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SYNTHETIC SUBSTANCES WITH MORPHINE-LIKE EFFECT

Relationship between Analgesic Action and Addiction Liability, with a Discussion of the Chemical Structure of Addiction-Producing Substances *

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SYNOPSIS

For compounds of the morphine, morphinan, pethidine, hexamethyleneimine, methadone, and dithienylbutenylamine groups, the analgesic and physical-dependence-producing properties are compared. On the basis of a parellelism in intensity of these properties, conclusions are drawn regarding their interrelationship and the chemical features common to substances with morphine-like addiction liability.

In the report on the sixth session (held in October 1955) of the WHO Expert Committee on Drugs Liable to Produce Addiction, it was said " that morphine, related substances, and synthetic drugs are equally useful for medical needs, and that there is a wide range of potency available among members of each group " and " that synthetic analgesic drugs differ from one another in addiction liability just as do drugs derived from natural substances such as opium; that members of each class must be considered individually with respect to inherent risk and therapeutic advantage; and that the risk of addiction through the use of synthetic drugs is neither greater nor less than the risk encountered through the use of morphine, related opium alkaloids, or substances derived therefrom." [68]

* This is the third 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 ",[6] and the second with " Relationship between Chemical Structure and Analgesic Action ".[5]

The present paper is directly related to these statements since it presents the available data on analgesic potency and addiction liability for all those substances, whether derived from morphine or produced synthetically, which have been evaluated quantitatively with respect to both properties. These data are examined for any possible clues to relationship between analgesic action and addiction liability. Furthermore, chemical structures and their modification which may be related to the production of addiction are reviewed. The question of therapeutic applicability will be discussed in another report.

Addiction to the opiates—to morphine and its derivatives, and to the synthetic analgesics with morphine-like effect—has three components, tolerance, physical dependence, and psychic dependence. The unmistakable proof of addiction to these substances lies in the demonstration of physical dependence, and physical dependence is shown by the development of a typical abstinence syndrome.

There are so far only two sources of information on addiction-producing and addiction-sustaining liability: (1) gradual accumulation of clinical experience after a new agent has been introduced which tells of danger and damage only after the damage has been done; and (2) the work of the National Institute of Mental Health Addiction Research Center at the Public Health Service Hospital at Lexington, Kentucky. In the latter case all observations are made on addicts and post-addicts, and the question has arisen repeatedly of the validity of predictions based on conclusions from work on such a population. There are two major justifications for the work and the conclusions drawn: (1) observations indicating the attractiveness of a new drug for the addict population are pertinent for prediction as to the likelihood of abuse, avoidance of abuse being one of the reasons for narcotics control; and (2) the predictions made to date from the work at Lexington have been fulfilled in clinical experience. This aspect of the problem will be discussed fully in the fourth study of this series.

Given a new drug whose addiction liability is to be determined, four types of experiment are carried out at Lexington:

1. *Single-dose administration for the detection of morphine-like (euphorigenic) effects:*

Starting with small doses based upon previous experience with the drug, the agent is administered to post-addicts by various routes, observations are made for the appearance of morphine-like or other effects, and note is taken of the individual's subjective reactions. The drug is given as an unknown, of course, but the patient is allowed to express his views on it, in comparison with his previous drug experience. He may say, for example, that it is like morphine, even like a certain dose of morphine or of some other drug which he has taken previously.

2. *Single-dose administration for effect on the morphine abstinence syndrome:*

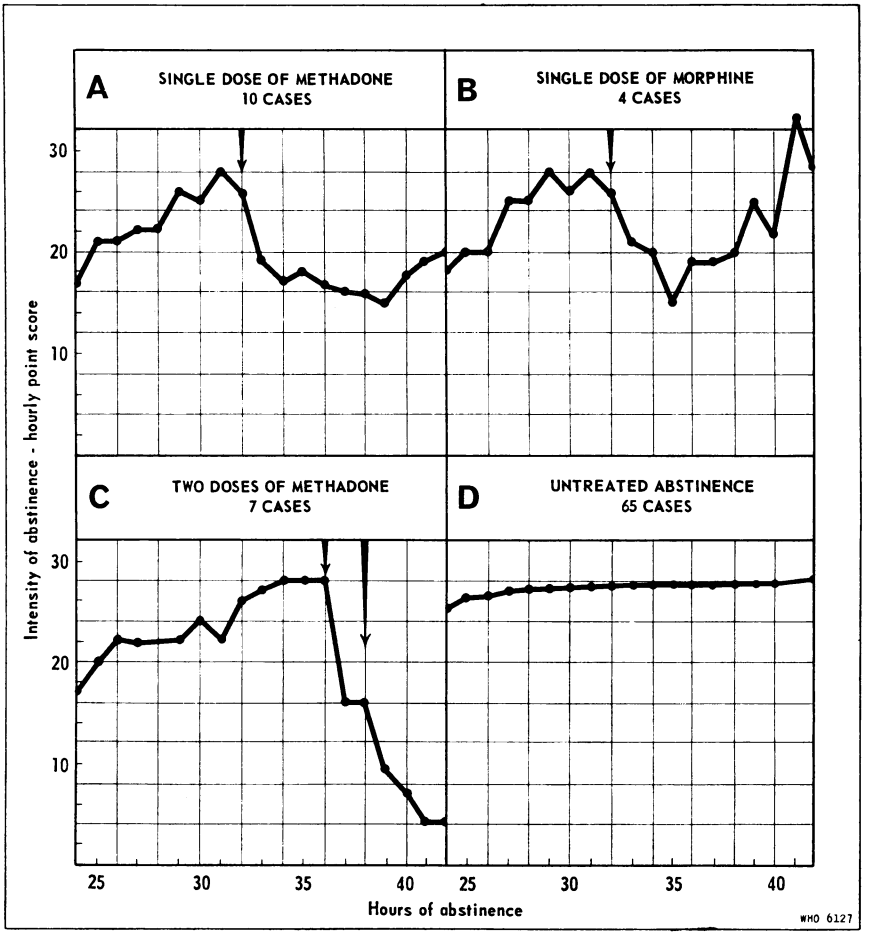
Individuals who have been receiving morphine regularly and who have been stabilized for not less than a week on a daily dosage of 200-300 mg are abruptly withdrawn from the drug. Approximately at the peak of the morphine abstinence syndrome, about the 30th hour of withdrawal, a dose of the experimental substance is administered, subcutaneously or orally. The size of this dose is based upon the morphine-like effects observed in the first experiment. Prior to administration of the experimental substance the abstinence syndrome has been evaluated according to the point-scoring system of Himmelsbach, and this evaluation is continued hour by hour to determine to what extent the new agent is able to suppress the morphine abstinence phenomena. The suppression, if any, is compared in degree and duration to that obtained with a 30-mg dose of morphine (see Fig. 1). In the Himmelsbach point-scoring system, arbitrary values are assigned to the various signs of physical dependence (abstinence phenomena) and the sum of these values as observed in a particular case permits a semi-quantitative estimate of the intensity of the abstinence syndrome. Daily scores of less than 15 are regarded as not significant; scores between 20 and 35 indicate mild, and scores of 50 to 60 severe, abstinence. An hourly point score of 30 would indicate severe abstinence for that particular hour. The signs and symptoms of abstinence and their numerical values, as given by Himmelsbach, [26, 51] based on observations on a large number of men with definite physical dependence (addiction), are shown in Table I.

3. *Substitution for morphine:*

The new drug is substituted for morphine in an individual stabilized on morphine as indicated in the second experiment. An attempt is made to substitute the new drug at such a dose and interval of administration as to maintain the individual's addiction, that is, to prevent completely the appearance of abstinence phenomena, which would otherwise occur because of the cessation of morphine administration. Usually after at least a week of substitution, the substituted drug is abruptly withdrawn and the ensuing abstinence syndrome is evaluated in comparison with the abstinence syndrome after abrupt withdrawal of morphine (see Fig. 2). This affords both a qualitative and a quantitative appraisal of the withdrawal symptoms after the substituted drug.

It should be pointed out that no substance has been found which will significantly suppress morphine abstinence phenomena—or which will substitute for morphine in an established addiction, maintaining the addiction and preventing the appearance of abstinence symptoms—but will not itself produce addiction. Therefore, sustaining, just as well as producing an addiction, defines a compound as addicting.

FIG. 1. RELIEF OF ABSTINENCE FROM MORPHINE BY METHADONE*



A. Average Himmelsbach point score of 10 subjects who received 21 mg of methadone subcutaneously at the 32nd hour of abstinence from morphine

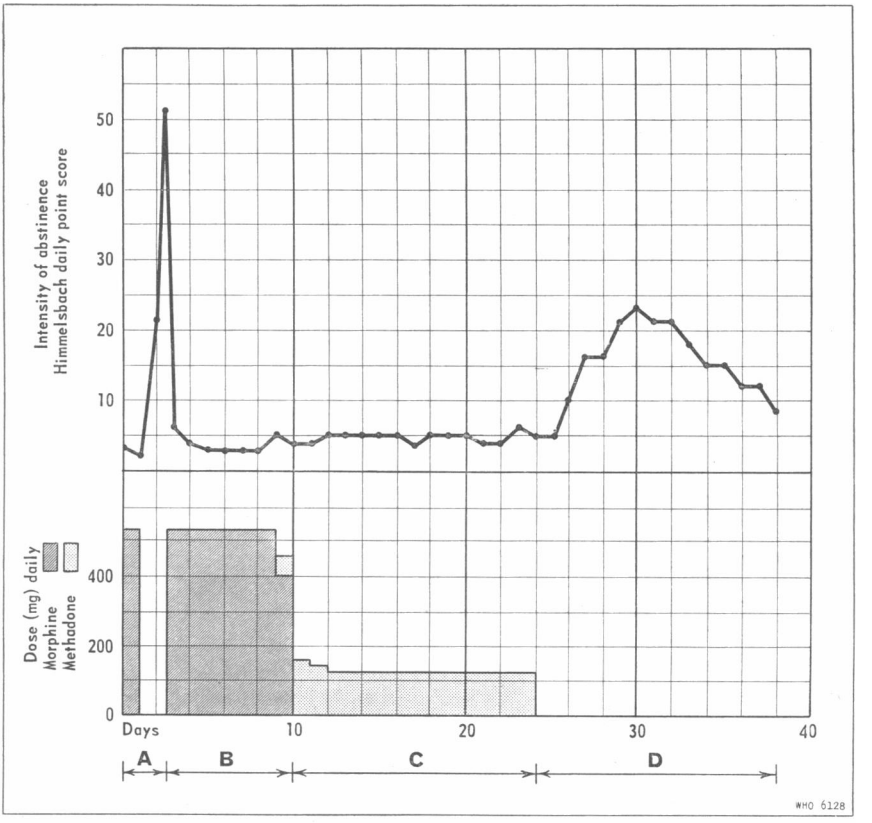
B. Average point score of four of the same subjects, who received 30 mg of morphine subcutaneously at the 32nd hour of a subsequent abstinence from morphine

C. Effect on morphine abstinence of two doses of methadone, given at the 36th and 38th hours of abstinence from morphine

D. Average course of untreated abstinence from morphine

* After Isbell & Vogel,[42] by kind permission of the editors of the *American Journal of Psychiatry*

FIG. 2. SUBSTITUTION OF METHADONE FOR MORPHINE : AVERAGE OF 12 CASES PREVIOUSLY STABILIZED ON MORPHINE *



A. Preliminary withdrawal of morphine
B. Restabilization on morphine
C. Substitution of methadone, 1 mg for each 4 mg of previous morphine dose
D. Withdrawal of methadone

* After Isbell et al.,[43] by kind permission of the editors of the *Journal of the American Medical Association*

TABLE I. HIMMELSBACH SYSTEM FOR SCORING ABSTINENCE SYNDROMES

Signs	*D (by day)*		*H (by hour)*	
	points	*limit*	*points*	*limit*
Yawning	1	1	1	1
Lacrimation	1	1	1	1
Rhinorrhoea	1	1	1	1
Perspiration	1	1	1	1
Mydriasis	3	3	3	3
Tremor	3	3	3	3
Gooseflesh	3	3	3	3
Anorexia (40% decrease in caloric intake)	3	3		
Restlessness	5	5	5	5
Emesis (each spell)	5		5	5
Fever (for each 0.1°C rise over mean addiction level)	1		1	10
Hyperpnoea (for each resp./min. rise over mean addiction level)	1		1	10
Rise in A.M. systolic B.P. (for each 2 mm Hg over mean addiction level)	1	15	1	10
Weight loss (A.M.) (for each lb. from last day of addiction)	1			

The total abstinence syndrome intensity per day or per hour is the sum of the points scored in the " D " or " H " columns, respectively, with due attention to the limits.

4. *Direct addiction:*

The fourth experiment is carried out with new chemical types or with agents likely to come into clinical use. To individuals previously addicted to morphine or related drugs and free of drugs for some months, the new agent is administered regularly around the clock at an interval and dose based upon the experience gained in this respect. The dose is increased as rapidly as possible, if cumulative effects or toxic reactions do not occur. Administration is continued for thirty days or more and is then stopped abruptly. The individual is observed for the appearance of abstinence phenomena, which again are evaluated, hourly at first, according to the Himmelsbach scale, and compared with the abstinence phenomena which occur after a similar period of administration of morphine. Fig. 3 shows a graph of the abstinence syndrome intensity observed after abrupt withdrawal of methadone in individuals addicted to that drug as described, and a graph of the abstinence syndrome after abrupt withdrawal of morphine.

Recently a procedure has been developed at Lexington which, in effect, combines the second and third experiments already described and results in a very great saving of time and clinical material. A group of individuals,

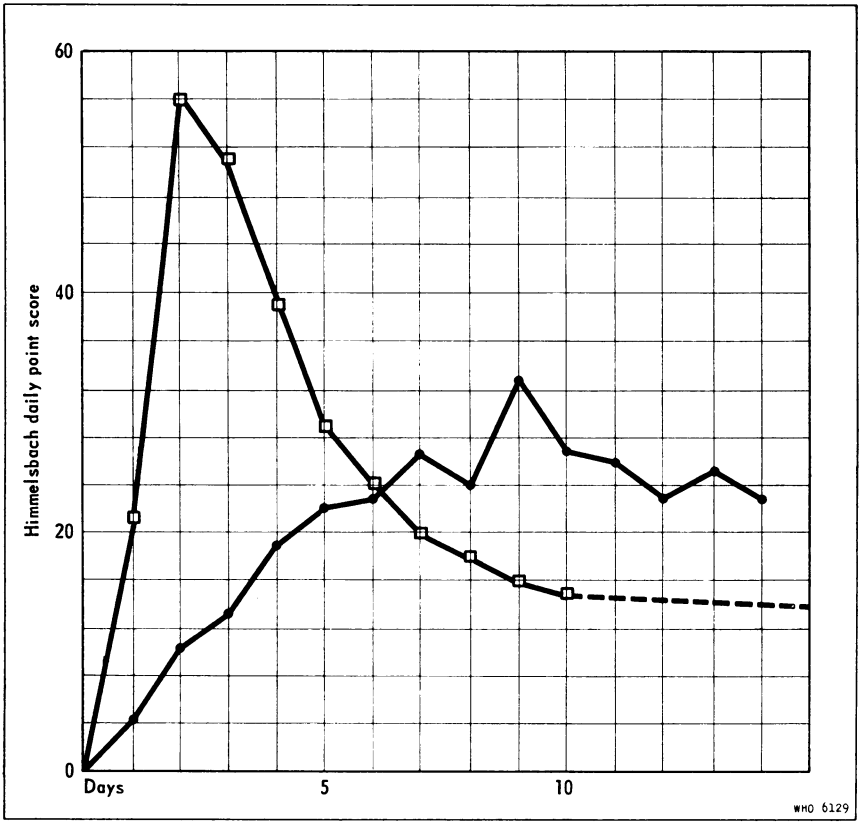
former addicts, usually 10 or 12 in number, receiving regular administrations of morphine are stabilized in the usual way at a daily dosage level of about 240 mg. Beginning with the evening dose and continuing through 24 hours a coded substance—that is, a substance given as an unknown—is administered in place of the regular doses of morphine. Beginning in the morning of the substitution period, 12-14 hours after the last dose of morphine, the individual is observed at regular intervals, the observations being recorded and evaluated according to the Himmelsbach scale for abstinence phenomena. The point scores are tabulated and those for an experimental drug are compared with those obtained for morphine and a placebo, both administered as unknowns in the same way in the same individual. At the end of the 24-hour substitution period the administration of morphine is resumed as before. The same 10 or 12 individuals can be used once a week for a 24-hour substitution test and can, therefore, be their own control by having administered to them in random order morphine, a placebo, and a series of experimental drugs.

If the drug is ineffective the graph of abstinence phenomena will coincide with that obtained after the administration of a placebo. If it is morphine-like in some degree, the graph of abstinence phenomena observed will approximate to that obtained after the administration of morphine during the substitution period or will fall between the morphine and placebo graphs, depending upon the dose used and its potency as a morphine-like agent. Fig. 4, 5, and 6 illustrate the results obtained with some experimental substances, one completely ineffective, the others varying in the intensity of their morphine-like effect.

The observations made at Lexington provide a qualitative and, to some extent, a quantitative comparison of a new substance with morphine in terms of its ability to produce morphine-like effects, to produce the subjective reactions which the addict values, to suppress morphine abstinence phenomena, to substitute for morphine in sustaining a morphine addiction, and, in some instances, to produce a direct addiction (physical dependence and tolerance) in a former morphine addict.

Early in the work at Lexington, Himmelsbach [26] questioned whether a comparison of only the physical dependence effects of two drugs would give a true picture of the relationship of their respective addiction liabilities. He expressed the opinion that comparisons of the relationships of both the physical dependence effects and the analgesic effects of narcotic drugs would be significant and that plotting the intensity and duration of these two facets of a drug's action could give an indication of the likelihood of addiction development in clinical practice. If, in a hypothetical compound, the intensity and duration of the analgesic effect exceeds the intensity and duration of the physical dependence or addictive action, the repeated administration of such a drug only for the relief of pain should be much safer from the standpoint of addiction than if these relationships are reversed.

FIG. 3. INTENSITY OF ABSTINENCE AFTER ADMINISTRATION OF METHADONE COMPARED TO THAT AFTER ADMINISTRATION OF MORPHINE *

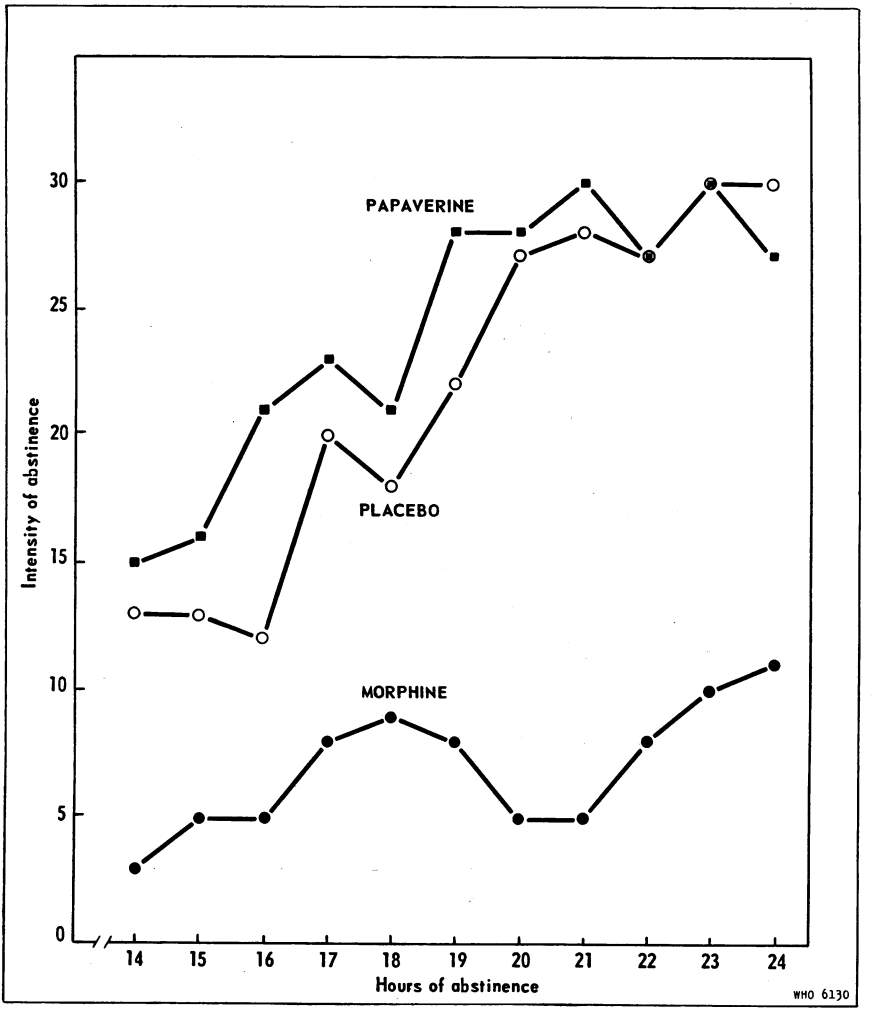


Abrupt withdrawal of methadone after 4½ to 6 months of administration. Average of 5 cases

Abrupt withdrawal of morphine in addictions of long standing and stabilization on morphine for two weeks or more. Average of 65 cases

* After Isbell et al.,[43] by kind permission of the editors of the *Journal of the American Medical Association*

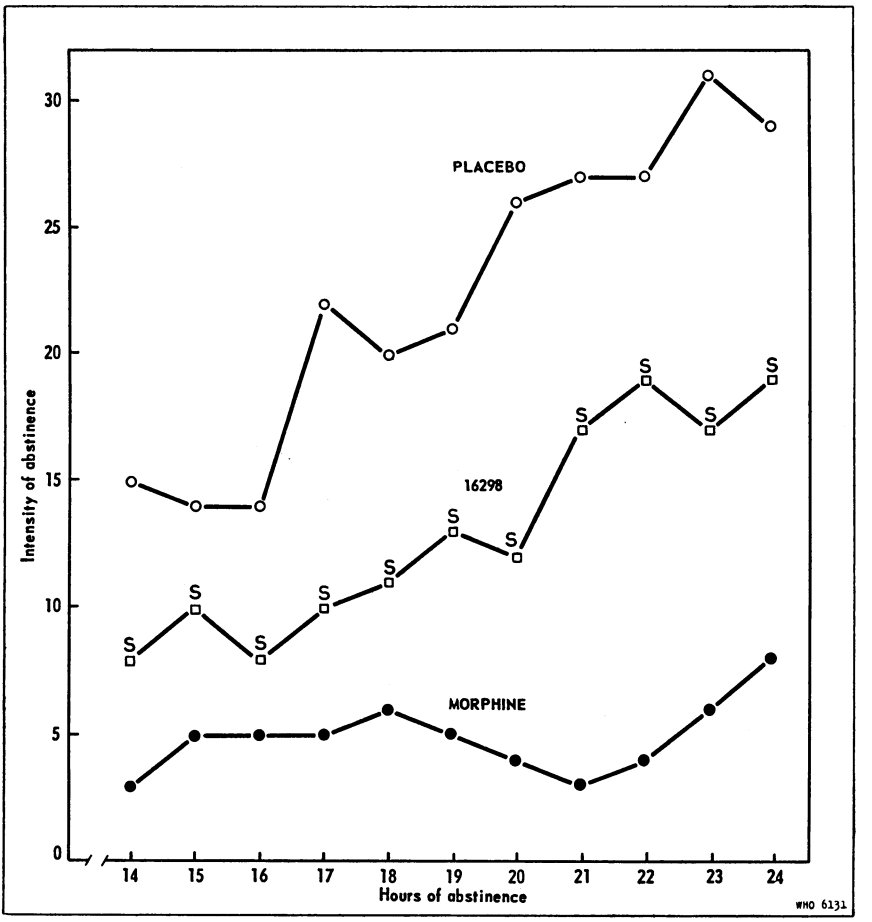
FIG. 4. 24-HOUR SUBSTITUTION IN STABILIZED MORPHINE ADDICTIONS TO TEST SUPPRESSION OF ABSTINENCE SYNDROME*



Papaverine, 50 mg subcutaneously, was administered 6, 14, 18, and 22 hours after last dose of morphine. The same individuals received 50 mg of morphine or a saline placebo at the same time-intervals during other withdrawals. Average of 5 cases.

* From unpublished material, by courtesy of Dr H. F. Fraser

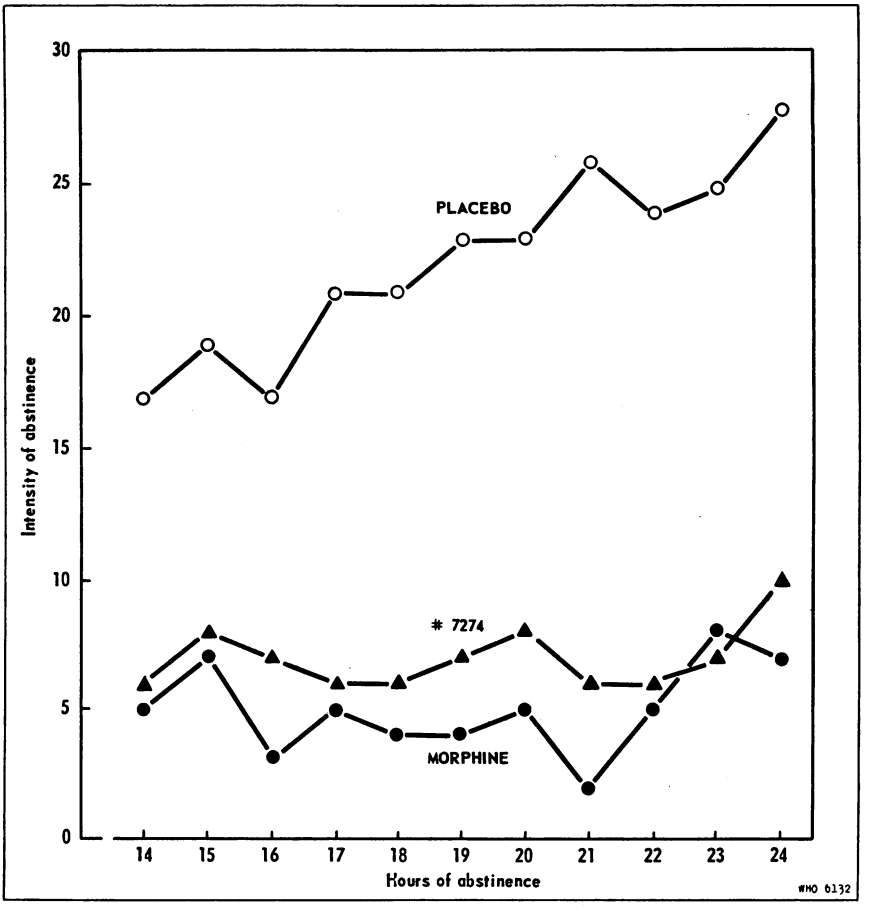
FIG. 5. 24-HOUR SUBSTITUTION IN STABILIZED MORPHINE ADDICTION TO TEST SUPPRESSION OF ABSTINENCE SYNDROME*



dl-1,2-Diphenyl-4-dimethylamino-3-methyl-2-propionoxybutane (code no. 16298), 400 mg orally, was administered every four hours, beginning four hours after last dose of morphine. The same individuals received 40 mg of morphine subcutaneously every four hours or a placebo capsule every four hours during other withdrawals. Average of 11 cases. The letter " S " signifies that the point is significantly different from the corresponding point for the placebo, indicating some suppressive effect on morphine abstinence.

* From unpublished material, by courtesy of Dr H. F. Fraser

FIG. 6. 24-HOUR SUBSTITUTION IN STABILIZED MORPHINE ADDICTION TO TEST SUPPRESSION OF ABSTINENCE SYNDROME*



l-3-Hydroxy-N-phenethylmorphinan (code no. 7274), 1.5, 1.5, 2.0, 1.5, and 1.5 mg subcutaneously, was administered 4, 8, 14, 18, and 22 hours, respectively, after last dose of morphine. The same individuals received 50 mg of morphine or a saline placebo subcutaneously at the same time-intervals during other withdrawals. Average of 8 cases. The curve for 7274 corresponds to that for morphine, indicating that the former substance is about 30 times as potent as the latter in suppressing morphine abstinence.

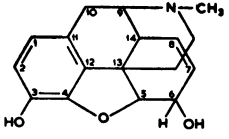
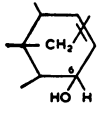
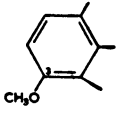
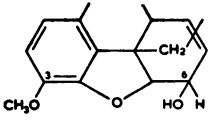
* From unpublished material, by courtesy of Dr H. F. Fraser

Himmelsbach apparently assumes that analgesic and physical dependence actions are independent properties of the drug and that, in the hypothetical case, the latter has waned completely before it is necessary to repeat the drug for pain relief. It is known that it is necessary for optimum development of physical dependence to repeat the administration at regular intervals, the length of which is not necessarily related to the duration of analgesic action. These relative durations of analgesic and physical dependence effects are significant for clinical practice, but are less so with respect to liability to abuse of a drug. For the latter, intensity of morphine-like effect is more important, though persistence of action may make a drug more attractive and extreme shortness of action, even of intense action, may make it less attractive and less liable to abuse because of the cost and difficulty of very frequent injections.

In contradistinction to Himmelsbach's suggestion, many addicted individuals seem to prize the waxing and waning of effect experienced particularly with intravenous administration of the addicting agent, and to get a greater satisfaction from an agent which builds up its effect rapidly, even though that effect may be of only brief duration, than from one which acts more slowly and less intensely even though the effect may be prolonged. The contrast is striking with methadone and diacetylmorphine. The former produces typical morphine-like subjective reactions which come on with only moderate rapidity but may be sustained for 12 to 18 hours. The subjective response to diacetylmorphine, on the other hand, reaches a greater intensity more rapidly but is sustained for a shorter period. Experience at Lexington indicates that many addicts prefer the intenseness of the diacetylmorphine reaction to the prolonged effect of methadone. It may be that a drug which has a long duration of analgesic action and a shorter duration of physical dependence effect is less likely to produce physical dependence in clinical practice because the drug will be repeated in terms of the analgesia produced. It is equally probable that a drug with a short, rapid, intense morphine-like subjective effect is likely to be abused, developing physical dependence rapidly, because it will be repeated at short intervals for its intense effect.

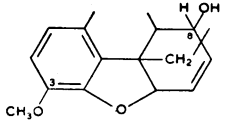
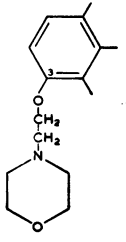
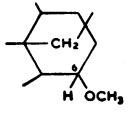
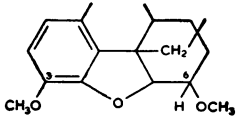
The data available to throw some light on the relationship between analgesic action and addiction liability are shown in Table II, which has been constructed to present the information as precisely as possible and for this reason has been limited to those substances which have been tested at Lexington. The data for morphine and its derivatives and for morphinan, pethidine, hexamethyleneimine, methadone, and dithienylbutenylamine derivatives have been arranged in that order. Besides the names of the compounds, the significant differences in chemical structure, figures for potency and duration of analgesic action and, so far as possible, figures for potency and duration of physical dependence action (addictive action) are included.

TABLE II. QUANTITATIVE DATA ON ANALGESIC EFFECTIVENESS AND ADDICTION LIABILITY

		Analgesic activity		*Physical dependence property*		*Bibliographica references*
		ED_{50} subcutaneously in mice	*duration of effect*	*equivalence to 50 mg of morphine sulfate for maintenance of addiction*	*time from last dose to 50% o peak abstinence intensity*	
		(mg/kg)	*(minutes)*	*(mg)*	*(hours)*	
	Morphine and its derivatives					
	Morphine	2.1	129	50	14.4	11, 26
	α-Isomorphine	3.8	148	40	13.0	*, 27
	Codeine	14.2	67	259 (1)	16.2	*, 29
	Isocodeine	33.8	166	200	18.0	*, 27

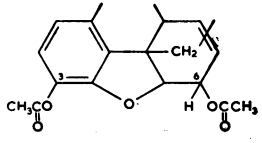
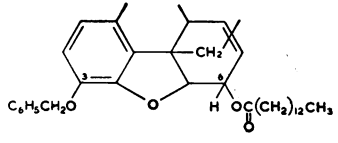
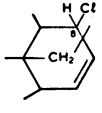
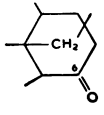
* Eddy, N. B., unpublished results
** Himmelsbach, C. K., unpublished results
*** Isbell, H., unpublished results
**** Fraser, H. F. & Isbell, H., unpublished results
(1) Even at the dose indicated substitution for morphine was not quite complete, mild abstinence symptoms appearing during administration of the substituted drug. Hence addiction-sustaining potency is somewhat less than the stated figure indicates.

TABLE II (*continued*)

	Analgesic activity		*Physical dependence property*		*Bibliographica references*
	ED_{50} subcutaneously in mice	*duration of effect*	*equivalence to 50 mg of morphine sulfate for maintenance of addiction*	*time from last dose to 50% of peak abstinence intensity*	
	(mg/kg)	*(minutes)*	*(mg)*	*(hours)*	
Morphine and its derivatives (*continued*)					
 Pseudocodeine	431.0	145	780	16.0	*, **
 Morpholinylethylmorphine (pholcodine)	176.0	88	>750 (2)		*, 33
 Dihydroheterocodeine	0.5	117	14	7.5	*, **, 65
 Dihydrocodeine methyl ether	3.3	123	72	17.5	*, **, 65

(2) 500-750 mg orally or subcutaneously every 4-6 hours, after abrupt withdrawal of morphine from stabilized addicts, substituted so poorly for morphine that during its administration an abstinence syndrome developed almost as intense as when morphine was abruptly withdrawn without substitution.

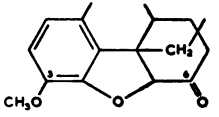
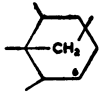
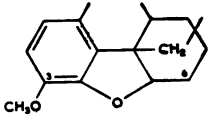
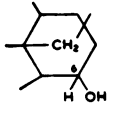
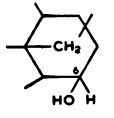
TABLE II (*continued*)

		Analgesic activity		Physical dependence property		Bibliographical references
		ED_{50} subcutaneously in mice	duration of effect	equivalence to 50 mg of morphine sulfate or maintenance of addiction	time from last dose to 50% of peak abstinence intensity	
		(mg/kg)	(minutes)	(mg)	(hours)	
	Morphine and its derivatives (*continued*)					
	Diacetylmorphine	0.9	69	18	7.0	*, 9
	Benzylmorphine myristyl ester	none		(3)		*, 20
	β-Chloromorphide	1.2	77	> 133 (4)	< 10.0	*, **, 65
	Dihydromorphinone (hydromorphone)	0.3	133	7	7.0	*, 27, 49

(3) No morphine-like effect was produced by doses of 25-600 mg orally. Also, 100 mg orally every 6 hours, after abrupt withdrawal of morphine from stabilized addicts, failed completely to substitute for morphine or to prevent the appearance of the morphine abstinence syndrome.

(4) 800 mg/day in 6 doses, administered subcutaneously after abrupt withdrawal of morphine from stabilized addicts, failed to substitute completely for morphine. With smaller amounts and fewer doses per day, abstinence symptoms of moderate intensity appeared during the substitution. After abrupt withdrawal of the substituted β-chloromorphide an abstinence syndrome developed rapidly, reaching 50% of peak intensity within 10 hours.

TABLE II (*continued*)

		Analgesic activity		*Physical dependence property*		*Bibliographical references*
		ED_{50} subcutaneously in mice	*duration of effect*	*equivalence to 50 mg of morphine sulfate or maintenance of addiction*	*time from last dose to 50% of peak abstinence intensity*	
		(mg/kg)	*(minutes)*	*(mg)*	*(hours)*	
	Morphine and its derivatives (*continued*)					
	Dihydrocodeinone (hydrocodone)	3.2	85	> 50 (5)	18.0	*, 16
	Dihydrodesoxymorphine-D	0.18	103	10	4.5	*, 10, 26
	Dihydrodesoxycodeine-D	2.9	90	70	8.5	*, 26
	Dihydromorphine	1.8	154	15	19.2	*, 26
	Dihydro-α-isomorphine	1.7	238	27	18.0	*, 27

(5) Figure is based on direct addiction for 38 days. Subsequent abstinence syndrome milder than would have been expected after addiction to equivalent dosage of morphine, but more severe than after codeine.

TABLE II (*continued*)

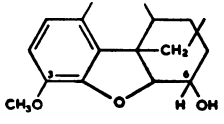
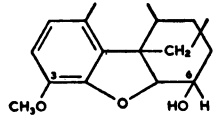
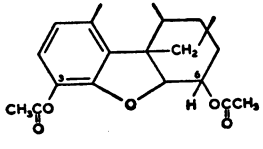
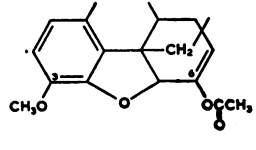
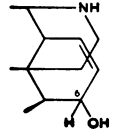
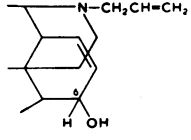
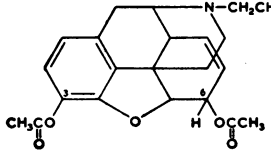
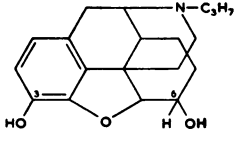
		Analgesic activity		*Physical dependence property*		*Bibliographical references*
		ED_{50} subcutaneously in mice	*duration o effect*	*equivalence to 50 mg of morphine sulfate for maintenance of addiction*	*time from last dose to 50% of peak abstinence intensity*	
		(mg/kg)	*(minutes)*	*(mg)*	*(hours)*	
	Morphine and its derivatives (*continued*)					
	Dihydrocodeine	12.4	130	175	24.0	*, 27
	Dihydroisocodeine	11.1	147	194 (1)	13.0	*, 27
	Diacetyldihydromorphine	1.6	153	25	17.5	*, **, 65
	Dihydrocodeinone enol acetate	1.3	89	60	24.0	*, **, 65

TABLE II (*continued*)

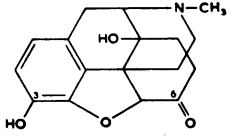
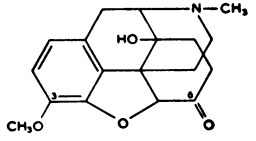
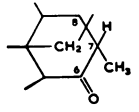
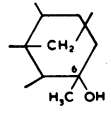
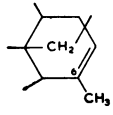
		Analgesic activity		*Physical dependence property*		*Bibliographical references*
		ED_{50} subcutaneously in mice	*duration of effect*	*equivalence to 50 mg of morphine sulfate for maintenance of addiction*	*time from last dose to 50% of peak abstinence intensity*	
		(mg/kg)	*(minutes)*	*(mg)*	*(hours)*	
	Morphine and its derivatives (*continued*)					
	Normorphine	38.3	161	(6)		*, ***
	N-Allylnormorphine (nalorphine)	73.0 (7)	96	(8)		*, 19, 35
	Diacetyl-N-allylnormorphine	none		(8)		*, 19
	N-Propyldihydronormorphine	none		(8)		*, 19

(6) 5 mg subcutaneously induced in post-addicts flushing, nausea, and rumbling in the gastro-intestinal tract of brief duration, but did not produce a morphine-like euphoria. It did not suppress morphine abstinence symptoms. The compound was judged to have no addiction liability.

(7) Never completely effective; maximum effect observed was 7 out of 10 animals affected with a dose of 60 mg/kg.

(8) Antagonist to morphine. Will not substitute for morphine, but promptly precipitates a typical abstinence syndrome when administered to addicts stabilized on morphine.

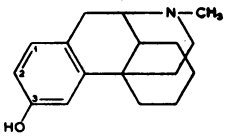
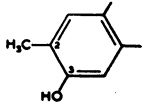
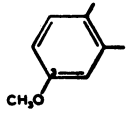
TABLE II (*continued*)

	Analgesic activity		*Physical dependence property*		*Bibliographical references*
	ED_{50} subcutaneously in mice	*duration of effect*	*equivalence to 50 mg of morphine sulfate for maintenance of addiction*	*time from last dose to 50% of peak abstinence intensity*	
	(mg/kg)	*(minutes)*	*(mg)*	*(hours)*	
Morphine and its derivatives (*continued*)					
 Dihydrohydroxymorphinone	0.17	122	5	4.0	*, 20
 Dihydrohydroxycodeinone (oxycodone)	0.6	169	66	14.5	*, **, 20
 Methyldihydromorphinone (metopon)	0.5	156	7	4.5	*, 26
 6-Methyldihydromorphine	5.4	140	>50 (9)	~20.0	*, 16
 6-Methyl-Δ^6-desoxymorphine	0.2	52	6 (10)	<6	*, 34

(9) Single doses of 90-100 mg had less effect on the morphine abstinence syndrome than would have been expected from 50 mg of morphine. After 30 days of direct addiction to 60 mg three times daily, the abstinence syndrome was slightly milder than that after addiction to codeine.

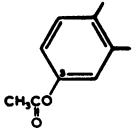
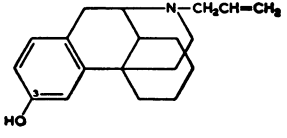
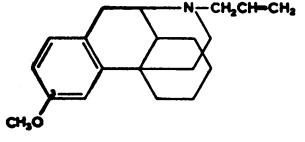
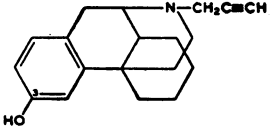
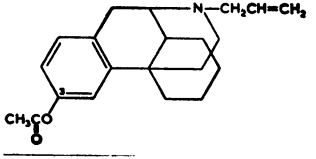
(10) Doses of 6-8 mg caused definite suppression of abstinence symptoms in patients addicted to 70-120 mg of morphine four times daily. A moderate abstinence syndrome followed withdrawal after direct addiction to amounts increasing to 6 mg eight times daily for only 15 days.

TABLE II (*continued*)

		Analgesic activity		*Physical dependence property*		*Bibliographical references*
		ED_{50} subcutaneously in mice	*duration o effect*	*equivalence to 50 mg of morphine sulfate for maintenance of addiction*	*time from last dose to 50% of peak abstinence intensity*	
		(mg/kg)	*(minutes)*	*(mg)*	*(hours)*	
	Morphinan derivatives					
	*dl*-3-Hydroxy-N-methylmorphinan (racemorphan)	0.9	119	>15-<50 (11)	16	*, 16
	l-3-Hydroxy-N-methylmorphinan (levorphan)	0.5	124	>7.5-<25 (12)	16	*, 38
	d-3-Hydroxy-N-methylmorphinan (dextrorphan)	58.2	80	(13)		*, 38
	*l*-3-Hydroxy-2,N-dimethyl-morphinan	9.1	164	>60 (14)	~4.0	*, ***
	d-3-Hydroxy-2,N-dimethyl-morphinan	none		(13)		*, ***
	*dl*-3-Methoxy-N-methylmorphinan (racemethorphan)	8.1	111	43	48	*, 38
	l-3-Methoxy-N-methylmorphinan (levomethorphan)	3.0	136	21.5 (15)	48	*, 38
	d-3-Methoxy-N-methylmorphinan (dextromethorphan)	(16)		(13)		*, 38

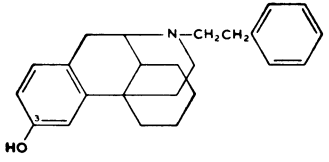
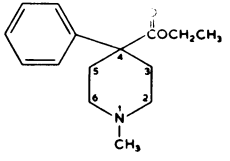
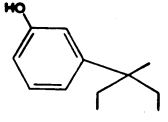
(11) After direct addiction to 15 mg four times daily for 38 days, the abstinence syndrome was less severe but more prolonged than the morphine abstinence syndrome.
(12) Figures are one half the values for racemorphan. Single doses of 14 mg of the *l*-isomer produced dramatic relief of morphine abstinence. Based on this the equivalent figure could be <14.
(13) Does not produce a morphine-like effect in post addicts nor does it suppress the morphine abstinence syndrome. Has no addiction liability.
(14) Doses of 60 mg every four hours suppressed the morphine abstinence syndrome partially.
(15) Figure is one half the value for racemethorphan. A single dose of 22 mg of the *l*-isomer was very effective in suppressing the morphine abstinence syndrome.
(16) Not completely ineffective; 5 out of 16 animals affected at 75 mg/kg.

TABLE II (*continued*)

		Analgesic activity		Physical dependence property		Bibliographical references
		ED_{50} subcutaneously in mice	duration o effect	equivalence to 50 mg of morphine sulfate for maintenance of addiction	time from last dose to 50% of peak abstinence intensity	
		(mg/kg)	(minutes)	(mg)	(hours)	
	Morphinan derivatives (*continued*)					
	*d*-3-Acetoxy-N-methylmorphinan	none		(13)		*, ***
	*l*-3-Hydroxy-N-allylmorphinan (levallorphan)	none		(8)		*, 35
	d-3-Hydroxy-N-allylmorphinan	none		(17)		*, 19
	*l*-3-Methoxy-N-allylmorphinan	none		(8)		*, 19
	*l*-3-Hydroxy-N-propargyl-morphinan	38.9	226	(8)		*, 19
	*l*-3-Acetoxy-N-allylmorphinan	none		(8)		*, 19

(17) Not an antagonist; nor does it produce a morphine-like effecti n post-addicts. Does not suppress the morphine abstinence syndrome and has no addiction liability.

TABLE II (*continued*)

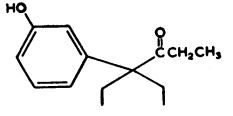
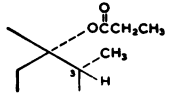
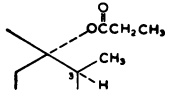
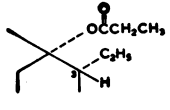
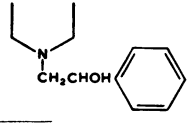
		Analgesic activity		*Physical dependence property*		*Bibliographical references*
		ED_{50} subcutaneously in mice	*duration o effect*	*equivalence to 50 mg of morphine sulfate for maintenance of addiction*	*time from last dose to 50% of peak abstinence intensity*	
		(mg/kg)	*(minutes)*	*(mg)*	*(hours)*	
	Morphinan derivatives (*continued*)					
	*l*-3-Hydroxy-N-phenethyl-morphinan	0.14	124	1.5 (18)		*, ***
	Pethidine and its derivatives					
	1-Methyl-4-phenyl-4-carbethoxy-piperidine (pethidine)	9.9	125	>120 (19)	4.5	*, 28
	1-Methyl-4-(*m*-hydroxyphenyl)-4-carbethoxypiperidine	6.6	100	>500 (20)	<6	*, 32

(18) 24-hour substitution carried out. Five doses in 24 hours substituted completely for morphine see Fig. 6).

(19) Dose indicated would not suppress the morphine abstinence syndrome completely.

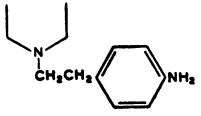
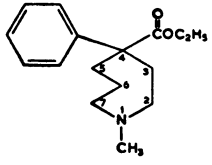
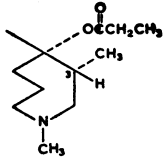
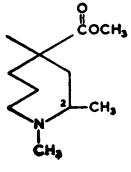
(20) 300 mg administered at the 30th hour of morphine abstinence followed by 500 mg at the 34th hour caused definite suppression of the abstinence syndrome, which, in the case of the 500-mg dose, was nearly as great as would be expected from 50 mg of morphine.

TABLE II (*continued*)

	Analgesic activity		Physical dependence property		Bibliographical references
	ED_{50} subcutaneously in mice	duration of effect	equivalence to 50 mg of morphine sulfate for maintenance of addiction	time from last dose to 50% of peak abstinence intensity	
	(mg/kg)	(minutes)	(mg)	(hours)	
Pethidine and its derivatives (*continued*)					
 1-Methyl-4-(*m*-hydroxyphenyl)-4-piperidyl ethyl ketone (ketobemidone)	1.6	127	50	7.5	*, 32
 *dl*-α-1,3-Dimethyl-4-phenyl-4-propionoxypiperidine (alphaprodine)	1.9	88	>75 (21)		*, 32
 *dl*-β-1,3-Dimethyl-4-phenyl-4-propionoxypiperidine (betaprodine)	0.7	128	35 (22)		*, 32
 *dl*-α-1-Methyl-3-ethyl-4-phenyl-4-propionoxypiperidine (alphameprodine)	1.3	96	35 (22)		*, 32
 1(β-Hydroxy-β-phenylethyl)-4-phenyl-4-carbethoxypiperidine	3.0	110	(23)		****, 59

(21) Doses of 60-90 mg at the 34th hour of morphine abstinence suppressed the abstinence syndrome only partially.
(22) Doses of 50-70 mg at the 30th hour of morphine abstinence suppressed the abstinence syndrome effectively.
(23) 24-hour substitution carried out.

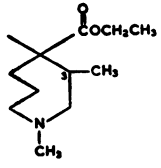
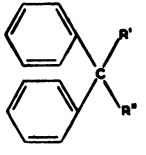
TABLE II (*continued*)

	Analgesic activity		*Physical dependence property*		*Bibliographical references*
	ED_{50} subcutaneously in mice	*duration of effect*	*equivalence to 50 mg of morphine sulfate for maintenance of addiction*	*time from last dose to 50% of peak abstinence intensity*	
	(mg/kg)	*(minutes)*	*(mg)*	*(hours)*	
Pethidine and its derivatives (*continued*)					
 1-[β-(*p*-Aminophenyl)-ethyl]-4-phenyl-4-carbethoxypiperidine	3.1	88	143 (24)		*, ****, 58
Hexamethyleneimines					
 1-Methyl-4-phenyl-4-carbethoxy-hexamethyleneimine	42.6	94	(13)		*, ***
 *dl*-α-1,3-Dimethyl-4-phenyl-4-propionoxyhexamethyleneimine	1.0	103	200 (25)	~3.0	*, ****
 1,2-Dimethyl-4-phenyl-4-carb-methoxyhexamethyleneimine	23.6	73	(13)		*, ***

(24) Despite the difference in the figures this compound isj udged more effective than pethidine. At the dose indicated it suppressed the morphine abstinence syndrome completely, whereas pethidine did not.

(25) 24-hour substitution carried out, 200 mg subcutaneously every 4 hours. The morphine abstinence syndrome was completely suppressed.

TABLE II (*continued*)

		Analgesic activity		Physical dependence property		Bibliographica references
		ED_{50} subcutaneously in mice	duration of effect	equivalence to 50 mg of morphine sulfate for maintenance of addiction	time from last dose to 50% of peak abstinence intensity	
		(mg/kg)	(minutes)	(mg)	(hours)	
	Hexamethyleneimines (*continued*)					
	1,3-Dimethyl-4-phenyl-4-carbethoxyhexamethyleneimine	20.5	87	(13)		*, ***
	Methadone and its derivatives					
	*dl*-4,4-Diphenyl-6-dimethylamino-3-heptanone (methadone)	1.6	70	12	60	43, 56
	l-4,4-Diphenyl-6-dimethylamino-3-heptanone	0.8	80	6	60	37, 56
$R' = COCH_2CH_3$ $R'' = CH_2CH(CH_3)N(CH_3)_2$	*d*-4,4-Diphenyl-6-dimethylamino-3-heptanone	25.7	74	(13)		37, 56
$R' = COCH_2CH_3$ $R'' = CH(CH_3)CH_2N(CH_3)_2$	*dl*-4,4-Diphenyl-5-methyl-6-dimethylamino-3-hexanone (isomethadone)	2.5	97	37	16	37, 56
$R' = CH(OH)CH_2CH_3$ $R'' = CH_2CH(CH_3)N(CH_3)_2$	α-*dl*-4,4-Diphenyl-6-dimethylamino-3-heptanol	18.9	213	>120 (26)		37, 56
	β-*dl*-4,4-Diphenyl-6-dimethylamino-3-heptanol	7.2	84	(13)		36, 56

(26) No morphine-like effects were seen after 100 mg subcutaneously in post-addicts and no suppression of the abstinence syndrome after 60-120 mg at the 28th and 32nd hour of morphine abstinence. However, slow onset of action of this type of compound was not appreciated or taken into account when these tests were done.

TABLE II (*continued*)

		Analgesic activity		Physical dependence property		Bibliographical references
		ED_{50} subcutaneously in mice	duration of effect	equivalence to 50 mg of morphine sulfate for maintenance of addiction	time from last dose to 50% of peak abstinence intensity	
		(mg/kg)	(minutes)	(mg)	(hours)	
Methadone and its derivatives (*continued*)						
$R' = COCH_2CH_3$ $R'' = CH_2CH_2N(CH_3)_2$	*dl*-4,4-Diphenyl-6-dimethyl-amino-3-hexanone	2.5	54	50		12, 41
	α-*dl*-4,4-Diphenyl-6-dimethyl-amino-3-acetoxyheptane	1.2	101	>15-<50 (27)		17, 18, 56
$R' = CH(OCOCH_3)CH_2CH_3$ $R'' = CH_2CH(CH_3)N(CH_3)_2$	α-*l*-4,4-Diphenyl-6-dimethyl-amino-3-acetoxyheptane	1.8	196	33 (28)	> 84	***, 17, 18, 56
	α-*d*-4,4-Diphenyl-6-dimethyl-amino-3-acetoxyheptane	0.3	127	16 (29)		17, 18, 56
	dl-Ethyl 2,2-diphenyl-4-dimethylaminovalerate	18.0	156	>73 (30)		*, 21, 40
$R' = COOCH_2CH_3$ $R'' = CH_2CH(CH_3)N(CH_3)_2$	*l*-Ethyl 2,2-diphenyl-4-dimethylaminovalerate	24.0	120	>73 (31)		*, 21, 40
	d-Ethyl 2,2-diphenyl-4-dimethylaminovalerate	5.4	331	>73 (30)		*, 21, 40

(27) Doses of 15-50 mg at the 28th and 34th hour of morphine abstinence suppressed the abstinence syndrome completely.

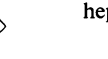
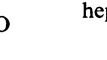
(28) More effective orally than subcutaneously. Smooth substitution for morphine in stabilized addicts was attained by oral administration of one dose daily of 1.0 mg for each 6-8 mg of the morphine stabilization dose. Substitution was also attained by an oral dose of 60 mg every third day with smooth maintenance of addiction. The figure given is that which suppressed abstinence phenomena when one dose was given daily to a patient who had been addicted to 50 mg of morphine four times daily.

(29) Substitution for morphine in stabilized addictions was satisfactory. Patients were returned to morphine without a withdrawal period after the substituted drug.

(30) Up to 73 mg subcutaneously or orally this compound did not induce morphine-like euphoria and did not relieve morphine abstinence symptoms, but did produce pupillary constriction. Its addiction liability was judged to be not greater than that of codeine.

(31) Up to 73 mg subcutaneously or orally this compound did not induce definite morphine-like euphoria, did not relieve morphine abstinence symptoms, and did not produce pupillary constriction. It was judged to have little or no addiction liability.

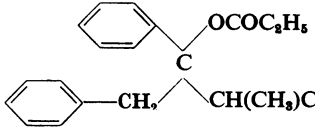
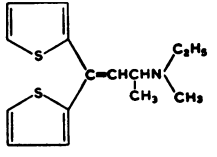
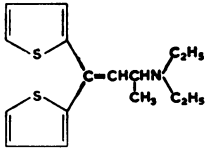
TABLE II (*continued*)

		Analgesic activity		*Physical dependence property*		*Bibliographical references*
		ED_{50} subcutaneously in mice	*duration of effect*	*equivalence to 50 mg of morphine sulfate for maintenance of addiction*	*time from last dose to 50% of peak abstinence intensity*	
		(mg/kg)	*(minutes)*	*(mg)*	*(hours)*	
	Methadone and its derivatives (*continued*)					
$R' = COOCH_2CH_3$ $R'' = CH_2CH_2N(CH_3)_2$	*dl*-Ethyl 2,2-diphenyl-4-dimethylaminobutyrate	9.3	115	>73 (31)		*, 21, 40
$R' = COCH_2CH_3$ $R'' = CH_2CH(CH_3)N$ 	*dl*-4,4-Diphenyl-6-piperidino-3-heptanone	2.0	98	50	(29)	*, ***
$R' = COCH_2CH_3$ $R'' = CH_2CH(CH_3)N$ 	*dl*-4,4-Diphenyl-6-morpholino-3-heptanone (phenadoxone)	1.1	48	<60 (32)	1.0	***, 12
$R' = COOCH_2CH_3$ $R'' = CH_2CH_2N$ 	*dl*-Ethyl 2,2-diphenyl-4-morpholinobutyrate	6.4	109	143 (33)		*, ****
$R' = CH(OCOCH_3)CH_2CH_3$ $R'' = CH_2CH(CH_3)N(CH_3)_2$	*β-d*-4,4-Diphenyl-6-dimethylamino-3-acetoxyheptane	4.6	319	33 (28)	>84	***, 40, 56

(32) 60 mg subcutaneously (or 15 mg intravenously) produced spectacular relief of abstinence when given 28-38 hours after abrupt withdrawal of morphine. The effect, however, lasted only one hour. After direct addiction for 30 days to doses increasing to 35 mg every three hours, abstinence intensity on abrupt withdrawal was not significant, probably because the drug could not be given at sufficiently short intervals.

(33) Substitution dose in only one patient because of delayed toxic reaction (mental confusion). Single doses of 100 and 200 mg at 20 and 20.5 hours after abrupt withdrawa of morphine effectively suppressed the abstinence syndrome, but were also followed by delayed toxic reactions.

TABLE II (*concluded*)

	Analgesic activity		Physical dependence property		Bibliographical references
	ED_{50} subcutaneously in mice	duration of effect	equivalence to 50 mg of morphine sulfate for maintenance of addiction	time rom last dose to 50% of peak abstinence intensity	
	(mg/kg)	(minutes)	(mg)	(hours)	
Methadone and its derivatives (*continued*)					
 *dl*-1,2-Diphenyl-4-dimethylamino-3-methyl-2-propionoxybutane	27.3	328	>400 (34)		*, ***
d-1,2-Diphenyl-4-dimethylamino-3-methyl-2-propionoxybutane	8.3	135	>200 (35)		*, ***
Dithienylbutenylamines					
 3-Ethylmethylamino-1,1-di-(2′-thienyl)-1-butene (ethylmethylthiambutene)	2.4	97	50	(29)	11, 39
 3-Diethylamino-1,1-di-(2′-thienyl)-1-butene (diethylthiambutene)	4.2	80	50	(29)	11, 39

(34) Single doses of 50-400 mg orally did not induce morphine-like effects in post-addicts. 400 mg orally every 4 hours did produce significant reduction in the intensity of the morphine abstinence syndrome (see Fig. 5). The compound was judged to have addiction liability no greater than that of codeine.

(35) Doses of 200 mg orally every 4-6 hours caused definite reduction in the intensity of the morphine abstinence syndrome. Withdrawal after direct addiction to 825 mg daily (divided into three oral doses) was followed by abstinence symptoms milder in degree than those which follow abrupt withdrawal of codeine. Its addiction liability was judged to be less than that of codeine.

The intensity of the analgesic activity is expressed as the ED_{50}, the dose in mg/kg which produces a significant analgesic effect in 50% of the animals (mice) used, and the duration of analgesic action in minutes averaged for all affected experimental animals, under the conditions of a specific laboratory procedure.[11] These data have been selected for the purpose as most comparable because they were obtained by the same procedure in one laboratory. Comparison with analgesic data for man would be better, but comparable figures for man have been obtained under controlled conditions in relatively few instances and any figure for the analgesic effect of a substance in man is too often unavailable. Usually, but not in all cases, the order of analgesic effectiveness in mice and man (see Table III) is reasonably close, though obviously the absolute doses are very different.

TABLE III

Substance	*Analgesic action*				*Physical dependence property*	*Bibliographical references*
	mice		*man*		*man*	
	ED_{50} subcutaneously (mg/kg)	*order of effectiveness **	*equivalence to 10 mg of morphine (mg (total))*	*order of effectiveness **	*order of effectiveness **	
Morphine	2.1	17	10	10-14	12-15	7
Codeine	14.2	25	60-120	26	25	52
Diacetylmorphine	0.9	8-9	3-5	6	8	1,62
Dihydromorphinone (hydromorphone)	0.3	3	2-5	4	3-4	8
Dihydrocodeinone (hydrocodone)	3.2	20	15	15-16	16-17	50
Dihydrodesoxymorphine-D	0.18	2	1-2	2	5	54,61
Dihydrocodeine	12.4	24	30	19-20	23	3
Dihydroisocodeine	11.1	23	30-60	23	24	3
Dihydrocodeinone enol acetate	1.3	12	10	10-14	19	13
Dihydrohydroxymorphinone	0.17	1	1.5	1	1	30
Dihydrohydroxycodeinone (oxycodone)	0.6	6	15	15-16	20	14,48
Methyldihydromorphinone (metopon)	0.5	4-5	3.5	5	3-4	46
6-Methyldihydromorphine	5.4	21	30	19-20	16-17	46

TABLE III (*continued*)

Substance	*Analgesic action*				*Physical dependence property*	*Bibliographical references*
	mice		*man*		*man*	
	ED_{50} *subcutaneously* (*mg/kg*)	*order of effectiveness* *	*equivalence to 10 mg of morphine* (*mg* (*total*))	*order of effectiveness* *	*order of effectiveness* *	
dl-3-Hydroxy-N-methylmorphinan (racemorphan)	0.9	8-9	5-10	8	10	44,45,66
l-3-Hydroxy-N-methylmorphinan (levorphan)	0.5	4-5	2-3	3	7	31,60
d-3-Hydroxy-N-methylmorphinan (dextrorphan)	none	29	none **	29	27-28	63,64
1-Methyl-4-phenyl-4-carbethoxypiperidine (pethidine)	9.9	22	50-100	25	22	52
1-Methyl-4-(*m*-hydroxyphenyl)-4-piperidyl ethyl ketone (ketobemidone)	1.6	13-14	5-15	9	12-15	4,57
dl-α-1,3-Dimethyl-4-phenyl-4-propionoxypiperidine (alphaprodine)	1.9	15	15-60	21	21	2,23,24,55
1-Methyl-4-phenyl-4-carbethoxyhexamethyleneimine	42.6	27	>200	27-28	27-28	22
dl-4,4-Diphenyl-6-dimethylamino-3-heptanone (methadone)	1.6	13-14	10	10-14	6	7
l-4,4-Diphenyl-6-dimethylamino-3-heptanone	0.8	7	4-6	7	2	7
dl-4,4-Diphenyl-5-methyl-6-dimethylamino-3-hexanone (isomethadone)	2.5	19	26-30	18	11	7
l-4,4-Diphenyl-5-methyl-6-dimethylamino-3-hexanone . . .	1.2	11	10	10-14	9	7
dl-4,4-Diphenyl-6-piperidino-3-heptanone	2.0	16	18	17	12-15	3,30

TABLE III (*concluded*)

Substance	*Analgesic action*				*Physical dependence property*	*Bibliographical references*
	mice		*man*		*man*	
	ED_{50} *subcutaneously* (*mg/kg*)	*order of effectiveness* *	*equivalence to 10 mg of morphine* (*mg* (*total*))	*order of effectiveness* *	*order of effectiveness* *	
dl-4,4-Diphenyl-6-morpholino-3-heptanone (phenadoxone)	1.1	10	60	24	18	46
dl-1,2-Diphenyl-4-dimethylamino-3-methyl-2-propionoxybutane	27.3	26	>200	27-28	26	25
3-Ethylmethylamino-1,1-di-(2′-thienyl)-1-butene (ethylmethylthiambutene)	2.4	18	50	22	12-15	15
N-Allylnormorphine (nalorphine)	73.0	28	10	10-14	29	47,51

* In each instance where a range of figures is given, different drugs appear to have the same effectiveness. The numbers indicating the order of effectiveness are different from the order numbers in Table IV, since Table III refers to a smaller number of substances.

** Slomka and associates have reported that the *d*-isomer not only has no analgesic effect in man, but also, administered simultaneously, interferes with the analgesic effect of the *l*-isomer or of morphine.

In Table II, the data on physical dependence potency are expressed in mg as the amount of the drug which produces a suppressive effect on morphine abstinence phenomena, or an addiction-sustaining effect, equal to that of 50 mg of morphine. The figure for duration of physical dependence effect has been derived, as recommended by Himmelsbach,[26] from the observations on the abstinence syndrome which follows abrupt withdrawal of the drug after it has been substituted for morphine. It is the time in hours from the last dose of the drug to the time of occurrence on the graph of abstinence phenomena of 50% of the maximum abstinence intensity. The numerous footnotes to Table II indicate the difficulties of attempting to reduce physical dependence activity to a single figure, and the additional information in the footnotes is taken into account in placing the drugs in their order of effectiveness. All of the data on physical dependence action are derived from observations on post-addicts at the National Institute of Mental Health Addiction Research Center.

To facilitate consideration of the data in Table II in the search for a relationship, a parallelism perhaps, between analgesic effectiveness and addiction liability, two procedures have been tried: (1) calculation of ratios

of effectiveness to that of morphine as 100 with respect to both analgesic and physical dependence activity, and (2) assignment of a number to each compound indicative of its order of effectiveness, the most effective being number 1, the next most effective number 2, etc., again for both analgesic and physical dependence properties (see Table IV).

The ratios are certainly helpful for relating the compounds one to another and to morphine with respect to either property separately, but should not be considered as entirely reliable for direct comparison of the two properties in the same compound, because of important differences in the origin of the two sets of data. The doses for analgesic effectiveness (ED_{50}) are derived from statistical analysis of data obtained in experiments on animals (mice), using a method which gives reproducible results.[11] On the other hand, the doses for physical dependence effectiveness are derived from experiments on man. It was not possible to extend these experiments to the establishment of a precise dose-effect relationship which could be subjected to statistical analysis. Consequently the figures presented cover a great deal of individual variability, but are nevertheless the most homogeneous data available on the physical dependence property. These differences in the data, as well as the uncertainty with regard to species differences inherent in any comparison of data from experiments on animals and on man, must qualify any inferences from a study of the ratios in Table IV.

It is pertinent to the question of reliability of the data to point out that the 24-hour substitution procedure developed recently at Lexington cancels out individual variability because it is carried out on a group of about ten subjects, each of whom is his own control. The data obtained can be subjected to statistical analysis, and, if a sufficient range of dosage is used in repeated tests, can establish very precisely the relationship of a new substance to morphine in terms of addiction-sustaining power. The new method has the disadvantage that it does not provide for abrupt withdrawal of the substituted drug. It fails to afford, therefore, any information on the abstinence syndrome of the new drug.

The simple ranking of the compounds of Table II in the order of their effectiveness and comparison of these orders for analgesia and for production of physical dependence (addiction liability) are probably as far as one should go with the data in seeking a relationship between these properties. A parallelism in the orders of effectiveness would seem to indicate that physical dependence is related to analgesic potency. Conversely, complete absence of parallelism would imply that there is no such relationship. A wide divergence in the orders of effectiveness for a few compounds, when there is otherwise general parallelism, would suggest that in those particular instances some other property is involved which overshadows the relation between analgesia and addiction. It may also mean that the two properties are not as closely related as the general parallelism seems to indicate, or, again, species differences may be the determining factor.

TABLE IV

Substance	*Analgesic action*		*Physical dependence property*	
	ratio to morphine	*order of effectiveness* *	*ratio to morphine*	*order of effectiveness* *
Morphine	100	29	100	24-29
α-Isomorphine	55	39	120	21
Codeine	15	54	<19	49-51
Isocodeine	6	62	25	54
Pseudocodeine	0.5	69	6	58
Morpholinylethylmorphine (pholcodine)	1	68	<6	57
Dihydroheterocodeine	354	9-10	359	9
Dihydrocodeine methyl ether	64	38	69	39
Diacetylmorphine	233	13-14	278	13-14
Benzylmorphine myristyl ester	(1)	71-79	(2)	61-72
β-Chloromorphide	175	17-18	<38	43
Dihydromorphinone (hydromorphone)	700	5-6	714	5-6
Dihydrocodeinone (hydrocodone)	66	37	<100	30-31
Dihydrodesoxymorphine-D	1166	3	500	7
Dihydrodesoxycodeine-D	72	33	71	38
Dihydromorphine	117	25-26	333	10
Dihydro-α-isomorphine	124	24	277	13-14
Dihydrocodeine	17	53	21	52
Dihydroisocodeine	19	52	<26	47
Diacetyldihydromorphine	131	21-23	200	16
Dihydrocodeinone enol acetate	162	19-20	83	35
Normorphine	5	63	(3)	61-72
N-Allylnormorphine (nalorphine)	3	67	(4)	73-79
Diacetyl-N-allylnormorphine	(1)	71-79	(4)	73-79
N-Propyldihydronormorphine	(1)	71-79	(4)	73-79
Dihydrohydroxymorphinone	1235	2	1000	2
Dihydrohydroxycodeinone (oxycodone)	350	9-10	76	37
Methyldihydromorphinone (metopon)	420	7-8	714	5-6
6-Methyldihydromorphine	39	42-43	<100	30-31
6-Methyl-Δ^6-desoxymorphine	1050	4	833	3-4
dl-3-Hydroxy-N-methylmorphinan (racemorphan)	233	13-14	>100-<333	17-18
l-3-Hydroxy-N-methylmorphinan (levorphan)	420	7-8	>200-<666	12
d-3-Hydroxy-N-methylmorphinan (dextrorphan)	4	66	(5)	61-72
l-3-Hydroxy-2,N-dimethylmorphinan	23	49	<83	36
d-3-Hydroxy-2,N-dimethylmorphinan	(1)	71-79	(5)	61-72
dl-3-Methoxy-N-methylmorphinan (racemethorphan)	26	47	116	23

TABLE IV (*continued*)

Substance	Analgesic action		Physical dependence property	
	ratio to morphine	order of effectiveness *	ratio to morphine	order of effectiveness *
l-3-Methoxy-N-methylmorphinan (levomethorphan)	70	34-35	239	15
d-3-Methoxy-N-methylmorphinan (dextromethorphan)	(1)	70	(5)	61-72
d-3-Acetoxy-N-methylmorphinan	(1)	71-79	(5)	61-72
l-3-Hydroxy-N-allylmorphinan (levallorphan)	(1)	71-79	(4)	73-79
d-3-Hydroxy-N-allylmorphinan	(1)	71-79	(6)	73-79
l-3-Methoxy-N-allylmorphinan	(1)	71-79	(4)	73-79
l-3-Hydroxy-N-propargylmorphinan	5	64	(4)	73-79
l-3-Acetoxy-N-allylmorphinan	(1)	71-79	(4)	73-79
l-3-Hydroxy-N-phenethylmorphinan	1500	1	3333	1
1-Methyl-4-phenyl-4-carbethoxypiperidine (pethidine)	21	51	<42	41-42
1-Methyl-4-(*m*-hydroxyphenyl)-4-carbethoxypiperidine	32	45	<10	56
1-Methyl-4-(*m*-hydroxyphenyl)-4-piperidyl ethyl ketone (ketobemidone)	131	21-23	100	24-29
dl-α-1,3-Dimethyl-4-phenyl-4-propionoxy-piperidine (alphaprodine)	111	27	<66	40
dl-β-1,3-Dimethyl-4-phenyl-4-propionoxy-piperidine (betaprodine)	300	11	142	32-33
dl-α-1-Methyl-3-ethyl-4-phenyl-4-propionoxypiperidine (alphameprodine)	162	19-20	142	32-33
1-(β-Hydroxy-β-phenylethyl)-4-phenyl-4-carbethoxypiperidine	70	34-35	33	46
1-[β-(*p*-Aminophenyl)-ethyl]-4-phenyl-4-carbethoxypiperidine	68	36	35	44-45
1-Methyl-4-phenyl-4-carbethoxy-hexamethyleneimine	5	65	(5)	61-72
dl-α-1,3-Dimethyl-4-phenyl-4-propionoxy-hexamethyleneimine	210	15	25	48
1,2-Dimethyl-4-phenyl-4-carbmethoxy-hexamethyleneimine	9	58	(5)	61-72
1,3-Dimethyl-4-phenyl-4-carbethoxy-hexamethyleneimine	10	57	(5)	61-72

TABLE IV (*continued*)

Substance	*Analgesic action*		*Physical dependence property*	
	ratio to morphine	*order of effectiveness* *	*ratio to morphine*	*order of effectiveness* *
dl-4,4-Diphenyl-6-dimethylamino-3-heptanone (methadone)	131	21-23	416	8
l-4,4-Diphenyl-6-dimethylamino-3-heptanone	263	12	833	3-4
d-4,4-Diphenyl-6-dimethylamino-3-heptanone	8	60	(5)	61-72
dl-4,4-Diphenyl-5-methyl-6-dimethylamino-3-hexanone (isomethadone)	84	31-32	136	22
α-*dl*-4,4-Diphenyl-6-dimethylamino-3-heptanol	11	56	<42	41-42
β-*dl*-4,4-Diphenyl-6-dimethylamino-3-heptanol	29	46	(5)	61-72
dl-4,4-Diphenyl-6-dimethylamino-3-hexanone	84	31-32	100	24-29
α-*dl*-4,4-Diphenyl-6-dimethylamino-3-acetoxyheptane	175	17-18	>100-<333	17-18
α-*l*-4,4-Diphenyl-6-dimethylamino-3-acetoxyheptane	117	25-26	151	19-20
α-*d*-4,4-Diphenyl-6-dimethylamino-3-acetoxyheptane	700	5-6	300	11
dl-Ethyl 2,2-diphenyl-4-dimethylamino-valerate	12	55	<68	49-51
l-Ethyl 2,2-diphenyl-4-dimethylamino-valerate	9	59	<68 (7)	59-60
d-Ethyl 2,2-diphenyl-4-dimethylamino-valerate	39	42-43	<68	49-51
dl-Ethyl 2,2-diphenyl-4-dimethylamino-butyrate	23	50	<68 (7)	59-60
dl-4,4-Diphenyl-6-piperidino-3-heptanone	105	28	100	24-29
dl-4,4-Diphenyl-6-morpholino-3-heptanone (phenadoxone)	191	16	<83	34
dl-Ethyl 2,2-diphenyl-4-morpholino-butyrate	33	44	35	44-45
β-*d*-4,4-Diphenyl-6-dimethylamino-3-acetoxyheptane	46	41	151	19-20
dl-1,2-Diphenyl-4-dimethylamino-3-methyl-2-propionoxybutane	8	61	<12	55
d-1,2-Diphenyl-4-dimethylamino-3-methyl-2-propionoxybutane	25	48	<25	53

TABLE IV (*concluded*)

Substance	*Analgesic action*		*Physical dependence property*	
	ratio to morphine	*order of effectiveness* *	*ratio to morphine*	*order of effectiveness* *
3-Ethylmethylamino-1,1-di-(2′-thienyl)-1-butene (ethylmethylthiambutene) . .	88	30	100	24-29
3-Diethylamino-1,1-di-(2′-thienyl)-1-butene (diethylthiambutene)	50	40	100	24-29

* In each instance where a range of figures is given, different drugs appear to have the same effectiveness.

(1) No analgesic effect.
(2) None; see note (3), Table II.
(3) None; see note (6), Table II.
(4) Antagonist; see note (8), Table II.
(5) None; see note (13), Table II.
(6) None; see note (17), Table II.
(7) Little or no addiction liability; see note (30), Table II.

It is apparent from Table IV that there is a general similarity in the order of effectiveness in this group of compounds in regard to their analgesic and physical dependence potencies. There are, however, some notable exceptions. The degree of parallelism and the exceptions are seen more clearly in Table V, in which the compounds have been rearranged in two main groups in the order of their analgesic activity. One group comprises those compounds which are more effective than morphine in one respect or the other; the other group contains those compounds which are less effective than morphine.

TABLE V

Compounds which are more effective than morphine in one or other property	*Order of effectiveness* *	
	analgesic action	*physical dependence property*
l-3-Hydroxy-N-phenethylmorphinan	1	1
Dihydrohydroxymorphinone	2	2
Dihydrodesoxymorphine-D	3	7
6-Methyl-Δ^6-desoxymorphine	4	3-4
Dihydromorphinone (hydromorphone)	5-6	5-6
α-*d*-4,4-Diphenyl-6-dimethylamino-3-acetoxyheptane	5-6	11
Methyldihydromorphinone	7-8	5-6
l-3-Hydroxy-N-methylmorphinan (levorphan)	7-8	12
Dihydroheterocodeine	9-10	9
Dihydrohydroxycodeinone (oxycodone)	9-10	37
dl-β-1,3-Dimethyl-4-phenyl-4-propionoxypiperidine (betaprodine)	11	32-33
l-4,4-Diphenyl-6-dimethylamino-3-heptanone	12	3-4
Diacetylmorphine	13-14	13-14
dl-3-Hydroxy-N-methylmorphinan (dextrorphan)	13-14	17-18
dl-α-1,3-Dimethyl-4-phenyl-4-propionoxy-hexamethyleneimine	15	48
dl-4,4-Diphenyl-6-morpholino-3-heptanone (phenadoxone)	16	34
β-Chloromorphide	17-18	43
α-*dl*-4,4-Diphenyl-6-dimethylamino-3-acetoxy-heptane	17-18	17-18
Dihydrocodeinone enol acetate	19-20	35
dl-α-1-Methyl-3-ethyl-4-phenyl-4-propionoxy-piperidine (alphameprodine)	19-20	32-33
Diacetyldihydromorphine	21-23	16
1-Methyl-4-(*m*-hydroxyphenyl)-4-piperidyl ethyl ketone (ketobemidone)	21-23	24-29
dl-4,4-Diphenyl-6-dimethylamino-3-heptanone (methadone)	21-23	8
Dihydro-α-isomorphine	24	13-14
Dihydromorphine	25-26	10
α-*l*-4,4-Diphenyl-6-dimethylamino-3-acetoxyheptane	25-26	19-20
dl-α-1,3-Dimethyl-4-phenyl-4-propionoxy-piperidine (alphaprodine)	27	40
dl-4,4-Diphenyl-5-methyl-6-dimethylamino-3-hexanone (isomethadone)	31-32	21-22
l-3-Methoxy-N-methylmorphinan (levomethorphan)	34-35	14
α-Isomorphine	39	21-22
β-*d*-4,4-Diphenyl-6-dimethylamino-3-acetoxyheptane	41	19-20
dl-3-Methoxy-N-methylmorphinan (racemethorphan)	47	23

TABLE V (*continued*)

Compounds which are equally effective with morphine in both properties	*Order of effectiveness* *	
	analgesic action	*physical dependence property*
dl-4,4-Diphenyl-6-piperidino-3-heptanone	28	24-29
Morphine	29	24-29
3-Ethylmethylamino-1,1-di-(2′-thienyl)-1-butene (ethylmethylthiambutene)	30	24-29
Compounds which are less effective than morphine in one or other property		
dl-4,4-Diphenyl-6-dimethylamino-3-hexanone	31-32	24-29
Dihydrodesoxycodeine-D	33	38
1-(β-Hydroxy-β-phenylethyl)-4-phenyl-4-carbethoxypiperidine	34-35	46
1-[β-(*p*-Aminophenyl)-ethyl]-4-phenyl-4-carbethoxypiperidine	36	44-45
Dihydrocodeinone (hydrocodone)	37	30-31
Dihydrocodeine methyl ether	38	39
3-Diethylamino-1,1-di-(2′-thienyl)-1-butene (diethylthiambutene)	40	24-29
6-Methyldihydromorphine	42-43	30-31
d-Ethyl 2,2-diphenyl-4-dimethylaminovalerate	42-43	49-51
dl-Ethyl 2,2-diphenyl-4-morpholinobutyrate	44	44-45
1-Methyl-4-(*m*-hydroxyphenyl)-4-carbethoxy-piperidine	45	56
β-*dl*-4,4-Diphenyl-6-dimethylamino-3-heptanol	46	none
d-1,2-Diphenyl-2-dimethylamino-3-methyl-2-propionoxybutane	48	52
l-3-Hydroxy-2,N-dimethylmorphinan	49	36
dl-Ethyl 2,2-diphenyl-4-dimethylaminobutyrate	50	59-60
1-Methyl-4-phenyl-4-carbethoxypiperidine (pethidine)	51	41-42
Dihydroisocodeine	52	47
Dihydrocodeine	53	54
Codeine	54	49-51
dl-Ethyl 2,2-diphenyl-4-dimethylaminovalerate	55	49-51
α-*dl*-4,4-Diphenyl-6-dimethylamino-3-heptanol	56	41-42
1,3-Dimethyl-4-phenyl-4-carbethoxy-hexamethyleneimine	57	none
1,2-Dimethyl-4-phenyl-4-carbmethoxy-hexamethyleneimine	58	none
l-Ethyl 2,2-diphenyl-4-dimethylaminovalerate	59	59-60
d-4,4-Diphenyl-6-dimethylamino-3-heptanone	60	none
dl-1,2-Diphenyl-2-dimethylamino-3-methyl-2-propionoxybutane	61	55

TABLE V (*concluded*)

Compounds which are less effective than morphine in one or other property	*Order of effectiveness* *	
	analgesic action	*physical dependence property*
Isocodeine	62	53
Normorphine	63	none
l-3-Hydroxy-N-propargylmorphinan	64	none
1-Methyl-4-phenyl-4-carbethoxyhexamethyleneimine	65	none
d-3-Hydroxy-N-methylmorphinan (dextrorphan)	66	none
N-Allylnormorphine (nalorphine)	67	none
Morpholinylethylmorphine (pholcodine)	68	57
Pseudocodeine	69	58

* In each instance where a range of figures is given, different drugs appear to have the same effectiveness.

The instances in which analgesic effectiveness seems definitely to exceed physical dependence potency, exceptions to relative parallelism, are oxycodone (9-10: 37), betaprodine (11: 32-33), the alphaprodine analogue in the hexamethyleneimine series (15: 48), phenadoxone (16: 32), β-chloromorphide (17-18: 43), alphameprodine (19-20: 32-33), dihydrocodeinone enol acetate (19-20: 35), and alphaprodine (27: 40). The figures in parentheses are the order of effectiveness numbers for analgesic action and physical dependence property, respectively. There are some exceptions of opposite character in which the physical dependence potency seems to exceed notably the strength of analgesic action: methadone (21-23: 8), dihydromorphine (25-26 : 10), α-isomorphine (39 : 21), β-*d*-4,4-diphenyl-6-dimethylamino-3-acetoxyheptane (41: 19-20), levomethorphan (34-35: 15), and racemethorphan (47: 23). The physical dependence figure for β-chloromorphide is uncertain, since smooth substitution for morphine was never attained with this compound because of its shortness of action. The physical dependence figures for the acetoxyheptane compound and for methadone are small because of their prolonged addiction-sustaining action. Other apparent exceptions may be explained in part at least by species differences in analgesic effectiveness. For example, relative to morphine, alphaprodine, oxycodone, and phenadoxone are poorer analgesic agents in man than in mice (see Table III). The possibility cannot be excluded, however, that some of these exceptions may represent a real dissociation of the two properties under consideration.

In addition to the exceptions already noted there are some instances in which analgesic action has been demonstrated in the laboratory but no

addiction-sustaining action has been found in the work at Lexington. One of these compounds apparently lacking addiction liability—namely, *β-dl*-4,4-diphenyl-6-dimethylamino-3-heptanol—has one-third the analgesic potency of morphine in animals; another—namely, 1-methyl-4-phenyl-4-carbethoxyhexamethyleneimine (the analogue of pethidine in the hexamethyleneimine series)—has been reported to have a useful degree of analgesic effect in man.[22] However, even in this group one might assume a parallel decrease in analgesic and addiction-producing effectiveness, the determination of the latter not being practicable because of the toxic side-effects which would be produced by the necessarily high doses. The conclusion of the absence of addiction liability, therefore, may not be absolute, but for practical purposes is real.

Conversely, it has been reported that N-allylnormorphine has an analgesic effectiveness in man equal to that of morphine [47,53] although laboratory methods have not detected any such activity. This substance is an antagonist to morphine, and in morphine addiction precipitates an abstinence syndrome instead of substituting for morphine and maintaining the addiction. It seems to represent a complete dissociation of analgesic action and physical dependence property.[47]

Reference was made earlier to the suggestion of Himmelsbach that long duration of physical dependence action relative to duration of analgesic effect would increase, whereas the reverse situation would decrease, the likelihood of addiction development. To test this hypothesis with the experimental data available, the duration of effect data and order of physical dependence effectiveness (from Table IV) for two groups of compounds are presented in Table VI. The first group consists of those compounds in which the duration of physical dependence action is shorter than the duration of analgesic effect; the second group comprises those compounds in which physical dependence action is prolonged. According to Himmelsbach's suggestion, the order of addiction-sustaining power (physical dependence property) might be expected to be below that of morphine in the first group of substances and above that of morphine in the second group. This is certainly not consistently so. It may still be that Himmelsbach's suggestion is valid for clinical practice, where duration of analgesic action determines the interval of administration.

TABLE VI

Substance	*Duration of effect*		*Order of physical dependence effectiveness from Table IV*
	analgesic action (minutes)	*physical dependence property (hours)*	
α-Isomorphine	148 (115)	13 (90)	21
Pseudocodeine	145 (113)	16 (111)	58
Dihydroheterocodeine	117 (91)	7.5 (52)	9
Hydromorphone	133 (103)	7 (49)	5-6
Metopon	156 (121)	4.5 (31)	5-6
Dihydrodesoxymorphine-D	103 (80)	4.5 (31)	7
Dihydro-α-isomorphine	238 (184)	18 (125)	13-14
Dihydroisocodeine	147 (114)	13 (90)	47
Dihydrohydroxymorphinone	122 (95)	4 (28)	2
Oxycodone	169 (131)	14.5 (101)	37
Pethidine	125 (97)	4.5 (31)	41-42
Ketobemidone	127 (98)	7.5 (52)	24-29
Morphine	129 (100)	14.4 (100)	24-29
Codeine	67 (52)	16.2 (113)	49-51
Dihydrocodeine methyl ether	123 (95)	17.5 (121)	39
Hydrocodone	85 (66)	18 (125)	30-31
Dihydromorphine	154 (119)	19.2 (133)	10
Dihydrocodeine	130 (101)	24 (167)	52
Dihydrocodeinone enol acetate	89 (69)	24 (167)	35
6-Methyldihydromorphine	140 (109)	20 (139)	30-31
Racemorphan	119 (92)	16 (111)	17-18
Racemethorphan	111 (86)	48 (333)	23
Isomethadone	97 (75)	16 (111)	22
Methadone	70 (54)	60 (417)	8
l-Methadone	80 (62)	60 (417)	3-4
β-*d*-4,4-Diphenyl-6-dimethylamino-3-acetoxyheptane	319 (250)	>84 (583)	19-20

Figures in parentheses relate duration of effect to that of morphine as 100.

Chemical Structure of Addiction-Producing Substances

In the report on its second session, the WHO Expert Committee on Drugs Liable to Produce Addiction expressed the opinion " that the fundamental structure of an addiction-producing drug is that particular arrangement of atoms within the molecule which is responsible for the addiction properties of the drug. In the present state of our knowledge it is not possible to say what part of the molecule of a drug is responsible for its addiction properties." [67]

This is still the case. Addiction-producing properties, as well as analgesic action, have now been demonstrated not only in morphine and its derivatives, but also in morphinan, pethidine, hexamethyleneimine, methadone, and dithienylbutenylamine derivatives. It has been deduced that the general parallelism in the intensity of the physical-dependence-producing property and analgesic action for compounds of each of these types may indicate a relationship between the two properties. Therefore, to the extent that such a relationship exists, the features possessed in common by compounds exhibiting a morphine-like analgesic effect may be considered also characteristic of compounds having morphine-like addiction liability. These features, as set forth in the second study of this series,[5] are as follows:

(*a*) A tertiary nitrogen, the group on the nitrogen being relatively small. (Reference to the small size of the group on the nitrogen must now be modified somewhat, since a phenylethyl-like substituent on nitrogen enhances analgesic activity markedly; and also enhances addiction-sustaining potency, in one instance to the same extent as the increase in analgesic action.)

(*b*) A central carbon atom none of whose valences are connected with hydrogen.

(*c*) A phenyl group, or a group isosteric with phenyl, which is connected with the central carbon atom.

(*d*) Maximum activity is obtained when the central carbon atom is connected with the nitrogen by a two-carbon chain.

The euphorigenic effect and the physical-dependence-producing property of morphine and morphine-like agents are, like the analgesic effect, antagonized to some extent at least by N-allylnormorphine and other similar morphine antagonists. Also, these antagonists are able in most instances to precipitate an abstinence syndrome if physical dependence has been produced by morphine or a morphine-like drug. (The antagonists do not precipitate an abstinence syndrome during prolonged administration of pethidine unless the daily dose of pethidine is very large.)

The statement with respect to the possession of the above features by an addiction-producing drug must be qualified, again as was done in connexion

with the presence of such features in analgesic drugs. Compounds possessing the features outlined may not exhibit morphine-like addiction liability and, therefore, the presence of those conditions cannot be made a basis for prediction of addictive properties.

Since a relation between the analgesic action and the physical dependence property (addiction liability) has been postulated because of the general parallelism of the orders of intensity of the two properties, modification of chemical structure should be expected to have, in the main, a similar modifying effect on analgesic action and addiction liability. Himmelsbach [27] discussed this question in 1941 with respect to the morphine derivatives which he had tested at that time. The present data now afford further evidence on the problem (see Table VII). For example, methylation of a phenolic hydroxyl reduces, whereas methylation or acetylation of an alcoholic hydroxyl enhances, both the analgesic and the physical dependence action. Also, removal of the alcoholic hydroxyl from dihydromorphine or dihydrocodeine or changing the hydroxyl to a ketone increases both properties markedly and about equally. Another striking parallelism is to be seen in the effect of removal of a double bond by hydrogenation of morphine and its derivatives. This change increases the analgesic and the physical dependence action in all instances but one which are available for comparison. In the exception, the change from diacetylmorphine to diacetyldihydromorphine, both effects are decreased.

TABLE VII. EFFECT OF CHANGES IN CHEMICAL STRUCTURE ON ANALGESIC ACTION AND PHYSICAL DEPENDENCE PROPERTY

	Analgesic action ED_{50} *(mg/kg)*	*Physical dependence property* *addiction-sustaining dose (mg)*
Methylation of a phenolic hydroxyl		
Morphine	2.1	50
Codeine	14.2	>259
α-Isomorphine	3.8	40
Isocodeine	33.8	200
Dihydromorphine	1.8	15
Dihydrocodeine	12.4	175
Dihydro-α-isomorphine	1.7	18
Dihydroisocodeine	11.1	>194
Dihydrohydroxymorphinone	0.17	5
Dihydrohydroxycodeinone (oxycodone)	0.6	66
Dihydromorphinone (hydromorphone)	0.3	7
Dihydrocodeinone (hydrocodone)	3.2	>50
l-3-Hydroxy-N-methylmorphinan (levorphan)	0.5	> 7.5-<25
l-3-Methoxy-N-methylmorphinan (levomethorphan)	3.0	21.5

TABLE VII. EFFECT OF CHANGES IN CHEMICAL STRUCTURE ON ANALGESIC ACTION AND PHYSICAL DEPENDENCE PROPERTY (*continued*)

	Analgesic action ED_{50} *(mg/kg)*	*Physical dependence property* *addiction-sustaining dose (mg)*
Methylation or acetylation of an alcoholic hydroxyl		
Dihydromorphine	1.8	15
Dihydroheterocodeine	0.6	14
Dihydrocodeine	12.4	175
Dihydrocodeine methyl ether	3.3	72
α-*dl*-4,4-Diphenyl-6-dimethylamino-3-heptanol	18.9	>120
α-*dl*-4,4-Diphenyl-6-dimethylamino-3-acetoxyheptane	1.2	>15-<50
Removal of an alcoholic hydroxyl or its change to a ketone		
Dihydromorphine	1.8	15
Dihydrodesoxymorphine-D	0.18	10
Dihydrocodeine	12.4	175
Dihydrodesoxycodeine-D	2.9	70
Dihydromorphine	1.8	15
Dihydromorphinone (hydromorphone)	0.3	7
Dihydrocodeine	12.4	175
Dihydrocodeinone (hydrocodone)	3.2	>50
α-*dl*-4,4-Diphenyl-6-dimethylamino-3-heptanol	18.9	>120
dl-4,4-Diphenyl-6-dimethylamino-3-heptanone (methadone)	1.6	12
β-*dl*-4,4-Diphenyl-6-dimethylamino-3-heptanol	7.2	none
dl-4,4-Diphenyl-6-dimethylamino-3-heptanone (methadone)	1.6	12
Removal of a double bond by hydrogenation		
Morphine	2.1	50
Dihydromorphine	1.8	15
α-Isomorphine	3.8	40
Dihydro-α-isomorphine	1.7	18
Codeine	14.2	>259
Dihydrocodeine	12.4	175
Isocodeine	33.8	200
Dihydroisocodeine	11.1	>194
Diacetylmorphine	0.9	18
Diacetyldihydromorphine	1.6	25

TABLE VII. EFFECT OF CHANGES IN CHEMICAL STRUCTURE ON ANALGESIC ACTION AND PHYSICAL DEPENDENCE PROPERTY (*continued*)

	Analgesic action ED_{50} *(mg/kg)*	*Physical dependence property* *addiction-sustaining dose (mg)*
Addition of a nuclear substituent to a morphine type		
Dihydromorphinone (hydromorphone)	0.3	7
Dihydrohydroxymorphinone	0.17	5
Dihydrocodeinone (hydrocodone)	3.2	>50
Dihydrohydroxycodeinone (oxycodone)	0.6	66
Dihydromorphinone (hydromorphone)	0.3	7
Methyldihydromorphinone (metopon)	0.5	7
Dihydromorphine	1.8	15
6-Methyldihydromorphine	5.4	>50
Change in the substituent on nitrogen		
Morphine	2.1	50
N-Allylnormorphine (nalorphine)	73.0	none
l-3-Hydroxy-N-methylmorphinan (levorphan)	0.5	>7.5-<25
l-3-Hydroxy-N-allylmorphinan (levallorphan)	none	none
l-3-Hydroxy-N-methylmorphinan (levorphan)	0.5	>7.5-<25
l-3-Hydroxy-N-phenethylmorphinan	0.14	1.5
1-Methyl-4-phenyl-4-carbethoxypiperidine (pethidine)	9.9	>120
1-[β-(*p*-Aminophenyl)-ethyl]-4-phenyl-4-carbethoxy-piperidine	3.1	143
1-Methyl-4-phenyl-4-carbethoxypiperidine (pethidine)	9.9	>120
1-(β-Hydroxy-β-phenylethyl)-4-phenyl-4-carbethoxy-piperidine	3.0	
dl-4,4-Diphenyl-6-dimethylamino-3-heptanone (methadone)	1.6	12
dl-4,4-Diphenyl-6-piperidino-3-heptanone	2.0	50
dl-4,4-Diphenyl-6-dimethylamino-3-heptanone (methadone)	1.6	12
dl-4,4-Diphenyl-6-morpholino-3-heptanone (phenadoxone)	1.1	<60
dl-Ethyl 2,2-diphenyl-4-dimethylaminobutyrate	9.3	almost none
dl-Ethyl 2,2-diphenyl-4-morpholinobutyrate	6.4	143
3-Diethylamino-1,1-di-(2′-thienyl)-1-butene (diethylthiambutene)	4.2	50
3-Ethylmethylamino-1,1-di-(2′-thienyl)-1-butene (ethylmethylthiambutene)	2.4	50

TABLE VII. EFFECT OF CHANGES IN CHEMICAL STRUCTURE ON ANALGESIC ACTION AND PHYSICAL DEPENDENCE PROPERTY (*concluded*)

	Analgesic action ED_{50} *(mg/kg)*	*Physical dependence property* *addiction-sustaining dose (mg)*
Change in the hydrocarbon chain of methadone types		
dl-4,4-Diphenyl-6-dimethylamino-3-heptanone (methadone)	1.6	12
dl-4,4-Diphenyl-5-methyl-6-dimethylamino-3-hexanone (isomethadone)	2.5	37
dl-4,4-Diphenyl-6-dimethylamino-3-heptanone (methadone)	1.6	12
dl-4,4-Diphenyl-6-dimethylamino-3-hexanone	2.5	50
dl-Ethyl 2,2-diphenyl-4-dimethylaminovalerate	18.0	codeine-like
dl-Ethyl 2,2-diphenyl-4-dimethylaminobutyrate	9.3	almost none
Change from an ethyl ketone to an ethyl ester		
1-Methyl-4-(*m*-hydroxyphenyl)-4-piperidyl ethyl ketone (ketobemidone)	1.6	50
1-Methyl-4-(*m*-hydroxyphenyl)-4-carbethoxy-piperidine	6.6	>500
dl-4,4-Diphenyl-6-dimethylamino-3-heptanone (methadone)	1.6	12
dl-Ethyl 2,2-diphenyl-4-dimethylaminovalerate	18.0	codeine-like
dl-4,4-Diphenyl-6-dimethylamino-3-hexanone	2.5	50
dl-Ethyl 2,2-diphenyl-4-dimethylaminobutyrate	9.3	almost none
Two changes simultaneously in pethidine or hexamethyleneimine types		
1-Methyl-4-phenyl-4-carbethoxypiperidine (pethidine)	9.9	>120
dl-α-1,3-Dimethyl-4-phenyl-4-propionoxypiperidine (alphaprodine)	1.9	>75
dl-β-1,3Dimethyl-4-phenyl-4-propionoxypiperidine (betaprodine)	0.7	35
dl-α-1-Methyl-3-ethyl-4-phenyl-4-propionoxy-piperidine (alphameprodine)	1.3	35
1-Methyl-4-phenyl-4-carbethoxyhexamethyleneimine	42.6	none
dl-α-1,3-Dimethyl-4-phenyl-4-propionoxyhexa-methyleneimine	1.0	200

Table VII presents still other examples of the effect of a chemical change on the two properties being compared, and includes also some interesting exceptions to parallelism in the effects produced. Note, for instance, that in alphaprodine, betaprodine, and alphameprodine analgesic action, compared with that of pethidine, has been increased without significant change in the addiction-sustaining dose. In the alphaprodine analogue in the hexamethyleneimine series analgesic effect, compared with that of the pethidine analogue in the same series, has been increased 40 times. Some physical dependence effect has appeared but the required dose is relatively large.

The demonstration of some analgesic activity in compounds which do not seem to have any addiction liability is another interesting exception to the general appearance of parallel results brought about by chemical changes. Taking the instances of both parallelism and exceptions to it into account, one must admit that the two properties may be independent in spite of the general appearance of interrelationship. Our present knowledge is not sufficient for a more exact appraisal of the situation.

Summary

Quantitative data have been presented for the intensity and duration of analgesic action and physical dependence production of morphine, morphinan, pethidine, hexamethyleneimine, methadone, and dithienylbutenylamine derivatives. There is a general parallelism in the order of intensity of the two effects, but there are also some important exceptions: compounds in which analgesic action is of a higher order than physical dependence production; others in which the order of physical dependence production is the higher; and compounds in which analgesic action has been demonstrated but with which no addiction liability has been found. The analgesic action in the third group is less, usually much less, than that of morphine, except in the case of nalorphine. It is reported that nalorphine has an analgesic effect equal to that of morphine in man, yet it is a morphine antagonist and has no addiction liability.

The parallelism between the order of intensity of analgesic action and that of physical dependence production may indicate a relationship between these two properties, but, at the same time, the exceptions suggest the possibility that the two properties are independent. Our present knowledge does not permit clarification of these points.

In so far as a relationship seems to exist between analgesic action and physical dependence production (addiction liability), the features which have been found to be possessed in common by morphine-like analgesic drugs may be considered also characteristic of those compounds which produce morphine-like addiction—namely, (*a*) a tertiary nitrogen; (*b*) a central carbon atom none of whose valences are connected with hydrogen; (*c*) a phenyl group, or a group isosteric with phenyl, which is connected

with the central carbon atom; and (*d*) maximum activity when the central carbon atom is connected with the nitrogen by a two-carbon chain. Compounds possessing these features may not exhibit morphine-like addiction liability and, therefore, the presence of these conditions cannot be made a basis for prediction of addictive properties.

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RÉSUMÉ

L'étude qui précède est la seconde d'une série consacrée aux médicaments synthétiques à effet morphinique. Elle présente des données quantitatives sur l'intensité et la durée de l'action analgésique et de l'effet de dépendance physique (aptitude à engendrer la toxicomanie) exercés par la morphine, le morphinane, la péthidine, l'hexaméthylèneimine, la méthadone, la dithiénylbuténylamine et leurs dérivés respectifs. Il existe un parallélisme général dans l'ordre d'intensité de chacune de ces propriétés, mais on rencontre aussi certaines exceptions importantes: il y a des substances dont l'action analgésique est plus intense que l'effet de dépendance physique, d'autres pour lesquelles c'est l'inverse qui se produit, d'autres encore dont on a pu mettre en évidence le pouvoir analgésique sans qu'elles se soient révélées aptes à engendrer la toxicomanie. Les substances de ce troisième groupe ont un pouvoir analgésique plus faible, et même en général beaucoup plus faible que la morphine. La nalorphine fait cependant exception. Il a été signalé que cette substance a, sur l'organisme humain, un effet analgésique égal à celui de la morphine, tout en étant antagoniste de la morphine et dépourvue d'aptitude à engendrer la toxicomanie.

Le parallélisme mentionné ci-dessus peut indiquer qu'il existe un rapport direct entre les deux propriétés considérées, mais, en même temps, les exceptions laissent supposer que ces deux propriétés sont peut-être indépendantes. Nos connaissances actuelles ne nous permettent pas d'élucider ce point.

On constate, pour autant qu'il existe un rapport entre l'action analgésique et l'aptitude à engendrer la toxicomanie, que les caractères communs aux substances analgésiques à effet morphinique sont également ceux que l'on rencontre chez les substances susceptibles d'engendrer une toxicomanie de type morphinique. Ces caractères sont les suivants: *a*) un atome d'azote tertiaire; *b*) un atome de carbone central dont aucune des valences ne fixe d'hydrogène; *c*) un groupe phényle ou isostérique du phényle, qui est lié à l'atome de carbone central; et *d*) un maximum d'activité quand l'atome de carbone central est lié à l'azote par une chaîne comportant deux carbones.

Toutefois ces caractères se rencontrent dans des substances qui ne sont pas susceptibles d'engendrer une toxicomanie du genre de la morphinomanie, si bien qu'on ne peut conclure de leur présence que telle ou telle substance sera toxicomanogène.

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