administration was the same for both drugs, namely 4 times a day; administration was always subcutaneous. Substitution was completely satisfactory. On abrupt withdrawal of the substituted drug an abstinence syndrome developed at approximately the same time and with the same severity as morphine abstinence. On the basis of this experiment the addiction liability of oxycodone would be judged to be close to that of morphine.

SUMMARY

Oxycodone has an analgesic potency approximately the same as that of morphine, with a usual dose of 10 mg and a similar duration of action. The incidence of most side-effects appears to be less for oxycodone than for morphine, but its respiratory depressant effect and its addiction liability are not materially different from these effects of morphine. Either of these effects should preclude its use as an antitussive.

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15. Oxymorphone[a] (dihydrohydroxymorphinone)

Oxymorphone bears the same relation chemically to oxycodone that morphine does to codeine. It has been tested against chronic pain at two institutions. In both (R. W. Houde & S. L. Wallenstein[b]; L. E. Lee, jr, N. B. Eddy & J. Lieberman[c]) the plan of the experiment was the same. A placebo, two doses of a standard (morphine 8 mg and 12 mg), and two doses of oxymorphone, constituting a quintet, were administered in random order, one medication per day to the same patient. The technique was double-blind and a nurse observer determined the degree of the patient's pain before and at 30- or 60-minute intervals after administration, usually until the pain returned to the level before administration. Successive quintets were used in which placebo and standard remained the same but the doses of oxymorphone varied; the ratio between the two oxymorphone doses, however, remained the same in each instance as the ratio between the doses of standard. An attempt was made to administer each quintet twice to each patient and only the results of administration of complete quintets were included in calculations. All patients had more or less continuous chronic pain and when pain recurred, after a coded preparation had been given, throughout the remainder of the 24 hours it was relieved by whatever medication was ordered by the hospital staff, usually morphine or pethidine. The categories of pain were given numerical values—severe pain 4, moderate pain 3, slight pain 2, no pain 1—and a pain relief score per dose per patient was obtained by adding together the difference between the value of the pain before injection and that recorded at each post-injection observation. In these two experiments the method of calculation of regression slopes for morphine and oxymorphone and of dose of oxymorphone equivalent to 10 mg of morphine was the same. The mean pain relief scores of all drug doses were significantly different from the pain relief scores for placebo and the regression slopes for morphine and oxymorphone were essentially parallel. Houde & Wallenstein estimated 1.12 mg of oxymorphone to be equivalent to 10 mg of morphine; Lee, Eddy & Lieberman estimated equivalence at 1.15 mg of oxymorphone for 10 mg of morphine. In the latter experiment the average duration of effect of 1.0 mg

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[a] International non-proprietary name; for other designations, see *Estimated World Requirements of Narcotic Drugs in 1958* (United Nations document E/DSB/15).

[b] Personal communication, 1956

[c] Unpublished data, 1957

of oxymorphone was 266 minutes and that of 12 mg of morphine was 277 minutes. At these two doses, respectively, 4.11% and 4.95% of doses failed to give any relief.

Coblenz & Bierman (1956) reported the administration of more than 9000 doses of oxymorphone by the parenteral route to 200 hospital patients, all of whom had neoplastic diseases. A double-blind test on eight patients showed, according to the authors, that a dose of 2 mg of oxymorphone was equivalent to 16 mg of morphine. 100 mg of pethidine or 4 mg of hydromorphone. Fifty-one patients received 1 mg of oxymorphone plus 0.4 mg of atropine as pre-operative medication. No untoward events attributable to the drug were observed. Post-operatively oxymorphone afforded 3-6 hours of effective analgesia, which could be maintained with continued regular use at these intervals. Respiratory and circulatory effects were minimal with doses up to 5 mg in patients who were not debilitated. Hypotension and severe respiratory depression were described as occurring after larger doses or in debilitated individuals; they were rapidly reversed by administration of nalorphine.

L. E. Lee, jr, N. B. Eddy & J. Lieberman [a] tabulated the side-effects reported as occurring after 230 doses of oxymorphone, 231 doses of morphine and 111 placebo injections. These are shown in Table XVIII.

With doses of 1 mg or more of oxymorphone the kind and incidence of side-effects were not materially different from those seen with morphine. Besides, serious respiratory depression occurred five times after 2 mg of oxymorphone, in two instances requiring the administration of nalorphine. Similar respiratory depression was seen in three cases when the dose of morphine was 12 mg. All these respiratory depressions were seen in the debilitated type of case referred to by Coblenz & Bierman, but nevertheless the superiority of oxymorphone over morphine with respect to side-effects was not demonstrated.

Coblenz & Boerman (1956) said that there could be no doubt that prolonged administration of oxymorphone represented considerable addiction liability. They found that individuals dependent on (addicted to) other narcotics were able to withstand large doses of oxymorphone, up to 20 mg, and the new drug could be effectively substituted for other narcotics in addicted individuals. When oxymorphone had been so substituted, withdrawal syndromes could be precipitated by nalorphine administration.

Fraser & Isbell (1955) found that 1.5-2.0 mg of oxymorphone subcutaneously induced intense morphine-like effects in 5 non-tolerant former addicts, and 6 mg of the drug every 3 hours completely suppressed abstinence in two individuals who had been receiving 60 mg of morphine every 6 hours. Three non-tolerant former addicts received oxymorphone subcutaneously every 3 hours for 18 days, the individual dose being increased

a Unpublished data, 1957

TABLE XVIII. SIDE-EFFECTS WITH OXYMORPHONE

Side-effects	Pla-cebo (111 doses)	Oxymorphone (mg/dose)						Morphine sulfate (mg/dose)	
		0.5 (17 doses)	0.66 (32 doses)	1.0 (84 doses)	1.33 (32 doses)	1.5 (34 doses)	2.0 (31 doses)	8.0 (114 doses)	12.0 (117 doses)
None reported	95 (85.5%)	10 (58.8%)	22 (68.4%)	49 (58.3%)	16 (50.0%)	21 (61.7%)	12 (38.7%)	75 (65.7%)	62 (53.0%)
Drowsiness and/or sleep	15	6	9	28	9	4	12	29	36
Nausea	1		1			6	1	1	10
Vomiting						5		1	2
Dizziness and/or lightheadedness	1			6	3	6	4	3	4
Headache	1						1		1
Sweating				1	2		3	1	1
Itching			1		2		2		1
Euphoria									2
Confusion				1				1	2
Apprehensiveness or nervousness								2	1
Grogginess			1	1			1		2
Feeling of numbness							2	1	
Feeling of warmth						1		1	1
Blurred vision					1				
Abdominal distension						1			
Fullness in chest			1	1					
Difficulty in breathing	1	1		1					2
Respiratory depression							5		3
Nalorphine given					1		2		1

from 0.5 mg to 4.0 mg. Nalorphine towards the end of the period precipitated abstinence phenomena and abrupt withdrawal of oxymorphone was followed by a severe abstinence syndrome, evident in 6 hours. Fraser & Isbell concluded that the addiction liability of oxymorphone was high.

SUMMARY

Oxymorphone is a very potent analgesic; it is estimated that 1.12-1.15 mg is equivalent to 10 mg of morphine. The duration of action of the

two drugs is similar. In the experience reported 1.0 mg or more of oxymorphone did not produce a lower incidence of side-effects than equivalent doses of morphine. Oxymorphone has high addiction liability.

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16. Pethidine [a] (1-methyl-4-phenyl-4-carbethoxypiperidine)

The objective of the synthesis which led to pethidine was the production of an atropine-like compound, and pharmacological tests showed that to some extent this objective was attained. That the drug had morphine-like properties as well was a fortuitous and most unexpected discovery. The chemists had, without a doubt, made something which combined features of both of these important alkaloids, and as a result pethidine could be introduced into medicine, hardly 20 years ago, as an analgesic, a sedative and a spasmolytic. All of the early reports stressed pethidine's triple character.

Early reports

The first reports in 1939 on the use of pethidine were, naturally, in the German literature. The following are typical. Althoff (1939) treated 44 patients with mild or moderate pain of various sorts and said the result was satisfactory in 37 with an oral dose of only 25 mg of pethidine 3 times a day. In another 47 cases of pain due to spastic conditions, biliary colic, etc., the result was satisfactory in 39 with a dose of 100 mg subcutaneously. The effect was prompt and lasted 2-4 hours. Althoff reported a calming effect and good symptomatic relief in 14 of 16 patients with circulatory disturbances. He saw no evidence of cumulation, tolerance or dependence and no significant side-effects. Dietrich (1939) described his experience with 150 cases of many types of pain, including spasmogenic, neuritic, etc. He used a dose of 100 mg by various routes, oral, rectal, intramuscular and intravenous. The effect was prompt both as an analgesic and a spasmolytic. Dizziness and euphoria were seen sometimes but no addiction, even on prolonged administration. Schäfer (1939) reported on the use of pethidine in 308 surgical patients. He also used a dose of 100 mg by various routes, except oral. He said that the effect of a single dose might last as long as 7 or 8 hours and that no tolerance occurred in patients receiving as many

[a] International non-proprietary name; for other designations see *Estimated World Requirements of Narcotic Drugs in 1958* (UN document E/DSB/15).

as 40 doses over an extended time. In four or five cases a pre-collapse-like syndrome—nausea, dizziness, sweating and faintness—was seen. Schlungbaum (1939) found that pethidine in doses of 75 mg or 100 mg, sometimes 150 mg, would relieve severe pain in 20-25 minutes, the effect lasting 4-5 hours. No tolerance was observed after weeks of oral administration. Vogt (1940), Sostmann (1940) and Heydner (1940) said that pethidine could replace morphine in its various uses. Vogt's experience was in internal medicine, Sostmann's in gynaecological practice and Heydner's in heart disease. In Vogt's cases no antitussive action was seen. In one of Heydner's patients some tolerance occurred after 50 doses so that this had to be increased from 100 mg to 150 mg. Sostmann commented on the spasmolytic as well as analgesic action and Vogt mentioned a euphoric effect in some cases.

Dobos (1941) reported the use of pethidine with very satisfactory results in 15 neurological cases. The dose was 100 mg subcutaneously. Side-effects occurred in 10 of the patients but they appreciated the pain relief so much that they wished to continue the drug despite the side-effects. Grigorescu (1941), too, said that pethidine was very effective in 40 cases of migraine and other cephalalgias and in his experience there were no side-effects other than dryness of the mouth.

Izar & Lenzi (1941) concerned themselves particularly with the use of pethidine in conditions in which a spasmolytic action would contribute to its effectiveness. They cited two cases of asthma, two of biliary colic and two of intestinal spasm in which attacks were cut short by intravenous administration of pethidine and recurrence was diminished or prevented by continuing oral doses. They said that similar results were obtained in other cases without side-effects.

Early papers on pethidine in the English literature were those of Climenko (1942), Christie (1943) and FitzGerald & McArdle (1943). Climenko found only a slight sedative but a marked analgesic action both with the Wolff-Hardy-Goodell pain-threshold technique and by clinical observation. He said that the drug frequently produced a marked euphoria which persisted for about an hour after administration. Christie reported on the use of pethidine in 335 cases, and his results were somewhat more quantitative than those in earlier accounts. The drug was given orally in a dose of 50 mg or 100 mg, or 25 mg every 4 hours for 6 doses. The 50-mg dose gave the best result—partial or complete relief of pain in 74% of 158 trials. The 100-mg dose and the repeated doses of 25 mg produced about the same effect—68% relief in 121 trials with the former, 66% partial or complete relief in 56 trials with the latter. Side-effects were most frequent (in 15 cases) with the 100-mg dose, and their occurrence may have affected the estimation of relief. The 50-mg dose was judged to be less effective than 10 mg or 15 mg of morphine in 13 patients who received both drugs. It was superior to a codeine compound in 50, equal in 23 and inferior to

codeine in 36 patients. FitzGerald & McArdle gave pethidine to 12 cases of severe pain due to neurological conditions. The dose was 50 mg or 100 mg and was administered intravenously in 10 of the cases. Relief was excellent in 8, considerable but not complete in 3, and there was one failure, an individual who was accustomed to taking considerable amounts of opiates and who resented the trial of something else. Ten of these neurological patients showed transient giddiness, pallor and sweating.

Benedek & Juba (1943) drew attention to the greater susceptibility to pethidine of persons over 60 years of age. A dose of 75 mg was satisfactory in 83% of patients in this older age-group, whereas it was insufficient in 60% of cases in the 20-60-year age-group. Most of these patients complained of dryness of the mouth or thirst. Three of the older patients were too depressed, with a respiratory rate of 12-16 per minute; in the others the respiratory rate was normal and the blood pressure unchanged.

Branwood (1943) said that a dose of 50 mg of pethidine was invariably successful in relieving pain associated with smooth muscle spasm, but almost entirely without effect in other cases, thus emphasizing the spasmolytic element in the drug's action. According to Szirmai (1955) excellent analgesia and an antispasmodic effect on the cervix uteri were obtained with 100 mg of pethidine intramuscularly in 33 cases of uterine difficulties, mostly abortions. Coagulation time was unchanged or increased. Szirmai thought that pethidine could contribute to the prevention of thromboembolisms.

Batterman has studied and written extensively on the effectiveness, advantages and disadvantages of pethidine. In one report (1943b) he said that control of pain, regardless of etiology, was achieved completely by parenteral administration of pethidine in 85% of 996 trials on 881 patients. An additional 10% experienced moderate relief. With oral doses there was complete control of pain in only 60.5% of 772 trials on 604 patients. Parenterally 100 mg of pethidine were equivalent in analgesic potency to 10 mg of morphine. In another paper (1945), Batterman described the effects of pethidine in 183 hospitalized and 73 ambulatory patients with arthritic pain. Effectiveness amounted to 87.5% and 59.8% complete relief of pain with a 100-mg dose parenterally or orally, respectively. Some relief was obtained in all patients with parenteral doses, but 10% of the cases got no relief when the drug was given orally. Batterman (1944) recommended a dose of 100 mg of pethidine intramuscularly for moderate, and 150 mg for severe pain. If the latter dose was not effective, higher doses or comparable doses of morphine were usually not effective either.

Hecht, Noth & Yonkman (1943) and Noth, Hecht & Yonkman (1944) observed only 64% complete relief of pain with pethidine in 123 patients. The dose was 100 mg, usually intramuscularly, and results were better with this route of administration than with oral use. Relief was better than with codeine but not as good as with morphine.

Analgesic action

There have been numerous attempts at quantitative estimation of the analgesic effectiveness of pethidine, with some attention paid to control of the procedure, the use of single- or double-blind techniques, and comparison with a placebo or with another analgesic agent. Some of these attempts, which could be considered at least semi-quantitative, have already been referred to. Others will be described briefly in approximate chronological order.

Batterman (1943a), presumably using a single-blind technique (that is, the observer but not the patient knew the nature of the medication), reported on the trial of pethidine in 1119 hospitalized, unselected patients, the only indication for the use of the drug being pain of whatever cause. The doses ranged from 50 mg to 150 mg and were given intramuscularly and orally. His criteria of relief were: (1) complete = C = complete control of pain for 3 or more hours, or almost complete relief for several hours, with minimal untoward reactions; (2) moderate = M = complete relief and almost complete relief for less than 3 hours, or partial relief for 3 hours or more, or as in (1) but with disturbing side-reactions; (3) slight = S = partial relief for less than 3 hours, or as in (1) and (2) but with moderately severe side reactions; and (4) none = N = failure to obtain pain relief, or as in previous categories if untoward reactions were severe. His results in percentages according to these criteria are shown in Table XIX.

The optimal dose would appear to be 100 mg by either route of administration, though the incidence of complete relief was definitely greater when the drug was given intramuscularly. It should be remembered that Batterman's criteria of effectiveness took into account the occurrence of side-effects as a factor in the satisfactoriness of relief and that side-effects were seen more frequently with oral administration, especially with the larger doses. However, in another place (1944) Batterman said that 100 mg of pethidine intramuscularly raised the pain threshold 80%, whereas the same dose orally raised the threshold only 50% (Wolff-Hardy-Goodell technique).

TABLE XIX. PERCENTAGE OF PAIN RELIEF WITH PETHIDINE OBTAINED BY BATTERMAN (1943a)

Dose	Intramuscular administration					Oral administration				
	trials	C	M	S	N	trials	C	M	S	N
50	83	67.4	22.0	7.2	2.4	235	54.4	20.4	13.6	11.5
75	222	81.9	13.0	3.1	1.8	39	46.1	28.2	17.9	7.7
100	643	88.4	8.4	1.4	1.7	431	65.9	23.9	4.9	5.3
150	40	85.0	10.0	—	5.0	14	42.9	57.1	—	—

Glazebrook & Branwood (1945) used a device which exerted pressure over the tibia. The threshold was the amount of pressure in mm Hg required to evoke pain and observations were made on six groups of normal subjects, 20 in each group. In random order each subject received a tablet containing codeine (5 mg), aspirin (130 mg) and phenacetin (130 mg), a subcutaneous injection of 100 mg of pethidine or of β-pethidine, or no medication. The technique was double-blind; neither observer nor patient knew what medication was employed. Repeated observations on the same subject on the same day without medication showed only minor variations in the pain threshold (maximum 2.2 mm Hg). Each of the 20 subjects in a group were affected at 1 and 2 hours after administration of each of the pethidines; the maximum elevations of threshold were 7.5 mm Hg and 6.5 mm Hg with pethidine and β-pethidine, respectively, but only 9 were affected after the codeine mixture, with a maximum rise in threshold of 4 mm Hg. The effect of pethidine was more persistent than that of β-pethidine. These authors said that both pethidines had a curiously variable, unpredictable action in patients with deep-seated and chronic pain.

Nickerson & Goodman (1947) made observations on eight medical students, determining pain thresholds by three methods: (1) the time required for pain to develop with the hand in water at 4°C; (2) the amperage to produce pain when current was applied to a metallic dental filling; and (3) the voltage to evoke a painful sensation by the Wolff-Hardy-Goodell technique. All subjects had had previous experience of all three end-points. Criterion of effect was percentage rise in threshold. Drugs were given orally several days apart with placebos interspersed. 100 mg of pethidine raised the threshold for the three methods, respectively, 55%, 67% and 30%. 20 mg of amphetamine raised the first threshold 76%. When pethidine and amphetamine were given simultaneously this threshold was raised 102%, but an additive effect of these drugs on the other two thresholds was not observed.

Christensen & Gross (1948) employed the Wolff-Hardy-Goodell radiant heat technique in 11 normal subjects and compared the percentage rise in threshold produced by subcutaneous and intravenous administration of graded doses of morphine, methadone and pethidine. The subjects were not informed of the identity of the drug received; after some experience, however, they were able to differentiate them by their side-effects. At least one week elapsed between the administration of two doses of the same drug to any subject; not all subjects received all doses. The figures in Table XX for the results of subcutaneous administration were derived from the graphs of the report.

100 mg of pethidine, 10 mg of morphine and 2.5 mg of methadone were alike in peak effect on the pain threshold and mainly the same in duration of action. Comparing the same doses given by the two routes, peak effect was less for methadone, greater for pethidine and about the

TABLE XX. EFFECT OF PETHIDINE, MORPHINE AND METHADONE ON PAIN THRESHOLD AS SEEN BY CHRISTENSEN & GROSS (1948)

Drug	Dose (mg)	Number of subjects	Peak effect (%)	Duration of effect (hours)
Pethidine	50	4	11	3.25
	100	6	17	5.50
	150	2	22	6.00
Morphine	5	6	8	3.00
	10	6	17	4.50
	15	6	23	6.00+
Methadone	1.25	9	10	4.50
	2.50	7	16	5.00
	5.00	5	26	6.00+

same for morphine, and duration of effect was less for all three drugs for intravenous as against subcutaneous administration. Simultaneous injection of atropine decreased the duration of action of pethidine, whereas neostigmine increased both intensity and duration of pethidine's analgesic action.

Keele (1952), using a method which he and his associates had described previously (Hewer & Keele, 1948), produced ischaemic pain in five normal subjects, a pain of rising intensity resulting from rhythmic closing and opening of the hand with the blood supply to the forearm cut off by a pressure cuff about the upper arm. Drugs were given intravenously and an attempt was made to determine the minimal dose which would check significantly the rising pain intensity. This threshold dose varied from subject to subject: for morphine from 0.5 mg to more than 2.0 mg; for methadone from 0.5 mg to 3.0 mg; and for pethidine from 5.0 mg to 10.0 mg. Drug interrelationship was not the same from subject to subject.

Wilson et al. (1950) also compared the effect of morphine, methadone and pethidine on ischaemic pain. They adopted two criteria of effect: the time to the appearance of pain; and the time to exhaustion, which was the time until 6 successive hand-closing efforts failed to develop a minimal pressure in a bulb being squeezed. Potency was indicated by the number of times in 30 trials that pain failed to develop before exhaustion time was reached. Doses were 10 mg and 15 mg of morphine, 10 mg and 15 mg of methadone, 100 mg and 150 mg of pethidine and 2 ml of saline as a

control. All administrations were subcutaneous. Time to exhaustion after drug administration (except in one instance, after 10 mg of methadone) did not differ significantly from time to exhaustion in the controls. Figures for absence of pain up to exhaustion time in 30 trials were: for the saline control, 3; for morphine 10 mg, 3, for 15 mg, 8; for pethidine 100 mg, 5, for 150 mg, 7; and for methadone 15 mg, 11. On this basis 15 mg of morphine, 150 mg of pethidine and 15 mg of methadone were nearly equally potent.

Deneau, Waud & Gowdey (1952, 1953) produced pain in normal subjects by rapidly inflating a cuff about the calf of the leg. The threshold was the pressure in the cuff in mm Hg when pain occurred and the criterion of effect the percentage rise in threshold. Medications were given orally. The following results were derived from the published graphs:

	Number of subjects	*Percentage change in threshold*		
Time of observation (minutes)		30	60	120
Placebo	93	2.5	4.0	3.0
Aspirin, 1700 mg	105	12.0	17.0	18.0
Codeine, 32.5 mg	18	20.0	32.5	21.0
Pethidine, 100 mg	27	9.0	25.0	25.0

By this method codeine and pethidine were about equally effective, a little more effective than a very large dose of aspirin.

Gaensler (1951) inserted a T-tube in the common bile duct in patients who had undergone cholecystectomies and related operations. The tube was connected to a pressure system and the pain threshold—the rise in pressure in the system in mm of water which evoked pain—was determined. This threshold was raised for periods of 3-6 hours after subcutaneous administration of analgesic drugs; for 3 hours with pethidine, for 6 hours with methadone and for intermediate times with the other drugs. For comparative purposes the rise in threshold was expressed in percentage of the normal, and the over-all analgesic effect in per cent./hours, the area under the curve when the percentage rise in threshold was plotted against time. The results are shown in Table XXI.

In another series of observations Gaensler gave graded doses of morphine and of pethidine to determine dose-effect relationship, as follows:

Drug	*Dose (mg)*	*Over-all analgesic effect (per cent./hours)*
Morphine sulfate	4	22
	8	86
	10	140
	16	269
	20	301
	32	329

Drug	Dose (mg.)	Over-all analgesic effect (per cent./hours)
Pethidine hydrochloride	25	43
	50	114
	100	172
	200	239

Beyond 16 mg of morphine sulfate or 100 mg of pethidine hydrochloride there was no further increase in the peak threshold elevation but some increase in duration of effect.

TABLE XXI. PEAK THRESHOLD ELEVATION AND OVER-ALL ANALGESIC EFFECT WITH PETHIDINE AND OTHER DRUGS AS SEEN BY GAENSLER (1951)

Drug	Dose (mg)	Number of patients	Number of observations	Peak threshold elevation (%)	Over-all analgesic effect (per cent./hours)
Morphine sulfate	10	30	40	56.5	140
Codeine sulfate	60	22	27	11.9	40
Hydromorphone hydrochloride	3	11	11	41.9	112
Metopon hydrochloride	7.5	7	7	46.4	98
Methadone hydrochloride	7.5	10	10	33.2	168
Pethidine hydrochloride	100	37	50	22.9	70

Working with 75 patients with chronic pain, Nathan (1952) attempted to establish equivalence in analgesic effectiveness of one drug with another in the same patient. The usual procedure was to administer a drug for 3 days, a second drug for 2 days and the first drug again for a day. In any comparison there were at least 10 administrations of the same dose, often as many as 40 or 50. Nathan said that for practical therapeutics, taking side-effects into account, 16 mg of morphine were equivalent to 12 mg of methadone or to 125 mg of pethidine. The lower therapeutic limit, the lowest dose which had a practical analgesic effect, was 11 mg for morphine, 5 mg for methadone and 50 mg for pethidine; the upper therapeutic limit, the dose at which intolerable side-effects occurred, was 65 mg for morphine, 30 mg for methadone and 250 mg for pethidine. The limits were the same for oral or subcutaneous administration.

Lasagna & Beecher (1954) compared morphine, codeine and pethidine for analgesic potency against post-operative pain. All doses were injected subcutaneously; 10 mg of morphine were given alternately in the same patient with varying doses of codeine or pethidine. The double-blind technique was employed, and the results were determined by a trained

observer at 45 and 90 minutes after drug administration. The criterion of effect was at least 50% relief of pain at both observation times and the result was expressed as the percentage of doses giving that degree of relief. The results with codeine and morphine were as follows:

Number of patients	*Codeine phosphate*		*Morphine phosphate*	
	dose (mg)	*percentage relief*	*dose (mg)*	*percentage relief*
30	30	43.7	10	65.3
23	60	59.9	10	70.9
31	90	41.9	10	55.5
24	120	65.8	10	71.8

With pethidine and morphine the results obtained were:

Number of patients	*Pethidine hydrochloride*		*Morphine phosphate*	
	dose (mg)	*percentage relief*	*dose (mg)*	*percentage relief*
23	25	45.7	10	74.5
27	50	62.2	10	64.1
34	100	61.9	10	50.6

50 mg or 100 mg of pethidine or 120 mg of codeine were equivalent in this experiment to 10 mg of morphine; the duration of analgesic effect of these doses was also approximately the same.

Bachrach, Godholm & Betcher (1955), also in post-operative patients, compared pethidine with alphaprodine. Half of 478 cases received one drug, half the other. No opiate had been used for premedication. The doses of pethidine were 50, 75 and 100 mg; those of alphaprodine were 30, 40 and 60 mg. All doses were given subcutaneously. The analgesic effect of pethidine was rated as marked in 50.3%, moderate in 43.5%, slight in 5.3% and none in 0.9%. The effect of alphaprodine was marked in 54.8%, moderate in 37.6%, slight in 5.9%, and none in 1.7%. The average duration of effect of pethidine was 4 hours and 7 minutes, and that of alphaprodine 2 hours and 50 minutes. The onset of effect was quicker with alphaprodine (average 11.9 minutes) than with pethidine (average 19.4 minutes).

Other actions

Pethidine was synthesized as an antispasmodic but, in spite of reports of benefits from its use in conditions involving spasm of smooth muscle structures,[a] more or less direct measurements have indicated both spasmolytic and spasmogenic effects.

Intestine. Batterman (1943a) made kymographic records of the activity of various portions of the gastro-intestinal tract from balloons introduced into the canal by intubation. Doses of 50-100 mg of pethidine intra-

[a] See references to such effects in the earlier reports quoted and in the section on special uses, page 770

muscularly had a spasmolytic effect in 23 of 27 subjects, appearing usually within 10 minutes and lasting 15-90 minutes. The stomach was most affected; the colon least. Yonkman, Noth & Hecht (1944) also recorded gastro-intestinal movements in 15 experiments on five subjects who had colostomies or in whom balloons were introduced by intubation. In one patient only and on one occasion only (there were four other experiments on this patient), pethidine appeared to stimulate the intestine. In two experiments it failed to check an increase in intestinal tonus due to morphine. This patient was given 250 mg of pethidine orally per day for 4 days followed by 200 mg intramuscularly. In the other patients pethidine usually caused a decrease in peristaltic frequency without a decrease in tone, except in one instance. It could on occasion relax a hyperactive intestine. This was illustrated by a partial relaxation of a morphine-stimulated intestine; 200 mg of pethidine were given after 15 mg of morphine, both subcutaneously. In a single case of fistula of the caecum, through which a balloon was inserted into the small intestine, Kewitz, Remmer, & Engelhardt (1951) found that morphine, 10 mg intravenously, increased intestinal tonus, but pethidine, 100 mg intravenously, or methadone, 7.5 mg intravenously, did not. In contrast to the above, Chapman, Rowlands & Jones (1950) said that morphine and pethidine were qualitatively similar in their effect on the gastro-intestinal tract. They inserted multiple balloons by intubation in eight subjects, five of whom received both drugs. Pethidine decreased propulsive activity by 12% in 15 minutes and by 70% in 45 minutes, the effect continuing for an additional 30 minutes. Up to this point the effects of pethidine and morphine were identical; then the pethidine effect declined while the morphine effect continued. Intermittent spasms, increases in tone, occurred after both drugs. During 2-hour periods of observation after injection in the same subjects, these spasms were seen twice with placebos, 10 times with pethidine and 24 times with morphine.

Biliary tract. Utendorfer & Bergh (1946) measured the resistance of the sphincter at the opening of the common bile duct into the intestine. In patients who had undergone operations on the biliary tract, a tube was inserted into the common bile duct and connected to a reservoir, the height of which was adjusted so that the column of fluid was just supported without inflow by the sphincter resistance. The height of the column of fluid, representing intrabiliary pressure or sphincter resistance, before drugging varied between 9 cm and 23 cm, usually between 12 cm and 15 cm, and was quite stable in the same individual for periods of 15-30 minutes. Drugs were given intramuscularly and sphincter resistance was measured minute by minute for an hour. 50 mg of pethidine decreased sphincter resistance in 3 and had no effect on it in 8 other patients; 100 mg of pethidine produced a definite elevation of sphincter resistance in 10 and no effect in one patient. The increase in resistance became evident in

5-12 minutes, reached its maximum in 12-17 minutes and persisted to the end of the hour in 8 of the 10 cases. The maximum increase amounted to 5-12 cm of water. 50 mg of pethidine given simultaneously with 60 mg of codeine, or 100 mg of pethidine given with 10 mg of morphine, had no influence on the spasmogenic effect, increase in sphincter resistance, provoked by the latter drugs. The authors concluded that pethidine, like morphine, must relieve biliary colic by a central action rather than by any direct effect on the biliary tract.

The work of Gaensler (1951), showing that pethidine caused an elevation of the pain threshold when pain was evoked by pressure in the common bile duct, has been noted. He and his associates (1948, 1950a, 1950b) also recorded the direct effect of pethidine and other analgesic agents on pressure in the biliary tract. A T-tube, inserted in the common bile duct in patients who had undergone cholecystectomies or related operations, was connected to a water manometer and pressure in the system stabilized before drug administration. Each of the agents tried had a spasmogenic effect as follows:

Drug	*Dose (mg) and route*	*Number of subjects*	*Average rise in pressure (mm of water)*
Morphine	10 s.c.	40	121
Hydromorphone . .	3 s.c.	14	107
Metopon	7.5 s.c.	16	112
Codeine	60 s.c.	25	48
Methadone	7.5 s.c.	16	91
Pethidine	100 i.m.	40	82

On some occasions the spasm in the biliary tract produced by pethidine, as well as that produced by morphine, was sufficient to precipitate an attack of biliary colic. Two such cases were reported (Gaensler, McGowan & Henderson, 1948). Contrariwise, Curry (1946) reported a case of gallstones in a man of 62, where 10 mg of morphine subcutaneously brought on a brief bout of gallstone colic and 100 mg of pethidine subcutaneously two days later had no untoward result. Gaensler noted that the spasmogenic effect of pethidine appeared within 5 minutes, reached its peak in about 20 minutes, and lasted 90-120 minutes. If it was given consecutively with one of the other opiates the spasmogenic effect of one was superimposed upon that of the other. Pethidine spasm could be relieved significantly by aminophylline or amyl nitrite (Gaensler & McGowan, 1950b).

Uterus.[a] Solomons & Widdess (1943) measured the force of uterine activity by connecting an intra-uterine balloon with a mercury manometer. In five of six patients who received pethidine uterine activity was increased, in one only relaxation was observed. Nevertheless pethidine was given orally to 10 patients with spasmodic dysmenorrhoea. Eight were unanimous

[a] See also section on obstetric analgesia, page 748.

in saying it was the most effective medication for pain relief; two found it no better than other agents tried. Szirmai & Sillo (1955) used pethidine in 33 patients prior to dilatation of the cervix uteri for curettage or other operative procedure. The dose was 100 mg injected into the portio vaginalis or intramuscularly. In 24 the drug facilitated dilatation of the cervix without pain; in 6 the result was poor, and in 3 there was no apparent effect.

Ureter. Climenko & Berg (1943) recorded the tone and contractions of the ureter by means of a catheter introduced during cystoscopic examination. 75 mg of pethidine injected intramuscularly in 14 cases decreased the tone and amplitude of ureteral contractions within 10 minutes. The greater was the initial activity of the ureter, the more marked was the effect.

Metabolism. The few statements which have been made on the effect of pethidine on basal metabolism are conflicting. Lenzi (1941) said that intravenous administration was followed by an increase in the basal metabolic rate persisting for at least 55 minutes, but the effect was less if the rate was already high and in one instance was followed by a noteworthy decrease. Batterman (1943a) found the basal metabolic rate unaffected by pethidine, and Butturini & Arduini (1945) reported divergent results. In 10 cases whose metabolic rates were normal initially, the injection of one ampoule of pethidine (presumably 100 mg) was followed in an hour by an average decrease from −7.5% to −8.1%. In 37 cases of thyroid disease whose metabolic rates averaged above normal, eight showed no change or some increase after the same dose of pethidine, and the others showed a decrease which averaged about 10%. The latter group were quieted by the drug and reported a good night's sleep; the others experienced marked side-effects including nausea and vomiting and no sedation.

Abreu et al. (1950) measured blood pressure, cerebral blood flow and oxygen and glucose uptake after intramuscular injection of codeine phosphate (65 mg), pethidine hydrochloride (100 mg), methadone hydrochloride (5 mg) and morphine sulfate (10 mg), in small groups (7-9) of psychiatric patients. Individual variations were considerable but the trend was towards an increase in cerebral blood flow and metabolism with pethidine and morphine, a decrease with codeine and no significant change with methadone.

Brown & Volpitto (1950) found that, in 25 parturient mothers given 80-190 mg (average 150 mg) of pethidine intramuscularly together with small doses of scopolamine (average 0.96 mg), there was a significant increase in blood carbon dioxide content. In only two babies was the umbilical vein oxygen tension below normal. In both instances the normal progression of labour had been interrupted. the babies were cyanotic and required resuscitation.

Secretion. Consistent with the atropine-like aspect of the action of pethidine, dryness of the mouth, often accompanied by thirst, has been frequently complained of in connexion with the use of this drug. Lenzi (1941) found that intravenous injection of pethidine decreased gastric secretion and decreased the gastric secretory response to histamine if the histamine was given a half-hour after the pethidine. Brown, Hodges & Bradbury (1950) reported that 16 mg of morphine subcutaneously or intravenously decreased renal plasma flow and urinary volume output in normal pregnant women; other drugs (alphaprodine, pethidine, codeine and levorphanol) in comparable sedative doses had qualitatively similar effects. Ferrer & Sokoloff (1947) compared the antidiuretic effect of morphine and pethidine. Both drugs were given to the same two patients after urine flow had been increased by mercupurin. 10 mg of morphine and 75 mg of pethidine were similar under these circumstances in their antidiuretic effect.

Histamine liberation. According to King, Elder & Dripps (1952) the intradermal injection of pethidine was followed within 10 minutes in each of seven subjects by the formation of an extensive wheal, suggestive of histamine liberation. In this respect the drug was similar to morphine. Finer & Partington (1953) described a "triple response", itching and discolouration of a vein spreading along the course of the vein, a red flare in the skin over the vein, and wheal formation, after intracutaneous or intravenous injection of pethidine, especially with partial occlusion of the local circulation. This response was diminished by anti-histaminics, indicating that it was due to histamine liberation. The authors thought it unlikely, however, that histamine liberation would account for the occasional hypotensive effect (see below) of pethidine.

Vestibular function. Gutner, Gould & Batterman (1951, 1952) investigated vestibular function in normal subjects (5 per drug) by means of two tests: (1) the cold microcaloric test, i.e., the production of nystagmus by the injection of ice water into the external auditory meatus; (2) galvanic stimulation of the mastoid area, i.e., the milliamperage required to cause tilting of the head. Increased labyrinthine sensitivity was produced by morphine, methadone and pethidine; it was reduced by codeine, and unchanged by aspirin. Increased sensitivity was evidenced by prolongation of induced nystagmus, increase in the ratio of onset of nystagmus to its duration, and decrease in the milliamperage required to effect tilting. The dosages employed were: morphine 10 mg, methadone 10 mg, pethidine 50 mg, codeine 60 mg and aspirin 600 mg; all subcutaneously except aspirin. The effect of pethidine was greater when the subject was upright rather than in the supine position. The authors suggested that this effect on vestibular function might be a factor in the production of

side-effects. Andersen, Jepsen & Kristiansen (1953) said that in normal subjects inferior vertical nystagmus invariably occurred shortly after the beginning of intravenous injection of pethidine (based on observation of 500 cases). The minimal dosage for this effect as determined in 74 patients was 20-80 mg. Since the nystagmus was elicited presumably by action on the vestibular nucleus, if it did not occur a lesion in that nucleus might be assumed.

Psychomotor function. Kornetsky, Humphries & Evarts (1957) gave pethidine orally to 10 normal subjects and concluded that at the doses employed, 50 mg and 100 mg, the drug did not impair psychomotor function; the results with it did not differ from those with a placebo. The tests used were: speed of addition, speed of copying numbers, pursuit rotor test, tactual threshold and adjective check-list for effect on mood. A pleasant subjective reaction was experienced by the majority of the subjects. In contrast to this negative result in normal individuals, Nathan (1952) asserted that pethidine, as well as morphine, methadone or phenadoxone, could not be relied on to give analgesia without depressing the patient's alertness. Orkin, Bergman & Nathanson (1954) injected pethidine intravenously with or without scopolamine and 15 minutes later injected thiopental sodium at a constant rate to the point of unconsciousness. Pethidine and scopolamine were synergistic so far as the production of amnesia was concerned but orientation, ability to perform simple calculations, tactile perception and ability to carry out commands were unimpaired. The amount of thiopental required to produce unconsciousness was significantly reduced.

Local irritant effect. The subcutaneous injection of pethidine is painful due to local irritant action. This is largely avoided by employment of the intramuscular route.

Side-effects [a]

The earlier reports quoted above mentioned the occasional occurrence of side-effects with pethidine but generally gave the impression that these occurred less frequently than with morphine and related substances. Some later investigators have studied this aspect of the drug's action more quantitatively and their results need to be considered in some detail for a better appraisal of the situation.

Hecht, Noth & Yonkman (1943) tabulated the side-effects which were seen in 132 patients after administration of pethidine at a dose of 100 mg, usually intramuscularly. Mild sedation occurred in about 50% and side-effects of some kind in 27% of the patients. The following figures give the numbers of patients showing the symptom; the figures in parentheses are

[a] See also sections on obstetric analgesia (page 748) and supplementation of anaesthesia (page 737)

the numbers in which the symptom was severe enough to cause discontinuance of the drug:

Vertigo	10 (1)
Dryness of mouth	10
Euphoria	8
Nausea only	3
Nausea and vomiting	5 (3)
Sweating	2
Circulatory collapse	1 (1)
Insomnia and restlessness	1 (1)
Palpitation and dysphoria	1 (1)
Sleep induced	67
Mild sedation without sleep	22
Induration of tissue at site of injection	10

Batterman (1943a) also tabulated the side-effects observed after pethidine according to the route of administration and found their incidence greater with oral doses and in ambulatory patients (Table XXII). The

TABLE XXII. SIDE-EFFECTS WITH 50-150 mg (RARELY 200 mg) OF PETHIDINE (BATTERMAN, 1943a) IN PERCENTAGE OF PATIENTS SHOWING SYMPTOMS

	Parenteral doses (996)	Oral doses (722)	Oral doses in ambulatory patients
Dizziness	59.5	71.1	87.0
Sweating	54.7	37.0	30.4
Euphoria	22.3	15.6	14.1
Dryness of mouth	16.7	27.7	27.2
Nausea	22.6	19.7	38.0
Vomiting	10.4	5.8	17.4
Weakness	0.3	2.3	15.2
Visual disturbance	1.0	2.9	5.4
Headache	1.0	5.2	8.7
Nervousness	0.3	2.3	—
Palpitation	—	0.6	—
Anxiety	0.3	0.6	—
Depression	—	0.6	2.2
Disorientation	0.7	—	—
Tremors	1.0	—	7.6
Urinary difficulty	0.7	—	—
Respiratory depression	0.7	—	—
Syncope	—	1.2	7.6

latter result should be compared with that recorded by Comroe & Dripps (1948) for administration of morphine to ambulatory subjects (Table XXIII). Comroe & Dripps said that only 12% of 68 bed-patients given 15 mg of morphine subcutaneously were nauseated.

Batterman (1943a) drew attention to the absence of changes in the pupil or in pupillary reflexes after pethidine, but the corneal reflex was abolished in 80% of the cases. He also said that the occurrence of side-effects with pethidine was unpredictable; they might occur after the first dose or only occasionally after several doses had been given. They tended to decrease in intensity (except in ambulatory patients) with continued administration and might subside entirely. On the other hand, Lenzi (1941) said that, if drowsiness and dizziness followed the first dose of pethidine, they would occur in that patient with each successive dose.

Bachrach, Godholm & Betcher (1955) compared the incidence of side-effects after pethidine and after alphaprodine in post-operative patients. The pethidine dosage ranged from 50 mg to 100 mg, the alphaprodine

TABLE XXIII. SIDE-EFFECTS AFTER PLACEBOS AND MORPHINE IN AMBULATORY SUBJECTS (COMROE & DRIPPS, 1948) IN PERCENTAGE OF SUBJECTS SHOWING SYMPTOMS

	Placebo	Morphine					
		subcutaneous			intra-venous	oral	
Dosage (mg)	—	8	15	20	15	15	30
Number of subjects	26	11	25	10	12	64	14
No symptoms (%)	88	9	0	0	0	41	14
Nausea (%)	—	36	40	90	85	11	36
Vomiting (%)	—	9	16	30	44	1.5	14
Dizziness (%)	—	36	84	100	75	18	21
Feeling of warmth (%)	—	18	57	60	75	0	14
Itching (%)	—	36	32	70	25	0	7
Drowsiness, fatigue or mental depression (%)	4	45	79	60	70	22	21
Euphoria (%)	—	27	8	40	60	0	0
Visual blurring (%)	—	9	25	50	25	3	7
Minor gastro-intestinal complaints (%)	—	18	25	40	17	25	28
Headache (%)	4	0	12	40	40	12	29
Dryness of mouth (%)	—	27	8	20	7	1.5	0

dosage from 30 mg to 60 mg. Both were given parenterally and there were 239 patients in each group. The following figures were obtained:

Side-effects	*Pethidine*	*Alphaprodine*
Nausea	37	35
Vomiting	12	9
Sweating	17	24
Respiratory depression	5	3
Headache	2	4
Mental confusion	1	1
Dizziness	4	1
Itching	2	3
Weakness	9	5

Batterman & Mulholland (1943) found no significant respiratory depression after pethidine in 488 post-operative patients. They said that other side-effects in such patients were less frequent than with morphine and judged pethidine to be more satisfactory on this account than morphine or any of its derivatives for relief of post-operative pain. Curry (1946) too said that there was little respiratory depression with pethidine in post-operative patients and that the occurrence of constipation and urinary retention was less than when morphine was used. Nevertheless, Curry urged caution with respect to the use of pethidine in cases of intracranial injury because respiratory depression might occur. Batterman (1943a) thought that the absence of an effect of pethidine on pupillary reflexes would permit its use in head injuries. Guttman (1944), however, reported on 20 patients with intracranial lesions to whom pethidine had been given, usually 100 mg intramuscularly: in 7 the respiratory rate fell to 12 or below for 15 minutes or more; in one the rate fell to 8 and in another to 4 per minute. Guttman believed this was too high an incidence of respiratory depression to warrant the use of pethidine in intracranial cases. Also the pupils were constricted in 7 of the 20 cases.

Wilson et al. (1950) found that dizziness, nausea and vomiting occurred less frequently in normal subjects with 150 mg of pethidine than with 15 mg of morphine or 15 mg of methadone. Narodick & Steele (1948) tested the relative side-effect incidence after morphine and pethidine by a sort of cross-over experiment. Each of 105 patients, who were to undergo elective thoracic surgery, was given 10 mg of morphine sulfate subcutaneously, several days before operation. Eighty-six showed no side-effects. Those patients who were sensitive to morphine became increasingly so with repetitions. Of the 19 who were intolerant to morphine 15 showed no symptoms after a test dose of 100 mg of pethidine; the other 4 were nauseated and vomited with pethidine as well as with morphine.

Hoffman (1943) expressed the opinion that the absence of an hypnotic effect with pethidine made the drug particularly applicable to the treatment of pain in ambulatory patients and would allow such patients to continue at their regular occupations.

Some unusual side-effects have been noted occasionally after the administration of pethidine. Batterman (1944) reported the occurrence of tremors and incoordination with therapeutic doses of pethidine and convulsions with doses exceeding 200 mg every two hours, particularly in morphine addicts. Flipse & Flipse (1949) described a case of urinary tract infection and subsequent phlebitis who was proven to have a febrile reaction associated with the administration of pethidine either intramuscularly or orally, proportional to the dose given, and accompanied by headache, nausea, vomiting and anorexia. She gave a marked local reaction to a pethidine skin-test, and it was found later that some antihistaminics would greatly diminish the febrile response while others exaggerated it. 50-mg doses of pethidine every 3 hours, parenterally or orally, begun when the patient was afebrile, raised her temperature to above 104°F.

Steinberg (1945) reported the occurrence of oedema of the uvula and glottis 1¼-24 hours after delivery in three obstetric cases who had received pethidine and scopolamine. The labours were prolonged. The pethidine total dosage was 700, 200 and 300 mg and the scopolamine dosage 1/15, 19/600 and 33/600 grain. The author thought the œdema was due to the scopolamine but a contributory role for pethidine could not be excluded. Jack & Taylor (1948) described another similar case and said three others had come to their attention. Their case had received 100 mg of pethidine and 0.5 mg of scopolamine intramuscularly near the end of the first stage of labour and the oedema occurred about 2 hours later during post-delivery repair.

Seneque & Huguenard (1953) described a case in which oedema and dry gangrene of the fingers followed injection of pethidine into and along a vein. The pethidine was combined with diparcol. Hecht, Noth & Yonkman (1943) mentioned induration of tissue at the site of pethidine injection in 10 of 123 patients.

Feghali (1954), discussing the use of pethidine in paediatrics, said that the drug was badly borne by children less than one year of age.

It is pertinent at this point to take a closer look at the statements which have been made with respect to a euphoric effect of pethidine.[a] Glazebrook & Branwood (1945) said that the euphoric effect was sometimes pronounced. They did not give figures for its incidence. Wilson & Hunter (1948) reported a pleasant feeling of detachment in normal subjects after phenadoxone, methadone and pethidine and this amounted to a marked euphoria with pethidine in the majority of cases. Batterman (1944) said that, when pethidine was administered to normal pain-free individuals, " a good number " experienced unpleasant dreams, but " the majority " experienced a sense of well-being or euphoria. This incidence of euphoria, he said, was much

[a] See also early reports (page 712) and tabulations of side-effects (pages 726 et seq.)

higher than in therapeutic use. Cimoch & Wirts (1953) found that relaxation and co-operation were better with pethidine than with morphine prior to gastroscopy. The pethidine was given intravenously and a definite euphoric effect occurred in 15 of 146 patients. Nickerson & Goodman (1947) reported that the euphoric effect of pethidine in normal subjects correlated with the maximum rise in pain threshold which it produced, and Kornetsky and his associates (1957) noted a pleasurable reaction to pethidine in their normal subjects without any change in psychomotor function.

Circulatory and respiratory effects

A collapse-like syndrome, as an unusual occurrence after the use of pethidine, was noted quite early (Schäfer, 1939), and has been reported occasionally by others (Hunt, 1946; Bieter & Hirsh, 1948; Comroe & Dripps, 1948; Batterman, 1943a). Branwood (1943) gave a 50-mg dose of pethidine intravenously, intramuscularly or subcutaneously, three subjects for each route of administration, and recorded the effect on blood pressure. Systolic pressure fell 66, 45 and 70 mm Hg when the dose was given intravenously, 35, 50 and 24 mm Hg when injection was intramuscular, and 30, 18 and 13 mm Hg after subcutaneous injection. Branwood thought at that time that intravenous administration would be better avoided as having no advantage and because of the unpleasant sensations of giddiness and faintness it tended to produce.[a] Karatygin & Kalyabina (1943) said that pethidine caused a slight to moderate fall in blood pressure (averaging about 10 mm Hg, as much as 29 mm Hg in one case only) in about half of the cases observed. The dosage ranged from 50 mg to 200 mg and administration was subcutaneous.

King, Elder & Dripps (1952) observed the effect of pethidine, 100 mg or 150 mg intravenously, on 26 subjects, medical students or ambulatory hospital patients, on a tilt-table, with constant recording of blood pressure and pulse rate. In the supine position pulse rate increased and blood pressure changed variably before tilting, with a fall in 7, an increase in 14 and no change in the others. When the subject was tilted to the head-up 60° position, the hypotensive effect of tilting was increased after pethidine in 5 of 19 subjects. This was significantly less than in similar trials after morphine. Of patients over 40 years of age 60% fainted when tilted after morphine (Drew et al., 1946) whereas in the present series only 14% of a comparable age-group fainted when tilted after pethidine. Dizziness was commonly reported after the pethidine injections but was not related to changes in blood pressure. According to Lenzi (1941), Batterman (1943a) and Johnstone (1951), the electrocardiogram was unaffected by therapeutic doses of pethidine.

[a] See section on supplementation of anaesthesia, page 737.

Batterman (1943a, 1943b), Batterman & Mulholland (1943), Wilpert (1941), Weinstein (1953) and others have said that respiratory depression with therapeutic doses of pethidine was rare or negligible, but some clinical observations and quantitative measurements have not been entirely consistent with these statements.

Prescott et al. (1949) gave a number of analgesic drugs intramuscularly to each of eight medical students and recorded the total volume of gas respired during the breathing of 5% carbon dioxide after the drug as a percentage of the gas respired before the drug. The degree of depression of the response to carbon dioxide was expressed as a ratio to the depressant effect of morphine. The doses and the ratios were:

	Dose (mg)	*Ratio*
Morphine . .	10	1.0
Pethidine . . .	100	0.15
Methadone . .	10	1.4-2.0
Isomethadone .	10	0.5-0.7

In this experiment methadone was the most depressant to respiration and pethidine the least. In the doses used morphine and pethidine had a sedative effect on all subjects, methadone and isomethadone had none. Remy & Wolsby (1950) also measured the response to the breathing of carbon dioxide (8%-10% in the inspired air) in 10 normal men and said that carbon dioxide respiratory stimulation was reduced equally and significantly by 10 mg of morphine, 10 mg of methadone or 100 mg of pethidine. Loeschke and his associates (1953) gave morphine 10 mg, pethidine 150 mg or saline subcutaneously to six normal men at rest breathing room-air or carbon dioxide at partial pressures increasing from 4.1% to 6.1%. Tidal volume and minute volume under the influence of carbon dioxide were decreased significantly below the saline control by both drugs. A decrease in respiratory rate was produced by pethidine only and with the higher concentration of carbon dioxide only. With the doses used the depressant effect of pethidine was twice that of morphine. The authors concluded that in equivalent analgesic dose pethidine should be at least as depressant to respiration as morphine. According to Stroud et al. (1955) the respiratory depression could be largely prevented by giving aminophylline intravenously immediately after the pethidine, 150 mg intramuscularly in normal subjects at rest.

Orkin, Egge & Rovenstine (1955) studied the effects of morphine, pethidine and alphaprodine on respiratory activity in man during the breathing of oxygen. The subjects were 30 healthy adults scheduled for minor surgery. Morphine (total dose, 10 mg) and pethidine (total dose, 100 mg) were given intravenously; alphaprodine (60 mg) was given subcutaneously. Oxygen uptake, respiratory rate, tidal volume and minute volume were measured.

After morphine or pethidine there was an immediate marked fall in respiratory rate and tidal volume. With morphine the tidal volume then returned to above normal while the rate remained slow; with pethidine the rate returned to above normal and the tidal volume remained reduced. 100 mg of pethidine depressed the minute volume more than did 10 mg of morphine. 60 mg of alphaprodine depressed minute volume approximately as much as 100 mg of pethidine. Oxygen uptake was not significantly altered by these analgesic agents.

Very recently Wendel & Lambertsen (1957) have confirmed the greater respiratory depressant effect of pethidine compared to morphine relative to their analgesic potency. The observations were made on small groups of healthy men (6-8 per dose). Morphine 5, 10 and 15 mg and pethidine 50 mg and 100 mg per 70 kg were given intramuscularly. Respiratory minute volume was measured at a constant pCO_2 (46 mm Hg), and the mean peak effects were plotted against molar free base. The dose-effect curves for the two drugs were parallel; 25, 56, 82 and 106 mg of pethidine had an effect equivalent to 5, 10, 15 and 20 mg of morphine for a potency ratio of 5.4 : 1. Since the ratio of equi-analgesic doses was 8-10 : 1, the authors calculate pethidine to be 1.3 times more depressant to respiration than morphine relative to analgesic action.

Rodman (1953) found that pethidine, 50 mg intravenously in patients under thiopentone/nitrous oxide anaesthesia, reduced the respiratory rate without change in tidal volume but with a marked reduction in minute volume and decreased response to carbon dioxide. Nalorphine, 3 mg intravenously after the pethidine, promptly restored the respiratory rate and minute volume to normal. A second dose of 50 mg of pethidine after the nalorphine failed to develop its respiratory depressant effect. Hamilton & Cullen (1953), more interested in the effect of another antagonist, levallorphan, gave deliberate overdosages of morphine or pethidine intravenously to patients under nitrous oxide/oxygen anaesthesia. The morphine dosages were 40, 45, 60 and 65 mg; the respiratory rate fell from about 20 to as low as 5 or 6 per minute. The pethidine dosages were 175, 200, 200 and 350 mg; the respiratory rate fell to zero in two of the four cases. After morphine or pethidine, levallorphan intravenously restored the respiratory rate approximately to normal and subsequent doses of either opiate did not depress respiration.

Megirian & White (1957) have also studied this effect of levallorphan on the action of pethidine, using a more nearly normal dose of the latter. The subjects were 62 post-operative patients who had received spinal or local anaesthesia. Minute ventilation, respiratory and pulse rates and blood pressure were recorded for 60 minutes or longer after the drugs were given. The dose of pethidine was 1.5 mg/kg (approximately 100 mg or less per patient). It was given alone or with levallorphan. The ratios of the latter to pethidine were 1 : 120, 1 : 60, 1 : 30 and 1 : 15. Levallorphan alone and

saline injections were given as controls. Ten patients were used per drug dose and administration was always intravenous. Levallorphan alone or saline did not alter respiratory function. Pethidine alone decreased minute ventilation to 74%-79% of saline control value for 40 minutes after the drug and respiratory rate to 82%-91% of the control value for 20 minutes.

When the 1 : 60, 1 : 30, and 1 : 15 mixtures were used, respiratory ventilation was not significantly different from the saline controls, except that the respiratory rate was above normal with the 1 : 15 ratio. The 1 : 120 ratio was only partially effective in preventing respiratory depression. In patients with severe pain the 1 : 60 ratio was effectively analgesic without causing significant changes in respiration, pulse rate or blood pressure.

McDermott & Papper (1950) and Meyer & Oehmig (1956) have also cited cases in which doses of 50-100 mg of pethidine injected intravenously produced respiratory depression even to the point of apnoea in anaesthetized patients.

Premedication

Burdick & Rovenstine (1942), Weinstein (1953), Rovenstine (1948) and Hunter et al. (1947) were among those who attested the satisfactoriness of pethidine as pre-anaesthetic medication. Weinstein said it could be used safely as a synergist with all types of anaesthesia. Rovenstine said that pethidine was more satisfactory than methadone but that with it not all patients came to operation in the proper psychic state. With opiates given properly this was less frequently the case. The most favourable cases for pethidine premedication were the elderly and those for whom opiates were contra-indicated. Pre-operative pain was not as well controlled with pethidine as with morphine. Oral doses of pethidine were unsatisfactory; 100 mg subcutaneously would be effective in 50% of the cases, somewhat more so in the elderly. Hunter compared the effect of 75 mg (57 cases) with that of morphine 10 mg (55 cases). Both were given subcutaneously one hour before the anaesthetic was started. In the pethidine group 8.8% and in the morphine group 9.1% were judged to be inadequately prepared. The incidence of post-operative nausea and vomiting was 22.4% when pethidine was the premedication and 17.0% when morphine was used. Hunter and his associates concluded the advantages of pethidine as premedication to be: (1) satisfactory analgesic and sedative effects affording ease in induction of anaesthesia; (2) little or no respiratory depression; (3) desirability in the older age-group; (4) atropine-like effect helping to dry secretions (but they recommended the addition of a small amount of atropine); (5) usefulness in morphine-sensitive patients (one case cited). They listed the contra-indications for pethidine as: (1) patients with severe pain especially if they had been taking considerable amounts of opiates; (2) intracranial lesions; and (3) children under 12 years of age.

Kirtland & Dedenbach (1946) described the use of pethidine in a large group prepared for nitrous oxide/oxygen anaesthesia supplemented with local anaesthesia at the site of operation and in a smaller group where local anaesthesia only was used. All of the latter group were sufficiently depressed and comfortable during the operative procedure. Of the others in 292, or 50%, induction and maintenance were smooth and quiet; in 109, or 22%, sedation was insufficient, and 18, or 4%, were apprehensive, noisy and excited during both induction and maintenance. The pethidine dose was usually 100 mg accompanied by 1/150 grain of scopolamine (both reduced for small individuals and extremes of age), given 15-45 minutes before induction of anaesthesia. Most patients described a feeling of warmth and well-being. Seven were nauseated. Dryness of the mouth, respiratory depression and sweating were mild in a few cases.

Weiss et al. (1956) were interested particularly in the value of chlorpromazine as an adjunct to premedication, but since it was used in all groups their results afforded an interesting comparison of the other premedications. Anaesthesias were of all types. The patients were grouped according to the agents used as follows:

Group A (520 patients)	Pentobarbital	100 mg	intramuscularly	90	minutes before operation
	Chlorpromazine	50 „			
	+ atropine	0.4 „	„	60	„ „ „
Group B (50 patients)	Pentobarbital	100 mg	orally	120	minutes before operation
	Chlorpromazine	25-50 „	intramuscularly	60	„ „ „
	Morphine sulfate	5-6 „			
	+ scopolamine	0.4 „	„	60	„ „ „
Group C (120 patients)	Chlorpromazine	50 mg	intramuscularly	90	minutes before operation
	Morphine sulfate	5 „			
	+ scopolamine	0.4 „	„	60	„ „ „
Group D (35 patients)	Chlorpromazine	50 mg	intramuscularly	90	minutes before operation
	Pethidine hydrochloride	50 „			
	+ scopolamine	0.4 „	„	60	„ „ „

The results in percentages were:

	Group A	*Group B*	*Group C*	*Group D*
No complications	73	76	69	54
Hypotension	4.5	8	16	34
Sedation:				
Good	89.2	80	80.9	85.5
Poor	1.6	4	1.6	8.5
Preparation satisfactory (anaesthetist's judgement)	84.2	78	74	74
Patients' reports:				
Awake and relaxed at time of operation	70.8	74	66.7	66
Apprehensive at time of operation	11.5	20	21.7	26
Post-operative nausea and vomiting	28	8	10	14

Rovenstine & Batterman (1943) compared pethidine with morphine as premedication. The pethidine dosage was 50, 75 or 100 mg according to whether 1/8, 1/6 or 1/4 grain of morphine would have been given. About a sixth of the patients received pethidine alone, the others pethidine plus scopolamine. The authors classed the result as satisfactory if the patient at the time of operation was calm without evidence of emotional disturbance but not depressed to the point that he would not respond to ordinary questions, and as unsatisfactory if he was apprehensive or if depression was so great that he was not easily aroused. Of 166 patients who received 100 mg of pethidine with scopolamine, 76% were judged satisfactory, 15% were not sedated, 5% were apprehensive and 3% were too depressed. Morphine gave a satisfactory result in 81%, and 9% were too depressed.

If patients in whom local anaesthesia was to be used were awake and restless, Barclay (1952) gave 100 mg of pethidine slowly intravenously. Originally this was given with or after 10 mg of morphine (by inference the morphine not having given sufficient sedation) but the combination occasionally caused gross respiratory depression, so that the addition of morphine was abandoned. Used on several hundred patients the pethidine promptly produced sound sleep. Barclay said: " The intelligent use of pethidine has, I believe, advanced the art of premedication for local anaesthesia a long way toward perfection."

Copen (1947), Lubit (1949), Slavin (1950), Nepola (1951) and Abramson (1952) have reported on the use of pethidine in conjunction with local anaesthesia for dental procedures. Copen combined 25 mg of pethidine with the first local anaesthetic injection. Almost immediately the patient relaxed and lost his fear of the procedure. The effect lasted ½-1 hour. Dryness of the mouth was noted in all cases. Pethidine was omitted from subsequent injections of the local anaesthetic if these were necessary, since it was given for its relaxing effect and not for analgesia. Nevertheless, in two control cases given the pethidine and local anaesthetic mixture the pain threshold (Wolff-Hardy-Goodell technique) was elevated by 30% in 30 minutes, returning to normal in about 70 minutes. Lubit used doses of 12.5-50 mg, usually 25 mg, given with the local anaesthetic. Usually the patient was calmed and relieved of his anxiety. There were two failures among ten cases cited. No side-effects were noted. Slavin tabulated his results in 50 cases who were given pethidine orally in comparison with 50 controls. The dose was 50-75 mg for children under 16, 100 mg for all others. The figures in the following tabulation are numbers of cases:

	Control group	*Pethidine group*
Hysterical talk or fear	9	3
Fear of needle	15	8
Pain on injection	18	17
Nervousness after injection	8	1
Syncope after injection	3	0

	Control group	*Pethidine group*
Condition during operative procedure:		
Calm	29	38
Nervous	21	12
Co-operative	44	47
Uncooperative	6	3
Gag reflex:		
Normal	19	6
Sensitive	18	2
Insensitive	13	42
Salivation:		
Normal	45	10
Excessive	5	0
Decreased	0	40

Four of Slavin's pethidine cases were euphoric. Nepola reported 140 cases, using doses of 25-50 mg combined with the local anaesthetic. 71% of the apprehensive, nervous, hysterical patients were relaxed and another 17% were relaxed but still nervous; 13, or nearly 10%, were euphoric. The antisialogogue effect was marked and the local anaesthetic effect better than average. Abramson claimed four years' experience in the use of pethidine in combination with the local anaesthetic for dental procedures in more than 4000 cases. He said that the result was a relaxed patient for about 45 minutes and a more profound local anaesthesia.

Another new field of application of pethidine was in the preparation of patients for endoscopy. Hufford (1944) reported on 38 ambulatory cases prepared for gastroscopy. The dose was 75-100 mg intramuscularly according to weight and degree of apprehension. Pantocaine was applied to the throat and upper oesophagus. The relief of nervous tension and apprehension was fair but not complete; it was better than with 1/2 grain of codeine. There was fair skeletal and smooth muscle relaxation in most cases and marked diminution of the gag reflex. Salivary secretion was decreased. Only one patient was nauseated, none vomited, and 5 complained of dizziness.

The other authors (Gammeltoft, Johnsen & Ruben, 1951; Ruben & Gammeltoft, 1953; Cimoch & Wirts, 1953; Rypdal, 1953; Gammeltoft, Johnsen & Ruben, 1953; Andersen, Jepsen & Sorensen, 1954) reporting on the use of pethidine for endoscopies administered the drug intravenously. In their first report Gammeltoft and associates (1951) had given doses of 100-200 mg to 104 patients. In about 3 minutes there was a selective effect on the pharyngeal and laryngeal reflexes lasting 10-20 minutes. Complete relaxation of the essential muscles made the procedure easier. There were no side-effects except a slight decrease in respiratory rate. In their second report (1953) the dosage of pethidine was reduced to 50-100 mg injected slowly without premedication and without the use of a local anaesthetic. The results were good in 28 oesophagoscopies and 24 gastroscopies. Again

there were no side-effects except a slowing of respiration in a few cases. The pharyngeal reflex was absent for about 10 minutes but the swallowing reflex was not completely abolished. A third series of 482 cases (1953) were given 50 mg of pethidine intravenously in preparation for cystoscopy. The drug was very rapidly effective and there were no complications. Additional doses of 25 mg were given in some cases. The analgesia was insufficient in 8 patients only. Cimoch & Wirts (1953) had used morphine previously before gastroscopy, 15 mg plus 1/150 grain of atropine, and a tetracaine gargle. Side-effects were minimal but sedation was often unsatisfactory because of difficulties in maintaining uniformity in time, type and amount of medication. In their series of 146 patients given pethidine intravenously there was good analgesia, relaxation and co-operation, better than previously. The results were unsatisfactory in 14 patients or 9.5%. The dose of pethidine varied from 50 mg to 150 mg; it was 100 mg in 78% of the cases. An additional 110 cases were mentioned as showing a similar result. Rypdal (1953) reported on 82 cases, 77 of them bronchoscopies, the others oesophagoscopies. The patients were premedicated with morphine and scopolamine and then given 100-200 mg of pethidine intravenously. Analgesia and relaxation were satisfactory and the amount of surface anaesthetic needed was reduced. The principal side-effect was respiratory depression, which, the author said, could be avoided by care in dosage.

Supplementation of anaesthesia (see Table XXIV)

In 1941 Garcia-Huidobro reported on the intravenous administration of pethidine in 30 cases with production of sufficient analgesia so that cervical dilatation and curettage could be carried out in 29 of them without additional anaesthesia. The dose was 150 mg in two cases only, 100 mg in all the others. All the patients were drowsy, dizzy and fell into a light sleep. The analgesia was at its height in 5-7 minutes and lasted about 15 minutes. Six patients were nauseated and two developed an urticaria along the vein. The blood pressure was recorded in 21; it was unchanged in 6, rose slightly in 1 and fell 10-30 mmHg in the other 14. This hypotensive effect the author considered the only disadvantage to an otherwise convenient procedure for patients not amenable to general anaesthesia. From time to time others have tried pethidine intravenously for a rapid analgesic effect, especially in obstetrics, and in 1947 Neff and his associates reported on its use with nitrous oxide anaesthesia. They were trying out curare to improve muscular relaxation and were convinced that painful stimuli during the operation were not completely obtunded. Evidence for this was contraction of muscles not completely paralysed by curare (facial grimace, etc.) and a rise in pulse rate and blood pressure in response to tugging on the viscera, etc. Intravenous morphine would prevent these responses but tended to produce respiratory depression. They tried instead pethidine

TABLE XXIV. SUPPLEMENTATION OF ANAESTHESIA BY PETHIDINE INTRAVENOUSLY

Author (year)	Number of cases	Type of case	Premedication	Induction	Anaesthesia	Other medication	Pethidine dosage	Result and remarks
Brotman & Cullen (1949)	317	37% over 60 years of age; only 96 considered to be in good physical condition	Pethidine, 100 mg i.m., adjusted to weight and condition; average 88 mg	Nitrous oxide	Nitrous oxide/oxygen	Pentothal or pentobarbital in all but 69 patients	Divided dose, each not exceeding 25 mg, average 3 doses when barbiturate given, 2.5 in others; average 1st hour 107 mg, average total 220 mg	Safe and convenient supplementative even in elderly and patients in poor physical condition
Mushin & Rendell-Baker (1950)	>100		Papaveretum	Thiopentone 0.5–0.7 g	Nitrous oxide/oxygen	Flaxedil. Intubation + controlled respiration with oxygen	50 mg first dose + 25 mg about every 20–30 minutes	Very prompt recovery at end of operation and noticeable absence of post-operative pain and restlessness
Griffiths (1950)	500	Operations of many types	Omnopon 22 mg (11 mg in patients over 60) + scopolamine	Thiopentone	Nitrous oxide/oxygen	Muscle relaxant as necessary	25 mg repeated not oftener than 25–30 minutes	In a few cases respiration decreased in rate; prompt recovery, often in operating room; reduced post-operative pain; reduced post-operative complications
Dauri & Paoletti (1950)	70	Mostly abdominal operations		Thiopentone	Nitrous oxide/oxygen	Curare	100 mg	Reduction of shock, early return of reflexes; fewer post-operative complications
Johnson (1951)	>200	Unselected	Pethidine 100 mg + scopolamine 0.42 mg i.m.	Thiopentone	Nitrous oxide/oxygen		Slowing of 10 mg/ml or slow i.v. drip; total dose 50–225 mg	Absence of respiratory depression; bronchi relaxed; rapid return to consciousness and prolonged post-operative analgesia

TABLE XXIV. SUPPLEMENTATION OF ANAESTHESIA BY PETHIDINE INTRAVENOUSLY (continued)

Author (year)	Number of cases	Type of case	Premedication	Induction	Anaesthesia	Other medication	Pethidine dosage	Result and remarks
Johnstone (1951)	50				Trichlorethylene		25 mg	Tachypnoea and cardiac arrhythmia promptly restored to or towards normal; pulmonary resistance to inflation decreased
Pearce (1951)	330	All types of surgery, broad age distribution	Morphine 10 mg+atropine 0.6 mg, patients 16 and over; under 16 atropine only	Thiopentone i.v.; average dose 250 mg	Nitrous oxide/oxygen	Usually muscle relaxant	15–50 mg just before nitrous oxide started, repeated with signs of reflex activity; average total dose 70–80 mg/hour	No change in blood pressure; marked fall in respiratory rate in 2 cases; prompt awakening; adequate oxygenation at all times of greater importance than keeping down dose of pethidine
Ruben & Andressen (1951)	50	Mostly elderly, poor operative risks	Morphine 5–15 mg + scopolamine	Pethidine 1 % solution, 60 mg/minute; total 50–80 mg	Nitrous oxide/oxygen started as soon as patient asleep		50 mg one minute after nitrous oxide started, further doses as necessary; total 40–200 mg	Laryngeal reflex abolished in large proportion, facilitating intubation; respiration often fell to 6-8/minute, chief disadvantage; prompt regaining of consciousness with little aftermath of anaesthesia
Haxholdt (1951)	100						75–550 mg in 1 % solution, slow injection	Prompt awakening; shock, if any, due to blood loss
Blazeby (1951)				Thiopentone	Nitrous oxide/oxygen	Flaxedil as necessary	20–50 mg first dose; subsequent doses 10–25 mg at intervals of not less than 30 minutes	

TABLE XXIV. SUPPLEMENTATION OF ANAESTHESIA BY PETHIDINE INTRAVENOUSLY (continued)

Author (year)	Number of cases	Type of case	Premedication	Induction	Anaesthesia	Other medication	Pethidine dosage	Result and remarks
Murphy (1951)	40		Omnopon	Thiopentone i.v.; average dose 300 mg	Nitrous oxide/oxygen	Flaxedil	25 mg when respiration regular under nitrous oxide; repeated in only 5 cases	Advantages: prolonged analgesia without respiratory depression and post-operative analgesia without mental depression; no depression of cough reflex, constipation or urinary retention. Disadvantage: slow development of full analgesia delaying beginning of surgery
Randall, Belton & Leigh (1952)	>1000		Pethidine + hyoscine s.c.; or morphine or barbiturate	Thiopentone	Nitrous oxide/oxygen		Slow drip; 100 mg in 500 ml 5 % dextrose; 20–40 mg injected rapidly, then rate adjusted to depth of anaesthesia	See text for listing of advantages and disadvantages
Verne (1952)	180	Simple office procedures lasting 5–22 minutes	Pethidine 50 mg + scopolamine 0.4 mg slowly i.v.	Immediately through same needle 2.5% thiopentone to unconsciousness	Nitrous oxide/oxygen or local anaesthesia			Prevention of pre- and post-operative psychic trauma, smooth intubation and maintenance, decreased mucous secretion; usually able to leave office with escort in 30 minutes
Jaquenoud (1952)	100	Mostly abdominal surgery	Sometimes barbiturate		Nitrous oxide/oxygen		Average dose 200 mg; should be reduced if barbiturate given as premedication	

TABLE XXIV. SUPPLEMENTATION OF ANAESTHESIA BY PETHIDINE INTRAVENOUSLY (continued)

Author (year)	Number of cases	Type of case	Premedication	Induction	Anaesthesia	Other medication	Pethidine dosage	Result and remarks
Auld (1952)	12	Children	None for children under 5–10 years		Nitrous oxide/oxygen	Flaxedil to the point of apnoea, then intubation and controlled respiration	I.v. drip, 5 mg; a pause of 1 minute; then another 5 mg continuing until child is asleep; then nitrous oxide started	Children fitter during operation, withstand long procedures better, and are better post-operatively than with other methods
Cyran (1952)	105	General surgery	Morphine or pethidine		Evipan i.v.		100 mg followed in 3 minutes by 5% solution of evipan	Significant respiratory and circulatory depression in 10% of cases but only 4 cases required stimulants
Buschkens (1953)	44		Pantopon 15–25 mg + atropine 0.5 mg	Thiopentone	Nitrous oxide/oxygen or trichlorethylene		Alternate cases given pethidine 38.9 mg during first half hour and 65.7 mg (total, mean figures)	Coughing was significantly reduced
Wolfers (1953)	100		Papaveretum 20 mg + scopolamine 0.4 mg	Thiopentone i.v.; 300 mg average	Nitrous oxide/oxygen	Relaxants as needed + additional thiopentone	25 mg or 50 mg repeated not oftener than at 20-minute intervals	See text for details
Preston (1953)	32		Papaveretum 20 mg	Thiopentone	Nitrous oxide/oxygen		First dose as soon as nitrous oxide started, 25–50 mg; 25 mg additional when anaesthesia lightens; average 132 mg	
Herington & James (1953)	289	Abdominal surgery	Omnopon 20 mg + scopolamine or morphine, + atropine in elderly	Thiopentone 300–500 mg i.v.	Nitrous oxide/oxygen	Succinyl choline to point of apnoea with controlled respiration	10–20 mg before peritoneum opened, repeated at most traumatic parts of operation; total 20–75 mg	Minimizes reflex disturbances and adds greatly to post-operative well-being

TABLE XXIV. SUPPLEMENTATION OF ANAESTHESIA BY PETHIDINE INTRAVENOUSLY (concluded).

Author (year)	Number of cases	Type of case	Premedication	Induction	Anaesthesia	Other medication	Pethidine dosage	Result and remarks
Pryor (1953)	100	Abdominal surgery		Thiopentone 400–600 mg i.v.	Nitrous oxide/oxygen	Curare; intubation; controlled respiration	20–25 mg as effect of thiopentone wanes, usually one dose sufficient; additional 20–40 mg may be given in 20–30 minutes	Low incidence of pulmonary complications because of prompt awakening, and decrease in post-operative vomiting
Rodman (1953)				Thiopentone	Nitrous oxide/oxygen		50 mg, single dose	Reduces respiratory rate, minute volume and response to carbon dioxide
Franks (1954)	222	Nose and throat operations	Papaveretum 20 mg + scopolamine 0.4 mg	Thiopentone 150–300 mg i.v.	Nitrous oxide/oxygen + small amount of trichlorethylene	Relaxant	15–25 mg+10–15 mg whenever cough reflex threatens; total dose 25–150 mg	Smooth anaesthesia without respiratory depression with carefully timed repetition of dose
Morel-Fatio (1955)	200	Facial surgery	Belladonna preparation + barbiturate		Local anaesthesia with xylocaine	Phenothiazine + diparcol	Divided doses, average total dose less than 100 mg	Excellent result in 170, good in 23, unsatisfactory in 7
Widdowson, Aquino & Virtue (1955)	82		Morphine 10 mg + scopolamine 0.4 mg	Thiopentone, average dose 328 mg i.v.	Nitrous oxide/oxygen		Divided doses; total 50–500 mg	Earlier recovery
Ausherman, Nowill & Stephen (1956)	800	Other than intra-abdominal or intrathoracic mainly	Morphine 8–15 mg or pethidine 50–100 mg; some also barbiturate and/or atropine or scopolamine	Thiopentone	Nitrous oxide/oxygen	Relaxant	0.5 % solution in 5 % dextrose, rapidly until respiration began to slow, not intended to go below 10, then more slowly; average dose 72.3 mg	Drip method gives smoother anaesthesia and less danger of respiratory depression; materially reduced amount of thiopentone required

intravenously in doses of 50 mg or 100 mg and found that it had the desired result, with the respiration depressed less and for a shorter period than with morphine. From this beginning others have developed the use of pethidine by various procedures to supplement anaesthesia and their results are summarized briefly in Table XXIV.

Among the earliest accounts of this supplementation procedure were those of Brotman & Cullen (1949, 1950), Brotman, Cullen & Wilkins (1950) and Mushin & Rendell-Baker (1949, 1950, 1951). Both groups found improved anaesthesia and commented on the prompt recovery of the patients and a noticeable lengthening of the post-operative period, during which there was absence of pain and restlessness. In their second paper Brotman & Cullen compared the intravenous use of pethidine with that of morphine and of racemorphan, 50 patients in each group, with the following results, analysed later statistically by Wilkins, Cullen & Brotman (1951):

	Supplementation with:		
	pethidine	*morphine*	*racemorphan*
Pentothal used (mg)	242	389	259
Total drug (mg)	324	33.4	9.7
Percentage of total given in first hour	77	95	94.8
Time from last dose to end of operation (minutes) . .	78	125	152
Duration of anaesthesia (minutes)	197	164	184
Recovery time,[a] (minutes) .	45	39	56
Analgesia,[b] (hours/minutes) .	12/31	17/48	17/59
Patients receiving no analgesic in first 24 hours	11	27	29

[a] From end of anaesthesia to response to spoken word
[b] From end of anaesthesia to first administration of analgesic

Mushin (1951) also compared pethidine with other agents. He said that morphine, heroin, methadone and phenadoxone produced more (too much) respiratory depression. He tried ketobemidone but was unable to decide upon its superiority. Pethidine by slow intravenous drip to a total of 100-200 mg or until the respiratory rate was reduced to 12 per minute was not as satisfactory as the earlier procedure of divided doses.

Sanchez Hernandez (1949) gave sedol (morphine 6 mg, scopolamine 0.2 mg and sparteine 20 mg) or pethidine slowly intravenously before and during general anaesthesia. Both reduced markedly the amount of anaesthetic required, but also caused respiratory depression and occasionally a fall in blood pressure; the latter was greater with pethidine. These adverse effects, however, were easily controlled. Contrary to the last statement, Zuck (1951) reported a case in which a prolonged apnoea and a profound fall in blood pressure followed the injection of only 25 mg of pethidine after induction with thiopentone and gallamine. Johnson (1951), however,

emphasized, as did others, that if the pethidine was given slowly respiratory and circulatory changes were largely avoided, and Johnstone (1951) said that the tachypnoea and cardiac arrhythmia which occurred during trichlorethylene anaesthesia would be restored to or towards normal by 25 mg of pethidine intravenously. It was assumed that a bronchiolar spasm existed which the pethidine relaxed. Also a factor in the cardiac arrhythmia might be retention of carbon dioxide and the author thought pethidine acted indirectly to facilitate elimination of carbon dioxide. In spite of the relief of the dysrhythmia by intravenous pethidine Johnstone said that cardiac inhibition occurred more quickly with cyclopropane if the patients had been premedicated with pethidine, consequently premedication should be limited to atropine. Curiously, Jonstone found that 50 mg of pethidine intravenously followed in 10 minutes by 0.65 mg of atropine intravenously, in 15 subjects with normal respiratory and cardiovascular systems, caused no change in the cardiogram, no evidence of a narcotic effect and no change in respiration—a most unusul result with that dose.

Randall, Belton and Leigh (1952) summed up the advantages of pethidine supplementation as rapid recovery from narcosis, diminution of post-operative pain and restlessness, relatively few post-operative complications, decrease in the amount of anaesthetic agent required, little or no effect on the cardiovascular system (unless large amounts were given quickly), and more adequate analgesia with less residual depression in long operations; and the disadvantages as a definitely depressant effect on respiration (in many cases it was necessary to assist the respiration), less muscular relaxation and more reflex straining or coughing, not quickly remedied by increasing the rate of injection.

Wolfers (1953) compared 100 patients supplemented with thiopentone only with two groups of 50 each, one of which received initial and subsequent doses of 25 mg of pethidine and the other initial and subsequent doses of 50 mg. The results were as follows (figures are means):

	Controls (thiopentone only)	*Pethidine groups*	
		25-mg doses	*50-mg doses*
Total dose of thiopentone (mg) . .	78	597	412
Thiopentone dose per minute (mg).	12.0	9.7	6.4
Total dose of pethidine (mg) . . .	—	76	102
Pethidine dose per minute (mg) . .		1.0	1.4
Number responding to command before leaving operating room . .	32	56	
Post-operative vomiting	11	21	
Time to first analgesic dose post-operatively (hours)	6.0	7.7	

Respiratory depression, presumed to be due to pethidine, was seen in 9 cases, in most of which some assistance was necessary. Temporary wheal, redness or flare along the vein was seen 11 times, severe hypotension

3 times. He concluded that intravenous pethidine did not appear to carry any special risks. This would depend, of course, upon the significance to be attached to the respiratory and circulatory depressions.

Siker et al. (1954) compared pethidine with alphaprodine as an adjunct to thiopentone/nitrous oxide/oxygen anaesthesia, with and without added relaxant. The criteria of effectiveness were the amount of thiopentone required and the percentage of patients responding to auditory and tactile stimuli within five minutes of completion of surgery. The results in the first group (with no muscle relaxant) are shown in Table XXV.

TABLE XXV. PETHIDINE AND ALPHAPRODINE FOR ANAESTHESIA SUPPLEMENTATION

Duration of anaesthesia (minutes)	Pethidine, 200 cases			Alphaprodine, 290 cases		
	thiopentone (mg/min.)	analgesic (mg/min.)	percentage of patients responding	thiopentone (mg/min.)	analgesic (mg/min.)	percentage of patients responding
0-30	39.4	1.39	36	17.3	0.60	62
30-45	24.2	0.98	48	13.4	0.57	67
45-60	19.2	0.72	41	9.8	0.49	77
60-90	16.7	0.65	60	7.7	0.44	84
90-120	12.5	0.58	61	5.9	0.35	87
120-150	10.5	0.43	64	4.5	0.29	88

Similar results in favour of alphaprodine were obtained when a relaxant was given only to intubation or was given for maintenance of relaxation.

Ausherman, Nowill & Stephen (1956) reviewed 800 cases in which pethidine in the form of an intravenous drip was used, and compared the results with those in 200 controls. The amount of thiopentone used was materially reduced from 675 mg per hour in the controls to 375 mg per hour in the pethidine group, or in long operations (more than 4 hours) from 350 mg to 247 mg per hour. The authors thought the drip procedure superior to intermittent dosage, since it gave smoother anaesthesia and, they said, less danger of respiratory depression. Respiration was depressed occasionally, however, because they spoke of the use of remedial measures such as nalorphine. Patients in the pethidine group awoke more quickly and were less confused. Using the response to questions as the criterion, 66% were able to respond at the conclusion of anaesthesia in the pethidine group, 43% in the control group.

Widdowson, Aquino & Virtue (1955) paid particular attention to recovery time in 82 patients given pethidine, compared with 142 patients in whom supplementation was by thiopentone alone. Criteria were ability to talk

and recognize in three successive trials a few seconds apart simultaneous light contact with one cheek and opposite hand. In the pethidine group recovery time averaged 43.5 minutes (0-120 minutes), in the control group it averaged 107 minutes (0-300 minutes). Also, in the pethidine group, once the patient recovered he remained alert, whereas in the control group he tended to relapse into drowsiness. The duration of operation averaged 145 minutes in the pethidine group, 108 minutes in the controls. The thiopentone dose averaged 328 mg for induction in the pethidine group, 800 mg for induction and supplementation in the controls.

Morel-Fatio (1955) supplemented local anaesthesia for facial surgery with intravenous pethidine with very satisfactory results. He said the advantages were calmness during the operation, post-operative amnesia and post-operative analgesia for periods up to 12 hours. Also the swallowing reflex was retained. Sanchez Hernandez (1956) gave pethidine in an intravenous drip with chlorpromazine in 15 obstetrical cases. Flaxedil was given also when dilatation of the cervix was complete and cyclopropane for termination of the delivery. Analgesia and amnesia were good to excellent in all and the author said there was no adverse effect on the infant.

Other reports on pethidine intravenous supplementation have been published by Hofmann (1950), Wylie (1951), Boisson (1952), Goldblat, Chevalier & Leroy (1952), Auvinen (1952), Remler (1953), Rizzi (1953), Forti (1953), Collados (1953), Kunz (1953), and DeBlasi & Rubino (1954).[a]

Recently Hamilton & Cullen (1955) and Swerdlow (1957) have extended their trials of pethidine supplementation, attempting to offset respiratory depression by the simultaneous use of levallorphan. Hamilton & Cullen reported on 30 cases. The initial dose of pethidine ranged from 25 mg to 450 mg; in half the patients it was not more than 150 mg. Apnoea was observed 20 times and a respiratory rate of 8 or less in all of the others. As soon as respiratory depression developed, levallorphan, usually 1, 1.5 or 2 mg, was injected with prompt restoration of the respiratory rate to the normal range and maintenance of normal tidal volumes. Both drugs were given intravenously. Anaesthesia appeared to become lighter in nine cases but, in the few individuals in whom an increased muscular tone followed the pethidine injection, this disappeared after levallorphan. A second dose of pethidine after levallorphan caused little or no respiratory depression.

Swerdlow reported on 60 cases. Twenty received pethidine alone, 20 pethidine plus levallorphan in the ratio of 50 : 1, and 20 pethidine plus levallorphan in a 100 : 1 ratio. Pethidine and levallorphan were pre-mixed. All subjects were about to undergo operation and had been premedicated with 8-10 mg of morphine plus 0.64 mg atropine. Thiopentone was injected intravenously, an airway inserted and nitrous oxide/oxygen administered.

[a] See also section on premedication, page 733

Pethidine and the pethidine-levallorphan mixtures were injected intravenously five minutes after the thiopentone, the pethidine dose in all cases being 0.6 mg/kg. Respiratory activity was measured before and at intervals after pethidine with the results shown in Table XXVI.

TABLE XXVI. RESPIRATORY ACTIVITY WITH PETHIDINE ANAESTHETIC SUPPLEMENTATION (SWERDLOW, 1957)

Drug	Respiratory activity	Time after thiopentone (minutes):				
		5 [a]	9	11	13	15
Pethidine alone	Respiratory rate per minute	19.1	10.6	9.9	10.1	9.2
	Respiratory minute volume	5361	3269	3318	3648	3429
	Respiratory tidal volume	282	302	331	363	377
Pethidine + levallorphan 50:1	Respiratory rate per minute	17.4	13.5	13.5	13.7	13.9
	Respiratory minute volume	6044	4984	5169	5408	5440
	Respiratory tidal volume	348	380	391	404	396
Pethidine + levallorphan 100:1	Respiratory rate per minute	18.3	13.7	13.7	13.4	13.6
	Respiratory minute volume	5715	4524	4679	4766	4993
	Respiratory tidal volume	315	343	355	366	378

[a] Pethidine or pethidine mixture given immediately after 5 minutes' observation, 20 patients in each group.

While some respiratory depression still occurred following the pethidine-levallorphan mixtures, the effect was greatly diminished by the addition of the antagonist. The optimal ratio of antagonist, however, could not be concluded from this work because its effect was practically the same with both ratios employed.

As a corollary to these observations, it may be noted that Schiffrin, Balagot & Sadove (1957), in a small group of patients with chronic pain, measured the response to 5% carbon dioxide and the degree of pain relief when pethidine was administered alone or in combination with levallorphan. The dose of pethidine was 50 mg or 100 mg according to the condition of the patient, and the ratio of pethidine to levallorphan was 100 : 1, 100 : 1.5 or 50 : 1. Injection was intramuscular or subcutaneous. The technique was double-blind and each patient received pethidine with and without the antagonist at 24-hours intervals, so that he served as his own control. The respiratory response, expressed as a percentage of the control value, for each patient and each dose is shown in Table XXVII.

It was evident that pethidine in the usual dose for pain relief in supine patients could produce respiratory depression detectable in 15 minutes and persisting sometimes for at least 90 minutes. Also levallorphan in the

TABLE XXVII. RESPIRATORY RESPONSE TO 5% CARBON DIOXIDE WITH PETHIDINE ALONE OR IN COMBINATION WITH LEVALLORPHAN (SCHIFFRIN, BALAGOT & SADOVE, 1957)

Patient	Lev-allorphan ratio	Pethidine dose (mg)	Route	Respiratory response to 5% CO_2 at minutes shown [a]			
				15	30	60	90
G.B.	None	100	i.m.	—	82.3	110	—
J.M.	None	100	i.m.	—	64.6	71.7	104
J.J.	None	100	i.m.	—	77.7	75.7	109
C.W.	None	100	s.c.	84.8	105	96.1	97.2
S.D.	None	50	s.c.	95.0	103	111	130
G.A.	None	50	s.c.	80.6	80.2	—	89.3
C.W.	100: 1	100	s.c.	113	131	117	113
S.D.	100: 1	50	s.c.	82.0	101	—	—
G.A.	100: 1	50	s.c.	115	104	102	—
G.B.	100: 1.5	100	i.m.	—	105	115	—
J.M.	100:1.5	100	i.m.	—	103	116	126
J.J.	100: 1.5	100	i.m.	—	96.0	117	143
C.W.	100: 1.5	100	s.c.	117	102	128	103
S.D.	100: 1.5	50	s.c.	104	121	122	—
G.A.	100: 1.5	50	s.c.	115	99.7	—	106
G.B.	50: 1	100	i.m.	—	114	132	—
J.M.	50: 1	100	i.m.	—	151	129	128
J.J.	50: 1	100	i.m.	—	109	98.6	—

[a] Expressed as percentage of control value.

ratios used prevented this depression. Levallorphan did not interfere with the analgesic effect of the pethidine nor—except perhaps in the 100 : 1 ratio where the number of cases was too small for certainty—did it diminish the incidence of other side-effects.

Obstetric analgesia

Physicians in general, with few exceptions, have been and continue to be strongly of the view that morphine as an obstetric analgesic involves a major risk for the infant. For example, Irving, Berman & Nelson (1934) compared the effect of morphine and scopolamine with that of various barbiturate combinations. They treated groups of 100 consecutive cases, unselected except for elimination of those with known complications. The medication in the various groups, the degree of amnesia attained, and the effect on the infant are shown in Table XXVIII.

TABLE XXVIII. COMPARISON OF EFFECT OF MORPHINE DERIVATIVES WITH THAT OF VARIOUS BARBITURATES

Medication	Amnesia (%)				Babies breathing immediately (%)
	complete	partial	none	excitement	
1. No medication			100		98.1
2. Nitrous oxide/oxygen/ether					80.0
3. Pantopon 20 mg+scopolamine 0.4 mg, the latter only repeated as often as necessary	39	34	27	10	33.0
4. Pantopon 20 mg + rectal ether + magnesium sulfate	18	47	35	4	53.0
5. Barbiturate only	42	43		15	53.0
6. Amytal + scopolamine	80	20		17.5	61.0
7. Pentobarbital+scopolamine	86	14			53.0
8. Amytal + rectal ether	72	25	3		59.0
9. Pentobarbital + rectal ether	66	28	6	4	53.0
10. Pentobarbital+paraldehyde	64	20		24	50.0

When pantopon was given labour was prolonged in primipara but not in multipara. The authors concluded that morphine or any of its derivatives had no place during labour because of the delay which resulted in infant respiration. The barbiturate combinations in this respect were a little better but not much. Taylor (1947) used morphine, scopolamine and nembutal routinely with excellent analgesic and amnesic effects, but in many cases the mothers were restless and uncooperative and the babies sometimes were resuscitated with much difficulty and were slow in learning to nurse. Searles (1954) said that morphine not only produced respiratory depression but also caused delay in emptying of the uterus. If it was used at all it should be restricted to a single small dose near the end of the second stage. Donnelly (1944) dissented; according to his experience, with careful supervision and adequate resuscitative facilities, morphine could be used safely. Nevertheless, it was little wonder that pethidine, reputed to be less depressant to respiration generally, should be tried in obstetrics. Many reports on its use appeared as a result from many parts of the world. A considerable number of these have been summarized briefly in Table XXIX.

These reports cover at least 25 000 cases, but, unfortunately for the clearest interpretation of the effectiveness and safety of pethidine, in considerably more than half scopolamine or barbiturates or both, and sometimes morphine, were used, and in a great many some form of terminal anaesthesia. However, these same adjuncts have been used similarly where

TABLE XXIX. PETHIDINE IN

Author	Number of cases	Dosage (mg)		Administration			Other agents
		initial	maximum	route	time started	repetition	
Benthin (1940)	ca 400	100 or 200	300 or 600	i.m. rectal		Once or twice.	None in 250.
Sonnek (1941)	200	100 or 200	300 or 600	i.m. rectal		Once or twice.	
Fuchs (1941)	200	100 or 200		i.m. or rectal			
Dobos (1941)	6	90		s.c.	When cervix partly dilated.	Repeated once in five cases only.	
Erbslöh (1943)	250	200 + 100		i.m. rectal			
Bisping (1943)		100 or 200	200 to 600	i.m. or rectal		One to three times.	
Roby & Schumann (1943) and Schumann (1944)	1000	100 i.m. or 100 i.v.		i.m. usual route		q. 4 h.	Scopolamine 0.65 mg with first pethidine dose; subsequently 0.3 mg q. 3 h.
Gilbert & Dixon (1943)	100	100	650	Oral or i.m.		1–6 times	Barbiturate (seconal) given in 72 cases. In these amnesia excellent in 8, good in 36, slight in 27, none in 1. Dose required for amnesia less than without pethidine. Terminal anesthesia (caudal or nitrous oxide) in all but one case.
Sontag Gandara & Monti (1943)	7	100 + 200		s.c. + rectal	When cervix fully dilated	Rectal dose once	

* Abbreviations : i.m. = intramuscular; i.v. = intravenous; s.c. = subcutaneous; q. 4 h. = every 4 hours; breathing = immediate breathing and cry without resuscitative effort. Scopol. = scopolamine.

OBSTETRIC ANALGESIA *

Analgesic effectiveness	Amnesia	Side-effects	Effect on labour	Effect on infant	Remarks
Satisfactory		Drowsy but not dopey	Dilatation of cervix facilitated; labour shortened.	Asphyxia in 3.2 %; three deaths	Other causes for two of the deaths.
Very satisfactory		None	Accelerated.	Asphyxia in three only	Asphyxia with excessive dosage (300–400 mg) only.
Good for 2–3 hours		Sleep for 2–3 hours		None	
Sa 50 % N 25 %			Shortened.	Asphyxia in one	Inferior to oxycodone in analgesic effect.
				Severe asphyxia in four with one death. Lesser asphyxia more often. Baby cries but then needs stimulation to improve breathing.	Safest of analgesics but damage to infant can occur. Doses close to delivery have greater effect on infant.
Good except in one case.		Drowsiness	Immediate decrease in pains, vigorous again in 1–2 hours. Over-all effect: shortening by muscular relaxation, most in primipara.	Asphyxia less frequent than formerly. Vigorous resuscitation not necessary.	Harmless for infant. Babies more resistant to pethidine than to morphine.
C 33.8 % P 53.6 % N 12.6 %	C 33.8 % P 36.7 % S 16.9 % N 12.6 %	Vomiting with i.v. doses if given too rapidly. Nausea in 25 % with slow injection.	Not shortened, possibly lengthened slightly.	Spon. breath. 82 %; delayed breathing needing slight stimulation 12 %; slow, needing vigorous resuscitation 3.3 %.	Authors say no demonstrable depressant effect on full-term or premature infant.
Good 65 % Slight 35 %	None when pethidine given alone	Drowsiness, lightheadedness and nausea; dryness of mouth; euphoria.	Generally shortened, at least when labour normal or dilatation incomplete when drug given. Haemorrhage not increased.	66 of 70 pethidine alone breathed spontaneously; 3 needed resuscitation. 69 of 80 pethidine plus seconal breathed spontaneously; 10 needed resuscitation.	Addition of barbiturate increased depressant effect on infant. Oral administration less rapid and uniform than i.m.
Good but incomplete.				All cried immediately.	Safe for mother and child even in hands of midwife.

C = complete; Sa = satisfactory; P = partial or moderate; S = slight; N = none; Spon. breath. = spontaneous

TABLE XXIX. PETHIDINE IN

Author	Number of cases	Dosage (mg)		Administration			Other agents
		initial	maximum	route	time started	repetition	
Mackenzie (1943)	2	50		i.m.		None	
Gallen & Prescott (1944)	150	100	400	usually i.m., rarely i.v.		q. 1 h.	Scopolamine or other depressants added in some cases. If first dose i.v. other doses were given i.m.
Spitzer (1944)	80	25 or 50	25 to 75	Oral		1–3 times at ½-hour intervals; 2nd dose 25 mg.	
Hori & Gold (1944)	50	100			At onset of labour	q. 4 h.	Scopolamine also given in half the cases, increasing effectiveness and giving fair amnesia.
Cripps, Hall & Haultain (1944)	102	100	400	i.m.	When cervix partly dilated.	q. 1–2 h. 44% one dose only.	Hyoscine given with pethidine in 6 cases only.
Venters (1944)		50 (Potassium bromide and chloral to all cases followed by 50 mg pethidine in some cases according to severity of pain and length of labour.)					
Carter (1945 and 1946)	ca 2700	100	200+	i.m.	When cervix partly dilated.	In 2–3 h.	A barbiturate given orally at beginning of labour; 0.4 mg scopolamine given with each dose of pethidine. Most often not more than 2 doses.

For key to abbreviations, see pages 750-751.

OBSTETRIC ANALGESIA (continued)

Analgesic effectiveness	Amnesia	Side-effects	Effect on labour	Effect on infant	Remarks
Satisfactory			In both cases cervix dilating slowly: 10 mg morphine had been given: three hours sleep. Pethidine had calming effect with relaxation and labour progressed rapidly.		
C 10 % Sa 50 % P 34 % N 5 %	One case only	Vomiting 28 %. Transient rise in blood pressure common. Dizziness, dryness of mouth often.	Dilatation of cervix facilitated but labour not shortened, possibly lengthened.	Spon. breath. 91 %. 9 % required resuscitation.	I.v. faster but i.m. just as satisfactory.
C 17.5 % Sa 72.5 % N 10 % C 22 % with larger dose.		Vomiting in two cases.	Dilatation of cervix rapid in 25, normal in 44, slow in 11.	Mild asphyxia in five.	
Sa 60 % P 22 % S 9 %	P. when scopolamine was added.	Vomiting or dizziness occasional.	No interference.	Spon. breath. 84 %, others vigorous resuscitation.	
Sa 79 % P 10.5 % N 10.5 %		No toxic effects.	Hastened in 33 cases through relaxation. Contractions stopped for several hours in 9. Forceps rate slightly increased.	Spon. breath. 80. 4 only required vigorous resuscitation.	Not harmful to mother or child. No ill effect following use of pethidine.
			Facilitates relaxation and may hasten labour.	No increase in usual number of slow to breathe.	As good as any other analgesic and less danger to mother and child.

TABLE XXIX. PETHIDINE IN

Author	Number of cases	Dosage (mg)		Administration			Other agents
		initial	maximum	route	time started	repetition	
Irving (1945)	2446	100		i.m.			Scopolamine given with pethidine.
Grogan (1945)		100	400 to 500	i.m.		q. 4–6 h.	Scopolamine 0.65 mg with first pethidine dose; subsequently 0.3 mg q. 3 h.
Garcia-Bird (1945)	50	100	500	i.m.	At beginning of labour.	In 1 h. then q. 4 h. Average 3 doses.	Scopolamine 0.65 mg with first pethidine dose; subsequently 0.3 mg q. 3 h.
Hamrick (1946)							
Hunt (1946)	ca 1500	100	400	i.m.		q. 3–5 h.	Barbiturate usually given first.
Mallia (1946)	160	100		i.m.		q. 3 h.	Scopol. 0.3 mg with each dose.
Volpitto (1946)							
Fitzgerald & McArdle (1943)	> 200	100	216.5 (average)	i.m., a few i.v.		In 1 h., then q. 3 h.	Hyoscine and sometimes amytal.
Maxinov (1946)	300	100	400	i.m.	As soon as patient complained of pain.	q. 3 h.; 250 one dose only.	Scopol. 0.4 mg.
Marion (1946)	ca 250						

For key to abbreviations, see pages 750-751.

OBSTETRIC ANALGESIA (continued)

Analgesic effectiveness	Amnesia	Side-effects	Effect on labour	Effect on infant	Remarks
	C + Sa 70 %	Respiratory difficulty in two.		Soon breath. 82 %.	
				Little effect on baby: it cried immediately.	
C 90 %		Rapid i.v. injection always causes vomiting with irregular pulse; avoided if injection given slowly.	Aided dilatation of cervix but did not necessarily shorten labour. Average lengthened slightly.	Two deaths where there was long delay with head on perineum.	Recommended use of forceps as soon as cervix fully dilated; then baby cried immediately.
Usually satisfactory	None		Undetermined. Use of forceps not increased; haemorrhage not increased.	Not ideal analgesic for baby.	No danger to mother.
Usually satisfactory. Oral doses relatively ineffective; 6 of 10 complete failures.		None		Delayed asphyxia five or six times. Baby cried but then needed stimulation to maintain regular breathing.	Did not maintain relief in hard labour as well as morphine but less depressant.
Satisfactory	C 65 %		Dilatation of cervix facilitated in a little more than half of cases. Contraction stimulated by 200 mg i.v. (18 cases).	In six cases where three doses given in 1 ½ hours, all babies drowsy needing resuscitation.	
					Pethidine superior to morphine.
C 16.5 % Sa 52 % N 1.5 %	C 7.5 % Sa 46 % P 15 % N 1.5 %	Nausea, vomiting, flushing, faintness, sweating in some cases.	Did not depress uterine contractions appreciably, did not prolong labour. Operative deliveries not increased.	Almost immediate breathing 73.4 %, delayed breathing 21.8 %, prolonged resuscitation 4.6 %.	Degree of depression less than any effective sedative used so far.
C 42 % Sa 44 % S 14 %	C 42 % S 14 %	Dryness of mouth 82 %, nausea 28 %, dizziness 14 %, sweating 12 %.	Shortened slightly.	Only unusually slow-breathing babies when both drugs were given within an hour of delivery, none with pethidine alone.	Safe for mother and child. Most satisfactory analgesic combination employed.
			Not interfered with. Dilatation of cervix facilitated.	Breathed spontaneously but greater tendency to sleep during first few hours.	Less depressant to baby than morphine.

TABLE XXIX. PETHIDINE IN

Author	Number of cases	Dosage (mg)		Administration			Other agents
		initial	maximum	route	time started	repetition	
Gauthier (1946)	Several hundred	100	700	i.m. or i.v.	When cervix partly dilated.	In ½ and 1 ½ h. then q. 3 h.	
Senarclens (1946)	167	100		i.m.	Early, when cervix partly dilated.	q. 4 h.	
McNeill (1946)	100	100	600 (1 dose only in 40 %)	i.m.	When labour well established.	¾ and 1 ¾ h. and then q. 1 h.	
Turner (1946)	1000	100		i.m.	In first or second stage.	q. 2–4 h. Spinal anaesthesia given when cervix fully dilated. Pethidine given i.v. if labour expected to terminate within two hours.	Scopol. 0.6 mg.
Cardus (1946)	22	50–100		i.m.			
Cameron (1947)	ca 4000	200		i.m.			
Barnes (1947)	500	100	600	i.m.		1 or 2 doses only in 468.	
Prescott & Ransom (1947)	30	100	200	i.m.		q. 1 h.	
	55	150	250	i.m.		100 mg in 1 h.	
Barnes, Hapke & Holzaepfel (1947)	35	100		i.m.			
Hall (1947)	125	100	700	i.m.		q. 1 h.	Scopol. 0.4 mg with each dose.
	27	100		i.v.		Not repeated.	
Downs (1947)	397	100	450	i.m.		50 mg in 2 h., 100 mg q. 2 h. thereafter.	Scopol. 0.4 mg with first and third doses.

For key to abbreviations, see pages 750-751.

OBSTETRIC ANALGESIA (continued)

Analgesic effectiveness	Amnesia	Side-effects	Effect on labour	Effect on infant	Remarks
		Vomiting if i.v. injection given rapidly; transient nausea in some others.	Not affected.	Breathing may be retarded but artificial respiration seldom needed.	Scopolamine added caused too much depression of infant.
C 20 % P 50 % S 11 %		Somnolence 60 %, nausea 9 %, confusion 11 %, dizziness 9 %.	Frequency of contractions decreased 25 %. Duration of labour increased slightly.	Spon. breath. 82 %, drowsy 2.5 %, some asphyxia 8.0 %, stillbirths 3 %.	In all but two cases effect on baby easily explained otherwise than by drug.
		Minimal	If affected, slightly shortened.	Spon. breath. 80 %. Eight slightly retarded. 10 definitely retarded. Four stillbirths.	Safe for mother and child. Stillbirths due to other causes than drug.
Sa 90 %	Sa 80 %				With scopolamine, most comfortable first stage of author's experience.
			Facilitated relaxation and shortened labour.	None if dose limited to 100 mg.	
Satisfactory					100 mg is an insufficient dose.
Sa 55 % P 32 %	Very little; C in 21; S 13, N 304.	Transient dizziness, faintness, numbness, sweating, nausea.	Contractions increased in 118, unchanged 334, decreased 44; operative interference not increased.	Some asphyxia in 55.	Does not endanger mother. May contribute to slowness of babies to breathe; approaches ideal analgesic.
Sa 40 %	Sa in 3 only	Dizziness, thirst, nausea, feeling of well-being.	Lengthened.	Slight asphyxia in 5.	Less depressant to baby than methadone.
Sa 71 %	Sa in 4 only.		Lengthened.	Asphyxia in 11, other causes in 4.	
				No depressant effect if given 1 ½ hours or more before delivery.	
Sa 83 %			Probably shortened, especially in primipara.	Nine babies required some stimulation, usually slight.	Less depressant to baby than morphine.
Sa 75.5 % P 10.9 % N 15.6 %	Sa 50 %		Lengthened.	Breathing delayed in 77, cry delayed in 153, cyanosis in 172; 51 required resuscitation (24, other causes).	Less effect if not given within 2 ½ hours of delivery.

TABLE XXIX. PETHIDINE IN

Author	Number of cases	Dosage (mg)		Administration			Other agents
		initial	maximum	route	time started	repetition	
Collins (1947)	Many						
Hallijas, Tovell & Holt (1947)	Many			i.v.			With scopolamine.
Heyns (1947)							
Taylor (1947)	356	100		i.m.		q. 2 h. or oftener.	Nembutal, 3 grains orally, followed in 30–60 minutes by pethidine + scopolamine, 0.4–0.6 mg.
Beaton (1948)	90	200	1000	i.m.		150–200 mg in 4 h.; 51 one dose only; 33 received 300–400 mg; others 500–1000 mg.	Trilene
Hershenson (1948)		20	240	i.m.		As necessary.	Scopolamine
Roberts (1948)	500	100	500	i.m.	When contractions were regular.	In 1 h. then q. 4 h.	Scopolamine.
Brougher (1948)	348						Barbiturate or paraldehyde usually.
Van Zeller (1948)	2	100		i.m.			Before local anaesthesia.
Rustia & Almeda (1948)	200	100	100	i.m.	Usually at beginning of second stage.	Scopol. only q. 1 h. to 3 doses.	Scopol. 0.6 mg.
O'Reilly (1948)	153	100	400	i.m.	When cervix partly dilated.	In 1 h. then q. 4 h.	All given 3 mg heroin on admission. Pethidine when cervix partially dilated.
Steel (1948)		100 or 150	200	i.m.		Once in an hour. Usually not repeated.	

For key to abbreviations, see pages 750-751.

OBSTETRIC ANALGESIA (continued)

Analgesic effectiveness	Amnesia	Side-effects	Effect on labour	Effect on infant	Remarks
					Less depressant and less untoward effect on infant than the opiates.
			Operative interference increased.	No greater than barbiturate + scopolamine.	As satisfactory as barbiturate + scopolamine.
					Original promise has not been fulfilled. Best method of use not yet determined.
Sa 70 %	Sa 70 %		Not prolonged. Operative interference not increased. No increase in haemorrhage.	Spon. breath. 83 %. Others, minimum of stimulation.	Safe and efficient means of providing amnesia and analgesia.
C 12 % P 69 % N 2 %		Sleep in 57, nausea and vomiting in 30; mild dizziness sweating.	No change in duration, nor in forceps deliveries.	Asphyxia in 8, no difficulty in resuscitation. Four stillbirths, three otherwise explained.	Post-partum haemorrhage in six and in only three of equal number of controls.
	C 47 % P 43 %	Excitement 45 %, vomiting 13 %.	No change in duration.	Spon. breath. 29 %; slight delay 46 %; easy resuscitation 22 %, severe asphyxia 1.5 %.	Only 1.5 % of babies of unmedicated mothers do not breathe immediately.
Sa 480 S 18	C in some cases.	Nausea, vomiting, dizziness rarely.	Lengthened slightly. Some decrease in frequency and strength of contractions.	37 did not breathe spontaneously.	Effective with no untoward results if dosage minimum for effective relief.
Very satisfactory		None	Shortened slightly.	Two difficult to resuscitate.	
Satisfactory					
Sa 62 % P 23 % N 11 %	Sa 86.5 %	Dizziness in all; occasional nausea and excitement.		177 breathed immediately. Others some degree of resuscitation.	Six stillbirths believed unassociated with drug.
C 30 Sa 69 S 31 N 14		Dizziness and vomiting rare.	Hastened dilatation, accelerated delivery.	23, some degree of asphyxia.	Some increase in asphyxia of baby.
Usually good			Sometimes seems shortened; sometimes uterine action weakened.		

TABLE XXIX. PETHIDINE II

Author	Number of cases	Dosage (mg)		Administration			Other agents
		initial	maximum	route	time started	repetition	
Little & Tovell (1949)	> 1000						
Davis & Tupper (1949)	100	100		i.m.		Hyoscine only in 1 h. then q. 2–3 h.	Hyoscine 0.4 mg first dose, then 0.2 mg.
	100	100		i.m.		In 1 h. then q. 2–3 h.	Hyoscine 0.4 mg first dose, then 0.2 mg.
De Bellefeuille (1949)							
Brown, Volpitto & Torpin (1949)	92	61–86 average		i.v.		Repeated at smaller doses in most cases.	Sometimes premedication with morphine or barbiturate, in which case pethidine dose reduced by about 25 %.
Manson (1950)	700	100		i.m.		In 1 h. then q. 1–2 h.	Scopol. 0.6 mg. Usually not repeated.
Narcia (1950)		100 to 125	ca 300	i.v.	When cervix partly dilated.	Repeated as necessary.	Atropine + scopolamine.
Patterson (1950)							
Hughes et al. (1950)	30	100	300	i.m.			Scopolamine in most cases.
Marion & Gagnon (1951)							
Ingelbrecht (1951)				Oral or i.m.			
Cowden (1951)	205	50 to 100		i.v.	When cervix partly dilated.	Usually not repeated.	Barbiturate given previously and repeated as necessary. Scopolamine given with pethidine.

For key to abbreviations, see pages 750-751.

OBSTETRIC ANALGESIA (continued)

Analgesic effectiveness	Amnesia	Side-effects	Effect on labour	Effect on infant	Remarks
				Less delayed respiration and less need of resuscitation than with morphine.	Accumulated results from literature and authors' conclusion.
Sa 55 P 40 S 4	Sa 68 P 16 S 15	Nausea and vomiting. Excitement in 10.	Probably lengthened slightly.	Marked or severe asphyxia in 7.	
Sa 61 P 33 S 6	Sa 69 % P 16 % S 15 %	Excitement in four.	Probably lengthened slightly.	Mild to severe asphyxia in 12.	
				Increased asphyxia if dose repeated.	
C 2.2 % Sa 44.5 % P 33.7 % S 19.6 %	C 53.3 % Sa 32.6 % P 13.0 % S 1.1 %	Nausea in 6, vomiting 5, sweating 2, dizziness 1.	Temporary slowing of labour in 3. Over-all little change in duration.	Spon. breath. 90 %. 10 % required resuscitation.	
C ca 50 % Sa 16 % S ca 20 % N ca 7 %		22 mothers required catheterization.	Usually shortened. Low forceps used in 40.6 %.	Spon. breath. 93 %. 43 babies needed resuscitation. Three died during labour.	
Satisfactory	Satisfactory		Forceps delivery in 17.	Mild to marked asphyxia in 12 babies.	
				Less depressing to infant than opiates or barbiturates.	Should not be used i.v. because of fall in blood pressure.
Sa 17 P 7 N 6				Breathing delayed in 10; four drowsy first day.	Suppression of cortical activity (EEG) in 19 babies.
Used alone, insufficient in most cases.					See earlier report by Marion (1946).
		Minimal	Frequent uterine atony.	Depressant to foetus.	
N in 3 cases.	C in all.	Vomiting 2, restless 2.	71 required low forceps.	Mild asphyxia in 5 % to 6 %.	Author considers degree of asphyxia "usual".

TABLE XXIX. PETHIDINE IN

Author	Number of cases	Dosage (mg)		Administration			Other agents
		initial	maximum	route	time started	repetition	
Lund (1951)							
Lacomme et al. (1952)	175	100	100+	i.v. slow drip			
Divis & Kvoten (1952)	140						Oxytocin
Carey (1952)							
Rosenfeld, Lapan & Weinstein (1952)	25	100	200	i.v. rapid first dose		Second dose by slow i.v. drip.	Scopol. 0.32 mg.
Armand (1952)	121	100	400	i.m.		Usually 2 doses only.	
Helbing & Diegritz (1952)	>1000	100	300	i.m.		Repeated in ca 10 % only.	
Merger & Melchior (1953)	1284	100		s.c.	When labour well established.		Barbiturate at start of labour.
Chase Sosa (1953)	466	100		i.m.			Scopol. 0.4 mg.
Reekie (1953)	750	100		i.m.	When labour established, cervix partly dilated.	Usually 50–100 mg once.	Scopolamine.
Stephen, Novill & Martin (1952)							

For key to abbreviations, see pages 750-751.

OBSTETRIC ANALGESIA (continued)

Analgesic effectiveness	Amnesia	Side-effects	Effect on labour	Effect on infant	Remarks
					Safest of analgesics if dose 100 mg or less.
Sa 79 P 44			Accelerated in 52, retarded in 32.	Spon. breath. in 143; 16 delayed three minutes or more.	In control group 154 babies breathed spontaneously, 11 delayed 3 minutes or more.
			Accelerated labour, especially dilatation of cervix, where labour progressing slowly.	Infant depressed in 6.7 %.	Failed of accelerating effect on labour in two cases only.
				Asphyxia in 8 %, increased to 16.6 % if morphine and scopolamine or barbiturates added.	
C 22 P 3	Sa 18 P 5 S 2	Dizziness, nausea, vomiting.		Spon. breath. 22, 3 required resuscitation.	Believed i.v. superior to i.m. administration.
C 45			Shortened	18 % required some resuscitation.	Less depressant than morphine + scopolamine.
C 6.6 % P 88.1 % S 5.2 %			Contractions weakened 14.8 %, unchanged 84.4 %, stronger 0.8 %. Dilatation of cervix accelerated.	No increase in asphyxia over usual expectation.	
Satisfactory			No significant effect.	35 required resuscitation.	10 foetal deaths, other cause in at least 8.
					Neither better nor worse than trilene.
Sa 80 % to 90 %			When given at proper time is relaxing, shortening labour.	14 % sleepy, 4.9 % narcotized.	Principally due to terminal anaesthesia.
				Depressed foetal respiration almost as much as equivalent amount of morphine.	

TABLE XXIX. PETHIDINE IN

Author	Number of cases	Dosage (mg)		Administration			Other agents
		initial	maximum	route	time started	repetition	
Heckscher (1953)		100		i.m.		q. 3–4 h.	
Garcia et al. (1951 and 1953)	48	25–50	147 (average)	i.v. slow drip	When cervix partly dilated.		
	2500	25–50		i.v.	In second stage.	As necessary.	
Stevenson (1954)		75–100	150			In 3–4 hours.	
Rosenfeld et al. (1954)	121		400	i.v. slow drip	As soon as pains severe.		Scopolamine.
Passmore & Santa Cruz (1954)	917	100	2400	i.v. or i.m.		Usually q. 1–2 h.	
Krumbhaar (1954)		100				Second dose 50 mg.	Scopolamine
Paterson & Prescott (1954)	408	50–100	500				Morphine in some cases.
Fist (1954)		100		i.m.	When contractions were strong.		Scopolamine + magnesium sulfate.
Louros (1955)		50		i.m.		q. ¼ h. Repeated every 15 minutes as long as pain continues unless contractions diminish; then oxytocin and pethidine resumed when contractions resumed.	

For key to abbreviations, see pages 750-751.

OBSTETRIC ANALGESIA (concluded)

Analgesic effectiveness	Amnesia	Side-effects	Effect on labour	Effect on infant	Remarks
		None	Relaxes spasm of cervix.	No undesirable effect.	
Sa 31 P 17	Very little.		No effect on contractions or duration of labour. Low forceps in 3%.	Spon. breath. 37, slight delay 8, delay of 1 minute or more 3.	
		No untoward effect.		No untoward effect.	
			Spontaneous delivery in 92%.	Infant rarely needs resuscitation, then usually from other causes.	
C 87 Sa 28 P 5 S 1	C 85 Sa 23 P 9 S 4	Excitement 8, nausea 12, vomiting 7, sweating 2, dizziness 15.	Usually shortened, slowed in 2 only. Forceps (low) in 37%.	Spon. breath. 88%, slight delay 7%, resuscitation 5%.	Result not as good if scopolamine omitted.
			Low forceps used optionally as often as possible. Labour usually shortened.	No greater difficulties than with other methods. 5 of 17 had some delay in breathing.	
					Early reports over-enthusiastic. Useful if used carefully.
				62 failed to breathe within a minute. One death, which may have been due to drug.	Morphine in 11 of slow breathers.
				Asphyxia increased if barbiturate also given.	One of the safer analgesics.
C ca 63% P ca 34% N 3%					

reliance was placed upon morphine, or one of its derivatives, or upon the barbiturates mainly for analgesia and amnesia.

Dosage. The dose most commonly employed has been 100 mg and it has usually been given intramuscularly. The same or a larger dose has been given rectally, and sometimes the same dose intravenously, when a very rapid effect was desired or delivery was imminent. Probably in a third to one-half of the cases a single dose only was employed, with repetition in 1-3 hours in most of the others. Most frequently, administration has begun early in labour when pains were becoming regular and dilatation of the cervix was partial. The caution has often been expressed that a dose should not be given if delivery is expected within an hour or two. The reason for this precaution would seem to be avoidance of an additive effect between pethidine and the terminal anaesthetic. There have been many exceptions to this usual pattern of administration and reported total dosage has gone as high as 2400 mg; total dosages above 500 mg, however, were unusual. It should be borne in mind that absence of any apparent cumulative effect on the mother does not preclude a cumulative effect on the foetus.

Analgesia and amnesia. Complete analgesia with pethidine has been reported to occur usually in only a small proportion of the cases (see Table XXIX), but most authors have said that it was satisfactory or nearly complete in the majority and the percentage of failures, or only slight analgesia, has been, as a rule, remarkably small. Amnesia, on the other hand, rarely occurred when pethidine was used alone. For this reason scopolamine was very frequently given, as has already been mentioned, and in that case a good degree of amnesia often resulted. There was some indication that the scopolamine also increased the incidence of depression in the infant.

Harer (1956) analysed the results obtained in 500 cases of normal spontaneous labour conducted under pethidine, scopolamine and barbiturate analgesia and compared them with the results in a similar group of 500 cases who also received chlorpromazine. The amount of pethidine required was significantly less in the chlorpromazine group; in 64.5% of this group labour was conducted with less than 100 mg of pethidine whereas the dosage was so small in only 6.2% of the control group. Hypotension, in some amounting to a drop of 10-54 mm Hg occurred in 31% of the chlorpromazine group.

Effect on labour. Most authors have reported that pethidine seemed to facilitate dilatation of the cervix, to promote relaxation, and to improve co-operation in the expulsive effort, partly because of the relaxation, partly because of the decrease in pain. All these things tended to shorten labour. Offsetting them, however, at least temporary weakening of uterine contractions, sometimes their disappearance for a time, has been observed not

infrequently. The score for the over-all effect on the length of labour stands thus for the authors reporting on this point:

Unchanged	10
Unchanged or shortened	9
Unchanged or lengthened	5
Shortened	12
Lengthened	9
Sometimes lengthened, sometimes shortened	4

The trend is towards some shortening, but definite lengthening on account of weakening of uterine contractions has occurred and some authors have said that there was an increase in the need for operative interference (forceps deliveries). No evidence has been offered that the use of the drug has any tendency to increase post-partum haemorrhage; such an increase has been denied in a number of reports.

Effect on the infant. Although a few authors have said that pethidine had no untoward effect on the infant, the tabulation of results shows clearly that the incidence of asphyxia in most groups of cases was definitely above the 1.9% of Irving, Berman & Nelson (1934) for babies of undrugged mothers. The incidence was greater too when scopolamine and/or barbiturate was administered in addition to the pethidine; it was less, however, than when barbiturates and scopolamine were used alone in adequate amounts for amnesia, and less, as a rule, than with analgesic doses of morphine. It is noteworthy that several authors (Eddy, Halbach & Braenden, 1956; Hunt, 1946) observed that, although the baby breathed and cried promptly, muscular tone was poor and breathing became shallow or irregular, requiring stimulation. F. F. Snyder [a] has said that even a single dose of 100 mg of pethidine had a demonstrable depressant effect on the infant. His test was the administration of nalorphine, 0.5 mg intramuscularly, to the infant. Within five minutes of such an injection crying began and continued at intervals. Respiration and body reflexes were strikingly active in contrast to the somnolent state noted a few minutes earlier before the injection of the antagonist. Kymographic records of the respiration of the infant were made by means of a body plethysmograph before and after injection of nalorphine in a series of 50, where 100 mg of pethidine had been given to the mother about 2 hours before delivery. Respiration was deepened and quickened.

J. D. Myers [b] too has reported significant depression of the infant when the mother had received a 100-mg dose of pethidine. He had been studying the value of dihydrocodeine as an obstetric analgesic and observed a comparable group of presumably normal deliveries in which the only difference was administration of 100 mg of pethidine intramuscularly instead of

[a] Personal communication, 1956

[b] Personal communication, 1957

dihydrocodeine. All mothers in each group received an oral dose of 100 mg of Seconal. The time incidence of normal cry and respiration at successive time intervals after birth for the two groups was as follows:

	Normal cry and respiration			
	0-1 minute	*1-2 minutes*	*2-3 minutes*	*3-25 minutes*
Dihydrocodeine group . .	29	8	5	6 (12%)
Pethidine group	25	5	7	11 (23%)

The longest time in the dihydrocodeine group was 14 minutes as against 25 minutes in the pethidine group. Six of the 11 labours in which the cry was most delayed were associated with complications of labour or delivery, but in the remaining 5 no contributing factor other than medication was apparent; in 2 cases in which the cry was delayed for 19 and 25 minutes, respectively, nalorphine was administered to the infant.

Hughes et al. (1950) recorded electroencephalograms on babies born of mothers whose labours were considered normal and who had had no volatile anaesthetic. The drugs and dosage, numbers of babies and general results are show in Table XXX. In the group given 100 mg of pethidine 8 babies showed suppression of cortical activity (decreased amplitude of wave) on the first day, in 5 within 10 hours of the last dose of the drug.

TABLE XXX. RESULTS WITH PETHIDINE AND MORPHINE ON MOTHERS AND BABIES (HUGHES ET AL., 1950)

Drug	Dose (mg)	Number of babies	Delayed respiration in:	Active resuscitation in:	Drowsy 1st day [a]	Analgesic effect in mother		
						good	fair	poor
Pethidine	100	17	3	3	1	8	4	4
Pethidine	200	5	3	3	1	3	2	
Pethidine	300	9	4	3	2	6	1	2
Morphine	10	19	3	2	3	4	12	3
Morphine	15	17	5	4	3	11	6	

[a] Others alert and clinically normal in appearance.

Occasional slow bursts of high microvoltage were seen in 6 on the first day and in 3 others on the second day. In the 200-mg group 3 of the 5 babies showed the same changes in the electroencephalogram, including the bursts of slow waves. In the 300-mg group there was suppression of cortical activity in 8 babies; 2 of these were lethargic and one remained lethargic into the second day. In the group given 10 mg of morphine there was suppression of cortical activity in 13 on the first day, in 8 of these still on the second day, and 6 still showed suppression on the third day. Four showed this suppression for the first time on the second day and one not

until the third day. The bursts of high microvoltage were seen, but less frequently than in the pethidine groups. There were also occasional short runs of fast activity which may have been sleep spindles. There was suppression of cortical activity in 11 of the 15-mg group on the first day, in 6 on the second day (2 for the first time on that day) and in 5 on the third day (one for the first time on the third day). Except for the runs of fast activity the effect of the two drugs was similar, and for the degree of analgesia attained as much depression of the infant was caused by pethidine as by morphine.

Taylor et al. (1955) determined the oxygen saturation of the blood of infants born of mothers who (1) received no general anaesthetic or analgesic, 14 cases; or (2) received 100 mg of pethidine and 0.4 mg of scopolamine 2-4 hours before delivery plus regional anaesthesia for delivery, 38 cases. All babies appeared normal and cried spontaneously. The mean oxygen saturation, oximeter determinations on infant ear, were:

	Minutes after birth			*Extremes at birth*	*Extremes at 30 minutes*
	0	*6*	*30*		
Group 1	74%	90%	98%	53%-94%	90%-100%
Group 2	59%	76%	87%	30%-92%	65%-100%

Roberts et al. (1957) measured the respiratory minute volume of newborn infants of mothers who had or had not received pethidine. The results, corrected for variation in the weight of the infants, were as follows, grouped according to other drugs used:

	Nitrous oxide/air		*Trichlorethylene*		*No other drug*	
	No. of infants	*Min. vol. (ml)*	*No. of infants*	*Min. vol. (ml)*	*No. of infants*	*Min. vol. (ml)*
Pethidine group . . .	205	1025	20	1077	15	815
No pethidine	565	1164	24	1208	38	1162

The authors concluded a 10%-15% decrease in minute volume in the pethidine groups. They then attempted to offset this depression by the administration of levallorphan with the pethidine and compared the results in 177 cases in which pethidine was given alone (Group A) with 178 cases receiving pethidine plus levallorphan (Group B). In each group the initial dose of pethidine was 150 mg intramuscularly followed by 100 mg as required and nitrous oxide/air as required. The second group were given 1 mg of levallorphan in the same syringe with the first dose of pethidine and 0.5 mg in the same syringe with the later dose. The results were as follows:

	Group A		*Group B*	
Number of deliveries . .	177		178	
Normal deliveries . . .	162		168	
Anoxia at birth:				
Severe	6	17%	0	12%
Moderate	13		7	
Mild	11		15	

Relief from pain:	*Group A*	*Group B*
Good	124 (70%)	134 (75%)
Fair	42	37
Poor	8	8

The authors said that there was no improvement in minute volume of the infant when levallorphan was administered with pethidine. Severe and moderate anoxia in the infant, however, was less in the levallorphan group. It is noteworthy also that pain relief was reported to be as good with pethidine plus levallorphan as with pethidine alone.

Side-actions. Drowsiness and light sleep between pains seems to have occurred in almost all cases. Nausea, vomiting and dizziness were common, dryness of the mouth and thirst were very common, and sweating, numbness and a sense of well-being or euphoria were seen less frequently. In other words, side-effects were of the same kind and had a similar incidence to those seen when pethidine was used for other purposes—nausea and vomiting may even have occurred more frequently. Also, just as collapse-like symptoms have occurred occasionally after pethidine in other situations, such have been seen in obstetrics. Butler (1951) described a case. A woman of 24 was given 100 mg of pethidine intramuscularly at 6.30 a.m. At 9.40 she developed cyanosis, widespread urticaria, some oedema of the lips and eyelids, a feeling of faintness and a marked fall in blood pressure. The baby was born dead at 9.45, although the foetal heart sounds had been heard just before the attack. Later a 50-mg dose of pethidine in this patient caused the blood pressure to fall from 120/75 to 90/60. The author concluded that the severe reaction in this case was due to pethidine and remarked that even an ordinary dose of a widely used and usually safe agent can give rise to serious untoward reactions.

Other special uses of pethidine

Singultus. Brunner (1940) reported that the intravenous administration of 2-4 ml (probably 100-200 mg of pethidine) immediately stopped persistent hiccup. The effect lasted about 6 hours, or longer if the pethidine was given intramuscularly, though in the latter case the effect was not so promptly attained. Jessen (1941), Muller (1942) and Fongi (1943) reported similarly. Jessen and Fongi said that pethidine was effective when various other medications (morphine, scopolamine, pentobarbital, etc.) had failed.

Parkinsonism. According to Wiedemann (1941) and Curia (1944) pethidine relieved the muscular rigidity and tremors of Parkinsonism. The former described 6 cases, the latter one. Wiedemann gave at first 100 mg intramuscularly, then oral doses of 40-60 mg 3 times a day; Curia used the drug by injection only. Neither saw any evidence of dependence on the drug but Curia gave only 15 injections in 3 months.

Tetanus. Grant & McNeill (1953) treated a case of tetanus by a slow intravenous drip of 0.4% solution of thiopentone, continued for 11 days. Pethidine was given intramuscularly about every 6 hours, 100 mg at each dose. The pethidine alone would not control the spasms but it materially reduced the amount of thiopentone required.

Asthma. Batterman (1943b) said that, in contrast to the opiates, pethidine could be used without fear in patients with bronchial asthma. Douthwaite (1944), too, recommended its use, in a dose of 100 mg subcutaneously, and an anonymous correspondent in the *Journal of the American Medical Association* (1950) in reply to a query said that 50-75 mg intramuscularly every 6-8 hours for periods of 4 or 5 days only would be useful in patients who had become refractory to bronchodilators (epinephrine, etc.). The cumulative effect of pethidine on the bronchi and the central nervous system could effect relaxation of persistent bronchospasm and respiratory depression would not occur with the dose mentioned unless considerable amounts of barbiturates were also given. The limitation of the period of administration was to avoid development of dependence; the object of the drug's use was mainly to allow restoration of sensitiveness to the bronchodilators. However, considerable respiratory depression can occur with pethidine (see respiratory effect, page 730), and Unger & Unger (1952) have said more recently that neither pethidine nor morphine should be used during attacks of asthma. They pointed out that death has occurred in asthmatic patients to whom morphine was given. By implication it might occur with pethidine. Still more recently Herschfus, Salmon & Segal (1954) described the effect of pethidine in 14 cases of bronchial asthma. The dose was 50 mg or 100 mg intramuscularly. Hyperventilation was diminished and vital capacity increased in most. Slight respiratory depression occurred in one patient only. They thought that pethidine in proper dosage was safe and useful in acute attacks of asthma. 100 mg of pethidine intramuscularly had some antagonistic effect against histamine-induced bronchospasm in 6 cases and against mecholyl-induced spasm in 5 cases.

Antitussive action. Pethidine is generally considered to have little or no antitussive action. Lenzi (1941) provoked cough by intravenous administration of lobeline and compared the time to response on one day with that on the following day when 100 mg of pethidine had been given an hour previously. The time to response was definitely lengthened after pethidine; response was not prevented. Randall, Belton & Leigh (1952) said the tendency to cough was one of the disadvantages to the use of pethidine as a supplement to general anaesthesia.

Angina. Karatygin & Kalyabina (1943) reported very effective relief of anginal attacks in 5 cases. Pain was partially relieved in 10-20 minutes

and completely in 50-60 minutes and did not recur for 6-10 hours, sometimes not for 24 hours. Althoff (1939) too had found the drug effective in anginal attacks.

Cor pulmonale. Hove (1951) recommended the substitution of pethidine for morphine in cases of cor pulmonale, who are particularly susceptible to the toxic effects of the latter.

Burns. Kaye (1956) thought that pethidine should be used in place of morphine for sedation in patients with burns and, because absorption might be delayed in such patients, it probably should be given intravenously.

Artificial fever. Heldt and associates (1945) described 165 treatments in 22 patients, most of whom had syphilis of the central nervous system. Temperature was maintained around 105°F for about 5 hours. 100 mg of pethidine were given intramuscularly as the patient was placed in the heat cabinet; a second dose was given in 2 or 3 hours, and a third dose of 50 mg or 100 mg in another 2 or 3 hours in one-seventh of the treatments. Objectively and subjectively the patients were more comfortable than with other sedatives (barbiturates or paraldehyde). Apprehension which usually accompanied such treatment was noticeably allayed; there was little tendency to delirium, yet the patients were easily roused to co-operate in the treatment.

The "lytic cocktail". Shackman et al. (1954) described under this name a mixture of pethidine and chlorpromazine, used for premedication. Promethazine was given orally the night before, and 100 mg pethidine plus 50 mg chlorpromazine intramuscularly 2 or 3 hours before operation. Subsequently all three drugs were given together intravenously for supplementation.

Addiction liability

As had happened repeatedly with other new morphine derivatives, the first reports on pethidine maintained that no tolerance or addiction had been seen. A factor here is the short space of time usually covered by early reports, but too often such reports do not make clear this limitation. Nevertheless, German physicians discovered very early in 1940 that pethidine could be substituted for morphine in addiction to the latter drug (Reisinger, 1940). Also in 1940 Kucher reported two cases of unusual demerol consumption, one of whom showed definite withdrawal symptoms, and von Brücke (1940) described another case. As the use of the drug spread, at first with unrestricted sale, other reports of addiction appeared. Amark (1941) described three cases two of primary and one of secondary addiction to pethidine, and Garda (1941) noted that many patients experienced a feeling of well-being after pethidine and expressed a desire for it apart from

their need for pain relief. He knew of two addicts who supported their addiction, incompletely they said, by 12-20 injections of pethidine a day. Rojas & Belbey (1941) maintained that tolerance developed with repeated use of pethidine and warned that its use should be restricted to prevent abuse. About this time too Schiøler (1940), Lungwitz (1941), Schwarke (1941) and Wilpert (1941) were discussing the addiction liability of pethidine, though Wilpert maintained that direct addition had not yet been seen. Fórizs (1942) reported on five cases, most of them secondary to the use of morphine. Fórizs said that those who were constitutionally prone to addiction were in the greatest danger (with pethidine), but that there were many examples to show that persons who had hitherto given no sign of proneness to addiction also ran the same risk. Novarini & Fellmer (1942), however, told of a woman who increased her daily dose from 2 or 3 to 17 ampoules and used more than 1000 ampoules of pethidine in 5 months. She was withdrawn abruptly and suffered severe abstinence symptoms for 5 days, but did not demand the drug. She recovered completely. Zara's (1942) four cases started the use of pethidine for medical reasons and continued to the point of addiction. Nau (1942) reported that, of 66 addicts seen up to the middle of 1941, 35 were taking pethidine. He thought the number even then might have been greater if there were better means of recognizing addiction to the drug. Other early references to pethidine addiction are those of Galindez (1942), Lorant (1942, 1943), Zutt (1942), Rodriguez-Gallo (1943), Dalsgaard-Nielsen (1943) and Pita (1943). Pita mentioned nine known cases of pethidine addiction in Argentina, most of them primary.

A number of studies on the addiction liability of pethidine have been carried out at the Addiction Research Center at Lexington, Ky. In the first Himmelsbach (1942) stabilized 13 addicts on morphine and then substituted pethidine. The morphine stabilization dose ranged from 25 mg to 50 mg (mean 36 mg) 4 times a day; the pethidine substitution dose ranged from 60 mg to 120 mg (mean 85 mg) 6-12 times (mean 9 times) a day. Substitution was not quite complete, i.e., the men were not completely satisfied and mild abstinence symptoms appeared during the substitution. After 10 days pethidine was stopped abruptly and an abstinence syndrome appeared, somewhat milder than that usually seen after morphine withdrawal. A direct addiction experiment was carried out on a group of four post-addicts who were allowed to increase their dose as they wished through a period of 10-11 weeks. The peak dosages attained were 257, 135, 217 and 205 mg administered subcutaneously about every 2 hours. After the first week of administration the patients developed muscular tremors and twitches which continued until the third or fourth day after withdrawal. The reflexes were hyperactive and the subjects seemed to become startled by stimuli ordinarily not disturbing. One subject developed a mild toxic psychosis which cleared up on reducing the dose. Two of the patients had epileptiform seizures during the tenth week. All the patients considered

the effects of the drug to be nearly like morphine but less well sustained and all complained of dryness of the mouth throughout. After one month of administration pethidine was temporarily withheld for 22 hours. Very mild signs of abstinence appeared by the 10th hour and persisted until the drug was resumed. A 24-hour withdrawal after two months of administration resulted in definite but mild abstinence signs somewhat earlier, but the patients had no appreciable subjective discomfort. Following final withdrawal of the drug in the 10th or 11th week a definite abstinence syndrome appeared, reaching 50% of peak intensity in 4 hours. The whole picture was typical of but less severe than that of morphine withdrawal.

In another study, Himmelsbach (1943) sought to determine the degree of dependence which would develop if the pethidine dosage was held at a therapeutic level. The number of cases, dosage and administration regimen were:

Number of cases	*Individual dose (mg)*	*Doses per day*	*Period of administration*
3	100	8	2 weeks
4	75	4	3 months
1	75	4	2 months
1	75	8	2 weeks
2	75	8	1 month
3	100	8	1 month
2	75	8	2 weeks

Withdrawals were carried out after the shorter periods of administration or temporary withdrawal at the end of the month and at the end of the experiment in the others. At the outset the patients receiving 75 mg liked the drug but during the second or third month said that it had no " kick ". For comparison a 10-mg dose of morphine was given to each of five subjects 4 times a day for one month. The order of intensity of observed abstinence for the various dosage regimens, the mildest first, was as follows:

Pethidine :

75 mg 4 times a day for 3 months
75 mg 8 times a day for 2-4 weeks
75 mg 4 times a day for 2 months
100 mg 8 times a day for 2 weeks

Morphine :

10 mg 4 times a day for 1 month

Pethidine :

as in first experiment, 10-12 times a day for 10-11 weeks

Usual morphine addiction, stabilization :

4 times a day for 1 week or more

Abstinence intensity of the first two regimens above was below the level of clinical significance, that of the third and fourth regimens, and all others, of course, was clinically significant.

Batterman & Himmelsbach in 1943 reviewed the Lexington experiments and Batterman's clinical trials and concluded that, while physical dependence on pethidine could develop, in a group of 115 hospitalized patients receiving 42-492 doses of the drug within periods of 4-28 weeks no appreciable tolerance to its general clinical analgesic effect occurred, nor were signs of abstinence encountered when the drug was abruptly withdrawn in 47 of the 115 patients.

In 1953 Isbell & White described briefly the subjective effects of pethidine in post-addicts and the usual course of pethidine addiction. They said that the subjective effects induced by pethidine differed somewhat from those of morphine. Pethidine caused considerably more dizziness and a greater degree of elation. Because its length of action was short persons addicted to pethidine ordinarily took the drug subcutaneously or intramuscularly at intervals of only 2 or 3 hours both day and night. A significant degree of tolerance developed but was incomplete with respect to toxic effects, so that pethidine addicts might show twitching of the muscles, tremors, mental confusion, hallucinations and at times convulsions. These toxic signs have been reported by others (Fórisz, 1942; Hunter et al., 1947) as seen during the course of addiction. Mukherjee (1955) described a case of a physician, formerly an alcoholic, who, after taking pethidine for 8½ months, developed a temporary psychosis. This was characterized by irritability, restlessness, incoherence, emotional outbursts and occasional delusions. The symptoms began to clear within a week of withdrawal and had disappeared in 2 weeks.

Recently Isbell (1955) studied four pethidine addicts who had never been addicted to morphine, primary pethidine addicts whose histories were corroborated by their families or physicians. These subjects were stabilized on 1200-3200 mg of pethidine daily for 5-14 days and then abruptly withdrawn. Their abstinence symptoms differed from those observed after morphine in that signs of autonomic dysfunction were not as prominent, whereas restlessness and muscular twitching were more severe. Peak intensity of abstinence was reached in 7-12 hours. Objective symptoms disappeared rapidly, in 3-5 days. Nalorphine, which readily precipitated an abstinence syndrome in a morphine addict, was ineffective in precipitating abstinence in these pethidine addicts unless the daily pethidine dose was 1600 mg or more. Simultaneously, Isbell observed two patients addicted to pethidine who had previously been addicted to morphine or codeine. The symptoms and course following withdrawal of pethidine from these two secondary addicts were identical with those observed in the primary addicts. Isbell concluded that previous addiction to an opiate was not a necessary requisite for the development of physical dependence on pethidine.

Reviewing the work at Lexington, Ky., Eddy, Halbach & Braenden (1956) stated that a dose of more than 120 mg of pethidine was equivalent to 50 mg of morphine for the maintenance of addiction. The dose had to be stated

as more than 120 mg because pethidine, like codeine, seemed never quite completely to satisfy or sustain a morphine addiction.

Using the Wolff-Hardy-Goodell technique, Andrews (1942a) determined the rate of development and disappearance of tolerance to the pain-threshold-raising effect of pethidine. The observations were made on four former addicts who were allowed to increase their dose of pethidine at will but not above 300 mg at an interval of 1½ hours. Threshold determinations were made weekly before and at 15-minute intervals after the current dose of pethidine given not less than 1½ hours after the last preceding dose. Tolerance developed rapidly, almost reaching its maximum in 8 weeks. At the time the effect of a much larger dose was much less than that of the initial dose of 100 mg. After abrupt withdrawal of pethidine the 100-mg dose was tried at 15-day intervals. At 45 days this dose had no effect in one subject, a small effect in two and about the original effect in the fourth subject. Andrews concluded that disappearance of tolerance required more than 30 days.

Andrews (1942b) also recorded electroencephalographic changes and tremors in five post-addicts, who, starting with a subcutaneous dose of 100 mg of pethidine, were allowed to increase administration of the drug as in the tolerance study. By the second week the electroencephalogram showed mainly slow waves with bursts of waves of high potential. These slow waves became progressively slower and increased in amplitude. The tremor records only occasionally exhibited a frequency close to that of cortical activity. Twenty-four hours after withdrawal, the electroencephalogram showed less slow activity but had not returned to normal. The tremor records continued to show large amplitude movements with some rhythmic tremors even after the electroencephalogram was normal. When large doses of morphine were administered regularly there were few effects comparable to those described; slow waves were sometimes seen when tolerance was exceeded but these changes were mild compared to the large amplitude waves seen with pethidine.

Schaumann in 1949 reiterated the view that pethidine was less likely than morphine to produce addiction in clinical practice. American writers (Batterman, 1944, 1948; White, 1943, 1944; Hoffman, 1943; Powers, 1947; Van Dyke, 1949; Seevers, 1949) had been saying this, though usually with the admission that addiction could occur and with the advice that the risk was sufficient to warrant the taking of precautions against it (Tainter & Buchanan, 1949). Nevertheless, cases of pethidine addiction were reported in the English as well as the German literature. Hecht, Noth & Yonkman (1943) saw evidence of addiction, abstinence symptoms, in 9 of 21 patients tested by abrupt withdrawal; the abstinence symptoms became more severe the longer the period of administration. They said that pethidine substituted readily for codeine, less readily for morphine. Schneck (1944) described the case of a woman who had taken successively large amounts of pantopon,

dilaudid and then pethidine, the last because she was told that it was not " habit-forming ". Himmelsbach (1946) reported on the first case of primary pethidine addiction admitted to the Lexington hospital, and Wieder (1946) reported on three admissions to that hospital, two of them certainly and one probably primary pethidine addicts. Curry (1947) reported a single case and Romanoff (1951) a single case. The latter said he had previously had considerable experience in the use of pethidine in asthma, giving 50-100 mg orally or parenterally 3 times a day or oftener without encountering respiratory depression or inducing addiction. The case described was an asthmatic whose physician had taught her to administer the drug to herself.

Polonio (1947) collected 17 cases of pethidine addiction from the literature and claimed to have seen 15 others. He stressed that therapeutic use could cause addiction; tolerance and dependence were easily acquired, though abstinence symptoms were not as intense as with morphine. Hammes (1952) said, " It has been our experience since the end of World War II that Demerol [pethidine] is the most commonly implicated drug in cases of addiction ". Doane (1953) was of the opinion that 100 mg of pethidine twice a day for a week would be likely to produce a state of discomfort when discontinued, a definite craving for continuance. He had seen half a dozen pethidine addicts within a year and by way of comparison had seen only two cases of codeine addiction among 4000 addicts. Thigpen, Thigpen & Cleckley (1953) describing the use of electro-shock therapy in addiction, said that 6 of 35 addicts so treated used pethidine only and 5 others used pethidine along with other drugs.

Samter (1946) commented on the fact that in Germany physicians assumed for some time that pethidine was less addicting than morphine. Consultation with German medical officers in 1946 revealed, however, that they had at that time 40 cases of pethidine addiction in their files and that some hospitals had abandoned the use of the drug on account of their feeling about its addiction liability. Linz (1953) analysed the records of 381 cases of addiction in Berlin (1945-1952). Morphine was the only drug used by 62 and pethidine the only drug used by 23 individuals. Morphine was used with other drugs by 214 and pethidine with other drugs by 92 persons. The records of known addicts in England (*J. Amer. med. Ass.*, 1953) showed that, in 1953, 67% used morphine, 17% heroin and 18% pethidine. The total number was 301. In 1955 (*J. Amer. med. Ass.*, 1955) of 317 known addicts 65% used morphine, 16% heroin and 17% pethidine.

Voorhees & Browne-Mayers (1954) described eight pethidine addicts, including three physicians and a nurse; five of them were taking 1500-4000 mg of the drug a day; the others less. All claimed to have started on the drug because of physical illness and five admitted that they continued to use it to ease anxiety, tension, insomnia, fatigue and strong feelings of resentment. Fox (1954) deplored the fact that most physicians who are

becoming addicted have resorted to pethidine rather than to morphine on account of the continuing impression that it was less addicting. This trend was clear in the report by Rasor & Crecraft (1955) on pethidine addicts admitted to Lexington. From 1 July 1950 to 30 September 1953, 457 were admitted; 288, or 63%, were primary; 169, or 37%, were secondary addictions. Almost 50% were physicians, nurses, or members of related professions. About 60% claimed discomfort from a medical condition as the reason for starting the drug, and most of the individuals were getting the drug from a physician. It should be pointed out that in the same period a total of 12 682 addicts were treated at Lexington.

The literature quoted certainly demonstrates that addiction to pethidine can occur under conditions of clinical practice. The euphoric effect of the drug has been discussed and may play a role in the desire for continuance of administration. The persisting attitude of little risk with the drug is undoubtedly a factor, but if the same precautions are employed in its use as with morphine, pethidine should not be any more addicting. These precautions probably should include avoidance of repeated administration, except in terminal cases, if a euphoric effect is experienced, and avoidance of excessive dosage to get a greater analgesic effect.

SUMMARY

Pethidine was introduced as a " triple-threat " drug, an analgesic, a sedative and a spasmolytic. The optimal analgesic dose, effective against most types of pain, is 100 mg and that dose, injected intramuscularly, is approximately equivalent to 10 mg of morphine. A single dose probably should not exceed 150 mg, because if that dose fails larger doses are usually ineffective and side-effects are increased. Drowsiness and light sleep occur frequently after pethidine and the drug's calming effect suffices for its satisfactory use as pre-operative medication, in preparation for endoscopies, and in conjunction with local anaesthetics in dentistry and elsewhere. The duration of action of pethidine is a little less than that of morphine. Pethidine is not always spasmolytic. On the biliary tract its action is morphine-like; on the intestine it may be morphine-like or spasmolytic, and it appears to decrease contractions of the ureter, to facilitate relaxation of the cervix in obstetrics and sometimes temporarily to decrease uterine contractions. It produces little disturbance of urinary function and is less constipating than morphine. It has been used in bronchial asthma for a spasmolytic effect but is not free of respiratory depression.

The side-effects commonly seen after morphine—dizziness, sweating, nausea and vomiting—occur almost as frequently after pethidine. The incidence is increased in ambulatory patients and after oral administration. Dryness of the mouth and thirst are particularly common after pethidine. A euphoric effect occurs frequently, estimated at from 10% to the majority

of individuals; its incidence appears to be greater in pain-free normal subjects. Pethidine has a respiratory depressant effect relative to its analgesic action at least as great as that of morphine, and a hypotensive effect, especially when injected intravenously. Slow injection decreases the hypotensive effect.

Pethidine has been very widely used in obstetrics with moderate to satisfactory relief of pain in the majority of cases. It is not by itself amnesic and the addition of scopolamine to produce amnesia has tended to increase its depressant action. It facilitates relaxation and dilatation of the cervix but may decrease or suppress uterine contractions at least temporarily and does not necessarily shorten labour. Pethidine has a significant depressant effect on the infant, increasing the incidence of delay on the first breath and cry. This depression is less than when the barbiturates are used and probably less than with careful administration of morphine, but it is definite and should not be regarded lightly. The optimal dose of pethidine in obstetrics appears to be 100 mg intramuscularly, repeated not oftener than every two or three hours.

A new use which has given promising results is intravenous administration of repeated small doses or a continuous intravenous drip to supplement general anaesthesia, particularly with nitrous oxide/oxygen. The injection should be given slowly to avoid respiratory and circulatory depression. The depression can also be diminished by simultaneous administration of an opiate antagonist.

Addiction to pethidine has been reported from many quarters, more frequently, there is reason to believe, because it was introduced like heroin without due recognition of the risk involved. The euphorigenic and addiction-sustaining dose of pethidine has been shown experimentally to be close to the optimal analgesic dose. On this account one should expect its addiction liability relative to its analgesic action to be much like that of morphine and therefore its use might well be limited to acute needs, where it is most effective with the least risk.

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17. Pethidine derivatives

(*a*) Alphaprodine [a] (α-1,3, dimethyl-4-phenyl-4-propionoxypiperidine)

Alphaprodine was shown in the laboratory to be a more powerful analgesic than pethidine, to which its basic structure is related, but to have a relatively brief duration of action. Consequently, while efforts were made to confirm the strength of the analgesic effect in man, clinical trials were directed more particularly to possible replacement of pethidine in its special uses, for endoscopies, supplementation of anaesthesia, and obstetric analgesia, where briefness of action would not be a disadvantage.

Using the Wolff-Hardy-Goodell technique on normal volunteers who had been trained in the procedure for 10 days, Gross, Holland & Schueler (1948) compared the threshold-raising effect of alphaprodine with that of

[a] International non-proprietary name; for other designations see *Estimated World Requirements of Narcotic Drugs in 1958* (United Nations document E/DSB/15).

morphine. Each drug was given subcutaneously at three dose-levels and the result was expressed as a percentage change from the initial threshold. Observations were made at 20-minute intervals after drugging:

Drug	*Dose (mg)*	*Number of subjects*	*Peak rise in threshold (%)*	*Duration of effect (minutes)*
Morphine sulfate . . .	5	5	13.8	185
Morphine sulfate . . .	10	6	21.5	246
Morphine sulfate . . .	15	5	27.2	280
Alphaprodine HCl . .	5	6	7.6	119
Alphaprodine HCl . .	10	8	17.1	191
Alphaprodine HCl . .	15	7	21.4	235

In this experiment alphaprodine was almost as effective as morphine, but it was shorter acting. Alphaprodine was about as effective orally as subcutaneously, but the peak rise was attained more slowly with oral doses. It was more effective intravenously in terms of peak rise in threshold but its duration of effect was even shorter than with subcutaneous doses. Dizziness occurred in more than half the subjects with each dose of alphaprodine, in nearly all with the highest dose; nausea, however, occurred with the highest dose only and then in less than half the cases. The sum of all side-effects with alphaprodine was definitely less than with morphine.

Later, using the same technique in 6 normal subjects, Keasling & Gross (1956) compared 15 mg of alphaprodine with 50 mg of pethidine orally and intramuscularly. At these doses pethidine was slightly more effective than alphaprodine. With alphaprodine drowsiness was reported by 2 subjects, dizziness by 2 and numbness by 5; with pethidine drowsiness was reported by 2, droopiness by one and numbness by one.

Slaughter (1950) also used the Wolff-Hardy-Goodell technique and found the threshold-raising effect of alphaprodine unaffected by the addition of neostigmine; the latter did reduce the incidence of side-effects (dizziness, sweating, nausea, drowsiness and euphoria).

Lee & Hasegawa (1950) and, in another paper, Lee & Pfeiffer (1951) compared alphaprodine with morphine, racemorphan and a placebo for its effect on several pain thresholds in normal volunteers. The doses used were 20 mg and 30 mg of alphaprodine, 20 mg of morphine and 3 mg of racemorphan. Administration was subcutaneous. The thresholds were the initial sensation and pain evoked by electrical stimulation of a filled tooth, pain evoked by the application of the warm wire algesimeter to points on the forehead or wrist, and radiant heat stimulation of the finger pads or finger-nail bed. Morphine and racemorphan raised both the tooth and warm-wire thresholds and alphaprodine raised the tooth threshold only. Side-effects, nausea and vomiting particularly, were most frequent with morphine, nearly as frequent with racemorphan, and least frequent with alphaprodine. In this experiment alphaprodine was a less effective analgesic than morphine.

Houde, Rasmussen & LaDue (1948) tried alphaprodine in the chronic pain of cancer in a small group of patients. Dosage ranged from 15 mg to 40 mg, subcutaneously and orally. Only 4 of 18 patients were made comfortable, 4 got some relief, and 10 got none. Three of the patients who received alphaprodine for more than 2 weeks developed some tolerance to its analgesic effect.

Gottschalk, Orkin & Rovenstine (1954) tested alphaprodine against both experimentally produced and pathological pain. In the first group of patients graded doses were given prior to a minor surgical procedure, and at the time of the procedure the skin was pinched with a haemostat. The result was judged good if the pain of the pinch and of the procedure was tolerated, fair when the pinch was felt as well as some pain of the procedure, and poor when both the pinch and the procedure were painful. The dosages, given subcutaneously, and the results were as follows (atropine or scopolamine was given with alphaprodine in some instances):

Dose (mg)	*Number of patients*	*Result*		
		good	*fair*	*poor*
12	1	1		
18	2	2		
24	5	2	2	1
30	12	9	2	1
36	3	1	2	
45	11	9	1	1
60	10	8	2	
90	1	1		

30-45 mg would seem to have been optimal, but the authors said severe respiratory depression might occur with 45 mg and this depression was not paralleled by the degree of sedation. The respiratory depression was easily relieved by nalorphine if the patient did not become hypoxic. Alphaprodine did not appear to depress the circulation.

In a second group of 15 patients with chronic pain Gottschalk, Orkin & Rovenstine (1954) gave multiple doses per day of 15-24 mg. Seven patients obtained good relief with 2 doses, 3 with 3 doses a day and 4 were only partially relieved by 4-6 doses a day. The drug failed to give relief in one patient. In 5 of these patients the drug was continued for 10-24 days and then was stopped abruptly without the appearance of abstinence symptoms. The only side-reactions seen were nausea and dizziness after a first dose of 24 mg.

A third group of 19 post-operative patients were given doses of 15-24 mg and the results were compared with those of 50 mg of pethidine. Good, fair or poor relief of pain were given scores of 2, 1 and 0, respectively, and an average score for all doses was computed. The score for the 50-mg pethidine dose was 1.0, for the 15-mg alphaprodine dose 0.65, and for the

24-mg alphaprodine dose 1.60. Also, the results with alphaprodine were more uniform than with pethidine.

Bachrach, Godholm & Betcher (1955) also compared alphaprodine with pethidine in post-operative patients; half received one drug, half the other. The only pre-operative medication was phenobarbital and scopolamine; anaesthetic procedures were various:

	Alphaprodine		*Pethidine*	
	Doses (mg)	*No. of patients*	*Doses (mg)*	*No. of patients*
	30	16	50	12
	40	215	75	37
	60	6	100	190
Average doses per patient . .	5.1		3.9	
Onset of effect (minutes) . . .	11.9		19.4	
Duration of effect (hrs/min.) .	2/50		4/7	
Effect %:				
Marked	54.8		50.3	
Moderate	37.6		43.5	
Slight.	5.9		5.3	
None	1.7		0.9	

40 mg alphaprodine would seem to have been as effective as 100 mg of pethidine, more rapid in onset of effect but shorter in duration. Euphoria and sedation were infrequent; other side-effects were similar in kind and incidence for both drugs: nausea in 35 and 37, vomiting in 9 and 12, sweating in 24 and 17, and respiratory depression in 3 and 5 with alphaprodine and pethidine, respectively.

Mack (1956) reported on a series of 114 consecutive post-operative patients observed in the recovery room. All were considered to have recovered fully from the anaesthetic. Of 100 who received 20 mg or 30 mg of alphaprodine subcutaneously, 91 obtained complete relief in 12 minutes on the average, lasting 30 minutes to 2½ hours. Five patients experienced moderate relief and 4 no relief. Drowsiness accompanied the relief in 52 cases and dizziness occurred only once. Of the remaining cases, 10 received 40-60 mg subcutaneously and four 30 mg intravenously. All of these obtained complete relief of their pain promptly for an average duration of one hour. Four of the patients receiving the largest doses showed some decrease in respiratory rate and diminished respiratory minute volume.

White, Megirian & Marcus (1956) noted that in normal volunteers and conscious post-operative patients alphaprodine in doses of 20-40 mg intravenously reduced respiratory minute volume to 55% of normal before drug within 10 minutes. Minute volume was back to 75% of normal in 40 minutes. If the alphaprodine was combined with 1/75-1/100 of its weight of *l*-3-hydroxy-N-propargylmorphinan respiratory minute volume was 70% and 90% of normal at the 10- and 40-minute post-drug observation times. All subjects were intermittently or constantly asleep and had to be roused

for the observation after alphaprodine, and this narcotic effect was not decreased by the addition of the antagonist.

Later White, Megirian & Marcus (1957) compared alphaprodine with pethidine and morphine. Post-operative patients to whom narcotics would normally have been given received a saline injection or one of the drugs slowly intravenously. Respiratory and pulse rates, respiratory minute volume, blood pressure and reactivity were recorded. Alphaprodine at a dose of 0.38 mg/kg in 9 patients decreased respiratory minute volume to 60%-90% of normal (saline control) for 20 minutes but did not affect respiratory rate. Pethidine at 1.5 mg/kg in 10 patients decreased respiratory volume to 70%-80% of normal for 40 minutes and respiratory rate to 80%-90% of normal for 29 minutes. Morphine at 0.15 or 0.2 mg/kg did not significantly change volume or rate. The authors concluded that at their usual analgesic doses—10-15 mg for morphine, 27-53 mg for alphaprodine, 100 mg for pethidine—alphaprodine was most depressant to respiration, morphine least, and pethidine intermediate.

Auerbach & Coakley (1956) determined the effect of alphaprodine alone (27 patients) and in combination with levallorphan in various ratios (42 patients). In both groups the dose of alphaprodine was 40 mg for males and 30 mg for females. The ratios of alphaprodine to levallorphan were 10 : 1, 15 : 1, 20 : 1, 30 : 1 and 40 :1. All injections were given subcutaneously. Respiratory rate and minute volume were measured before and at 15-minute intervals after drug administration for one hour. Alphaprodine alone produced only a slight decrease in respiratory rate, but a decrease in minute volume to 78.4% of the control value 15 minutes after injection with little return toward normal during the 60-minute period. When alphaprodine was given with levallorphan respiratory rate was always above normal if the proportion of levallorphan was 20 : 1 or greater. Minute volume under these circumstances was less than control values but greater than when alphaprodine was given alone. However, if the ratio of the combination was 30 : 1, respiratory minute volume was depressed nearly as much, and, if the ratio was 40 : 1, it was depressed fully as much as by alphaprodine alone.

All the patients in this study were in need of analgesic medication and all were relieved completely whether or not levallorphan was administered. Most of the patients receiving alphaprodine alone were sleepy and complained of dizziness a few minutes after injection. One complained of generalized itching and one of nausea and vomiting. When levallorphan was also given side-effects were not reduced when the ratio was 10 : 1 or 15 : 1 and probably not with the 20 : 1 ratio; they appeared to be less with the 30 : 1 and 40 : 1 combinations.

In another respect alphaprodine was morphine-like. According to Brown, Hodges & Bradbury (1950) 16 mg of morphine subcutaneously or intravenously reduced renal plasma flow and increased tubular reabsorption

to decrease urine volume. Alphaprodine in a comparable sedative dose (the dose was not otherwise stated) had a qualitatively similar effect. The observations were made on normal pregnant women.

Premedication and supplementation of anaesthesia

Like pethidine, alphaprodine has been used preparatory to local anaesthesia, for endoscopies and as a supplement to nitrous oxide/oxygen anaesthesia. Weiner (1955) gave 40-60 mg of alphaprodine subcutaneously to 60 patients prior to oral surgery. The patient was allowed to recline for 20 or 30 minutes and when he became drowsy the surgical procedure was carried out under local block or nitrous oxide oxygen anaesthesia. The author said the rapidity and brevity of action of alphaprodine were advantageous. Anxiety was nearly always relieved; the patients were relaxed and tended to doze; analgesia was good in 53. Three patients felt faint following the injection of the local anaesthetic. After the procedure the patients were somewhat dull; there was nausea in 8, vomiting in 2 and dizziness in 5. Weiner considered the over-all effect excellent in 41, good in 12 and fair in 6.

Protell (1956) reported on the use of alphaprodine in dentistry. There were 29 cases in the study who required preparation of the teeth for full coverage and one case of extraction of six teeth. His results were summarized as follows:

Number of cases	30
Dose (mg)	48
Number of doses	84
Doses per patient, average	2.1
Onset of analgesia, average	19.5 minutes
Duration of analgesia, average	2 hours, 40 minutes
Effect (%):	
Marked	56.7
Moderate	33.3
Slight	10.0
None	0.0
Side-effects, incidence:	
Nausea	2
Vomiting	1
Respiratory depression	1
Headache	3
Dizziness	6
Mental confusion	1

Protell characterized his patients as neurotic individuals on whom the effect of prolonged grinding of the teeth would undoubtedly have been traumatic. He thought alphaprodine seemed to neutralize anxieties inherent in the dental situation.

As the result of a study of the use of alphaprodine in 128 cases of dental extractions in ambulatory patients, Bitte, Hale & Dunn (1956) summed up its advantages as rapid onset of action, adequate pain relief, lack of interference with the patient's ability to co-operate during the procedure, a total action not much longer than the operating time, and a minimum of side-reactions. They used the drug in combination with pentothal sodium to produce both analgesia and amnesia and said that it played a part in the relief of anxiety as well as pain as a supplement to local block.

Belinkoff (1955) used alphaprodine as premedication in 1000 surgical cases, mostly young healthy adult males. The routine procedure was pentobarbital sodium 1½ grains at bedtime the night before operation and repeated about 2 hours pre-operatively. Alphaprodine 60 mg and scopolamine 0.32 mg were given when the patient was called to the operating room. Most of the patients became sleepy and euphoric and tended to doze during operations done under some form of regional block anaesthesia. No significant respiratory depression was noted in any of these cases. However, the author noted that if intravenous pentothal was used following alphaprodine premedication very much smaller amounts of pentothal were required and respiratory depression and apnoea were easily produced. Itching of the nose or generalized itching was the only side-effect noted after alphaprodine premedication in this series. Belinkoff said that children withstood alphaprodine well when it was used as premedication in combination with scopolamine. He employed doses ranging from 10 mg for infants of 2-4 years, to 45 mg for children aged 12-15 years. A 3-year-old child inadvertently given 50 mg of alphaprodine was very sound asleep on arrival in the operating room with a respiration of 6-8 per minute. Following 1 mg of levallorphan subcutaneously the respiration rose to 22 per minute within 3 minutes and the child awoke and cried.

Bowman (1955) reported that, whereas seconal had been used previously as premedication for caesarian sections, for a year and a half alphaprodine in a dose of 30 mg subcutaneously with atropine 0.4 mg one hour before operation had been substituted for seconal with very satisfactory preoperative sedation and no ill effect on the newborn.

Walters, Mayer & Johnson (1956) described their results in 199 cases of different categories requiring relief of pain and/or anticipatory anxiety, in whom alphaprodine was the sole anaesthetic agent. The number and types of cases, the dosage and results are given in Table XXXI.

No side-effects other than drowsiness were seen. The authors also mention briefly more than 1000 cases in which alphaprodine was used as premedication or as an adjunct to anaesthesia. The only comment on results was that the use of alphaprodine reduced the amount of thiopental administered to achieve satisfactory anaesthesia.

There have been ten reports published on the use of alphaprodine preparatory to bronchoscopy (Halle et al., 1955; Gierson, Gottlieb &

TABLE XXXI. ANALGESIC EFFECT OF ALPHAPRODINE (WALTERS, MAYER & JOHNSON, 1956)

Number of patients	Dosage of alphaprodine	Procedure	Attitude of patient	Analgesic effect	
				satis-factory	unsatis-factory
93	30 mg	Cystoscopy	87, good	87	6 (pain on inserting scope)
20	30 mg	Urethral dilatation	18, good	18	2
48	30 mg (for adults; less for children)	Reduction and fixation of fractures	46, good	46	2
38	30 mg maximum for individual doses; 6 mg per minute	Dental surgery; reduction and fixation of mandibular and other fractures	35, good	35	3
199			186, good	186	13

Ruben, 1955; and Belinkoff, 1956) or to cystoscopy and other urological procedures (McCrea & Post, 1954; Garnes, 1955, 1956; Yow, Mathias & Bunts, 1955; Trifilio & Hudson, 1955; Chang & Graves, 1955; and Ashmore & Moon, 1955). Halle et al. (1955) gave 60 mg of alphaprodine an hour before or 30 mg subcutaneously half an hour before bronchoscopy; sometimes a second dose of 30 mg was given intravenously just before intubation. Gierson, Gottlieb & Ruben (1955) gave 15, 30 or 60 mg subcutaneously 15 minutes before examination. Belinkoff (1956) gave 60 mg of alphaprodine intravenously. Each of these investigators used local anaesthesia and, in addition, Gierson, Gottlieb & Ruben and Belinkoff gave their patients previously one or two doses of pentobarbital orally. The results were said to be excellent in most cases. Respiratory depression occurred occasionally with 60-mg doses so that the patient had to be reminded to breathe deeply. Of Halle's cases receiving the 60-mg dose, 40% were nauseated; this was reduced to 16% if the dose was 30 mg. Of Gierson's patients, 10% complained of dizziness and nausea. Belinkoff saw no undesirable side-effects. According to Halle the cough reflex was retained; Gierson thought it was better suppressed than with pethidine or morphine, and Belinkoff said that alphaprodine produced a pronounced desirable depressant effect on the laryngeal and pharyngeal reflexes. The last author remarked that the pronounced analgesic effect facilitated and speeded up laryngoscopy for the application of local anaesthetics to the respiratory passages.

Preliminary trials indicated to McCrea & Post that 30 mg of alphaprodine intravenously was the optimal dose for cystoscopy; this amount was used in 100 patients. Analgesia was marked in 40, moderate in 34, slight in 11 and none in 10; it was rapid in onset, within a minute in 58 and within three minutes in 15 others; it lasted on the average 16 minutes. Sedation was marked in 17, moderate in 11 and slight in 16; it lasted usually 20-30 minutes. The examination had to be postponed in five cases on account of the occurrence of side-reactions. Garnes reported 80 cases; Yow, Mathias & Bunts, 150. The dose in each case was 30 mg intravenously. Garnes gave a second dose of 20 mg if the examination had to be repeated. He said that analgesia was good in 69 (86.25%), moderate in 7 (8.75%) and poor in 4 (5.0%). There was little sedation and recovery was complete in all but three within 30 minutes. Yow said the result was excellent in 58% and good in 34%. He also reported little sedation. In both these groups of patients no other medication was used. Fourteen of Garnes' patients complained of dizziness and two of Yow's series were nauseated and vomited.

In his later report Garnes (1956) described 74 cases in which alphaprodine 60 mg plus levallorphan 0.25 mg were given intravenously preparatory to urological procedures, mostly cystoscopies. The analgesia was good in 70 and moderate in 4. The result was considered good when the procedure was accomplished without complaint from the patient. There was complete recovery from the sedative effect within 30 minutes. Nausea, vomiting and itching were absent in all cases, but 39 patients experienced some dizziness. There were no appreciable changes in blood pressure, pulse or respiration. Other ratios of alphaprodine and levallorphan gave less satisfactory results.

Trifilio & Hudson (1955) reported 100 trials of alphaprodine for cystoscopies and other urological procedures. The dose was 30-20 mg intravenously in 33 trials, 20-60 mg subcutaneously in the others. The analgesic effect was satisfactory in 94%. The result was improved by the addition of scopolamine 0.4 mg. Nausea developed in 15 trials, in 10 of which the dose was greater than 20 mg. Nausea occurred more frequently with subcutaneous than with intravenous administration and more frequently in females than in males. Some decrease in respiratory rate was seen in 15 cases but it was never marked or considered of clinical significance.

Chang & Graves (1955) used alphaprodine for cystoscopy in three series of cases. In 76 the drug was used alone, in 38 it was used with pentothal and in 21 with pentothal and nitrous oxide to complete anaesthesia. When alphaprodine was used alone there was no discomfort in 42% and only slight discomfort in 37%; the result was unsatisfactory in 13%. The dosage varied from 30 mg to 60 mg and was administered intravenously. In contrast to Trifilio & Hudson, Chang & Graves said that depression of respiration was marked chiefly through a decrease in rate which might drop to 6 per minute. This depression was increased by the addition of pentothal. However, the amount of pentothal used with alphaprodine as compared with

the amount when pentothal was used alone was markedly reduced from 711 mg and 620 mg, averages for males and females, to 260 mg and 117 mg. Other side-effects seldom occurred—dizziness four times, nausea and vomiting once.

Ashmore & Moon (1955) have reported on the use of alphaprodine for urological procedures on more than 1000 patients in office practice. They used 30 mg intravenously and said that it almost always produced immediate euphoria, as if the patients were becoming drunk. Nausea occurred in seven of the first 25 cases but subsequently was almost always prevented (reduced to about 1%) by the previous administration of 50 mg of Dramamine. Ashmore & Moon said that alphaprodine left the patient with the use of all of his faculties and completely free of fear and apprehension. They said it was the agent of choice to give prompt attainment of maximal analgesia.

Siker et al. in 1954 reported on the use of alphaprodine intravenously in 656 cases as a supplement to nitrous oxide/oxygen/thiopentone anaesthesia and compared the results with those obtained in 600 cases with pethidine. Siker, with others (Swerdlow, Foldes & Siker, 1955b ; Foldes, Swerdlow & Siker, 1955 ; and Foldes et al., 1956), later reported on supplementation with alphaprodine plus levallorphan. In the first series thiopentone was given intravenously in an amount sufficient to permit establishment of an oropharyngeal airway, then nitrous oxide/oxygen was begun and the first dose of the analgesic was given intravenously. The initial dose of alphaprodine was usually 7.5 mg (3.5 mg in debilitated individuals, 12 mg in the very robust). Subsequent fractional doses were given at 8-20-minute intervals on the appearance of signs of too light anaesthesia or a rise in the respiratory rate above 20. Evaluation was based on the mg per minute of thiopentone required and the percentage of patients responding to auditory and tactile stimuli within 5 minutes of the completion of surgery. The patients were classified in three groups: those in whom no muscle relaxant was used, those in whom a muscle relaxant was used up to intubation only, and those in whom a relaxant was used during maintenance of anaesthesia. The results with alphaprodine and with pethidine in each group are shown in Table XXXII.

The authors concluded that alphaprodine most closely approached the desiderata of a short-acting analgesic with minimal cumulative effect and, therefore, easy control. They pointed out, however, that, if the doses of alphaprodine indicated above were exceeded, respiratory depression occurred which was sufficiently severe to make it necessary to assist the respiration mechanically or manually, and hence the anaesthesia was less controllable.

In a second report Swerdlow, Foldes & Siker (1955b) described the effect of alphaprodine on cerebrospinal fluid pressure and the modification of that effect by levallorphan. There were four groups of patients, 15 in each

TABLE XXXII. COMPARISON OF EFFECT OF ALPHAPRODINE AS ANAESTHETIC SUPPLEMENT WITH THAT OF PETHIDINE

Duration of anaesthesia (minutes)	Thiopentone (mg/min.)	Analgesic (mg/min.)	Percentage of patients reacting within 5 minutes	Thiopentone (mg/min.)	Analgesic (mg/min.)	Percentage of patients reacting within 5 minutes
	Group 1: No muscle relaxant					
	Alphaprodine, 290 cases			**Pethidine, 200 cases**		
0-30	17.3	0.60	62	39.4	1.39	36
30-45	13.4	0.57	67	24.2	0.98	48
45-60	9.8	0.49	77	19.2	0.72	41
60-90	7.7	0.44	84	16.7	0.65	60
90-120	5.9	0.35	87	12.5	0.58	61
120-150	4.5	0.29	88	10.5	0.48	64
	Group 2: Relaxant to intubation only					
	Alphaprodine, 145 cases			**Pethidine, 200 cases**		
45-60	14.4	0.53	72	21.4	0.87	43
60-90	8.4	0.48	87	17.0	0.60	55
90-120	6.1	0.45	90	13.2	0.52	62
120-150	4.9	0.39	91	10.9	0.48	66
150-180	4.1	0.35	91	9.7	0.43	65
	Group 3: Relaxant throughout maintenance					
	Alphaprodine, 321 cases			**Pethidine, 200 cases**		
45-60	12.4	0.53	70	18.8	0.75	44
60-90	8.0	0.43	81	14.5	0.61	56
90-120	6.4	0.41	84	11.9	0.54	62
120-150	5.2	0.37	85	10.2	0.48	64
150-180	4.2	0.33	88	9.6	0.46	66
>180	3.2	0.28	89	8.2	0.33	66

group, who were to receive spinal anaesthesia. They were premedicated with thiopentone 1½ hours before and 5-10 mg of morphine plus scopolamine 1 hour before the observations were begun. Pressure was recorded from the spinal needle by means of a water manometer and the drugs were given intravenously. The dosage was 0.33 mg/kg of alphaprodine and 1/50 of that amount of levallorphan. In one group alphaprodine was given alone, in other groups it was given 5 minutes before or 5 minutes after levallorphan, and in the fourth group both drugs were given together. The dose of alphaprodine was considerably greater than the single doses of this narcotic recommended for supplementation of anaesthesia as outlined above. There was a high degree of scatter in the initial cerebrospinal fluid

(CSF) pressure in the individual patients, yet alphaprodine and levallorphan resulted in marked changes, which were expressed as percentages of the control value. The pressure was recorded at minute intervals after drug administration (see Table XXXIII).

TABLE XXXIII. CEREBROSPINAL FLUID PRESSURE CHANGES FOLLOWING ALPHAPRODINE ADMINISTRATION, EXPRESSED AS PERCENTAGES OF CONTROL VALUES

Sequence of drug administration	Time in minutes									
	1	2	3	4	5	6	7	8	9	10
Alphaprodine alone	10.3	32.8	54.5	62.4	69.4	67.4	64.7	66.1	66.2	58.2
Alphaprodine followed in 5 minutes by levallorphan	6.2	28.6	49.9	61.7	67.4[a]	61.2	47.2	35.0	27.7	24.1
Alphaprodine 5 minutes after levallorphan	−0.6	−3.0	−1.5	−3.1	−2.8[b]	0.1	16.3	27.7	41.1	43.1
Alphaprodine and levallorphan given together	8.5	16.6	26.3	41.2	45.0	47.0	47.1	49.5	37.4	41.6

[a] Levallorphan administered
[b] Alphaprodine administered

Alphaprodine caused a marked rise in CSF pressure, which was well maintained to the end of the 10-minute observation period. The rise was partially prevented or counteracted by levallorphan given shortly before, shortly after or together with the alphaprodine.

In another study Foldes, Swerdlow & Siker (1955) and Foldes et al. (1956) determined the effect of the supplemental alphaprodine in nitrous oxide anaesthesia on respiratory activity and the influence thereon and on the value of the supplementation of simultaneously administered levallorphan. Alphaprodine depressed respiratory rate to 40%, tidal volume to 45%, minute volume to 30%, and alveolar ventilation to 20% of control values (average of 30 cases). If levallorphan was given 4 minutes before the alphaprodine, 2 minutes after the latter respiratory rate was reduced only to 75%-80%, tidal volume to 60%, minute volume to 65%, and alveolar ventilation to 50%-60% of the control value (average of 10 cases). The giving of levallorphan with the alphaprodine in the proportion of 1:50 by weight permitted the use of larger doses of alphaprodine and there was a much greater reduction in the amount of thiopental required. In 92 of 852 patients no thiopental at all was required after the alphaprodine-levallorphan mixture. Also 95% of the patients responded to stimuli within 5 minutes of completion of surgery as compared with the 62% so

responding in the previous series of 756 patients given alphaprodine for supplementation.

Kepes & Margolius (1956) also employed alphaprodine for supplementation and levallorphan to counteract its respiratory depressant effect. They compared initially four groups of 20 patients each. Minimal premedicative relaxation was provided in all by 0.3-0.4 mg of atropine or scopolamine. In group 1 induction of anaesthesia was accomplished with 2.5% thiopental in a dose range of 50-300 mg (average 170 mg), and anaesthesia was maintained with nitrous oxide/oxygen supplemented with intermittent doses of alphaprodine. Individual doses of alphaprodine ranged from 6 mg to 24 mg and total doses from 18 mg to 336 mg (average 90.5 mg). Levallorphan was used as needed to overcome respiratory depression in an amount approximately 1/50 of the alphaprodine dose. In group 2 induction again was with 2.5% thiopental (average dose, 230 mg) and maintenance of anaesthesia was with nitrous oxide/oxygen plus intermittent doses of alphaprodine and levallorphan premixed in a 50:1 ratio. The individual doses of alphaprodine were as in group 1, with a total dose ranging from 12 mg to 174 mg (average 58.8 mg). In group 3 anaesthesia was induced with a continuous drip of 50:1 mixture of alphaprodine and levallorphan, 20-35 mg of alphaprodine per minute. For maintenance of anaesthesia (plus nitrous oxide/oxygen) the rate of infusion was decreased. In this group the total alphaprodine dose ranged from 100 mg to 490 mg (average 231.5 mg). In group 4 (controls) induction was with thiopental and maintenance with nitrous oxide/oxygen plus intermittent doses of thiopental. The total thiopental dose ranged from 200 mg to 1100 mg (average 650 mg).

Severe respiratory depression was noted in almost every instance in group 1 following the initial dose of alphaprodine but was easily controlled with levallorphan. Such severe respiratory depression was prevented in groups 2 and 3 where the two drugs were given together. Moderate depression only occurred with the initial dose or with institution of the drip but lasted only 2-5 minutes and respiratory function was adequate subsequently in both groups. The addition of the levallorphan permitted the use of substantially larger doses of alphaprodine than could be given otherwise without risk to patients, yet reactivity at the completion of surgery was excellent.

The satisfactoriness of alphaprodine plus levallorphan for supplementation of anaesthesia has been further confirmed by Lipson & Bradford (1957). In addition, these authors reported that satisfactory operating conditions were obtained with alphaprodine alone (8 cases) or in combination with a narcotic antagonist (76 cases) but without general, spinal or regional anaesthesia. They said that the feasibility of such a regimen attested to the high analgesic potency of alphaprodine but that it required high doses, which could be given safely if levallorphan were given conjointly. Levallorphan did not cause any considerable interference with analgesic action

and the reactivity of patients at the end of surgery was excellent. They recommended wider use of alphaprodine combined with levallorphan as the sole anaesthetic agent and to supplement nitrous oxide/oxygen/thiopental anaesthesia.

Stoelting & Hicks (1956) reported on 252 surgical patients to whom alphaprodine and levallorphan were given as a pre-mixed solution in a ratio of 50 : 1. In this group, 165 underwent major surgery. Premedication consisted of 3-15 mg of morphine sulfate and 0.15-0.4 mg scopolamine or atropine 60-90 minutes before surgery. Nitrous oxide/oxygen was used in 243 patients, supplemented occasionally by cyclopropane or ether. Nine operations were done under local blocks. Ten to 15 minutes before initiation of anaesthesia the alphaprodine-levallorphan mixture was given intravenously, the size of the initial dose corresponding to 30-60 mg of alphaprodine, depending on the age and physical state of the patient. Subsequent doses of 12 mg of alphaprodine and 0.24 mg of levallorphan were given and/or a 2.5% solution of thiopental intravenously as required. Succinylcholine was used for relaxation in 53 cases.

The total amount of alphaprodine varied from 6 mg to 240 mg (average 73.3 mg), and the total amount of thiopental from 50 mg to 775 mg. (average 194 mg), much less than is usual without the supplementation. In 154 of the 199 who did not receive a relaxant respiration was adequate throughout; the remainder experienced different degrees of respiratory depression, marked in 30 cases and requiring manual assistance. The first dose of the mixture sometimes reduced the minute volume by as much as 50% for 5 or 6 minutes. Minute volume then increased, approaching control values, and subsequent doses of the mixture had little depressant effect. Of the total, 164 patients were awake and reacted within 3 minutes, and 91% responded within 5 minutes of completion of surgery. There was no case of postoperative respiratory depression.

Foldes, Zeedick & Koukal (1957) extended the use of alphaprodine to supplementation in cases operated upon under subarachnoid or epidural block, giving the drug alone, prior to, after, or simultaneously with levallorphan or nalorphine and comparing the result with that obtained with pethidine similarly administered. There were 110 patients in the study, divided into 11 subgroups. Graphs were presented of the effects on respiratory rate, minute volume and alveolar ventilation. The dosage of alphaprodine was always 0.66 mg/kg; of pethidine, 2 mg/kg; of levallorphan, 0.03 mg/kg; and of nalorphine, 0.15 mg/kg. All were given intravenously. All patients had been premedicated with pentobarbital and with a combination of 50-100 mg of pethidine and 0.3-0.4 mg of scopolamine or atropine.

Alphaprodine and pethidine in the doses used, judged to be equi-analgesic, markedly decreased respiratory function, a depression which was more profound and more prolonged with alphaprodine. Both levallorphan and

nalorphine given without narcotic produced a slight depression of respiration. Both antagonists given 4 minutes after alphaprodine or pethidine promptly counteracted the respiratory depression, or given 5 minutes before the narcotic prevented respiratory depression to a considerable degree. A similar result was attained by the simultaneous administration of the narcotic and antagonist. Given before or after the narcotic, levallorphan or nalorphine seemed to have a somewhat greater antagonistic effect on the respiratory depression of pethidine than on that of alphaprodine.

Lancaster & Levin (1956) reported on the use of alphaprodine in combination with suxamethonium by continuous intravenous drip in 120 surgical cases. The patients were premedicated an hour before operation with 40 mg alphaprodine and 0.43 mg scopolamine. The purpose of this premedication was to determine whether there was any sensitivity to alphaprodine; none was encountered. But the combination proved a useful premedicant, especially where morphine was contra-indicated. Anaesthesia was induced with thiopentone intravenously in an average dose of 350 mg followed by nitrous oxide/oxygen and the alphaprodine 0.01%, suxamethonium 0.1% solution. The average dose of alphaprodine was 0.63 mg per minute or 37.8 mg per hour. The authors considered the maintenance of anaesthesia uniformly satisfactory. Among these patients, 47% awoke or could be roused before leaving the operating room, but they were comfortable and drowsy on removal to the ward and a notable feature was a residual analgesic effect which reduced restlessness in the immediate postoperative period.

Having determined the respiratory effect of pethidine, with and without levallorphan, in patients about to undergo surgery (1957a) (see page 746), Swerdlow (1957b) conducted a similar study with alphaprodine and levallorphan. There were 60 patients in the group, all in good general condition, who had been premedicated with 11 mg of morphine and 0.64 mg atropine subcutaneously 45 minutes before the test started. At zero time sodium thiopentone, 8 mg/kg, was injected intravenously, and nitrous oxide/oxygen was administered. In group 1 at zero plus 10 minutes a supplemental dose of thiopentone, 2 mg/kg, was given; in group 2 the supplemental dose, also at zero plus 10 minutes, was alphaprodine 0.15 mg/kg, and in group 3 levallorphan, 0.02 mg/kg, was given at zero time followed by alphaprodine, 1 mg/kg, at zero plus 6 minutes, thiopentone, 2 mg/kg, at zero plus 10 minutes and alphaprodine, 0.15 mg/kg, at zero plus 15 minutes. Respiratory function was determined initially and at intervals after the various medications with the results shown in Table XXXIV.

In all three groups respiratory function was depressed, and this depression in this series was not prevented by levallorphan. However, in the third group respiratory function at 15 minutes was comparable to that in the other groups although anaesthesia was deeper.

TABLE XXXIV. EFFECT ON RESPIRATORY FUNCTION OF ALPHAPRODINE WITH AND WITHOUT LEVALLORPHAN

Group	Respiratory function	Control	Minutes						
			3	5	9	12	15	18	20
Group 1: 20 patients	Respiratory rate	17.5	19.1	19.4	18.2	18.9	18.6		
	Minute volume	5146	5050	5458	5727	4600	5064		
	Tidal volume	294.1	264.4	281.3	314.7	243.4	272.3		
Group 2: 20 patients	Respiratory rate	17.8	18.3	18.0	17.1	10.9	9.9		
	Minute volume	5945	5587	6121	6425	3862	4035		
	Tidal volume	334.0	305.3	340.0	376.9	354.2	407.6		
Group 3: 20 patients	Respiratory rate	16.6	16.6	17.0	18.4	11.9	11.9	9.8	10.4
	Minute volume	5573	4695	5264	5605	3821	3873	3630	3978
	Tidal volume	335.7	282.9	309.8	269.3	321.1	325.5	370.4	382.5

Most recently, Foldes (1957) and Foldes and others[a] have advocated the production of controlled apnoea in connexion with anaesthesia by the administration of an overdose of alphaprodine, since it was possible to terminate the apnoea at will by the administration of levallorphan. The procedure consisted in the initial intravenous injection of a sleeping dose of thiopental and the intravenous injection of alphaprodine in divided doses until apnoea was produced. A single dose of succinylcholine was given for intubation and anaesthesia maintained by nitrous oxide/oxygen and by additional fractional doses of alphaprodine. Adequate respiratory exchange was maintained by manually or preferably mechanically controlled respiration. At termination of operation or at any other time when restoration of spontaneous respiration was desired, 0.02 mg/kg of levallorphan was injected intravenously and mechanical control suspended. Adequate spontanous respiration returned within 1½-3 minutes. The advantages claimed were (1) analgesia and apnoea were produced by the same agent; (2) if the level of anaesthesia was inadequate the patient was able to indicate this by movement or grimacing even though apnoea was present; (3) muscle relaxants did not need to be administered to the point of respiratory paralysis; (4) the respiratory depression was promptly reversible; (5) the patient regained consciousness within a few minutes of the completion of surgery; and (6) the danger of recurrence of respiratory depression was minimal since the duration of action of levallorphan was longer than that of alphaprodine.

In the later report, presented to the American Medical Association, Foldes et al. compared 219 patients who underwent various intraperitoneal

[a] F. F. Foldes et al. in a paper presented to the 106th Annual Meeting of the American Medical Association, 3-7 June 1957, New York, N.Y.

operations with controlled apnoea with a group of 321 patients who received alphaprodine for supplementation but without controlled apnoea (Foldes et al., 1956). In the former, the average amount of thiopental per minute was less and the average amount of alphaprodine used more than double that in the control group. Of the patients whose respiration was controlled, 98% reacted to auditory or tactile stimulation at the end of surgery; i.e., after the reversing dose of levallorphan had been administered.

According to Mazzia, Van Poznak & Artusio (1957) after a priming dose of 250-875 mg of thiopental, constant intravenous administration of a 1% or 2% solution of thiopental maintained the patient (7 subjects) in a constant state of light narcosis with a constant electroencephalographic pattern. Subsequent intravenous injection of 60 mg alphaprodine, 1 mg levallorphan, and 4 mg or 5 mg chlorpromazine had no effect on the electroencephalogram or on the rate of thiopental injection to maintain a constant pattern. Nevertheless the alphaprodine quieted previously restless patients and abolished responses to noxious stimuli, and levallorphan significantly improved respiratory activity. In spite of the negative effects on the electroencephalogram the authors confirmed the clinical changes brought about by alphaprodine, which made for more satisfactory operating conditions and a decrease in the amount of thiopental required for such conditions.

Eckenhoff & Funderburg (1954) gave alphaprodine during nitrous oxide/oxygen anaesthesia. At the conclusion of operation they measured respiratory minute volume and then gave 20 mg of nalorphine intravenously. Respiration had been depressed by the alphaprodine. After total doses of 80, 100 and 110 mg, the respiratory rate was only 6, 9 and 11 per minute and the minute volume 4350, 3400 and 4150 ml, respectively. After nalorphine the rate went to 17, 15 and 20 per minute and the minute volume to 8000, 9600 and 10 000 ml. The first patient was aroused by the antagonist, the second was aroused only partially and the third not at all.

Orkin, Egge & Rovenstine (1955) measured directly the effect of alphaprodine on respiratory function in comparison with morphine and pethidine. The subjects were 30 healthy adults scheduled for minor surgery. The alphaprodine dose was 60 mg subcutaneously; the morphine dose 10 mg and the pethidine dose 100 mg, each given intravenously. Alphaprodine depressed respiratory tidal volume and rate in 10-15 minutes. The depression of minute volume was approximately the same as with pethidine. Oxygen uptake was not altered by either agent.

Obstetric analgesia

Sixteen authors have reported on the use of alphaprodine as an analgesic in more than 4000 obstetrical cases, and their results have been briefly summarized in Table XXXV. Scopolamine has been used also, as with pethidine, but less frequently, perhaps in a third of the total. The optimal dose appeared to be 40-60 mg subcutaneously, and, while some said the

TABLE XXXV. ALPHAPRODINE

Author	Number of cases	Dosage and route of administration	Other agents	Analgesia
Smith & Nagyfy (1949)		10 + 20 mg s.c. 30 mg s.c. 30 mg oral 30 mg oral + 15 mg s.c. 20 mg s.c.	Scopolamine	Satisfactory, 451 Partial, 32
Hapke & Barnes (1949)	500	40 mg s.c. repeated at 2–2 ½-hour intervals.		Slight or none, 17
Thelen (1949)	54	20–40 mg s.c. (20 patients got 2 doses, totalling 50–70 mg; 4 got multiple doses to 80–200 mg.)	Usually scopolamine	Moderate to complete relief of pain in 5–10 minutes
Thelen (1950)	48	20–40 mg s.c. at any stage of labour; 20 mg could be repeated safely q.i.h.; 88 % 60 mg or less.		
La Forge (1951)	1000	40–80 mg, usually 60 mg, s.c. 746 had 1 dose only. Only 36 more than 2 doses.	Hyoscine in first third of cases	Satisfactory, 87 % None, 1.6 %
Lund (1951)				Irregular in its effectiveness
Powell & Savage (1953)	125	60 mg s.c. usually 30–60 mg i.v. in 19 cases.	Scopolamine	Satisfactory, 81 %
Taylor, Young & Hanson (1953)	100	40–60 mg s.c. repeated as necessary.	None	Satisfactory, 92 %
Kane (1953)	1000	60 mg s.c. optimal.	Scopolamine	Satisfactory, 98 %
Drouin (1954)	244	40 mg (rarely 60 mg) s.c.; subsequently, 30-mg doses as necessary. Second dose in 17.2 %. Second dose another analgesic in 17.5 %.		Satisfactory, 81.1 % Partial, 18.0 %
Hughes & Philpott (1954)	100	60 mg s.c. in 75. 10 mg repeated once or twice in 25.	None Scopolamine	
Ferron (1955)	113	30 mg s.c. inadequate. 60 mg i.m. repeated once in 38, twice in 3.		Satisfactory
Lagarde et al. (1955)		40–60 mg s.c.		Moderate
Emich (1955)	1000	40 mg s.c. One dose only in 834.	Scopolamine in some cases	Satisfactory, 831 Slight, 102 None, 67
Ekelman & Reynolds (1955)	30	20–60 mg i.v.	Nalorphine in 2 cases	Rapid and satisfactory in all
King (1956)	402	120–360 mg s.c., total	Scopolamine in many	Satisfactory in all but 18

IN OBSTETRIC ANALGESIA

Amnesia	Side-effects	Effect on labour	Effect on infant	Remarks
		Operative interference not increased.	Less depression than with other agents, but increased by addition of scopolamine.	Greater flexibility because of shortness of action.
	None		No detectable effect on infant if not given less than 2 hours before delivery. In 30 cases given 40 mg up to 5 doses q. 2 h. infant depressed.	Pain relief less than with 100-mg doses of pethidine.
			4 infants sleepy, the anaesthesia had been too deep in 2; the mother of 1 got the 200-mg dose.	"No deleterious effect attributable to drug."
			4 infants sleepy.	Confirmed view of previous report.
	Dizziness in 12; 1 delirious; 1 urticaria: sweating in several. Usually drowsiness and relaxation.	Possibly shortened slightly.	80% breathed spontaneously. Slight resuscitative effort in 18%. Others breathed within 3 minutes.	Improvement over anything used previously.
		Probably shortened.	Some depression in 16.6%.	I.v. use gave deeper and more rapid analgesia without foetal depression.
	None	Shortened.	None	Chief advantage: rapidity of action.
	Dizziness in 8 cases.		Respiratory depression 4.9%.	
		No slowing, accelerated in some.	5.5% required some resuscitation.	With other analgesics 14.5% required some resuscitation.
	Dizziness 23. Nausea 9, and 6 of these vomited.	Not shortened.	Spontaneous breathing 73%, asphyxia mild 9, moderate 4, marked 5.	Co-operative and mentally clear. A few had sensation of floating.
			1 minute or more required for regular breathing in 34.	Rapid and short-acting.
	Relaxation, drowsiness, slowed respiration.		No apparent effect.	Rapid onset. Duration about 2 hours.
	None	Contractions decreased in 96.	Respiratory depression in 9 only. Connexion with drug doubted.	Rapid onset and lack of effect on foetus are advantages.
None	Nausea and vomiting, dizziness in 1; profuse sweating in 2.	Contractions decreased in force, in most primipara and some multipara.	Slight depression in 6, responding to resuscitative measures within a minute.	1 neonatal death, small infant, breech extraction.
When scopolamine was added.	Marked euphoria (like alcoholic intoxication) in all.		Slight delay in cry in 26, none longer than 2½ minutes.	Dosage should not exceed 120 mg in 3 hours.

dose could be repeated at 1-2-hour intervals, the majority of the patients received one dose only. A satisfactory analgesic effect was attained rapidly in most cases with very few side-effects. The rapidity and shortness of action were cited as advantages by most of the authors. No definite effect on the duration of labour was noted as a rule; it might have been shortened slightly in some instances. Ekelman & Reynolds (1955) said that in most primipara and in some multipara alphaprodine decreased uterine activity. Uterine contractions were recorded by means of a tocodynamometer in 30 patients. The dose of alphaprodine was 20-60 mg intravenously. The force of the contractions was decreased most often, their duration less frequently, and their frequency very seldom.

Some depression of the infant was apparent, but this was rarely marked. It was more than would be expected when no analgesic medication was given; it was less than has been observed with morphine and probably less than with pethidine. Some reservation attaches to this conclusion, however, because the extent of experience with alphaprodine and with pethidine is not at this moment nearly comparable. It is noteworthy that satisfactory analgesia with alphaprodine and without any adjuvant medication has been reported in as high as 80%-90% of cases so treated (Taylor, Young & Hanson, 1953; Drouin, 1954).

Backner, Foldes & Gordon (1957) used a pre-mixed alphaprodine-levallorphan solution (ratio 50:1) for obstetric analgesia in 200 patients. The initial dose was 1 mg of alphaprodine per kg of prepregnancy weight; half this amount was given in 30 minutes and at 15-20 minute intervals as necessary thereafter. Scopolamine 0.4-0.6 mg was given intramuscularly at the time of the first alphaprodine dose and occasionally afterwards. The total dose of alphaprodine ranged from 48 mg to 330 mg; 54% of the mothers were given 1 or 2 doses only, 40.5% 3-6 doses and 5.5% 7-11 doses. Analgesia was excellent in 81.5%, good or fair in 13.5% and poor in 5%. Sixty-one per cent. of the patients were awake, 35% lightly asleep and 4% deeply asleep at the end of the first stage of labour. Respiratory or circulatory depression did not occur in the mothers and duration of labour was not longer than with other forms of analgesia. Eighty per cent. of the infants were delivered under saddle block anaesthesia, the others with nitrous oxyde/oxygen. The average breathing time of the infants in the saddle block group was 4.5 seconds, the crying time 8.5 seconds. For 100 infants delivered under saddle block where the mothers had received other analgesic medication, the average breathing time was 7.4 seconds, the crying time 11.7 seconds. According to the authors these differences were not significant. However, when the anaesthesia was nitrous oxide/oxygen, 67.5% of the infants breathed within 10 seconds when alphaprodine-levallorphan had been used; the average breathing time was 10.0 seconds for the group of 40. On the other hand, only 30% of 100 infants breathed within 10.0 seconds when delivered under this form of anaesthesia and the mothers had received

other analgesics; the average breathing time was 50.5 seconds, a very significant difference. For this group at least the mixture was superior.

Addiction liability

Isbell (1949) tested alphaprodine for morphine-like effects and for suppression of morphine abstinence by administration of single doses according to the usual techniques employed at Lexington (Eddy, Halbach & Braenden, 1956). Typical morphine-like euphoria—manifested by loquaciousness, slurring of speech, requests for more of the drug, increased motor activity, etc.—was produced by subcutaneous administration to post-addicts. The dose judged to be equivalent to 30 mg of morphine in this respect was 100 mg.

Single doses of alphaprodine were administered subcutaneously to men strongly addicted to morphine (stabilization doses of 240-360 mg of morphine sulfate daily) 30 hours after they had received their last dose of morphine and while they were showing signs of moderate to severe abstinence. Observations for withdrawal signs were made hourly from the 24th to the 40th hour. An additional dose was given at the 34th hour of abstinence. Four patients received 45-90 mg (average 72 mg) of alphaprodine at the 30th hour and 60-90 mg (average 75 mg) at the 34th hour. The initial dose was followed by only a minor degree of relief of abstinence, but the second dose produced a definite decrease in the intensity of abstinence as compared with the control level. Isbell judged the addiction liability of alphaprodine to be probably about equal to that of pethidine.

H. F. Fraser[a] carried out an additional test of the addiction-sustaining power of alphaprodine by the 24-hour substitution technique. 150 mg of the drug were given subcutaneously every 4 hours to four patients who had been stabilized on 70 mg of morphine 4 times daily. There was definite but incomplete suppression of abstinence, which permitted the calculation that 107 mg of alphaprodine were not quite equal to 50 mg of morphine in addiction-sustaining power. Comparatively, 120 mg of pethidine would not completely suppress the morphine abstinence syndrome. Again one should conclude that alphaprodine and pethidine are approximately equal in addiction liability.

SUMMARY

Alphaprodine is a moderately rapid, short-acting analgesic. The optimal dose subcutaneously is 40-60 mg. Its duration of action is definitely shorter than that of morphine or pethidine. Side-effects are minimal; certainly less than with morphine, not more and probably less than with pethidine. It has been used successfully preparatory to local anaesthesia, for endoscopies and as a supplement to nitrous oxide/oxygen anaesthesia by intravenous

[a] Personal communication, 1956

administration. By this route the drug produces respiratory depression which can be largely offset, apparently without significant diminution of analgesic action, by combining it with 1/50 of its weight of levallorphan. For endoscopies, 30 mg of alphaprodine was an adequate dose: for supplementation the intravenous dose per minute was approximately two-thirds the dose of pethidine for similar supplementation. Alphaprodine permitted a greater reduction than pethidine in the amount of thiopentone required per minute and a more rapid return to consciousness at the conclusion of the operation.

Alphaprodine has been used for obstetric analgesia, most commonly in a dose of 40-60 mg subcutaneously, with a satisfactory result in as high as 80%-90% of a series. Side-effects have been minimal; there has been little change in the duration of labour, but some depression of the infant—not more, possibly less, than with pethidine.

Alphaprodine is an addicting agent; its addiction liability is approximately the same as that of pethidine.

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17. Pethidine derivatives

(*b*) Anileridine[a] (1-[2-(p-aminophenyl)-ethyl]-4-phenyl-4-carbethoxypiperidine)

Weijlard et al. in 1956 described a new pethidine derivative which they said had shown in preliminary trials in man an analgesic potency at least twice that of pethidine. The modification of pethidine which had been effected was substitution of *p*-aminophenethyl for methyl on nitrogen and was particularly interesting because heretofore methyl had appeared to be the optimal substituent for analgesic activity (Braenden, Eddy & Halbach, 1955). The general pharmacology of the compound has been described by Orahovats, Lehman & Chapin (1957), and its analgesic effectiveness by Chang, Safar & Lasagna (1957), Dripps & Millar (1957), A. S. Keats, J. Telford & Y. Kurosu,[b] and others.

[a] International non-proprietary name.
[b] Personal communication, 1957

Dripps & Millar (1957) gave doses of 5-50 mg of anileridine intramuscularly and intravenously to relieve post-operative pain and/or restlessness and compared its effect with that of morphine and pethidine but apparently not in the same patients. Satisfactory results (moderate and marked relief) at the various doses were recorded as follows:

Dose (mg)	*Morphine*	*Anileridine*	*Pethidine*
		Intramuscular injection	
5	34 of 84 trials	—	—
10	17 of 20 trials	10 of 20 trials	—
15	—	22 of 42 trials	5 of 16 trials
25	—	27 of 31 trials	42 of 104 trials
50	—	3 of 3 trials	4 of 6 trials
		Intravenous injection	
5	13 of 16 trials	—	—
10	—	10 of 14 trials	—
15	—	10 of 16 trials	6 of 13 trials
25	—	2 of 14 trials	12 of 18 trials
50	—	—	1 of 2 trials

The authors judged equipotent dosage ratios for intramuscular injection to be morphine 1, anileridine 2-2.5, and pethidine 3.5-5. The duration of relief was 50 minutes for anileridine, 58 minutes for pethidine and 72 minutes for morphine. The duration of effect was even shorter for intravenous injection (20-25 minutes).

A. S. Keats, J. Telford & Y. Kurosu[a] also studied anileridine in post-operative patients (Table XXXVI). Graded doses were alternated in the same patient with 50 mg of pethidine and results expressed as the percentage of doses giving satisfactory relief (reduction of pain to 50% or less 45 and

TABLE XXXVI. EFFECT OF ANILERIDINE IN POST-OPERATIVE PATIENTS

Number of patients	Paired doses	Anileridine		Pethidine	
		dose (mg per 70 kg)	percentage of analgesic doses	dose (mg per 70 kg)	percentage of analgesic doses
28	73	10	52.1	50	64.4
44	81	20	70.4	50	76.5
29	56	40	85.7	50	58.9
37	78	50	85.9	50	60.3
33	60	75	86.7	50	70.0
30	50	50	92.0	100	78.0

[a] Personal communication, 1957

90 minutes after injection). Doses were per 70 kg of body-weight and were given intramuscularly during the first 30 post-operative hours. The technique was double-blind and observations were made by trained observers.

The dose-effect curve for anileridine intersected with the line representing the effect of 50 mg of pethidine at 21.3 mg, hence anileridine was estimated to be two and a half times as potent as pethidine, and 40 mg would be equivalent to 100 mg of the latter.

R. W. Houde[a] tested anileridine against chronic pain in cancer patients in comparison with morphine and pethidine. Each patient received subcutaneously on a double-blind basis a single dose of morphine, 10 mg, 2 doses of pethidine, 50 mg and 100 mg, and 2 doses of anileridine. The morphine and pethidine doses remained constant throughout but the doses of anileridine were raised or lowered from group to group as the study progressed to yield results in a range of effect approximately equal to that of the other drugs. In successive groups of patients the anileridine doses were 25 mg and 50 mg, 50 mg and 100 mg, 12.5 mg and 25 mg, and 25 mg and 50 mg. Eighty complete series of 5 doses were administered to 21 patients. Based on total analgesic effect over a 6-hour period, anileridine had 2.55 times the potency of pethidine, or 29.4 mg of the former were equivalent to 75 mg of the latter, and 31.0 mg of anileridine or 79.1 mg of pethidine were equivalent to 10 mg of morphine. Based on peak analgesic effect, anileridine had 2.59 times the potency of pethidine, and 23.7 mg of anileridine or 61.5 mg of pethidine were equivalent to 10 mg of morphine. The course of action of anileridine and pethidine was similar; both were shorter-acting than morphine.

Chang, Safar & Lasagna (1957) matched anileridine against pethidine as a supplement to nitrous oxide/oxygen anaesthesia. Each drug was given by intravenous injection, " blind ", and in random order to successive patients. 30 mg of anileridine were approximately as potent as 100 mg of pethidine in reinforcing the anaesthesia.

Other reports on the use of anileridine to supplement nitrous oxide/oxygen anaesthesia were those of J. T. Stage[b] and of R. I. Riffin and R. Preisig.[c] Stage compared the use of the drug in 100 cases with that of pethidine in 300 other operations. The most effective mode of administration for both drugs was continuous intravenous drip. Premedication consisted of a barbiturate the night before and 1½ hours pre-operatively and pethidine plus scopolamine 1 hour pre-operatively. Induction of anaesthesia was effected by intravenous injection of thiopental, followed by nitrous oxide/oxygen by a semi-closed system and *d*-tubocurarine intravenously and intermittently. Optimally, thiopental was discontinued 10 minutes after the surgical procedure was started, which facilitated early

[a] Personal communication, 1957

[b] In a paper presented to the Florida Society of Anesthesiologists, 17 November 1956, Jacksonville, Fla.

[c] In a paper presented to the annual meeting of the New Jersey State Medical Society, 29 April-3 May 1957, Atlantic City, N.J.

recovery of the patient from anaesthesia. Pethidine, 0.5 mg per ml, was given intermittently or continuously to a total dose on the average of 75 mg; the rate of injection decreased during the second hour of operation. When anileridine was used the procedure was the same except that the anileridine concentration was 0.3 mg per ml and the total dose ranged from 35 mg to 50 mg as compared with the usual 75-mg dose of pethidine. No difficulty attributable to the analgesic was encountered and post-operative analgesia of 2 or 3 hours' duration was observed.

Riffin & Preisig used anileridine to potentiate nitrous oxide in more than 300 patients. Anaesthesia had been induced with a short-acting barbiturate and succinylcholine administered in an apnoeic dose of 30-40 mg. After 10-12 minutes of nitrous oxide and oxygen, anileridine was administered intravenously, the usual dose being 10-12 mg. The same dose of anileridine was repeated whenever the respiratory rate exceeded 24 per minute. The depth of anaesthesia decreased but there was good maintenance of analgesia. The authors stated that 25 mg of anileridine invariably caused apnoea, whereas apnoea rarely followed the smaller doses of 10-12 mg, and when it did occur was of brief duration. In any case respiration was manually assisted throughout. The total dosage of anileridine rarely exeeded 37.5 mg.

Riffin & Preisig recorded electrocardiograms and electroencephalograms in small groups of patients receiving anileridine. In 10 of 16 cases there was no change in the electrocardiogram. In 3 the changes were inconsequential; in 2 there were minor changes in rhythm rapidly reverting to normal; and in one there was evidence of an ischaemic myocardial change superimposed upon an already abnormal pattern. In 8 of 14 cases there were no observable changes in the electroencephalogram and in the others the changes were minor, a slight change in the frequency (a decrease in 3, an increase in 3) of the background rhythm and either an increase or decrease in microvoltage.

In 278 patients, Riffin & Preisig compared anileridine with pethidine, alphaprodine, levorphanol and morphine with respect to pain relief and side-effects during the first three post-operative days. The several drugs were not used in the same patients. Also each patient received 30 mg of phenobarbital routinely 3 times a day. The procedure seems to have been single-blind, the observer but not the patient knowing that different drugs were employed. The results for the adult patients only were as follows:

Number of patients	*Agent*	*Usual dose (mg) and route*	*Percentage complete relief*	*Average number of doses in 3 days*
109	Anileridine	100 i.m.	99.5	2.73
84	Pethidine	100 i.m.	83.1	4.14
20	Alphaprodine	60 s.c.	85.0	4.60
23	Levorphanol	2 s.c.	95.6	3.30
22	Morphine	15 s.c.	95.0	2.90

The dose of anileridine reported is relatively large compared with that used by other investigators, but it is significant that a dose giving practically complete relief could be used with almost no side-effects (see below).

Keesling & Keats (1957) compared the effectiveness of oral medication given on a double-blind basis in random order to more than 100 dental surgical patients. Each individual was given a 24-hour supply of one medication to be taken at 4-hour intervals, was directed to report the result the next day, and was then given another drug. The medications and incidence of pain relief with each were as follows:

Placebo	62%
Aspirin, 0.6 g	71%
Dihydrocodeine, 30 mg	73%
Anileridine, 30 mg	70%
Anileridine, 60 mg	95%

The greatest number of side-effects, such as dizziness and nausea, followed the 60-mg dose of anileridine.

Respiration

Dripps & Millar (1957) noted respiratory depression with doses of 25 mg of anileridine intravenously during spinal or general anaesthesia. Eighty such injections were made. Apnoea occurred on four occasions and respiratory rates below 10 per minute were seen 20 times. The duration of depression, however, did not exceed 10 minutes, shorter than with pethidine. Chang, Safar & Lasagna (1957) reported similarly. They found the respiratory depression with doses required to maintain adequate anaesthesia greater with anileridine than with pethidine.

Each of three groups who have studied the analgesic potency of anileridine have measured its respiratory effect in normal volunteers. Dripps & Millar gave 50 mg of anileridine intravenously to one normal male volunteer and 60 mg intravenously to another. The response to carbon dioxide was depressed similarly to a comparable dose of pethidine but for a shorter period. Keats, Telford & Kurosu [a] compared the effects of 40 mg of anileridine and 100 mg of pethidine, each intramuscularly in the same five subjects at an interval of not less than 5 days. The decrease in minute volume and the decrease in response to carbon dioxide were similar for both drugs but the duration of effect was less for anileridine. Chang, Safar & Lasagna gave doses of 60 mg of anileridine and 100 mg of pethidine intravenously in random order to seven healthy volunteers. The response to carbon dioxide was depressed for more than 2½ hours with each drug, but the effect of anileridine was the greater.

Circulation

Dripps & Millar (1957) studied the effect of anileridine on the circulatory response of 12 volunteers to passive head-up tilt. Blood pressure and pulse

[a] Personal communication, 1957

rate were recorded continuously. After a control tilt anileridine was given into a 5% glucose intravenous infusion in doses of 20-60 mg and the tilt repeated in 10-15 minutes. The anileridine caused less hypotension than had been noted previously with comparable doses of morphine or pethidine. Also, in the patients who had received these narcotics post-operatively, anileridine caused a reduction in systolic pressure of 30 mm Hg or more in only 4 of 119 patients; morphine in the post-operative group caused a similar fall in pressure in 4 of 130 individuals, and pethidine caused a similar fall in 9 of 166 patients. Chang, Safar & Lasagna (1957), comparing 60 mg of anileridine with 100 mg of pethidine, each intravenously, on the response to head-up tilt in seven normal subjects, said that the drug did not cause fainting or significant arterial hypotension. Dripps & Millar, noting that anileridine intradermally showed no tendency to wheal formation, which has been interpreted as evidence of histamine liberation, thought this might be a factor in the drug's lesser hypotensive effect.

Side-effects

The incidence of post-anaesthetic nausea and vomiting was similar for anileridine and pethidine when these drugs were used to supplement nitrous oxide anaesthesia, but late nausea and vomiting occurred in six of seven subjects in the tilt tests after anileridine and in only one of the seven after pethidine (Chang, Safar & Lasagna, 1957). Only two of the 12 subjects in the tilt experiments of Dripps & Millar (1957) vomited after anileridine.

To study the subjective effects of anileridine the drug was given to pre-operative patients free of pain awaiting elective surgery (A. S. Keats, J. Telford & Y. Kurosu [a]). The dose was 50 mg intramuscularly, and for comparison other similar patients were given 100 mg of pethidine. The procedure was double-blind and the data were collected by technicians who interviewed the patients before and at 30, 60 and 120 minutes after drug administration. Forty patients received each drug. The percentage incidence of symptoms was as follows:

	Pethidine 100 mg intramuscular	*Anileridine 50 mg intramuscular*
Drunkenness	18	33
Lightheadedness	55	68
Dizziness	65	60
Shakiness	8	10
Visual difficulty	15	28
Nervousness	5	10
Restlessness	0	8
Psychic depression	3	20
Relief of depression	8	0
Cheerfulness	15	5

[a] Personal communication, 1957

	Pethidine 100 mg intramuscular	*Anileridine 50 mg intramuscular*
Absence of cheerfulness	0	8
Heavy limbs	13	5
Unpleasant dreams	8	0
Sweating	53	38
Nausea	25	43
Vomiting	5	13
Itching	5	28
Dryness of mouth	48	23
Dislike of drug effect	37	62

The technician's judgement of effects was:

	Pethidine 100 mg intramuscular	*Anileridine 50 mg intramuscular*
Euphoria	8	3
Little drug effect	13	10
Sedation	23	48
Marked sedation	65	30
Stimulation	8	15
Increased talkativeness	30	60
Unpleasant drug effect	50	70

In spite of the fact that the dose of anileridine was 20% greater than had been judged previously to be equivalent to 100 mg of pethidine, the incidence of side-effects with it was not significantly greater than with pethidine.

According to Riffin & Preisig very few side-effects were encountered in the use of anileridine, in spite of the fact that the dose was large. In 2 instances there was mild subjective vertigo preceding sleep, which did not recur when the dose was repeated. In 2 other patients nausea and itching, one with and one without a rash, were seen; and in 2 others nausea and vomiting occurred. In the pethidine group of 92 patients nausea and/or vomiting were reported 4 times. Other side-effects were absent, the authors thought, because of the routine administration of phenobarbital, given to the anileridine and pethidine groups alike.

Obstetric analgesia

I. Siegel[a] administered anileridine to 158 obstetric patients, always intravenously. The single dose varied from 30 mg to 100 mg but was most often 50 mg. Scopolamine, 0.4 mg or 0.6 mg, was given routinely with the initial dose only and 42 patients received only 2 doses of anileridine. The maximum for any patient was 155 mg in 5 doses over a period of 6½ hours. Amnesia was reported as complete or excellent in 31 patients, good in 63, none in 11 and partial (poor to moderate) in the others. Various types of

[a] Personal communication, 1957

anaesthesia, most often saddle block, were used for delivery. Elective low forceps were used 100 times and elective medium forceps or other procedure in 13 cases.

In five cases no note was made on the condition of the infant. Breathing was immediate in 141, or 89%, of the babies. There was, however, some evidence of depression in 29, or 25%. There were obstetrical complications which could have been at least contributory to the depression in 13 cases. Occasionally, even when breathing of the infant was initiated promptly, a period of delayed apnoea was noted.

Addiction liability

Single doses of 3-150 mg were given orally to non-tolerant post-addicts. Questionable morphine-like effects were seen with 75 mg and definite morphine-like effects with doses of 100 mg and 150 mg. Doses of 125 mg or above subcutaneously in other post-addicts produced effects equivalent to those of 15-30 mg of morphine similarly administered (Fraser & Isbell, 1956). These single doses of anileridine resembled morphine more closely than pethidine because they produced less central excitation than did the latter.

In another experiment Fraser & Isbell stabilized eight individuals on 280 mg of morphine daily. Each was given a total of 900 mg of anileridine in divided doses of 150, 150, 200, 200 and 200 mg at the 5th, 8th, 14th, 18th and 22nd hours of abstinence. The test was controlled by giving the same patients either placebo injections or regular doses of morphine at corresponding hours during two other withdrawals. Anileridine effectively substituted for morphine since abstinence scores (Himmelsbach hourly point score) were comparable to those observed when morphine was continued. Fraser & Isbell judged that anileridine had addiction liability like that of morphine and that, since it suppressed morphine abstinence completely whereas pethidine did not, in this sense it had addiction liability greater than that of pethidine. However, it might be significant that, as to dose, the analgesic potency of anileridine was about two and a half times and the addiction-sustaining potency was about of the same order as that of pethidine.

SUMMARY

Anileridine is an effective analgesic agent against post-operative pain and as a supplement to nitrous oxide/oxygen anaesthesia with a potency two to three times as great as that of pethidine. Its duration of effect is shorter than that of morphine and perhaps a little shorter than that of pethidine. It produces as much respiratory depression as pethidine but less circulatory depression, and its respiratory depression is of shorter duration than that of pethidine. The incidence of other side-effects is not greater

with anileridine than with pethidine and may be less when the drugs are given in equipotent analgesic doses. Anileridine has been used for obstetric analgesia in combination with scopolamine, administered intravenously. The results have, as a rule, been satisfactory for the mother, but some depression of the infant has been seen in about one quarter of the cases. Anileridine has morphine-like addiction liability. Its addiction-sustaining dose is of the same order as that of pethidine, but it is able to suppress morphine abstinence completely whereas pethidine is not.

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17. Pethidine derivatives

(*c*) Ketobemidone[a] (1-methyl-4-(m-hydroxyphenyl)-4-piperidyl ethyl ketone)

Ketobemidone was first prepared by Eisleb (1942) about 1942 and was tested for its pharmacological properties by O. Schaumann (quoted by Gross & Meier, 1949) and by Gross & Meier (1949). The first reference to its trial in man was by Scott, Robbins & Chen (1946). Using the Wolff-Hardy-Goodell technique, 7.5 mg of ketobemidone were equivalent to 5 mg of methadone or to 100-150 mg of pethidine in pain-threshold-raising effect. Bieter & Hirsh (1948) employed doses of 5, 7.5 and 10 mg of ketobemidone subcutaneously for relief of pain in 24 medical cases. The analgesic effect was good in 22, fair in 2. They found it equivalent to *l*-methadone in analgesic power and superior to methadone or *l*-isomethadone. It also had a greater sedative effect than methadone.

Bernstein (1949) reported on the use of ketobemidone in 161 patients, 81 by oral application, 45 by subcutaneous and 35 by oral and subcutaneous administration. The results obtained are shown in Table XXXVII. In the view of the author, 5-10 mg of ketobemidone were equivalent to 10 mg of morphine, 2 mg of hydromorphone or 50 mg of pethidine.

Linder & Vollmar (1950) used ketobemidone for post-operative pain in 122 patients. The dose was 7.5-10 mg, administration was subcutaneous, and the result was very satisfactory. In 10 cases of thoracic operations,

[a] International non-proprietary name; for other designations, see *Estimated World Requirements of Narcotic Drugs in 1958* (United Nations document E/DSB/15).

TABLE XXXVII. EFFECT OF KETOBEMIDONE IN 161 PATIENTS (BERNSTEIN, 1949)

Route	Dose	Number of cases	Analgesic effect [a]			Duration of effect	Side-effects	
			very good	good	insufficient			
s.c.	5	9	3	5	1			
s.c.	6.25	21	16	5		3–6, mostly 4 or 5 hours	Nausea and vomiting	1
s.c.	10	38	29	8	1	2–6, mostly 4 or 5 hours	,, ,,	2
s.c.	12.5	5	5			6 hours	,, ,,	3
s.c.	25	2	2			6 hours	,, ,,	2
oral	5	4	3	1				
oral	10	66	46	16	4	2–6, mostly 4 or 5 hours	,, ,,	4
oral	12.5	5	3	2			,, ,,	1
oral	20	1	1				,, ,,	1
oral	25	10	8	2		2–6 hours	,, ,,	3

[a] Very good = complete or almost complete freedom from pain; good = distinct improvement; insufficient = slight decrease of pain.

10 mg 3 or 4 times a day not only gave complete pain relief but relieved cough as well. Twenty-four patients with acute biliary or renal colic were given ketobemidone in the 10-mg dose. Pain began to abate in 10 minutes and was gone completely in 20 minutes. Duration of effect varied from 3 to 8 hours. Four of the patients had previously received 4 mg of dilaudid or 10 mg of methadone, or 100 mg of pethidine, without obtaining relief from pain. When the colicky pain recurred, a second dose of ketobemidone gave equally good relief without disturbing side-effects. Linder & Vollmar considered 10 mg of ketobemidone to be equivalent in analgesic potency to 15 mg of methadone or 15-20 mg of morphine. In chronic pain too they found the drug effective either orally or subcutaneously over a period of several months.

Blanke (1950) reported the results obtained with ketobemidone in 141 cases. The indication for its use was pain (traumatic, post-operative, colicky, pain of cancer, etc.) in each instance. For the younger patients the dose was restricted to 5 mg orally, 1-3 times within 12 hours. These oral doses did not give particularly good relief and the duration of effect was short. In other cases the drug was given by suppository (7.5 mg once or twice in 12 hours), dissolved in an enema (15 mg once or twice in 24 hours), or by subcutaneous injection (7.5 mg 2 or 3 times in 24 hours). Administration by enema was employed when injections were refused and a strong long-lasting analgesic effect was desired. The best results in intensity and duration of action were obtained with subcutaneous injections.

Kastranek (1950) used ketobemidone post-operatively in 200 patients, injecting 10 mg per dose intravenously or intramuscularly. The analgesic effect was rapid in onset and persisted for 4-8 hours.

Other noteworthy reports on the analgesic effectiveness of ketobemidone were those of Liessen (1951), 288 general surgery post-operative patients; Peregalli (1952), 54 cases after orthopaedic surgery and malignancies; Vara & Kinnunen (1951), 50 gynaecological post-operative cases; Villa (1951), 32 patients with severe pain of diverse origin; and Peltola (1952), 803 cases with pains of all sorts. Liessen gave 1 or 2 7.5-mg doses subcutaneously or 1 or 2 10-mg doses by suppository on the first post-operative days and 2 or 3 5-mg doses orally later. The duration of analgesic effect averaged 5-7 hours. Peregalli said the onset of analgesia with ketobemidone was fast, 10-20 minutes, and that pain relief continued for 4 or 5 hours. He said also that in chronic pain 3 injections of ketobemidone would do the work of 6 injections of morphine or 10 of pethidine. The effect of oral doses was a little slower in onset and slightly shorter. Villa also found the effect of oral doses less than that of injections, but pain relief was well maintained by oral doses if subcutaneous injections had been given previously. Ketobemidone was effective in extreme pain of long duration, more so than morphine, according to Peltola, and its effect lasted 4-6 hours. Ketobemidone was as effective as the opiates against cough and cardiac dyspnoea. Peltola used doses of 5-10 mg.

P. Peltola & P. Soisalo [a] carried out a cross-over experiment on 45 patients with chronic pain (mostly cancer) to determine the analgesic potency of ketobemidone relative to that of morphine. One of the drugs was administered for not more than a week, during which an attempt was made to find the minimal analgesic dose which could be used for at least 3 successive days without having to be increased. The patient was then treated with the other drug without being made aware of the change and the minimal analgesic dose was determined as in the first instance. If morphine was administered first (28 patients) the corresponding analgesic doses were 18.2 mg for morphine, 5.8 mg for ketobemidone; if ketobemidone was administered first (16 patients) the doses were 7.2 mg for ketobemidone and 22.0 mg for morphine. The authors maintained that for ketobemidone the analgesic dose was well below that which produced euphoria, whereas for morphine the analgesic and euphoric doses were approximately the same.

Obstetric analgesia

Lund (1947, 1948) compared ketobemidone with methadone as an obstetric analgesic. The former was used in 50 patients at a dose of 5-10 mg (usually 7.5 mg), the latter in 17 patients at a dose of 5-15 mg (also usually 7.5 mg). Ketobemidone gave good analgesia in 50%, fair analgesia in 40%,

[a] Personal communication, 1957

none in 10%. Forty-one of 51 babies breathed immediately; the delay in 6 of the others was from 2 to 5 minutes. The analgesic effect of methadone was poor and there was some foetal depression.

Käser, König & Etterich (1951) compared ketobemidone with pethidine. Both drugs were used both with and without scopolamine. Ketobemidone was used at a dose of 5-7.5 mg subcutaneously in about 100 cases and with scopolamine was effective 75% of the time. The authors thought the dose should not be repeated more than once nor given within 2 or 3 hours of delivery. The comparative dose of pethidine was 100 mg.

Møgelvang (1952) used Ketogan[a] in 946 obstetrical cases. The dose initially was 0.75 ml but when no harmful effect on the infant was observed this was increased to 1.0 ml (5 mg of ketobemidone). A second dose was given in only 15% of the cases. Labour was not retarded and there was no increase in post-partum haemorrhage. There were 4 stillbirths and 5 neonatal deaths, but the author attributed none of these to the drug; he believed that there was no harmful effect on the infant. Relaxation was better with Ketogan than with pethidine and there were no side-effects.

Pre-anaesthetic medication

Ketobemidone was tried by Linder & Vollmar (1950) as pre-anaesthetic medication in 39 patients. The dosage ranged from 7.5 mg to 15 mg. The lowest dose was most satisfactory, though it had less sedative effect than morphine; doses of 10 mg and 15 mg had the same disadvantages as other opiates.

Lorenzini (1950) employed ketobemidone for premedication for anaesthesia of various types:

(*a*) General anaesthesia with nitrous oxide/oxygen/ether (31 cases): 10-15 mg with 0.5 mg of atropine 45 minutes before induction. Good psychic tranquillity resulted and avoidance of coughing and laryngeal spasm which sometimes occur with too rapid administration of ether, but there was some cardiac slowing and some potentiation of the respiratory depression.

(*b*) Spinal anaesthesia (16 cases): 10 mg with ephedrine 30 minutes before spinal injection. In spite of the ephedrine blood pressure fell and vomiting occurred occasionally during recovery.

(*c*) Local anaesthesia (14 cases): 30 mg an hour before anaesthesia, an unusually high dose for the purpose.

(*d*) Intravenous barbiturate anaesthesia (18 cases): there did not seem to be any potentiation of respiratory depression but the result was no better than with morphine.

[a] Ketobemidone plus 1.1-diphenyl-3-dimethylamino-1-butene, manufactured and used principally in the Scandinavian countries.

(*e*) As basal anaesthetic 20 mg were given an hour before and 10 mg more 15 minutes before operation. Analgesia was good but not complete and there was severe respiratory depression in one case.

The drug was most satisfactory in the first and second groups, as to both rapidity and ease of induction of anaesthesia.

Ferrero (1951) also used ketobemidone as premedication according to the first four categories mentioned above at similar or smaller dosages and with similar results. For spinal anaesthesia (4 cases) he used only 10 mg, combined with ephedrine, and saw no fall in blood pressure. Crimini (1953) gave a dose of 7.5 mg of ketobemidone as pre-anaesthetic medication in 80 cases varying in age from 18 to 60 years with very satisfactory results. The systolic blood pressure fell slightly in those cases in which it was recorded, but never enough to be disturbing. Respiration was not depressed notably. Martinetto (1955) varied the dose for pre-anaesthetic medication in 164 patients from 7.5 mg to 15 mg subcutaneously an hour before or 10 mg intravenously 10 minutes before operation. The analgesic effect was good but the psycho-depressing action was weak. However, anaesthesia was easily induced and patients awoke normally. Antistin enhanced the effect of ketobemidone. Thompson & Neff (1950) said that ketobemidone had been used with uniformly satisfactory results in 66 unselected cases, including intra-abdominal and intrathoracic operations. In the earlier cases severe respiratory depression or complete apnoea and a fall of blood pressure occurred, but these effects were largely avoided when the concentration of the solution and the individual doses were reduced. Dosage ranged from 3 mg to 15 mg intravenously in divided doses, average 4.6 mg per patient. Relaxation was as good as with pethidine, and post-operative complications were not noticeably altered by the use of ketobemidone. In unanaesthetized patients it produced dryness of the mouth, mild relaxation and drowsiness, and dizziness but no euphoria. Later in a review of nitrous oxide/oxygen anaesthesia and its supplementation, Neff, Mayer & Thompson (1950) said that on account of the respiratory depression produced by comparable analgesic doses ketobemidone possessed no significant advantage over pethidine. Finally, in this connexion Mushin (1951) tried ketobemidone intravenously as a supplement to nitrous oxide/oxygen anaesthesia in comparison with pethidine but could come to no conclusion with respect to superiority.

Side-effects

In their observations on normal subjects, Scott, Robbins & Chen (1946) found the most frequent side-effect to be lightheadedness. Nausea or vomiting rarely occurred. Bieter & Hirsh (1948) saw nausea and vomiting in only three of their 24 patients after ketobemidone, 5-10 mg subcutaneously; there was a sedative effect in 16 cases.

Bernstein (1949) said that side-reactions, such as vomiting, and a euphoric effect, were less frequent with ketobemidone than with morphine. Ketobemidone, however, produced a pleasant sense of fatigue, relaxation and relief from anxiety. Marked euphoria was seen in three patients receiving the drug subcutaneously and in three cases after oral administration. Linder & Vollmar (1950) found ketobemidone to have less sedative action than morphine when used as pre-anaesthetic medication and a dose of 10 mg produced fewer side-effects than 20 mg of pantopon. Of 105 patients asked to compare the drug with other analgesics 20 preferred ketobemidone, in part at least because it produced fewer side-effects.

According to Blanke (1950), 40%-50% of his 141 patients experienced a very definite sedative effect and a tendency to sleep. Also a light euphoria was often seen. Severe side-reactions, however, occurred in only four cases, all acute cholelithiasis associated with pancreatitis. 10-mg doses subcutaneously, even once repeated, did not cause paralysis of intestinal peristalsis.

Bernsmeier & Heine (1950) said that side-effects, including euphoria, were less after ketobemidone than after morphine. Two groups of patients, 10 in each group, whose circulation and respiration were normal, were given ketobemidone intramuscularly, 7.5 mg and 15 mg, and respiratory rate, tidal volume and minute volume were recorded. Depression of minute volume, due principally to a decrease in tidal volume, always occurred. The effect was not very much greater with the larger dose but was more persistent.

Kastranek (1950) observed no disturbance of bladder or intestinal function, no alteration of circulation and only slight respiratory depression in 200 post-operative patients receiving 10 mg of ketobemidone intravenously or intramuscularly. The only side-effect noted by Liessen (1951) was dizziness in 9% of his patients; there were no respiratory or circulatory disturbances. According to Vara & Kinnunen (1951), 6 of 50 women complained of restlessness after administration of ketobemidone, sufficient in 2 cases to disturb sleep, and 4 of these patients complained of nausea.

Addiction liability

Bernstein (1949) did not encounter addiction to ketobemidone, but administration was continued for a month or more in a very few cases only. Tolerance to the analgesic effect was seen in 6 of 29 cancer patients. Blanke (1950) reported also that he had seen no addiction, although in a few cases administration had continued for more than 3 weeks. In one case of addiction to pethidine, ketobemidone was substituted, at a dose of 30 mg per day, and later withdrawn without difficulty.

Bernsmeier & Heine (1950) continued the administration of ketobemidone for more than 3 weeks in 27 of their 303 cases, and in 7 analgesic effectiveness diminished. In 4 of these 7 deterioration of the condition

(carcinomatosis) and worsening of the pain might have been a factor, but in the other 3 tolerance to the drug undoubtedly occurred. One patient became addicted to ketobemidone.

Liessen (1951) continued 28 of his patients on ketobemidone for 4 weeks and one patient for 6 months and then did not observe any withdrawal symptoms. Villa (1951) gave 74 of his patients ketobemidone for at least 20 days, averaging about 10 mg per day, orally, subcutaneously or by suppository. Administration was then suspended for 3-5 days and could be resumed at the original dose-level, indicating to the author that no tolerance had developed; nor were any abstinence symptoms seen in the drug-free interval. Neither the dose nor the time of administration was really sufficient for a conclusion on tolerance or dependence. Vara & Kinnunen (1951) made the surprising recommendation that ketobemidone should be used whenever the danger of the development of morphine habituation was "suspected" to be greater than usual. Unfortunately they did not give criteria for this "suspicion".

Stemplinger (1951) stated that three cases of ketobemidone addiction were known to him, allegedly taking up to 100 ampoules per day. Sattes (1951) described two cases of secondary addiction to ketobemidone; the patients had previously taken morphine and methadone. Dependence on ketobemidone developed rapidly, doses had to be given frequently to avoid abstinence phenomena and the withdrawal syndrome was severe. He said the euphoric effect of the drug was marked. Geller (1952) also reported two cases of ketobemidone addiction, both secondary to morphine, and Hamburger (1952) three additional cases, one previously addicted to dilaudid, the others to morphine. As in Sattes' cases, abstinence phenomena appeared quickly, within a few hours after a dose, and were severe on final withdrawal. One but not the other of Geller's cases experienced a euphoric effect with the drug. Cieslak (1952) described a case of primary addiction to ketobemidone, a 40-year-old physician who had not been addicted previously. He took the drug orally at first, then subcutaneously increasing from 0.5 ml (5 mg) 3 or 4 times a day to 90 mg per day in 4 months' time. For this patient the drug was dysphoric rather than euphoric and produced in him at times symptoms of excitation. Gerchow (1954) too reported a case of primary addiction to ketobemidone, also a physician, and Carriere (1953) reported 10 cases, 4 of them primary. It was noted that there was a strong desire to increase the dose rapidly so that toxic symptoms were likely to occur. The withdrawal syndrome was severe. Other cases of secondary addiction to ketobemidone have been described by Salm (1953).

Isbell (1949) found that 30 mg of ketobemidone subcutaneously produced morphine-like effects in former addicts equivalent to those of 30 mg of morphine. In a direct addiction experiment on five post-addict volunteers, morphine-like regressive behaviour developed as well as tolerance to some of the actions of ketobemidone. Administration was continued for about

60 days to a dosage level of 290-450 mg per day. On abrupt withdrawal a very severe abstinence syndrome developed very rapidly. Ketobemidone was on a par with morphine in physical dependence potency, but shorter and more rapid in its action.

P. Peltola & P. Soisalo [a] plotted the daily dosage of ketobemidone required for adequate relief in 25 patients with chronic pain over a period of 12 weeks. The dosage increased on the average from approximately 16 mg to approximately 28 mg per day. While part of this increase was probably associated with progress of the disease, part must have been due to the development of tolerance, which was remarkably low grade in this carefully controlled experiment. These authors also reported on the degree of cross-tolerance between morphine and ketobemidone. When morphine was administered for more than 3 months in 24 patients with notable development of tolerance approximately equivalent amounts of ketobemidone had to be given to maintain the comfort of the patients. On the other hand, when ketobemidone was administered for more than 3 months with development of the low grade of tolerance mentioned above, morphine could be substituted in about the 3 : 1 ratio of their relative analgesic potency in non-tolerant individuals. The authors believed that there was a significant spread between the doses of ketobemidone required to produce analgesia and euphoria and that this plus their observations on cross-tolerance indicated a low addiction liability for ketobemidone in clinical practice.

Altschul & Wikler (1951) described the effects of single doses of ketobemidone on the electroencephalogram of post-addicts and the changes in the record which occurred during addiction and withdrawal. The only effect of single doses was a drop in mean alpha frequency in 4 of 10 records. Some tolerance to this change occurred during addiction. Also there was an early rise in the percentage of delta waves which tended to subside again during maintained addiction. Paroxysmal high voltage slow waves appeared in two cases in whom the records were abnormal initially. These suggested that the drug might be dangerous in convulsive disorders. During withdrawal, frequency of the electrical waves spread in both directions with return to normal in about 3 days.

Ketogan

Høilund-Carlsen & Petersen (1952) used Ketogan for women who were unable to take morphine; it was continued for 3 months 3 times a day without side-effects. Altogether 362 patients were given 507 doses subcutaneously and 201 tablets orally. 612 doses (86%) gave excellent results, 51 good results and 45 no effect. The usual dose was 1 ml (5 mg of ketobemidone) subcutaneously or 1-2 tablets (5-10 mg of ketobemidone) orally.

Schmith (1952) used Ketogan for 32 patients with different types of pain, mainly chronic pain; 158 oral doses (1-2 tablets) were given and 104

[a] Personal communication, 1957

injections (1-2 ml) subcutaneously. Of the 158 oral doses results were good in 117 cases, medium in 35 and none in 6. They were effective after 15-30 minutes and the duration of effect was 4-6 hours. In the other series of 104 doses, 90 gave a good effect and the others a medium effect. Side-effects were very slight: dizziness in 5 cases, nausea in 3 and drowsiness in 3. The mixture was shown to have a good effect on patients who could not take morphine. No tolerance was seen. In 4 or 5 patients euphoria and the desire to continue the drug were observed. Withdrawal was, however, carried out without difficulty and abstinence symptoms were not of importance.

Kirchoff & Andersen (1952) used Ketogan for pre-anaesthetic medication in 50 patients for orthopaedic operations of various kinds. The dose was 1 ml subcutaneously 1½-3 hours before operation. Anaesthesia was provided by nitrous oxide/oxygen/ether supplemented with pethidine or pentothal. The analgesic effect was sufficient and sedation satisfactory in all, making induction easy. No respiratory depression was found and no nausea or vomiting were attributed to the drug.

SUMMARY

The analgesic dose of ketobemidone has varied mainly from 5 mg to 10 mg, 7.5 mg being commonly employed. Thus its analgesic potency is greater than that of morphine and the duration of its analgesic action is at least as long. It is effective by various routes of administration but best results have been obtained with subcutaneous doses. Morphine-like side-effects, including respiratory depression, are no greater than with morphine, probably less, except euphoria, which may be very intense. Ketobemidone is effective for premedication and has been used in obstetrics. It was reported to be superior to methadone and pethidine, but the latter comparison as well as the effect of ketobemidone on the infant need further study.

A quantitative comparison indicates slow development of tolerance to the analgesic effect of ketobemidone, little cross-tolerance to morphine, but a high degree of cross-tolerance to ketobemidone in morphine-tolerant individuals.

Ketobemidone is at least as addicting as morphine. Dependence on it either primarily or in patients addicted to other drugs develops rapidly and the subsequent abstinence syndrome is severe.

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17. Pethidine derivatives

(*d*) Properidine[a] (1-methyl-4-phenylpiperidine carboxylic acid, isopropyl ester)

Only one report on the clinical trial of properidine has come to our attention, although the substance has been marketed in Italy and in South America. Uccheddu (1944) reported on its use subcutaneously, orally, intravenously and rectally for pain of various origins. The usual subcutaneous dose was 5 mg. It acted promptly and had a duration of effect of 3-5 hours. Intravenous administration was followed by very rapid relief of pain and usually quiet sleep. Side-effects were minimal. The pulse rate was accelerated slightly and respiration slowed. The drug was most effective if the pain was due to spasm of smooth muscle structures. The author found properidine particularly effective in cardiac cases by intra-

[a] International non-proprietary name; for other designations, see *Estimated World Requirements of Narcotic Drugs in 1958* (United Nations document E/DSB/15).

venous injection followed by oral doses of 10 mg, because of the accompanying relief of anxiety as well as of pain. The author had insufficient experience to venture an opinion on addiction liability but believed that tolerance had occurred.

No specific tests on the addiction liability of properidine have yet been made. The Italian Government placed it under their regimen for narcotics' control prior to August 1954. The WHO Expert Committee on Drugs Liable to Produce Addiction (1955) said, with respect to properidine:

"The isopropyl and other esters of 1-methyl-4-phenylpiperidine-4-carboxylic acid must be suspected of having addiction-producing properties, because general pharmacological experience indicates that in compounds of this type the change from the ethyl to the isopropyl or other ester can effect no significant qualitative change in, and can be expected to effect no major quantitative change in, the action of the compound."

The Committee thought that all esters of 1-methyl-4-phenylpiperidine-4-carboxylic acid should be controlled like morphine.

SUMMARY

Properidine appears to be an analgesic agent, several times more potent than pethidine, and, like the latter and morphine, capable of relieving anxiety as well as pain. Its reported effective dose is 5-10 mg. Properidine must be classified as an addiction-producing agent.

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17. Pethidine derivatives

(*e*) Trimeperidine [a] (1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine)

After thorough pharmacological investigation, reported upon by Nazarov et al. (1952) and Kruglikova-Lvova (1953), Promedol (trimeperidine) was used clinically before operations under local anaesthesia, post-operatively, and in many other types of pain. It was injected subcutaneously in doses of 10-20 mg. Given 15-20 minutes before operation, the drug had a general soothing effect and, in some cases, produced drowsiness and sleep. It had a rapid analgesic effect even in cases of severe pain and, in addition to removing the pain, reacted favourably on the patients' general condition. For chronic pain, the preparation was given 2 or 3 times a day in doses of 10-20 mg subcutaneously. Relief lasting 4-6 hours was

[a] International non-proprietary name

observed and the patients' condition improved. It could be substituted completely for morphine, pantopon and other narcotics. Nazarov concluded that the normal therapeutic dose of Promedol should be 25-30 mg orally or 10 mg subcutaneously. In very severe pain the dose could be increased to 50 mg or 20 mg by the two routes, respectively.

Izosimov (1952) also reported on the use of Promedol pre- and post-operatively in gastro-duodenal ulcers, in inoperable cancer and in renal colic. It failed post-operatively in 7 of the first 22 cases; and, in 14 other patients, there was no effect in 5. The starting dose was 10 mg, but, since this was only partially effective, doses of 20 mg were given. With the latter, pain relief began promptly, in 10 or 15 minutes, and persisted for 3 or 4 hours.

According to Sigidin (1953), 25 mg of Prodemol orally 3 times a day did not produce adequate analgesia in a case of perigastritis or in another patient with neuroma of the brachial plexus. In his subsequent study of 36 cases, the drug was given subcutaneously. 128 doses of 10 mg and 91 doses of 20 mg. The pain was due to circulatory and neurological conditions. Analgesia was observed to be complete or almost complete in 63%, fair in 18.5%, slight in 10.5% and absent in 8% of the cases. Onset of effect varied from 3 to 90 minutes (average 15 minutes). The duration of effect was 4 hours or less in 13.5%, but more than 8 hours in 43.5% of the patients. However, it was noted that in some instances an analgesic effect might not occur until after the second or third dose had been given. Sigidin said the action of Promedol was stronger the more intense the pain and the shorter the duration of the pain syndrome.

Eidinova (1954) tested Promedol against pain of peripheral neurological origin, giving doses of 10 mg subcutaneously in 16 patients and of 25 mg orally in 12 others. The analgesic effect was good in all cases and if the dose was given in the evening restful sleep was promoted. Effect with the oral doses was less but nevertheless definite. The drug was used with satisfactory results in three cases of Parkinson's disease.

Obstetric analgesia

Nazarov (1952) gave 20-40 mg of Promedol subcutaneously to women in labour, with the rapid production of good analgesia, apparent strengthening of the uterine contractions and no harmful effect on mother or infant. Foi & Legostev (1953) also reported very good analgesia with Promedol in the parturient mother, better than with pethidine, and an acceleration of labour through a strengthening and quickening of uterine contractions. The optimal dose was 30 mg subcutaneously, followed in 15 minutes or less by drowsiness and maximal analgesia in about half an hour. Effective analgesia was obtained in 75% of more than 200 labours, persisting on the average 3-4 hours. Promedol was said to have no toxic effect on the

foetus even if a second dose was given 2 or 3 hours after the first. In some instances 5 mg of oxycodone were given with 30 mg of Promedol to enhance the analgesic action.

Spasmolytic action

Bazanova (1954a) employed Promedol in the treatment of 25 cases of dyskinetic constipation, due to spastic conditions in the intestinal tract, which had persisted often for many years. The symptomatology included abdominal pain, digestive disturbances and palpable signs of spasticity in addition to the chronic constipation. X-ray examination revealed that there was a marked retardation in the movement of intestinal contents, stasis in one or another part of the colon, haustral spasticity of the colon and sometimes sphincteric spasm and decreased motor activity of the small intestine. Most of the patients were also neurasthenic. The treatment consisted of 15-30 daily injections of 10 mg of Promedol. The acute pain due to spasm disappeared promptly and the dull persistent ache gradually subsided during the course of the treatment, disappearing completely in 18 of the 25 cases. All digestive disturbances abated and constipation was relieved in 15 patients. X-ray examination showed that time for passage of intestinal contents had been reduced almost to normal, accompanying disappearance of the haustral spasticity in the large intestine. Most of the patients put on weight and enjoyed untroubled sleep.

In another report, Bazanova (1954b) determined the effect of Promedol in various spastic conditions, biliary and renal colic, intestinal spasm, hypertension, etc. She used three routes of administration: 25-40 mg orally, 10-20 mg subcutaneously and iontophoresis with a 0.5% solution through the abdominal wall. In 105 cases the best analgesic results were obtained with 10 mg subcutaneously. Onset of relief was faster than with oral administration. The effect sometimes lasted as much as 12 hours. Cases of colic, renal or biliary, required, as a rule, the maximum dose. Analgesia was usually accompanied by calm, deep sleep. Single doses of Promedol cut short attacks of bronchial asthma in 4 cases. In only 2 of the 105 patients was Promedol completely ineffective.

Bazanova & Klementiev (1954) reported on the use of Promedol in 30 cases of duodenal or gastric ulcer associated, in most instances, with long-standing nervous and emotional troubles. All had pain, digestive disturbances and insomnia, and most had also neurasthenic symptoms. Administration of Promedol orally or by iontophoresis was unsatisfactory, so that all patients were given 10 mg subcutaneously once or twice a day. On this regimen the analgesic effect was good, usually accompanied by sleep. During the treatment gastric hyperacidity abated in 6 of 13 cases showing this symptom. Gastric hypertonicity apparent in 2 cases initially disappeared and gastric emptying time was shortened in 4 of 6 patients in whom it was abnormally long.

Gefter & Matusova (1955) and Sokolov (1955) combined Promedol with a papaverine-like substance[a] in the treatment of angina pectoris and other instances of coronary disease. Fifty-three patients were treated altogether. The Promedol dose was 25 mg orally 2 or 3 times a day for periods up to 14 days. The combination had less effect on acute anginal attacks, though it tended to decrease their frequency, than on more persistent dull aching pain. It was not a substitute for the quick relief afforded by nitroglycerin. Promedol by injection was, as a rule, effective against acute anginal attacks. The papaverine-like agent alone was ineffective. Gefter & Matusova noted that inequalities of blood pressure in the two arms and differences in skin temperature on the right and left sides during anginal attacks were reduced by the Promedol-tiphen treatment. Occasionally there was some reduction in electrocardiographic abnormalities. Most noticeable perhaps was the improvement in the patient's general condition, manifested by reduction in the fear of attacks and better and deeper sleep. For both groups of cases together results were good in 14, fair to satisfactory in 26. In three of Sokolov's cases side-effects were severe enough to cause cessation of the treatment after the first day.

Side-effects

According to Nazarov (1952), side-effects were entirely absent after doses of 10 mg and nausea only was seen in some cases with 20 mg subcutaneously. Izosimov (1952), however, noted slight dizziness, some euphoria, malaise, drowsiness and a feeling of slight intoxication. He used doses of 10-20 mg, also subcutaneously. The pulse and respiratory rates usually declined slightly and there might be a slight fall in blood pressure, not sufficient to contra-indicate the use of the drug. In cases of hypertension the fall in blood pressure, both systolic and diastolic, was sometimes considerable and persistent after doses of 20 mg. In one case the pressure fell from 220/110 (systolic and diastolic pressures, respectively) to 155/85 in 30 minutes; in another case the fall in pressure was from 165/105 to 130/80 in 2 hours. Such changes in blood pressure did not occur if the pressure was low initially; in that circumstance, it might even rise slightly.

Sigidin (1953) reported the following incidence of side-effects in percentage of injections with which they occurred:

Side-effects	*Dose* 10 mg	20 mg
None	70.0	24.8
Sensation of warmth	7.8	64.8
Euphoria	4.7	68.7
Dizziness	10.9	28.6
Drowsiness	4.7	20.0
Nausea	2.3	4.4
Sweating	0.8	28.5
Cardialgia	0.0	7.7

[a] Tiphen=β-diethylaminoethyl ester of diphenylthioacetic-acid hydrochloride.

In spite of the marked increase in side-effects (except nausea) with the larger dose, the author said they were not usually distressing to the patient and were severe enough to cause discontinuance of the drug in two cases only. The incidence of euphoria with the higher dose is especially striking. It persisted, as a rule, with repeated injections, whereas the other effects tended to occur with the first few doses, diminish and then disappear as the use of the drug was continued. This same trend has been noted with pethidine. Patients said their spirits rose after Promedol. Some felt a need for active movement while others experienced a pleasant muscular relaxation and still others an irresistible desire for sleep. Sleep, when it occurred, was deep and the patients awoke refreshed. Heart and respiratory rates declined after 39% and 42% respectively of 10-mg doses, and after 44% and 53% of 20-mg doses. The extent of the decrease in heart rate was from 2 to 10 or more, most often 4-6, beats per minute. The decrease in respiratory rate was only 2-4 per minute with 85% of the doses. Changes in blood pressure were noted by Sigidin as follows in percentages of injections (pressures were determined once or twice before injection and at 20-minute intervals afterwards):

Change	*Systolic pressure*		*Diastolic pressure*	
	10 mg	*20 mg*	*10 mg*	*20 mg*
Fall.	29.4	41.7	30.8	46.6
Rise	13.5	12.5	19.2	40.1
None	57.1	45.8	50.0	13.3

The amount of the fall in systolic pressure was 6-10 mm Hg with 45.4%, 11-15 mm Hg with 21.2%, 16-20 mm Hg with 21.2% and more than 21 mm Hg with 12.2% of injections. This was a greater fall in pressure than usually occurs with subcutaneous analgesic doses of morphine. The fall in pressure was not greater or persistent in cases of hypertension.

In only one of Eidinova's (1954) neurological cases were symptoms of nausea and dizziness observed, but these were so severe that the drug had to be discontinued although the patient's pain was relieved. Bazanova (1954b) too noted side-effects in only 2 of 105 patients and these were only brief dizziness and malaise.

Addiction liability

The various authors who have reported on the clinical use of Promedol have denied the occurrence of tolerance to its analgesic effectiveness and have said that they saw no signs of addiction to the drug. It should be remembered, however, that the periods of administration reported have been relatively short (the longest was 38 days), and usually repeated doses were given only once or twice a day. Nazarov (1952) said that Promedol could be substituted completely for morphine or pantopon, where the patients had been receiving these drugs, and Bin (1955) reported evidence of tolerance development in animals. Also, in the cases of Sigidin (1953),

a high incidence of euphoria was noted if the dose was increased to 20 mg. The close similarity in chemical structure and clinical activity between Promedol and pethidine and its derivatives, whose addiction liability is known, strongly suggests that addiction to Promedol must be expected if its administration is prolonged.

This has been confirmed in the annual report of the USSR Government on opium and other dangerous drugs for 1955 (United Nations, Commission on Narcotic Drugs, 1955). An analysis of 459 cases of addiction revealed that 4% were Promedol addicts.

Isopromedol[a]

Zherebtsov (1955) compared Isopromedol with Promedol in 56 patients, 26 of whom had pain associated with smooth muscle spasm, angina pectoris, biliary and renal colic, etc., while the others had pain of various other origins, particularly malignancies. The analgesic effect was fair to complete in about 80% of both groups of patients. The few failures were mainly in patients who had received considerable amounts of other narcotics previously. The duration of effect of Isopromedol lay between 6 and 9 hours. The dose was 10-20 mg subcutaneously, the principal difference being in the longer duration of effect with the larger dose. Four patients had attacks of nausea and vomiting after the injection and two others complained of headache, dizziness and tinnitus. There was a small decrease in respiratory rate after 62.5% of doses given. The author's over-all conclusion was that Isopromedol was superior to Promedol in strength and duration of action.

SUMMARY

The clinical analgesic dose of Promedol lies between 25 mg and 50 mg orally and 10 mg and 20 mg subcutaneously; at least by the latter route its potency is 5-10 times that of pethidine and its duration of action is somewhat longer, probably about the same as that of morphine. Its side-action liability is not materially different from that of pethidine, except that it seems to have a greater tendency to cause some fall in blood pressure. It appears to have some spasmolytic action and it has been used successfully as an obstetric analgesic. Addiction to Promedol has been reported and must be expected to occur if its administration is prolonged.

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[a] One of the stereoisomers of Promedol.

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18. Pholcodine [a] (β-morpholinylethylmorphine)

Chabrier, Giudicelli & Thuillier (1950; and in an unpublished report in 1949 [b]) prepared pholcodine, the morpholinylethyl ether of morphine, and found in animal experiments that it was considerably less toxic than codeine and other ethers of morphine. Unlike codeine, it did not produce convulsions, which was confirmed by Cahen, Groskinsky & Parisek (1956), nor did it increase the tonus and peristaltic movements of the guinea-pig's isolated small gut as morphine and codeine did. The general sedative action of pholcodine was superior to that of codeine. In rabbits pholcodine depressed the respiratory rate and volume less than morphine and somewhat more than codeine.

As Chabrier, Giudicelli & Thuillier demonstrated on the rabbit's ear, the analgesic effect of a threshold dose of pholcodine of 0.05 mg per kg body-weight was less than that produced by morphine, but always equal and sometimes superior to that of codeine, the doses being the same for all three drugs. In mice, however, the analgesic potency of pholcodine was not more than one-tenth that of codeine (see Eddy, Halbach & Braenden, 1956). In eight volunteer patients, the pain threshold by the radiant heat method (Wolff, Hardy & Goodell, 1940) was not changed by single subcutaneous doses of 50 mg of pholcodine; 100 mg elevated the pain threshold by 20%-30% 80 minutes after injection (Delay [c]).

Antitussive action

May & Widdicombe (1954) found that in cats the capacity of pholcodine to inhibit the expiratory efforts caused by mechanical irritation of the trachea was three times greater than that of codeine and one-half that of morphine.

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[a] International non-proprietary name; for other designations, see *Estimated World Requirements of Narcotic Drugs in 1958* (United Nations document E/DSB/15).

[b] Chabrier, P., Guidicelli, R. & Thuillier, J. (1949) Unpublished working document WHO/APD/15, Add.1

[c] Delay, J. (1951) Unpublished working document WHO/APD/27

In man, the cough produced by intravenous injection of 3-10 mg of lobeline was neutralized by 80-100 mg of pholcodine subcutaneously in the same way as by 100-150 mg of codeine as reported by Chabrier, Giudicelli & Thuillier (1950).

The first clinical trials with pholcodine as an antitussive were reported by Chabrier, Giudicelli & Thuillier[a] (1950). Cough of any origin—irritation of the upper respiratory tract, laryngo-tracheitis, reflex coughing in pleuro-pulmonary diseases or due to mediastinal compression—was always soothed by a single dose of between 10 mg and 80 mg. The average daily doses were of the order of 40-120 mg orally or by subcutaneous injection. For assessment of the antitussive effect, reports of the nursing staff and statements of the patients themselves were used. The onset of the action took place between 5 and 15 minutes after parenteral and 10-25 minutes after oral administration. The reduction of cough as produced by the minimum effective dose lasted from 90 minutes to 4 hours. In some cases of tracheitis in smokers, a single dose of 20 mg administered in the morning was capable of preventing an attack of coughing for the whole day. Three of the 10 typical case reports concerned whooping-cough and pertussoid tic in children; 3 daily oral doses of 5-10 mg had a significantly ameliorating effect.

Independently of the suppression of cough, a general sedative effect was also noticed, as indicated, for example, by better sleep.

Side-effects

Side-effects of pholcodine were not observed. As could be expected from pharmacological experiments (see above), therapeutic doses of this substance did not bring about abdominal distension, meteorism, constipation, or nausea, symptoms which used to occur with codeine.

Tolerance

Tolerance to the antitussive action did not develop in any of Thuillier's cases. There was no need to increase the minimum effective dose of pholcodine, even when the treatment lasted several months. Thus, in three cases daily doses of 40, 50 and 60 mg had a constant effect over 2, 3 and 4 months respectively. In another group of 10 patients, 60 mg of pholcodine a day remained effective against cough for 8 months.

Addiction liability

The addiction liability of pholcodine was tested by Delay[b] in the Psychiatric Hospital, Paris, and by Isbell[c] in the Addiction Research Center, Lexington, Ky. Eight volunteer patients did not feel depressed or eupho-

[a] Chabrier, P., Giudicelli, R. & Thuillier, J. (1949) Unpublished working document WHO/APD/15, Add.1

[b] Delay, J. (1951) Unpublished working document WHO/APD/27

[c] Isbell, H. (1951) Unpublished working document WHO/APD/28

rized by a single subcutaneous dose of 100 mg of pholcodine; 120 mg given to three patients caused headache in one and vomiting in another (Delay). In former morphine addicts pholcodine failed to produce euphoria, miosis, nausea or vomiting when given subcutaneously in doses of 50 mg and 100 mg; even 400 mg orally in two patients and 400 mg subcutaneously in two patients had no effect (Isbell). Six addicts physically dependent on morphine were abruptly withdrawn and, in the acute stage of the abstinence syndrome, received 50 mg of pholcodine (2 patients) and 100 mg (4 patients) respectively. Apart from a decrease in the respiratory rate, no changes in the withdrawal symptoms were noticed (Delay). Six of the addict patients at Lexington, stabilized on daily doses of between 120 mg and 300 mg of morphine were given pholcodine beginning 4 hours after complete withdrawal of morphine. Since single large doses of pholcodine did not affect the abstinence syndrome and were very irritating subcutaneously, five of the patients received total doses of between 3500 mg and 5200 mg orally distributed over a 40-hour withdrawal period, resulting in only little relief. Delay administered 60 mg a day to 10 patients with respiratory troubles for 3 months without noticing depression, euphoria or other behavioural changes; sudden withdrawal was not followed by abstinence phenomena nor was it after the regular medication had been carried on for another 6 months. The authors' conclusions were: pholcodine does not produce physical dependence and addiction (Delay); it should be considered as having less addiction liability than codeine (Isbell).

SUMMARY

The analgesic potency of pholcodine is too low for it to be used in therapy. Its antitussive action approximates that of codeine, hence its therapeutic antitussive dose is similar. As a centrally sedative agent it is somewhat superior to codeine. Pholcodine depresses the respiration less than morphine and a little more than codeine does. Other side-effects and addiction liability are practically absent.

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19. Propoxyphene [a]

(4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane)

The chemical name, 4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane, characterizes four stereoisomers. Only the alpha-racemate,

[a] International non-proprietary name for the racemic form

however, and its alpha-*d*-isomer, because the latter was shown in the laboratory (Robbins, 1955) to be responsible for the analgesic activity of the racemate, have been submitted to clinical trial. Hereafter, propoxyphene will designate the alpha-racemate and *d*-propoxyphene, the active isomer. In rats it required 20-40 mg per kg of propoxyphene subcutaneously for an effect on the pain threshold equivalent to that of 2 mg per kg of methadone; *d*-propoxyphene was twice as effective as the racemate. Both the racemate and the *d*-isomer were approximately twice as effective subcutaneously as orally.

In the first clinical test of propoxyphene (Gruber et al., 1955), a dose of 50 mg was compared with 32.5 mg of codeine, 325 mg of acetylsalicylic acid and a placebo. Each was given in a capsule orally, 1 or 2 every 4 hours, to patients with slight to moderate chronic pain. At the end of 24 hours on a particular medication the patient was questioned as to the number of hours of severe, moderate, slight or no pain in the preceding 24 hours. The intention was to have all patients receive all four medications at both dose-levels. Only 14 patients did so. To evaluate the results, each hour of severe pain was given a score of 3, each hour of moderate pain a score of 2, and each hour of slight pain a score of 1, thus permitting a daily pain score for each medication. These scores were lower for each of the analgesic medications than for the placebo and in each case lower when the dose was two capsules. There was no significant difference in the pain scores for the three analgesic medications. 50 mg of propoxyphene were judged to be equivalent to 32.5 mg of codeine. Side-effects occurred no more frequently with the analgesic medications than with the placebo.

In another series of observations, Gruber (1955, 1956, 1957) at seven co-operating institutions administered orally 32.5 mg and 65 mg of *d*-propoxyphene hydrochloride, 32.5 mg and 65 mg of codeine phosphate and a placebo to 101 patients, Either dose of either analgesic was given for the first 3 days (1, 2 and 3). This same analgesic was given at the other dose for the last 3 days (13, 14 and 15). The other drug was given in corresponding doses on days, 4, 5 and 6, and 10, 11 and 12, and the placebo was always given on days 7, 8 and 9. The pain scores, calculated as in the previous study, for the patients at each hospital and in total were as shown in Table XXXVIII. Pain was of various origins and no one category was better relieved than another by either drug. The two drugs were equally effective at each dose used. The incidence of side-effects with each dose is given in Table XXXIX. The figures are times observed during 303 hospital days per dose.

Only the 65-mg dose of codeine, according to the authors, was associated with a significant increase in gastro-intestinal side-effects. It may be important that the incidence of drowsiness with the 65-mg dose of each analgesic was nearly the same and the incidence of a rash was greater with the 65-mg dose of *d*-propoxyphene than with any other medication.

TABLE XXXVIII. PAIN SCORES RECORDED IN 101 PATIENTS WITH CODEINE, PLACEBO, AND *d*-PROPOXYPHENE

Hospital	Number of patients	Codeine		Placebo	*d*-Propoxyphene	
		65 mg	32.5 mg		32.5 mg	65 mg
A	12	724	863	914	758	615
B	22	300	260	270	222	215
C	8	276	413	496	424	416
D	8	355	302	360	344	310
E	14	319	542	542	586	423
F	20	232	271	477	356	291
G	17	783	1007	1270	956	915
Total	101	3099	3658	4519	3646	3185

In nine of the patients in the series just described (Gruber et al., 1956), nurses inquired at hourly intervals from 10.0 a.m. to 4.0 p.m. as to the degree of pain present and the pain categories of slight, moderate, severe and agony were given numerical values of 1, 2, 3 and 4, again to arrive at

TABLE XXXIX. SIDE-EFFECTS OBSERVED WITH CODEINE, PLACEBO AND *d*-PROPOXYPHENE

Side-effects	Codeine		Placebo	*d*-Propoxyphene	
	65 mg	32.5 mg		32.5 mg	65 mg
Loss of appetite	31	20	19	13	16
Nausea	71	34	22	33	25
Constipation	51	44	26	26	32
Abdominal pain	35	26	24	20	19
Dizziness	21	7	4	11	10
Drowsiness	43	32	24	33	41
Rash	5	2	4	2	8
Total	257	165	123	138	151

a pain-relief score per patient and per medication. These scores per hour per medication totalled for the nine patients were:

	Hour after medication							Total
	0	1	2	3	4	5	6	
Placebo	29	24	24	27	30	30	32	196
Codeine 32.5 mg	31	28	25	23	23	27	29	186
d-Propoxyphene 32.5 mg	26	24	23	21	23	27	28	172
Codeine 65 mg	28	23	20	19	20	26	27	163
d-Propoxyphene 65 mg	29	23	21	21	24	23	25	166

For the first 2 hours the patients were unable to distinguish between the placebo and either drug, but at 3 hours, when the peak effect of the drugs occurred, there was little relief from the placebo. There was no significant difference between codeine and *d*-propoxyphene at either dose-level, but with both drugs there was a significant difference in total relief between the 32.5-mg and 65-mg doses. The authors concluded that the two drugs were of equal potency, milligram for milligram.

Addiction liability

Since propoxyphene was irritating on subcutaneous administration, Fraser & Isbell (1956) used only the oral route in studying its addiction liability. Single doses of 50-400 mg were given to non-tolerant former addicts. No morphine-like effects were produced. Two subjects who were given 200 mg at 8.30 a.m. and an additional 400 mg at 9.0 a.m. even said it was like water. Both complained of a slight headache. Two of five subjects were slightly drowsy after a dose of 200 mg and two subjects complained of diarrhoea. Eleven subjects who had been stabilized on 240-280 mg of morphine per day were given a total of 1200 mg of propoxyphene during the first 24 hours after abrupt withdrawal of morphine. During another 24-hour withdrawal after re-stabilization the same subjects were given a total of 2400 mg of propoxyphene, 400 mg per dose. Intensity of abstinence was plotted hourly from the 14th to the 24th hour and compared with abstinence intensity during other 24-hour withdrawals when a placebo in capsule form was given at the same 4-hour interval or morphine at the usual dose was given as an unknown. The intensity of abstinence was significantly reduced by the propoxyphene substitution; the curve of abstinence intensity with propoxyphene lay about half-way between the curves for placebo and morphine administration. Two of the propoxyphene subjects were excessively sedated and one had a depressed respiration of Cheyne-Stokes type. There was some respiratory depression in each of the subjects on this high propoxyphene dosage. All the individuals felt that the propoxyphene was beneficial since they slept more and were less nervous than when no medication was given during withdrawal, but none of them experienced a morphine-like euphoria. At this time it was judged that propoxyphene had some addiction liability because of its partial suppression of

abstinence, but that its liability was no greater and probably less than that of codeine.

Direct addiction with propoxyphene orally was attempted by Fraser & Isbell in five subjects. Nalorphine in a dose of 10 mg did not precipitate an abstinence syndrome and signs of abstinence on abrupt withdrawal after 46 days of administration were insignificant.

300 mg of *d*-propoxyphene orally did not but 400-800 mg orally did induce behavioural changes in non-tolerant former addicts resembling those seen after 15-30 mg of morphine. Five subjects were given 3 oral doses of the drug a day, the total dose ranging up to 825 mg a day and continuing for 52 days. All the patients developed a great deal of somnolence, and some tolerance to this effect was observed. Nausea and vomiting occurred occasionally. 10 mg of nalorphine did not precipitate clear-cut objective manifestations of abstinence and abrupt withdrawal was followed by very mild abstinence phenomena. It was concluded that the *d*-isomer also had addiction liability of a very low order, less than that of codeine.

As a further test of the addiction-sustaining potency of *d*-propoxyphene, Fraser & Isbell (1957) conducted a cross-over substitution study in which on one occasion codeine and on another occasion *d*-propoxyphene were substituted for morphine in the same individuals. Ten former opiate addicts volunteered for the study. Morphine sulfate was administered in increasing amounts to a total of 280 mg per 80 kg of body-weight per day and the subjects were stabilized on that amount for 31 days. Then in five individuals codeine phosphate (total dose, 1600 mg per 80 kg per day) and in the other five *d*-propoxyphene (total dose, 800 mg per 80 kg per day) was substituted for morphine for 14 days and each in turn was substituted by a placebo. The codeine, *d*-propoxyphene and placebo were given in an equal number of capsules per dose 3 times a day. The conditions of substitution were double-blind. After 10 days of placebo administration the stabilization and substitution procedure was repeated; the subjects who had received codeine now received *d*-propoxyphene, and those who had received *d*-propoxyphene now had codeine substituted. The dose of *d*-propoxyphene was half that of codeine because toxic symptoms would be expected with larger doses.

d-Propoxyphene substituted partially for morphine, since during its administration the abstinence symptoms which appeared were less intense than would have been expected if morphine had been abruptly withdrawn. *d*-Propoxyphene, however, was far less effective than codeine in suppressing morphine abstinence symptoms. During the substitution of *d*-propoxyphene physical dependence on morphine largely disappeared because placebo substitution caused the appearance of only very mild abstinence phenomena. Codeine, on the other hand, maintained the addiction fairly well because an abstinence syndrome of moderate intensity followed the replacement of codeine by placebo. The patients did not classify the subjective effects of *d*-propoxyphene as resembling those of an opiate, whereas

they did so identify the effects of codeine. Fraser & Isbell concluded finally that the addiction liability of *d*-propoxyphene was less than that of codeine.

C. M. Gruber, jr,[a] reported that 130 patients had received propoxyphene on a continuous basis as their principal analgesic, usually 200 mg of the racemate or 260 mg of the *d*-isomer daily orally in divided doses. Twelve had received the drug for ½-1 year, 13 for 1-1½ years, 17 for 1½-2 years, and one patient had been on the drug for more than 2½ years. These patients usually received measurable relief with the drug and the same doses were continued for months without loss of analgesic activity. Eight patients voluntarily discontinued the drug and 12 others were given capsules, which looked identical, of acetysalicylic acid. In none were signs of physical dependence detected. Also, on no occasion during this prolonged administration was a euphoric effect reported. Two opiate addicts were given 200 mg or 300 mg of propoxyphene intravenously during withdrawal with an unsatisfactory effect on abstinence. One of these patients was given 800 mg of propoxyphene intravenously and 4050 mg orally in divided doses over a 48-hour period without complete relief of the withdrawal syndrome.

SUMMARY

Propoxyphene is effective against slight to moderate pain to about the same degree as codeine. *d*-Propoxyphene is as effective as codeine, milligram for milligram, when each is administered orally for chronic pain. At an oral dose of 65 mg the side-effects with *d*-propoxyphene are in most respects less than with the same dose of codeine. The addiction liability of propoxyphene or of its *d*-isomer is substantially less than that of codeine.

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20. Thebacon[b] (dihydrocodeinone enol acetate)

The basic pharmacology of thebacon was published by Behrens et al. in 1929. They speculated that for human beings its effectiveness should lie

[a] Personal communication, 1957

[b] International non-proprietary name; for other designations, see *Estimated World Requirements of Narcotic Drugs in 1958* (United Nations document E/DSB/15).

between that of codeine and that of morphine. The first clinical report was that of Nonnenbruch & Rischawy (1929), who confirmed the previous authors' expectation, though they placed thebacon rather closer to morphine than to codeine. Their report was based on the use of the drug in about 250 patients. The usual dose was 10 mg either orally or subcutaneously; only occasionally was the dose increased to 20 mg and the maximum per day was 50 mg orally or 30 mg subcutaneously. Oral doses were less effective and slower in the onset of their action. The drug was used for pain but more particularly as an antitussive. It was more effective than codeine in analgesic and sedative actions, about half as effective as morphine in these respects, and about four times more effective than codeine against cough. It was particularly valuable for haemoptysis because of its calming effect. If cough was accompanied by pain, as in pleurisy, the breathing became slower and deeper on account of the relief of the pain.

Bertram & Stoltenberg (1929) gave doses of 5 mg and 10 mg orally and 10 mg subcutaneously in a large number of cases (more than 1000) of cough of many types, both acute and chronic. They believed that it was as effective, sometimes even more effective orally than subcutaneously, as an antitussive and definitely more active against cough than the other common opiates. It was nearly as good an analgesic as but shorter-acting than morphine, 10 mg being equivalent to 7 mg of the latter for relief of pain. Thebacon had a sedative and sleep-promoting action over and above that which would follow the relief of cough.

Büssow (1929) too said that thebacon was as effective orally as subcutaneously for the relief of cough. He treated many tubercular patients, usually giving 10 mg orally per dose. 10 mg or 20 mg orally were very effective against acute as well as chronic cough. As an analgesic it was weaker and shorter-acting than morphine. It was less hypnotic than morphine also; a dose of 10 mg gave at the most 3 or 4 hours' sleep, whereas after 10 mg of morphine the patient slept the whole night through. The analgesic effect of thebacon was least when the pain was accompanied by or due to smooth muscle spasm. Yet these authors said that the drug regularly relieved the respiratory distress and its use resulted in subjective improvement in bronchial asthma. The effect of 10 mg in such cases lasted 1½-2 hours.

Narbeshuber (1929) and Paula (1929) reported very satisfactory results with thebacon as an antitussive. They used oral doses of 5 mg or 10 mg, more often the latter. It was usually, but not always, more effective than previously used morphine or codeine. Action was prompt but briefer than that of morphine. Paula said that thebacon was effective against many types of pain and caused no gastro-intestinal disturbance.

Crohn (1930), Curschmann (1936), Dalal (1931), Hegler (1934), Holdheim (1932), Rehfeldt (1931), and Reinwein (1936) all found thebacon superior to codeine as an antitussive. Most of them used a 5-mg dose

orally, increasing to 10 mg orally and to 10 mg subcutaneously only in the most severe cases. Crohn said that it was difficult to return to the use of codeine after thebacon because of the superiority of the latter. Holdheim recommended a starting dose of only 2.5 mg, finding this dose twice a day with a 5-mg dose at bedtime usually quite adequate. He seems never to have given more than 5 mg 3 times a day. Holdheim, like Nonnenbruch & Rischawy (1929), thought that thebacon was very useful in haemoptysis; it relieved the patient's anxiety without a notable narcotic effect. For this purpose he gave the drug subcutaneously.

Zischinsky (1937) was especially interested in the use of thebacon in children. He said it was the best antitussive of his experience because it had a quieting effect in addition to relieving the cough. He did not believe that children generally were more susceptible to opiates than adults. His dosage schedule was 1.25 mg for babies up to 2 years, 2.5 mg for children of 3-7 years and 5 mg for older children; the drug was always given orally.

Halasz (1931) used a 5-mg dose of thebacon as premedication for tonsillectomies and said that the results were as good as had been obtained previously with morphine, except that there was less tendency to sleep. The inclination to cough was reduced markedly and the quieting effect would persist for 5 hours. The effect could be extended to 12 hours by giving a second dose. An exciting effect was never seen.

Persch (1936) advocated the administration of thebacon by placing a tablet (5 mg) or part of a tablet beneath the tongue in cases of laryngeal tuberculosis where swallowing was particularly difficult. He said the action was rapid and adequate both with respect to cough and a general quieting effect.

Side-effects

Nonnenbruch & Rischawy (1929) said that the side-effects of thebacon were minimal and that it was, as a rule, better tolerated in circulatory disorders than morphine or other opiates. It was constipating but not sufficiently so to be used as an antidiarrhoeic. However, they reported two cases in which a collapse-like syndrome with vomiting occurred after the drug had been given orally. The symptoms disappeared spontaneously. According to Bertram & Stoltenberg (1929), most patients experienced few or no side-effects. If they did occur with a 10-mg dose, they would, as a rule, disappear when the dose was reduced to 5 mg and not again reappear. Profuse sweating was seen in some cases, and the usual morphine-like side-effects appeared in 18 of more than 1000 cases treated for cough. In all of these the dose was given orally and the patients were ambulatory. Respiration was not depressed by therapeutic doses and blood pressure and pulse rate were unaffected. The drug did not produce paralysis of intestinal peristalsis, so that a constipating effect with small doses was much less serious than with other opiates.

Büssow (1929) found that oral doses of thebacon only occasionally caused dizziness and headache and had practically no sedative effect. In two debilitated patients he saw a brief collapse-like syndrome, like that reported by Nonnenbruch & Rischawy (1929), after a dose of 7.5 mg.

Hegler (1934) said that thebacon was not constipating. He used doses of 2.5-5 mg orally 3 times a day.

Addiction liability

Nonnenbruch & Rischawy (1929) observed no tolerance to the action of thebacon. They were able, however, to replace morphine by thebacon in cases of morphine addiction. Bertram & Stoltenberg (1929) said that a euphoric effect was seen occasionally in their series of more than 1000 cases; they saw some tolerance but no evidence of addiction. Some of their patients received daily doses of 10-30 mg for 3 or 4 months. Paula (1929) did not encounter addiction to thebacon, but he found that it produced typical euphoria and was inclined to reserve its use for serious advanced tubercular cases.

Crohn (1930), Holdheim (1932), Persch (1936) and Rehfeldt (1931) claimed that no tolerance to the antitussive effect of thebacon occurred. Holdheim said that it was often possible to reduce the dose as the condition improved when the cough was relieved.

In spite of the mainly negative evidence of the earliest reports, except for Nonnenbruch's substitution of thebacon for morphine in addicts, cases of primary addiction were not long in appearing. Bieling's case, reported in 1931, was the first. The patient began the use of thebacon on account of a circulatory disturbance and an accompanying bronchitis. The dose was rapidly increased to 20 times 10 mg per day. The drug was injected subcutaneously and its use was continued for 13 months. The patient denied experiencing any euphoria but needed it for maintenance of his well-being. While taking these large doses he had difficulty in urination and was constipated. The drug was discontinued on a schedule of moderately rapid withdrawal, during which much psychic and motor unrest was experienced. This was followed by a period of great apathy with gradual recovery.

Also in 1931 Wenger reported a case of *acediconomanie*. The patient had begun the use of the drug on the advice of a physician, using at first oral doses of only 5 mg. The drug had a calming and euphoric effect, for which he continued its use, increasing the dose to 30-40 mg a day. Several times he tried to shift to eucodal but for him this drug was inferior. After six months of use the patient changed to subcutaneous administration and very quickly was using 1 g a day by this route. This man found voluntary withdrawal impossible because of sensations of great fatigue and the occurrence of severe cramps. Eventual withdrawal, with temporary substitution of small doses of dilaudid, was difficult and very painful. Afterwards the

patient would refer to his experience only with horror and to the drug as an infernal medicament.

In the third case of thebacon addiction reported in 1931 (Unverricht), the patient had been previously addicted to morphine but was believed to have been drug-free for some time when he began the new drug. Thebacon was given for cough by his physician in place of morphine because the patient was afraid of becoming addicted to the latter drug again. The dose was increased rapidly to 8 or 10 injections a day and again attempts at voluntary withdrawal were unsuccessful. Rapid withdrawal in hospital was accompanied by a severe abstinence syndrome.

Himmelsbach (Small et al., 1938) substituted thebacon for morphine in five stabilized morphine addicts. The amount used was 60 mg for each 50 mg of the morphine stabilization dose and it was given at the same interval, 4 times a day. Addiction was maintained with complete satisfaction to the patients and with complete absence of abstinence phemonena. On abrupt withdrawal of the substituted drug an abstinence syndrome as severe as that of morphine developed almost as rapidly as with morphine, in 18 hours as against 14 hours for morphine. On the basis of this experiment the physical dependence property of thebacon is almost the same as that of morphine, though a little slower in its development (Eddy, Halbach & Braenden, 1956).

SUMMARY

Thebacon is an effective antitussive; the optimal dose seems to be 5 mg orally. Doses of 10 mg orally or subcutaneously have been used in the more severe cases. Its analgesic effect is inferior to that of morphine and is less with oral doses. Except for the very occasional occurrence of brief collapse-like symptoms, side-effects have been mild, and it is reported to be less constipating than morphine or codeine. Cases of primary addiction were reported quite early in its use. It certainly produces more euphoria than codeine and, on the basis of substitution experiments, its physical-dependence-sustaining property is several times greater. Its over-all addiction liability is greater than that of codeine and approaches that of morphine.

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21. Thiambutenes [a]

The thiambutenes are a group of dialkyl derivatives of dithienylbutenylamine, differing in the nature of the alkyl group, which have been shown in the laboratory to have an analgesic effectiveness in some instances as great as that of morphine (Adamson & Green, 1950; Eddy & Leimbach, 1953; Green, 1953). In spite of their apparent dissimilarity, it can be shown that the thiambutenes possess structural characteristics which make them akin to the opiates (see Braenden, Eddy & Halbach, 1955). Keele and Flintan & Keele have studied the analgesic effectiveness in man of some of the thiambutenes in a number of ways.

In his first report Keele (1952) described the effect of four of the dithienyl compounds on ischaemic pain in normal subjects and the effect of one of them on the persistent pain of a cancer patient. Ischaemic pain was produced by causing the subject to clench and unclench his fist once a second with the blood supply to the forearm occluded by a sphygmomanometer cuff about the arm. The minimal dose injected intravenously required to check the rising intensity of pain and the number of contractions of forearm muscles required to elicit slight or moderate pain were determined. The threshold doses to check ischaemic pain varied considerably from subject to subject (see Table XL).

Ethylmethylthiambutene was less effective than morphine or methadone; the other members of the group were still less effective; but all were more effective than pethidine. Only diethylthiambutene (191C49) was tested for its effect on the number of contractions required to produce slight or moderate pain in the ischaemic forearm. The dose was 25 mg, compared with 10 mg of morphine, each intramuscularly. While in some subjects the thiambutene increased notably the number of contractions required to produce pain, sometimes even more than morphine, the results were not consistent and a conclusion on relative potency by this test was not drawn.

[a] International non-proprietary names: dimethylthiambutene, diethylthiambutene, ethylmethylthiambutene; for other designations, see *Estimated World Requirements of Narcotic Drugs in 1958* (United Nations document E/DSB/15).

TABLE XL. THRESHOLD DOSES (INTRAVENOUS) TO CHECK ISCHAEMIC PAIN

Subject	Morphine (mg)	Methadone (mg)	Pethidine (mg)	Dithienyls [a]			
				1C50 (mg)	268C49 (mg)	191C49 (mg)	489C49 (mg)
J	1.0	0.5	5.0	<2.5	5.0	5.0	7.5
R	1.0	2.5	10.0	7.5	>2.5	5.0	7.5
H	>2.0	2.0	10.0	1.0	2.5		5.0
F	>0.5	3.0	7.5	5.0	5.0		>5.0
L	>2.0	2.0	5.0	>2.5	2.5		2.5

[a] 1C50 = 3-Ethylmethylamino-1,1-di(2'-thienyl)-1-butene (ethylmethylthiambutene).
268C49 = The alkyl amine is pyrrolidine.
191C49 = The alkyl amine is diethylamine (diethylthiambutene).
489C49 = 3-Dimethylamino-1,1-di(2'-thienyl)butane.

Diethylthiambutene, apparently at the 25-mg dose, produced drowsiness or sleep in 17, euphoria in 8 and dizziness in 9 of 22 subjects; morphine produced drowsiness in 7, euphoria in 1 and dizziness in 4 of 13 subjects. In the one patient reported, 50 mg of 489C49 produced only slight relief of pain; 100 mg relieved pain completely and the patient slept for two hours.

Flintan & Keele (1954a, 1954b) administered the same four dithienyl compounds mentioned above for post-operative pain and to normal subjects for assessment of side-actions including respiratory depression. Injection was intramuscular in all cases and conditions were single-blind; i.e., the observer but not the patient knew the nature of the drug employed. In the patients comparisons were made, so far as possible, in the same individual, whenever more than one dose of an analgesic was required, with morphine or pethidine and between two dose-levels of the new agent. Placebos were not administered. Patients were queried by the observer half an hour and then hourly after injection as to the degree of pain relief. If the patient was asleep at any observation time complete relief of pain was assumed and he was not awakened. Satisfactory relief of pain was considered to be reduction of pain to zero or slight intensity.

268C49 was given in doses of 75 mg and 100 mg and in only 13 of 26 trials did it produce satisfactory relief of pain. 489C49 produced complete relief of pain on each of 10 trials at a dose of 50 mg, but the side-effects were too severe to warrant further use. Only a few doses of 191C49 were given to this series of patients, so that no further evidence on its analgesic effectiveness became available. 1C50, ethylmethylthiambutene, was the most effective of the group. The results are shown in Table XLI.

1C50 at the higher dose had a duration of effect like that of morphine, more than 5 hours on the average. It produced sleep accompanying pain relief more frequently than morphine or pethidine. Nausea, vomiting

TABLE XLI. RELIEF OF PAIN WITH ETHYLMETHYLTHIAMBUTENE (1C50)

Drug and dose	Pain before injection	Number of doses [a]	Doses giving complete relief		Doses giving satisfactory relief [b]	
1C50, 50 mg	Very severe	22 (11)	5	38 %	12	65 %
	Severe	47 (26)	21		33	
1C50, 100 mg	Very severe	14 (8)	7	75 %	13	98 %
	Severe	70 (37)	56		69	
Pethidine, 100 mg	Very severe	8 (6)	3	48 %	3	75 %
	Severe	48 (31)	24		39	
Morphine, 10 mg	Very severe	11 (6)	6	67 %	9	94 %
	Severe	25 (21)	18		25	

a Figures in parentheses show the number of patients.
b Satisfactory relief = pain reduced to slight or zero intensity.

and euphoria were seldom seen in these patients with the dithienyl compounds. Marked muscular weakness, particularly in the arms and hands, was seen in two of eight patients given 489C49. There was great difficulty in speaking and the weakness was accompanied by sweating and flushing and by considerable distress and restlessness. These symptoms were not seen with 268C49 or 1C50.

Observations on the effect of the dithienyl compounds on respiration and on side-effects in general were made on 12 normal subjects. For respiratory effect, pulmonary ventilation (respiratory rate × tidal volume) was plotted against time and the mean percentage change from the normal value was used as the criterion for comparison. From the graph of these means the degree of respiratory depression with the various drugs may be expressed in round numbers as follows:

Drug	*Dose (mg)*	*Main percentage change in pulmonary ventilation*
Saline		+1
268C49	25	−18
489C49	25	−27
Pethidine . . .	50	−33
Morphine . .	10	−41
1C50	25	−50

Other side-effects observed are shown in Table XLII. There are obvious disadvantages to all but 1C50, ethylmethylthiambutene. That compound is an effective analgesic, but it has no superiority over morphine except for the relative absence of nausea and vomiting, and it has a greater respiratory depressant effect. Nalorphine antagonized the respiratory depression.

TABLE XLII. SIDE-EFFECTS OBSERVED WITH THIAMBUTENES

Side-effects	Saline (37 doses)	Morphine 10 mg (29 doses)	Pethidine 50 mg (28 doses)	l-Metha-done 5 mg (13 doses)	489C49 25 mg (19 doses)	268C49 25 mg (18 doses)	1C50 25 mg (23 doses)
Drowsiness	5	21	23	9	19	14	21
Sleep		7	9		15	6	12
Uneasy stomach		6		1	2		
Nausea		16	3	2	2	1	1
Vomiting		2		1			
Pallor and sweating		7		1	1		
Faintness		4					
Ataxia		5			2		
Lightheadedness			2	2	4	1	2
" Drunkenness "		1			3		
Euphoria		7	10	6	5	3	11
Headache		3	1				
Photophobia					8		1
Dizziness		2	1	1	4	1	9
Visual difficulties		3	2	1	11	1	7
Warm glow		5	7		8	2	8
Itching			1				5
Dryness of mouth		5	7	1	8	2	8
Muscular weakness					9	1	4

Diethylthiambutene (191C49 of the previous report) and ethylmethylthiambutene (1C50) have been tested by Isbell & Fraser (1953) and Isbell, Fraser & Wikler (1953) for addiction liability. Single doses of 40-60 mg of each compound administered subcutaneously to non-tolerant former addicts produced typical morphine-like effects. The diethyl derivative at the dose indicated appeared to be equivalent to about 15 mg of morphine, whereas the ethylmethylamine produced an effect about like that of 30 mg of morphine. The ethylmethylamine at a dose of 60 mg produced as much depression of respiratory minute volume and almost as much pupillary constriction as 5 mg of hydromorphone. 60 mg of ethylmethylthiambutene, administered every 3 hours, beginning 3 hours after the last dose of morphine, substituted completely for morphine in 10 addicts who had been stabilized on 60-100 mg of morphine 4 times daily. On subsequent abrupt withdrawal of the thiambutene abstinence signs appeared promptly, within 4 hours, and reached peak intensity in about 14 hours. The abstinence syndrome was not as severe as after morphine and subsided more rapidly.

Diethylthiambutene also suppressed morphine abstinence signs, almost completely, when administered in doses of 60-70 mg every 3 hours after abrupt morphine withdrawal. A direct addiction experiment with ethylmethylthiambutene was carried out on three former addicts. The drug was given subcutaneously every 3 hours; the individual dose was increased from 15 mg to 60 mg in 14 days, and maintained at that level for an additional 16 days. Abrupt withdrawal resulted in an abstinence syndrome which differed in no way from that seen when the drug was substituted for morphine and then withdrawn. During the addiction the patients complained of " seeing and hearing things ", but were not greatly disturbed, nor did they ask to have the experiment discontinued. They also complained of dark, almost black, discolouration of the urine (noted also by Flintan & Keele), probably due to a metabolite, since no disturbance of kidney function was detected. Isbell & Fraser concluded that the thiambutenes examined possessed addiction liability similar to that of morphine.

Addiction to dimethylthiambutene occurs in certain regions, as might be inferred from seizures of considerable illicit amounts of this substance (called Ohton) in different parts of Japan during the last years.[a]

SUMMARY

The thiambutenes lie between morphine and pethidine in analgesic effectiveness, nearer to the latter. The most effective member, ethylmethylthiambutene, has an optimal dose, equivalent to 10 mg of morphine, of more than 50 mg. It has a respiratory depressant effect, however, at least as great as that of morphine and an addiction liability approximately the same as that of morphine. Its duration of action is similar as well as its side-effects, except that it produces less nausea and vomiting. Side-effects and weaker analgesic action are definite disadvantages of the other members of this group which have been examined.

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[a] See summaries 1 and 5 of United Nations document E/NS.1955 and summaries 1, 3 and 5 of United Nations document E/NS.1956.

DISCUSSION AND SUMMARY

General Therapy with Natural and Synthetic Morphine-like Agents

Brief summaries have been written at the end of each monograph, but it seems pertinent to review the whole picture in one place to determine, if possible, what is gained by the multitude of morphine-like agents now available. Opinion, to be sure, has differed widely on this point, with the argument focused for the most part on the relative advantages, or dangers, of " natural " and " synthetic " agents—the former meaning opium, morphine and substances derived therefrom, and the latter meaning substances wholly produced in the laboratory. Vaille & Stern (1951), for example, point out that France, having allowed the introduction of pethidine, decided in 1949 to prohibit the use in France of other new synthetic narcotic drugs unless they represent an important progress in therapy. They argue that this decision is based *inter alia* on a restriction in the recommendation of the League of Nations in 1935 on the issuance of new licences for the manufacture of narcotic drugs if medical needs were already being met. Vaille & Stern state that from a pharmacological standpoint the synthetic and natural products are on the same level, and further that the efficacy of control is in inverse proportion to the number of drugs to be controlled and thus to the difficulties in controlling their manufacture. Also, they say, many products have been put on the market without adequate warning to physicians of the dangers. This has been the case with morphine derivatives too; the introduction of heroin is an outstanding example. It has been argued that imposing this far-reaching prohibition because of possible difficulties in control would impede medical progress and could deprive therapeutics of most advantageous developments. Seevers (1956) has taken a very strong position on the opposite side of the question. He has said:

" The evidence in favour of the ' synthetics ' is so impressive when subjected to comparative analysis that the author is tempted to predict that the day is not far distant when the Commission [on Narcotic Drugs] will be confronted with resolutions which would propose to abolish all ' horticulturally derived ' narcotics."

Vaille & Stern (1956) were of the opinion that any superiority a synthetic drug might have over a natural drug with comparable analgesic properties could only lie in its distinctly weaker addiction-producing potency; it has been pointed out, however, that the necessity to consider therapeutically useful as well as undesirable side-effects (other than addiction liability) should not be overlooked when weighing the advantages against the disadvantages of different drugs. In this context Seevers (1956) referred to several synthetic drugs with less pronounced side-effects, such as respiratory depression and gastro-intestinal effect (pethidine), better oral effectiveness (levorphanol, methadone), greater duration of action (levorphanol), less tolerance development and less physical dependence and primary addiction

liability (methadone). He pointed out that, although no single agent possessed all these advantages, the above facts suggested that the search for such a compound having all these advantages might be successful. Some years ago Robsom & Nissim (1949) expressed the opinion that it might be a long time before the ideal analgesic is discovered, if, indeed, such a substance exists. They considered a very good alternative would be to have a large number of analgesics differing in their side-actions, i.e., in any effect other than the production of analgesia. This would afford a wide choice and the type of side-action could determine the suitability of a product for a particular occasion.

Anstee in 1951 considered morphine still supreme but was willing to concede that:

" Pethidine is less liable than morphine to cause nausea, vomiting or constipation. It is also the least depressant of the analgesics to respiration. Amidone [methadone] is a much more potent analgesic than pethidine, even a little more potent than morphine, but it is almost as depressant to respiration and often causes nausea and vomiting if given by mouth. It has hardly any of morphine's sedative effect."

More recently, Nordal (1956) has said:

" As far as their margin of therapeutic safety is concerned the natural drugs are by no means inferior to the synthetic ones." [He could just as well have phrased this the other way round.] " In fact morphine is in this respect superior to all known analgetics. In therapeutic value the natural and synthetic drugs are almost on a par with one another. The extent to which each is used, therefore, depends largely on such factors as therapeutic traditions, production costs, national interests, trade restrictions, etc."

Radouco-Thomas and colleagues (1956) also discussed the pros and cons of the synthetics and came to the conclusion that these products were entitled to a place of honour in therapeutics, but were not free of the danger of addiction. They stressed the physician's duty to use them, as well as the " natural " alkaloids, in such a way as to minimize this danger.

Isbell (1948), Brown & Volpitto (1950), Papper (1950) and Donatelli (1955) have compared from their respective viewpoints pethidine and methadone with morphine and its derivatives, pointing out what they considered to be special indications or limitations. Isbell considered that pethidine was most useful when pain accompanied spasm of smooth muscle, but that in its over-all effectiveness it was less reliable than morphine. Methadone, he thought, could be used in most instances in which morphine was indicated. Brown & Volpitto said that methadone was like morphine as an analgesic but produced less psychic sedation. They considered levo-isomethadone the best analgesic of the methadone series. Papper stressed the value of pethidine in pre-operative medication, in the control of post-operative pain and for analgesia in obstetrics. However, pethidine, valuable though it was, was not the ideal potent analgesic because of its addiction potential and limited safety in aged patients. Papper thought it merited the widespread usage it enjoyed. Concerning methadone, he believed there

were differences between it and morphine which offered utility to the clinician in favour of methadone. Papper said that therapeutic doses of methadone caused less circulatory depression, less sedation, less respiratory depression and infrequent euphoria in non-addicts as contrasted with morphine. It was valuable in the therapy of painful states which required a drug as potent as morphine. It was not advantageous in pre-operative medication because of the lack of euphoria, nor in obstetric analgesia because of depression of foetal respiration.

Donatelli (1955) reviewed at length many morphine derivatives and some of the synthetic analgesics and gave the following table of therapeutic dosages (in mg):

	Subcutaneous	*Oral*
Morphine	5-20	20-50
Codeine	50-100	—
Heroin	5-10	3-5
Hydromorphone	2	2.5-5
Oxycodone	10	2.5-5
Metopon	6	6-9
Desomorphine	2-4	—
Hydrocodone	—	5-10
Pethidine	50-100	25-150
Ketobemidone	7.5	5
Levorphanol	2	1.5
Methadone	5	2.5
Phenadoxone	10	10

Finally, to conclude these quotations of opinion, Pfeiffer (1951) set forth what he considered to be the desiderata of the ideal analgesic, as yet undiscovered: (1) it should not become ineffective through the development of tolerance and should not be habit-forming or addicting (absence of addiction-producing properties is certainly to be sought for, but an agent which promotes comfort could hardly be expected not to be habit-forming); (2) it should be safe, i.e., it should have a large therapeutic range or margin of safety; (3) it should be effective against all types of pain; (4) it should possess a short latent period and a long duration of action; in some instances (obstetric analgesia) a short duration of action is advantageous; (5) it should not alter sensory modalities other than pain; (6) it should not depress respiration or the cardiovascular system; (7) it should not affect the gastrointestinal tract; (8) it should be chemically stable and inexpensive; (9) it should be effective both orally and parenterally; (10) it should not be antidiuretic. Pfeiffer also gave his preferences among the analgesics for different indications; where more than one drug is mentioned, they are in the order of the author's preference: (1) severe pain (usually more effective in chronic than in acute pain situations): levorphanol, methadone, hydromorphone, morphine (subcutaneously); (2) obstetrical pain: alphaprodine, hydromorphone, pethidine (intramuscularly); (3) chronic pain, as of cancer:

methadone, levorphanol (orally); levorphanol, methadone, morphine (subcutaneously); (4) pre-anaesthetic medication: morphine, hydromorphone, levorphanol (subcutaneously); (5) sleep in the presence of pain: morphine, methadone, levorphanol; (6) to prevent vomiting: morphine (subcutaneously or slowly intravenously); (7) internal haemorrhage and shock: morphine (slowly intravenously); (8) cardiac asthma and pain of thrombosis: hydromorphone (subcutaneously); (9) cough: codeine (orally). Pfeiffer listed a few contra-indications: (1) head injury; (2) chronic allergic asthma; pethidine may be used occasionally but the patient should be kept in ignorance of the nature of the medication; (3) the aged and very young, with caution; (4) migraine headache; potent analgesic drugs are unphysiological but occasionally are needed.

In Table XLIII an attempt has been made to summarize concisely the data presented in the many individual monographs. The drugs are listed in the order of analgesic effectiveness. Where figures are given they are doses in mg; otherwise, comparisons are made with morphine (M) or codeine (C). The data as given for the antitussive, antispasmodic, and sedative action do not reflect the extent to which practical use is being made of these therapeutic effects. For example, methadone, although having no doubt a strong cough-depressing effect, is in most countries not widely used as an antitussive.

It is quite clear that the alternative of Robsom & Nissim (1949) is being built up, a wide variety of analgesic agents (and antitussives) being available with varying potency and a good deal of variation in side-action liability. It is noteworthy that many of the side-effects of natural and synthetic morphine-like analgesics are antagonized and their physical dependence symptoms unmasked or precipitated by substances like nalorphine and levallorphan. The non-addicting analgesic has not been found, except in so far as nalorphine meets this condition, and it has been pointed out that the side-actions of this drug make its common use impracticable.

Special Uses

Premedication

Morphine is the time-honoured pre-anaesthetic medication, commonly combined with scopolamine or atropine—the latter preferably, it is said, in elderly individuals and the very young, so that one must suppose a general belief in additive sedative effects of morphine and scopolamine. Morphine owes its value as a premedicant to its sedative action, to its ability to relieve anxiety, and only to a lesser extent to its analgesic action. Consequently the value of other morphine-like agents in premedication will depend upon their relative sedative and calming actions rather than upon their pain-relieving properties. Respiratory depression is the side-effect of greatest importance as a disadvantage to the use of a substance in premedication

TABLE XLIII.

Drugs in order of analgesic effectiveness	Analgesic effect		Antitussive action	Antispasmodic action
	potency *	duration		
Oxymorphone	1–2	Like M		
Desomorphine	1–2	< M		
Levorphanol	2–3	Like or > M		
Hydromorphone	2.5–5	< M	Good	
Metopon	3–6	Like or < M		
Racemorphan	5	Like or > M		
Heroin	5–10	< M	Good	
Ketobemidone	7.5	Like M		
Methadone	10	Like or > M	Good	
l-Isomethadone	10	Like M		
Oxycodone	10	Like or < M	Good	
Properidine	ca 10			Sometimes
Nalorphine	10–15	< M		
Trimiperidine	10–20			Sometimes
Thebacon	> 10	Like M	Good	
Hydrocodone	> 10	Like or < M	> C	
Phenadoxone	> 10	< M		
Alphacetylmethadol	10–50	> M		
Dipipanone	20–25	Like M		
Anileridine	25–30			
Dihydrocodeine	> 30 (*14*)	< M	Good	
Alphaprodine	40–60	< M		Sometimes
Ethylmethylthiambutene	> 50	Like or < M		
Pethidine	100	< M	Little or none	Sometimes
Propoxyphene	(*16*)	Like or < M		
Ethoheptazine	(*18*)	Like C		
Pholcodine	(*17*)		Like or > C	
Normethadone	(*19*)		Good	
Myrophine	(*20*)	Like or > M		
Dextromethorphan			Like or > C	

* Mg equivalent to 10 mg of morphine, unless otherwise stated.

** Mg equivalent to 50 mg of morphine in addiction sustaining potency, from Eddy, Halbach & Braenden (1956).

M = morphine; C = codeine.

(*1*) Marked in post-addicts; not reported in clinical trials.

(*2*) Considerable, on the basis of limited clinical experience; substitutes completely for other opiates in established addiction.

(*3*) In clinical practice like morphine or less. H. Isbell (personal communication, 1956) judges it to be like heroin in liability to abuse, if it were as generally available.

(*4*) Rapid disappearance of tolerance is particularly noteworthy.

(*5*) Very rapid development of physical dependence has been noted experimentally and clinically. Addicts to other agents very easily switch to ketobemidone. Abstinence is at least as severe as after morphine.

(*6*) Insufficient for pre-operative medication.

(*7*) Would be expected to be like morphine; there is as yet no clinical experience on this point.

(*8*) Nalorphine may have a morphine-like effect initially, but generally is dysphoric, especially if another narcotic has been given previously.

GENERAL SUMMARY

Sedative action	Euphoric effect	Respiratory depression	Other side-effects	Addiction liability	
				physical dependence potency **	clinical judgement
Like M	(1)	Like or > M	Like M	5	(2)
Like or > M	Like M	Like M	< M	10	Like M
< M	Like or < M	Like M	Like or < M	7.5–25	Like M
> M	Like or > M	Like M	Like or < M	7	(3)
< M	< M	Like M	< M	7	Like or < M (4)
< M	Like or < M	Like M	Like or < M	15–50	Like M
Like M	> M	Like or > M	Like or < M	18	> M
Like M	> M	Like M	Like or < M	50	> M (5)
< M (6)	< M	Like M	Like M	12	Like or < M
< M	< M	Like M	< M	18	(7)
Like M	Like M	Like M	Like or < M	66	Like M
Like M		Like M	< M		(9)
< M	(8)	Like M	> M	None	
					(9)
< M	> C	> C	Like C	60	Like or < M
< M	< M	> C	Like C	> 50	> C
Like M	Like M	Like of > M	Like or > M (10)	< 60	Like or < M
Like M	Like M	Like M	Like or > M (11)	15–50	(12)
< M	< M	Like M	< M	50	(13)
				150	(9)
< M	< M	Like M	< M	175	> C
Like M	< M	Like or < M	< M	> 75	(15)
< M	Like or < M	< M	Like M	50	Like M
Like M	Like M	Like or < M	Like M	> 120	Like M
< M	Almost none	< M	Like or < C	> 400	(17)
Like C	None	< M	Like or < C	None	
< C	None	< M, > C		None	(17)
Like C	Like or > C		Like or > C	50	< M, > C
< M	None	None	None	None	
< C	None		< C	None	

(9) Not determined; chemical and pharmacological similarity to pethidine would presume similar addiction liability.

(10) A very narrow margin between analgesic and toxic doses has been reported. Collapse-like symptoms can occur.

(11) Repeated subcutaneous doses of α-*l*-acetylmethadol have produced serious central depression. Side-effects with oral doses of the racemate are like those with morphine.

(12) Presumed to be like methadone. Addiction-sustaining effect is very prolonged.

(13) Presumed to be like methadone.

(14) Equivalent dose calculated to be about 70 mg. Optimal dose for moderate pain 30 mg, and at that dose side-effects are minimal.

(15) Recommended for acute use only. No evidence on prolonged administration.

(16) Never equivalent to morphine; equivalent to codeine mg for mg for mild to moderate pain.

(17) Substantially less than codeine.

(18) Never equivalent to morphine; 100 mg about equivalent to 60 mg of codeine for mild to moderate pain.

(19) Used as an antitussive only, admixed with Suprifen, in the preparation Ticarda.

(20) Substantially less than morphine.

since it may become additive with the effect of agents used subsequently for anaesthesia.

The more potent morphine derivatives have been found generally satisfactory for premedication. Lee (1942) and Schürch (1945) said that desomorphine was adequate for this purpose in spite of its briefness of action. Heroin and hydromorphone have been used to a considerable extent (see page 607 for reports on the latter), though their greater respiratory depressant action may be disadvantageous. This has not seemed to be too evident, however, with hydromorphone. Metopon is a notable exception. Lee (1942) reported that all too frequently, in 16 of 66 cases, where metopon was used prior to nitrous oxide/oxygen/ether anaesthesia, respiratory depression became so marked as to cause the anaesthetist concern for his patient. Lee thought metopon was definitely contra-indicated for premedication.

Methadone particularly, and those of its derivatives which have been tried, appear to be significantly inferior to morphine for pre-anaesthetic medication. (See page 627 for a discussion of the sedative effect of methadone.) Phenadoxone would be contra-indicated because of the narrow margin between its analgesic and potentially toxic doses. Pethidine, on the other hand, has been very commonly used for premedication before both general and local anaesthesia, with results usually reported to be satisfactory (see page 735). Its calming effect and the sense of well-being which it engenders are quite adequate for this purpose in most cases. Alphaprodine (page 790) and ketobemidone (page 818) have been similarly used with, for the most part, similar results, though relative to potential respiratory depression ketobemidone appeared to be inferior to morphine in sedative action (Linder & Vollmar, 1950).

Racemorphan and levorphanol, while perhaps somewhat inferior to morphine in sedative action, have been used satisfactorily for premedication (see pages 671 and 681). The difference in sedative action is not great enough here to be a disadvantage.

In general, morphine and its more potent derivatives (except metopon), members of the morphinan series and members of the pethidine series may be used more or less interchangeably for premedication, but methadone and its derivatives are unsatisfactory.

Supplementation of general anaesthesia

Many analgesics have been tried for supplementation (codeine, morphine, heroin, methadone, phenadoxone, ketobemidone), but those which have been used to the greatest extent are pethidine, alphaprodine alone and with levallorphan and levorphanol. Meals (1948) found morphine too depressant to respiration, pethidine not very effective but codeine remarkably successful. Codeine reduced the amount of thiopentone required by one-third and recovery time from hours to minutes. Mushin (1951) found

codeine as satisfactory as pethidine but not better and Brown (1953) also concluded that it had no advantages (over pethidine). Investigators generally have considered morphine too depressant to respiration but it might be mentioned that its use with an antagonist has not been exploited. Mushin (1951) reported that heroin, methadone and phenadoxone also were too depressant to respiration. and the narrow margin between safe and toxic doses of phenadoxone would seem to contra-indicate its intravenous use. Neff, Mayer & Thompson (1950) also said that methadone was too depressant and that while initial trials of ketobemidone were satisfactory, on account of respiratory depression produced by comparable analgesic doses, this drug possessed no significant advantage over pethidine.

Siker (1956) has recently reviewed the use of analgesic supplements to nitrous oxide anaesthesia with some very pertinent conclusions. He points out that these supplements are valuable because they " work ", but that the main difficulty in their exact appraisal is the lack of means to measure accurately how successfully they attain the goals sought. These goals appear to be safe production of adequate planes of anaesthesia and rapid post-anaesthetic recovery without post-operative restlessness. Measures which have been used to compare one analgesic with another in supplementation are: (1) the mg per minute of thiopentone used during maintenance of anaesthesia (Wolfers, 1953; Siker et al., 1954; Foldes et al., 1955); (2) the percentage of patients reacting at the end of the operation (Brotman, Cullen & Wilkins, 1950; Wolfers, 1953; Siker et al., 1954; Foldes et al., 1955; Lancaster & Levin, 1956); and (3) the duration of post-anaesthetic analgesia (Brotman, Cullen & Wilkins, 1950). The following figures have been reported for mg/min. of thiopentone used with different analgesic supplements:

		No analgesic	*Pethidine*	*Alphaprodine*	*Alphaprodine + levallorphan*
Wolfers (1953)		12.0	6.4		
Siker et al. (1954) Foldes et al. (1955)	No relaxant		20.0	9.8	4.1
	Relaxant for intubation		14.0	8.4	3.8
	Relaxant for maintenance		12.0	6.4	8.4

The figures reported for reactivity at completion of operation are shown in Table XLIV.

According to either measurement, alphaprodine plus levallorphan would seem to rate best. Neff, Mayer & Thompson (1950) and Siker (1956) have pointed out that with added experience the trend has been to diminish the dose of the supplement. and Siker quite properly says that:

" Only when more precise methods for measuring the effects of these supplements during anaesthesia are found, however, will we have an idea of their proper role in anaesthesia, whether one drug is preferable to another, or whether they need be used at all."

TABLE XLIV. PERCENTAGE OF PATIENTS REACTING TO AUDITORY AND TACTILE STIMULI AT COMPLETION OF OPERATION, WITH VARIOUS SUPPLEMENTS TO GENERAL ANAESTHESIA

Author	Criterion	No analgesic	Pethidine	Alphaprodine	Alphaprodine + levallorphan	Morphine	Levorphanol
Wolfers (1953)	Before leaving operating room	32	56				
Brotman, Cullen & Wilkins (1950)	On return to ward		28			31	39
Siker et al. (1954) and Foldes et al. (1955)	Within 5 minutes of completion of surgery:						
	No relaxant		53	77	98		
	Relaxant for intubation		59	87	94		
	Relaxant for maintenance		60	84	95		
Lancaster & Levin (1956)	In operating room			47			

Obstetric analgesia

There is no doubt that the view is widely held that morphine with or without scopolamine has too much of a depressant effect on the infant to be a safe obstetric analgesic. The same should apply to most morphine derivatives. Hydromorphone and heroin are at least as depressant relative to analgesic action. Pennell [a] reported satisfactory use of metopon by oral or rectal administration but too much depression of the foetus when the drug was given intramuscularly. Snyder,[b] on the basis of experimental studies, judged desomorphine to have less effect on the labour mechanism and less effect on the foetus than morphine or many other analgesics which he had tried. Perhaps its intense but brief analgesic action is the decisive factor. Snyder has strongly recommended its clinical trial. Most recently, J. D. Myers [c] has reported on the use of dihydrocodeine in a small group of normal labours, with adequate analgesia in almost all and with less effect on the foetus than with pethidine. The difference is great enough to warrant further trial of dihydrocodeine in obstetrics.

Where methadone has been tried for obstetric analgesia it has generally produced too much delay in initiation of respiration in the infant (see

[a] Thesis, St. Louis University School of Medicine, 1949
[b] Personal communication, 1954
[c] Personal communication, 1957

page 628). Perhaps the lesser effect of the drug in calming anxiety, noted in connexion with premedication, tending to augment the amount of drug used, is a significant factor.

Pethidine and some of its derivatives have been and are being very widely used in obstetrics. Pethidine has been discussed at length (page 748). It is clear that it is not without influence on the infant and this depressant effect is increased when scopolamine is also used. The depressant effect of pethidine, however, when used in moderation, appears to be less than that of morphine and its equipotent derivatives. Pethidine seems to facilitate dilatation of the cervix and may shorten labour but it can also interfere with uterine contractions at least temporarily. Alphaprodine has been used less frequently than pethidine in obstetrics, generally with a satisfactory analgesic effect, with no more and perhaps less effect on the labour mechanism and the infant. It is more rapid in its action, and somewhat less lasting, both qualities being useful in obstetric analgesia.

Levorphanol has been used little, if at all, in obstetrics, probably for fear of its having a profound effect on the foetus on account of its potency. Nalorphine has been used successfully to combat foetal depression due to morphine-like obstetric analgesia and it is probable that its wider use would increase the safety of these agents and allow the mother to have greater pain relief. Levallorphan could, of course, be similarly used. Also the successful use of levallorphan with analgesic supplementation of nitrous oxide/oxygen anaesthesia suggests the possibility of its similar use in obstetrics.

Antitussive therapy

As Table XLIII (pages 852-853) shows, one-third of the 30 drugs covered by the monographs in the second part of this study are capable of relieving cough to an extent sufficient to be exploited, but not all of them are being used therapeutically for this purpose. Reasons preventing the practical application are various. A high risk of addiction, as is connected with heroin and oxycodone, should preclude their use as antitussives. This risk is certainly not outweighed by the lower degree of certain undesired side-effects as compared with morphine, nor by their less frequent occurrence. Hydromorphone, although having four times the antitussive potency of morphine and comparatively fewer side-effects, is no longer widely used against cough. Whether this is due to its pronounced sedative action or to its previously favoured use in cases of tuberculosis cannot be said. Undesirably strong sedative or other side-effects may be the reason that methadone is not being exploited in this respect, although it is dose for dose a stronger antitussive than morphine.

In the remaining group of antitussives of morphine type, a clear distinction can be made between those with addiction-producing properties

(codeine, dihydrocodeine, hydrocodone, thebacon, normethadone) and those with very low addiction liability (pholcodine) or none at all (dextromethorphan). In this respect, the latter substance is joined by narcotine (noscapine), an opium alkaloid of isoquinoline type with good antitussive but no analgesic action which, therefore, was not included in the second part of the present study. A group of non-addicting morphine-like antitussive agents being available, the question arises whether any of the above-mentioned substances possesses properties which justify wide use as an antitussive in spite of their inherent capability of producing addiction.

With dihydrocodeine (see page 576), the nature and degree of undesirable side-effects appear to be approximately the same as with codeine or greater. Whereas the situation regarding therapeutic effectiveness, side-effects, and addiction liability is similar for codeine and dihydrocodeine and, with regard to respiratory depression, perhaps somewhat in favour of the latter, this is not so with hydrocodone (see page 595). Its side-effects are negligible in therapeutic dosage, but it is much more addicting than codeine, although the risk of addiction may be less when given orally and when its dose is restricted to the small amount recommended for cough relief. Similarly, thebacon (see page 838) has a high antitussive effectiveness and mild side-effects, in particular with regard to constipation—advantages which are outweighed by an addiction liability approaching that of morphine. It has been noted that methadone (see page 627), although having strong cough-relieving properties, is little used in practice as an antitussive. On the other hand, normethadone (see page 652), which is chemically in close relation to methadone, is being employed exclusively for cough relief. Its good antitussive effect, together with its practical lack of side-effects, is, however, accompanied by addictive properties equalling those of morphine, which are not diminished by the addition of a centrally stimulating sympathicomimetic substance, as, for example, in the antitussive preparation Ticarda.

Centrally acting antitussives without addictive potency and other undesirable side-effects are pholcodine (see page 831), dextromethorphan (see page 689), and narcotine. It is noteworthy that the latter two are also devoid of any analgesic potency. Pholcodine has a very low analgesic and addiction-producing potency, both under the level of those of codeine and thus without practical importance. Whereas pholcodine depressses the respiratory system a little more than codeine, dextromethorphan does not influence the respiration nor do therapeutic doses of narcotine, for which it has been shown in animals (Van Dongen, 1940) that the respiration can even be stimulated by large doses. In view of the well-known over-all stimulant action of narcotine on the central nervous system, the discovery in animals of an antitussive effect of the same order as codeine (Winter & Flataker, 1954; Konzett, 1955) was surprising, even though as early as 1851 an antitussive effect in the cat had been described by Hinterberger

(see Krueger, Eddy & Sumwalt, 1943). In experimental cough in man (Bickerman et al., 1957), the antitussive effect of narcotine was found to be of the same magnitude as that of codeine. H. A. Bickerman[a] administered narcotine orally to 37 ambulatory patients with chronic cough (bronchiectasis or chronic bronchitis associated with asthma). While the dose of 15 mg was obviously too low, 30 mg were more effective than 15 mg of codeine. Most patients preferred narcotine to the latter drug, the side-effects of 30 mg of narcotine being minimal whereas they increased materially if the dose of codeine was increased from 15 mg to 30 mg.

The question arises whether the antitussive potency of morphine-like substances is accompanied by a general sedation or a respiratory depression in particular. There seems to be some parallelism of cough relief and general sedation in the cases of hydromorphone, heroin, oxycodone, hydrocodone, and dihydrocodeine. Thebacon, methadone, and normethadone would seem to have a relatively lower centrally sedative action as compared with their antitussive effectiveness. In pholcodine the sedative action is distinctly inferior to the antitussive, whereas dextromethorphan lacks any sedation and the central effects of narcotine, if any, are of a stimulating nature. Thus, in the last group the absence of sedation is to be considered an additional advantage to the absence of addiction. The relation between antitussive action and respiratory depression appears to be similar to that between antitussive and centrally sedative action, except in the case of pholcodine, which depresses the respiration more than codeine. While for dextromethorphan respiratory effects have not been particularly mentioned, narcotine has been found to have in animals a stimulating effect, if any, on respiration.

As to the route of administration, it may finally be mentioned that preferences among the enumerated antitussive agents do not exist. All of them can be given orally and the aforementioned data and comparisons are based on oral doses.

Addiction Liability

In the main, the order of addiction-sustaining potency, in terms of the dose of the compound which is equivalent to a standard dose of morphine for the purpose, is the same as the order of analgesic potency. However, clinical impressions of addiction liability under conditions of therapeutic use do not always correspond. Heroin and ketobemidone, for example, in clinical practice have given evidence of developing physical dependence rapidly and are judged to be more liable to produce addiction than morphine. Methadone, on the other hand, which has a strong addiction-sustaining potency and a prolonged action in this respect, may be less likely to develop

[a] Personal communication, 1957

dependence under conditions of therapeutic use. H. Isbell[a] has pointed out the difficulties of reducing addiction potentiality of a drug to a single quantitative figure or even to a single rating statement. Too many variables are involved, such as the quality of the euphoric effect induced, the speed of onset and duration of that effect, the presence or absence of side-effects regarded as desirable or undesirable by the addict, the ability to suppress abstinence, the intensity of the abstinence syndrome at its peak after withdrawal, the duration of the abstinence syndrome, and the ability to continue using the drug either intravenously or subcutaneously. Furthermore, these qualities cannot be expressed in terms of dose without giving a false impression. An addict is just as satisfied with the euphoria induced by 30 mg of morphine as he is with the euphoria induced by oxymorphone at a tenth of that dose. Isbell mentions methadone and phenadoxone to illustrate his points in contrasting fashion. Methadone induces a marked euphoria in the post-addict, which, although it appears on subcutaneous injection more slowly than after morphine, persists for a longer time. Methadone suppresses abstinence completely. Nalorphine in the presence of methadone addiction precipitates a very severe abstinence syndrome. Abstinence intensity after abrupt withdrawal of methadone is low at its peak, but the abstinence syndrome is prolonged. Methadone rates low on one point only, intensity of the withdrawal phenomena. Therefore, its over-all addiction liability is high. Phenadoxone, on the other hand, induced marked euphoria of brief duration after intravenous injection but not when given subcutaneously in much larger dosage. Small single doses suppressed morphine abstinence markedly but very briefly. Attempts at direct addiction were followed by little or no abstinence phenomena on abrupt withdrawal of the drug, probably because it was not possible to maintain a schedule of injection of every hour or less throughout the day. Therefore, in spite of the high euphoric effect on intravenous injection and the marked but brief suppression of abstinence, phenadoxone must be rated as having a low over-all addiction liability.

Isbell has constructed a table of ratings of the various points which participate in addiction potentiality and from these ratings has arrived at a judgement of over-all addiction liability (see Table XLV).

In comparing the estimates of over-all addiction liability as stated in Table XLV with clinical impressions of addiction liability as stated in Table XLIII, it should be borne in mind that the former are based on experiments on post-addicts and the latter are the result of use of the substances in chronic disease. Undoubtedly, the former reflect the liability to abuse of the compounds so far as they may be available to an addict and foretell the possibility of addiction under conditions of prolonged administration. They do not necessarily express quantitatively the likelihood of addiction

[a] Personal communication, 1957

Drugs in order of analgesic effectiveness	"Euphoric" potency			Ability to suppress abstinence	Intensity of abstinence after nalorphine	Intensity of abstinence after abrupt withdrawal	Duration of abstinence after abrupt withdrawal	Over-all addiction liability
	quality and intensity	speed of onset	duration					
Oxymorphone	VS	Im	L	H				H
Desomorphine	S	F	Sh	H		Im	Im	H
Levorphanol	VS	Im	Im	H				H
Hydromorphone	VS	F	Im	H	H	H	Im	H
Metopon	Im	Im	Sh	H		Im	Im	H
Heroin	VS	F	Sh	H	H	H	Im	H
Ketobemidone	VS	F	Im	H		H	Im	H
Methadone	VS	Im	L	H	H	Lo	Lo	H
l-Isomethadone	S	Im	Im	Im		Im	Im	Im
Oxycodone				H		H	Im	H
Nalorphine	0			N		N		N
Thebacon				H		H	Im	H
Hydrocodone	VS	Im	Im	H		Im	Im	Im
Phenadoxone	H (i.v.) 0 (s.c.)	F	Sh	H		N*		L
Alphacetylmethadol	VS	Sl	L	H				H
Dipipanone	VS	Im	Im	H*				H
Anileridine	VS	F	Im	H				H
Dihydrocodeine	VS	Im	Im	H		Im	Im	Im
Alphaprodine	S	F	Sh	Im				Im
Ethylmethylthiambutene	S	F	H	S	H	Im	Sh	Im
Pethidine	S	F	Sh	Im	N (or mild)	Im	Sh	Im
Propoxyphene	P	Sl	Im	Lo	Lo	Lo	Sh	VL
Ethoheptazine	0			N				N
Pholcodine	0			Lo				Lo
Normethadone	S	Im	Im	Im				Im
Myrophine	0			N		N		N
Dextromethorphan	0			N		N		N

0 = No morphine-like effect. P = Poor. Im = Intermediate. S = Satisfactory. VS = Very satisfactory. F = Fast. Sl = Slow. Sh = Short. L = Long.
* = Dose schedule inadequate. VL = Very low. Lo = Low. H = High. N = None.

under conditions of careful therapeutic use, which can be derived only from long clinical experience. It should be emphasized, however, that whenever the tests on post-addicts have shown intermediate or high addiction liability, if the substance has been tried clinically in prolonged administration, evidence of physical dependence (addiction) has become apparent, and sometimes the parallelism in the results of the two types of experience, with heroin and ketobemidone, for example, is very striking. Methadone is a partial exception to parallelism in that primary addiction to it has developed less frequently than one would expect from its prolonged addiction-sustaining action, but it substitutes readily for other addicting substances and many cases of secondary addiction to it have been reported. It is worth noting that two analgesic agents with an effectiveness comparable to that of codeine have been reported; in the tests at Lexington, Ky., one had no addiction liability at all and the other an addiction liability substantially less than that of codeine.

Nalorphine warrants further discussion. It has been shown to be capable of relieving pain, in some circumstances at least as well as morphine. It can produce morphine-like side-effects and sometimes subjective effects which the individual interprets as extremely unpleasant. It is doubtful if physicians generally would subject their patients to the unpleasantness of nalorphine administration. Many patients would say, as many have already, they would rather have their pain. In this connexion, however, Keats & Telford (1957) make a very interesting point. Probably all would agree that desirable or pleasant or satisfying psychic effects facilitate repetition of administration, the first step towards addiction, and Keats & Telford remark that it is illogical to expect pleasant psychic effects without possible development of psychic dependence in some patients. They say that the critical question is, how pleasant can or should a drug be while still avoiding the dangers of psychic dependence. It is possible that psychic dependence can only be avoided through the use of drugs which are not pleasant to the patient. Nalorphine is not pleasant to the patient generally; it has not produced psychic or physical dependence; and it is a non-addicting analgesic, even though its use is impracticable. It is not too much to hope that a nalorphine-like drug may be found which can be used in practical therapeutics.

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RÉSUMÉ

Cette étude est la quatrième d'une série consacrée aux drogues synthétiques à effet morphinique. Dans deux des études précédentes, les relations entre la structure chimique et l'action analgésique, puis entre l'action analgésique et les propriétés toxicomanogènes, ont été envisagées du point de vue expérimental. Cette nouvelle étude examine la situation présente, sur la base d'expériences cliniques, d'après la documentation fournie par la pratique médicale courante, des observations contrôlées faites sur des malades (avec essai comparatif à blanc), et des observations sur des volontaires.

Les auteurs passent en revue 30 médicaments d'importance pratique mis dans le commerce pour remplacer la morphine et la codéine. Ils évaluent leurs avantages thérapeutiques et leurs effets secondaires dont le plus important est la capacité d'engendrer la toxicomanie.