Bull. World Hlth Org. 1949, **2**, 193-204
13

ON PETHIDINE AND METHADONE DERIVATIVES *

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From the medical point of view the international conventions on habit-forming drugs form an important means for the prevention of addiction in so far as the administrative control is concerned. It must, however, be very clearly stated that control implies in no sense prohibition of therapeutic administration or inhibition of research ; for the hope still exists—and nowadays perhaps with more justification than a decade ago—that the ideal substance may be found, which will possess all the therapeutically desirable qualities of morphine as a powerful analgesic, but without the side-effects of habituation and addiction.

It needs the practical experience of many years to arrive at a correct assessment of the therapeutic and addictive or non-addictive qualities of a substance. The history of our subject shows several examples of substances which seemed to present a notable advance towards the desired goal, but which afterwards proved to be clearly addictive. Of these, heroin is one : more than fifty years ago its discovery was enthusiastically welcomed, but this drug developed quickly into the most dangerous—or one of the most dangerous—substances of its type. Dihydrodesoxymorphine-D is another, more recent, example ; after a careful clinical trial with promising results, it showed addiction properties when employed later on a large scale, so that the US Government withdrew it. The latest instance is pethidine (dolantin, demerol), which certainly possesses a desirable therapeutic quality distinguishing it from the usual opiates : the combination of the analgesic effect with an antispasmodic effect ; but which is, nevertheless, a habit-forming drug. It is the most regrettable example of its kind, owing to the fact that in 1944 its original manufacturers were still emphasizing its addictive innocence through propaganda in some countries, although as early as 1941 it had been submitted by its country of origin (Germany) to the usual legal and administrative control for opiates with addictive qualities.

The general conclusion of the foregoing is that experience has taught us caution in declaring a substance to be non-addictive. It seems preferable, indeed, to submit a questionable compound — questionable in the sense of being addictogenic — to the usual legal and administrative control for habit-forming drugs, and to withdraw the restrictions later, when the substance

* Note submitted to the Expert Committee on Habit-forming Drugs at its first session, Geneva, 24-29 January 1949

** Now Secretary

in question, after a period long enough to guarantee certain security of judgement, has proved in practice to be non-addictive. This procedure seems preferable to that of applying restrictions to a product after it has been freely available for some time. The reason why the first procedure is by far preferable to the second lies in the considerable practical disadvantages of the latter; for it is easier to notify practising physicians of the repeal of a restriction than of a new restriction of a substance which has not previously been controlled.

It seemed necessary to outline these general considerations as a basis for the consideration of the new non-opiate, addicting analgesics of the pethidine and methadone series.

Pethidine and methadone, appear to present a notable therapeutical advance and are therefore of value and importance. Their addictive qualities have resulted or will result in their being submitted to the usual legal and administrative measures; this is easily accomplished through the usual channels. The situation becomes complicated, however, owing to the fact that they are merely the outstanding, and until now the best-known members of very large series of derivatives. Many of these are already known, while others are still available only to the chemists who have synthesized them, the range of theoretically producible derivatives being unlimited.

The danger of this situation has already been recognized in the recent Protocol bringing under international control drugs outside the scope of the Convention of 13 July 1931 for limiting the manufacture and regulating the distribution of narcotic drugs, signed in Paris on 19 November 1948.[22] Although this protocol has not yet received the necessary number of final signatures, it is expected to enter into force in the very near future.

The Expert Committee on Habit-forming Drugs of the World Health Organization has the task of considering these substances from the point of view of their liability to produce addiction or to be converted into a compound with addictive properties.

With regard to pethidine and methadone, there is no doubt that they are habit-forming, but few of the derivatives of either of these "parent substances" have so far been tested experimentally on animals and fewer still on human beings.

These tentative observations, however, do not solve the problem which the expert committee has to consider, i.e., their habit-forming properties, for the determination of the existence or non-existence of these properties demands much more extensive work—quantitatively as well as qualitatively—than, for instance, do the observations of other effects on the different systems, organs, etc. Consequently, such studies cannot make much progress while the development of these substances is still in its early stages.

For the task of the expert committee, however, this state of affairs is not so important as it may seem at first glance, as it would seem preferable

to place all possible derivatives of both types of substance under the usual legal and administrative control, until their non-addictive character has been adequately proved.

Such a general attitude is the only adequate guarantee that public health will not be menaced by a substance of this class which, after its appearance on the market, may exhibit addicting properties. It must always be kept in mind that all the derivatives under consideration are prepared with the sole object of ultimately obtaining a suitable substitute for morphine.

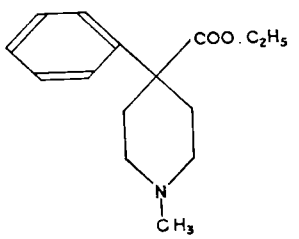
It must not be overlooked that in the course of these researches a derivative with other important therapeutic qualities may be discovered ; pethidine itself is an example of this. In such a case the cautious attitude of the expert committee as to the probable, or at least possible, addicting qualities of the compound in question would in no way hinder its use for other therapeutic purposes.

1. Pethidine Series [a]

As already mentioned, numerous derivatives of pethidine have been described. As early as 1940, Schaumann,[18] who was the first to analyse the effect of pethidine, mentioned 42 such new compounds, which Eisleb [3] had synthesized through modifications of the phenyl nucleus, the piperidine ring and the ester group and through the formation of amides, ketones, carbinols, etc. Lee *et al.*[12] described 113 derivatives, Randall & Lehmann [17] studied 50 pharmacologically, and Jensen *et al.*[10] investigated a number of esters of 4-phenyl-4-hydroxy-1-methyl-piperidine.

It is not the task of the expert committee to consider all these derivatives. Reference will be made only to those which, for one reason or another, may be of interest at the moment, or which, for particular reasons, have to be mentioned as examples.

I

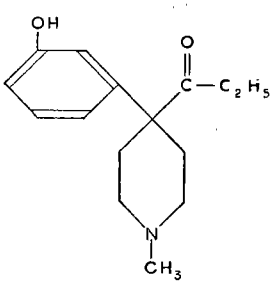


1-methyl-4-phenyl-piperidine-4-carboxylic acid ethyl ester ;
ethyl-4-phenyl-1-methyl-piperidine-4-carboxylate ;
pethidine, demerol, dolantin, dolosal, isonipecain, meperidin, etc.

[a] For the sake of brevity we have refrained from mentioning the corresponding salts (hydrochloride, etc.).

There exists a relative specificity of the ethyl-ester. Apart from the *iso*-propyl-, allyl- and, to a lesser degree, *n*-propyl-esters, no esters show any activity, or only an insignificant amount.[14] Neither, according to Schaumann,[18] do the amides, while ketones are active. The best known ketone derivative is No. 10720, or K4710 (Winthrop), with the formula :

II

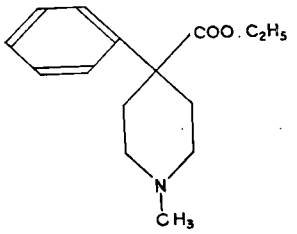
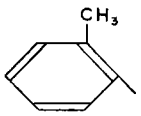


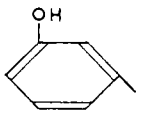
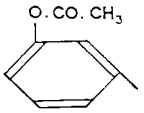
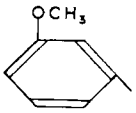
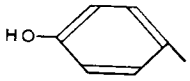
1-methyl-4-metahydroxyphenyl-4-propionyl-piperidine

This compound, called also "keto-bemidone", appeared, after a very limited trial, to merit further study, because it showed excellent analgesic properties with minimal side-effects.[11] In this group a strong analgesic effect must always lead to a suspicion of habit-forming properties. It seems that the ketone form is more potent than the ester form.[19]

Acyl derivatives of 4-phenyl-4-hydroxy-1-methyl-piperidine have considerable activity, the propionic acid derivative being the most active.[10]

1.1 *Effect of variations in the phenyl ring*

		Activity
III 	pethidine	1
IV 	2'-methyl-pethidine	1 ½

			Activity
V		3′-hydroxy-pethidine	1
VI		3′-acetoxy-pethidine	1
VII		3′-methoxy-pethidine	$^1/_2$
VIII		4′-hydroxy-pethidine	$^1/_3$

The characteristic properties of these derivatives are :

2′-methyl-pethidine, ethyl-4-(*o*-tolyl)-1-methyl-piperidine-4-carboxylate, is a more potent and lasting analgesic than pethidine itself. This increase in potency may be related to its closer approximation to the phenanthrene feature of morphine.

3′-hydroxy-pethidine, ethyl-4-(3′hydroxyphenyl)-1-methyl-piperidine-4-carboxylate. The intensity of analgesic effect is the same as that of pethidine. While this compound is substantially equal to pethidine itself, constitutionally it is nearer to morphine. The corresponding acetoxy-compound had activity of the same order.

3′-acetoxy-pethidine. The analgesic effect of this compound is as intense as that of pethidine (its composition is somewhat similar to that of heroin).

3′-methoxy-pethidine. The intensity of analgesic effect is half as great as that of pethidine.

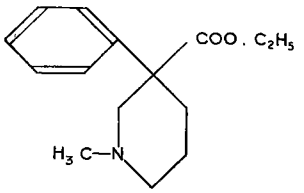
This shows a relationship similar to that between codeine and morphine or heroin. The greater stability of the methoxy-group to hydrolysis in vivo, as compared with that of the acetyl-group, would account for this phenomenon. The loss of activity following methylation (but not acetylation to acetoxy-pethidine) may be due to the same causes as the similar loss of activity following methylation of the phenolic OH of morphine.

1.2 Iso-*series*

With regard to the piperidine ring itself, in pethidine it has been shown that the relative position of the nitrogen and the point of attachment of

the two substituent groups is not of special importance, as β-pethidine is nearly as powerful an analgesic as pethidine. Again, as in pethidine itself, the specificity of the ethyl ester group is dominant.[5, 14]

IX



1-methyl-3-phenyl-piperidine-3-carboxylic acid ethyl ester, β-pethidine, *iso*-pethidine, *iso*-dolantin

In this β-pethidine series, there is an asymmetric carbon atom ; the *l*-form of N-nor-β-pethidine is much more active than the *d*-form.[14]

The effect is similar to pethidine ; there is hardly any difference in the antispasmodic properties. This compound is less soporific, less sedative than pethidine, and euphoria, sometimes so pronounced an effect of ordinary pethidine, did not seem to be produced by β-pethidine to any noticeable degree. No withdrawal symptoms have been observed in the few cases recorded.[5]

Methyl-iso-*pethidine*, *methyl*-iso-*dolantin*. The intensity of analgesic

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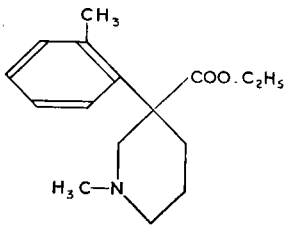


effect is three-quarters that of pethidine. The action is delayed but prolonged.

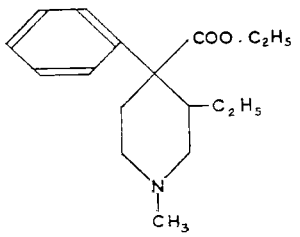
In this *iso*-series, as in the pethidine series itself, the activity appears to be enhanced by introducing a 2′-methyl group into the phenyl ring.

1.3 *Effect of variations in the N-group*

Compounds obtained by substitution of the methyl radical by butyl (NU-830) or *iso*-propyl (NU-896) are highly active and have considerably less effect in developing tolerance than morphine.[4]

Maximal analgesic potency is attained by introducing an alkyl group into the 3-position of the 1-,4-,4-substituted piperidines. Qualitatively these compounds resemble morphine in pharmacological action ; four of them are from four to eight times as potent as morphine. These are : *dl*-β-1,3-dimethyl-4-phenyl-4-propionoxy-piperidine hydrochloride (NU-1779) ; *d*-β-1,3-dimethyl-4-phenyl-4-propionoxy-piperidine *d*-acid tartrate (NU-1831) ; its *l*-form (NU-1832) ; and 1-methyl-3-ethyl-4-phenyl-4-propionoxy-piperidine (NU-1932), also called 3-ethyl-dolantin.[17] As an example the configuration of this last compound is given :

XI



In morphine, breaking the piperidine ring leads to almost complete loss of analgesic properties. This also holds good in the pethidine series, as shown by the very slight activity of ethyl-α-phenyl-α-methyl-γ-dimethyl-amino butyrate, and the corresponding γ-piperidine compound.[14]

It is important to note, however, that, when the α-methyl group in the latter compound is replaced by a phenyl group, the activity is increased to about one-half of that of pethidine.[14,15] Therefore, the introduction of a second phenyl group restores the analgesic power to a certain extent.

The degree of analgesic potency of certain compounds is also determined by the steric configuration. This influence of stereo-isomerism is indeed most striking. A good example of this influence is found in the *cis*- (NU-1196) and *trans*- (NU-1779) forms of 1,3-dimethyl-4-phenyl-4-propionoxy-piperidine. The analgesic potency of the *cis*-form in dogs (technique of H. G. Wolff) is slightly greater than of morphine, whilst the *trans*-form is about four to six times as potent as morphine. In man the *cis*-form is somewhat less than, the *trans*-form about equal to, morphine in analgesic potency ; the duration of the analgesic effect of the *cis*-form is shorter than, that of the *trans*-form about equal to, that of morphine. The *cis*-form gives a mild sedation which is more marked with the *trans*-form. The *cis*-form causes few side-effects (dizziness, etc.), which are, however, marked with the *trans*-form.[2]

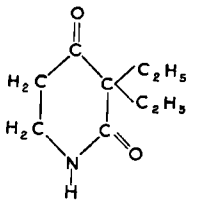
The potency of NU-1779, however, is surpassed by its *laevo*-antipode, NU-1832. However, substitution in the 3-position has not consistently

increased activity ; NU-1333 is more potent than the corresponding 3-substituted compound NU-1215. It seems that the steric arrangement of the substituents in the 3- and 4-positions determines the degree of analgesic potency. According to Lee (personal communication to Randall & Lehmann [17]), it is highest when the configuration of the substituents in the 3- and 4-positions resembles that of morphine, as is apparently the case with NU-1779, but not with its diastereomer, NU-1196.

There are many more recent synthetic attempts in this field. Some of them are original and some inspired by the success of pethidine. Amongst the latter are the esters of diphenylacetic acid and fluorenecarboxylic acid, the α-position of which is substituted by β′-amino-alkyl-radicals. Their preparation is described by Bockmühl & Ehrhart (German patent no. 711,069) and they are said to be useful spasmolytics and analgesics. A representative of this series, ethyl-α, α-diphenyl-γ-N-piperidinobutyrate, when compared with pethidine by Macdonald *et al.*,[14] was found to possess definite analgesic activity, though to a lesser degree.

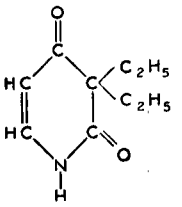
Another derivative of piperidine must be mentioned, although it is of simpler constitution and does not belong to the pethidine series : 3,3-diethyl-2,4-dioxopiperidine, also called NU-1510, or " sedulon ".[16] It seems to give good or fair sedation ; 0.25 g. was administered three times daily for three to five months. One patient, after one month, " was apprehensive about continuing the drug " ; it was stopped several days later. This drug, therefore, seems at least sufficiently suspect of habit-forming qualities.

XII



3,3-diethyl-2,4-dioxopiperidine, sedulon, NU-1510

XIII

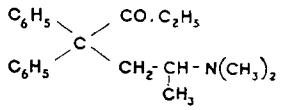


3,3-diethyl-2,4-dioxotetrahydro-pyridine, NU-903

The great variety of derivatives with analgesic action, of which only a small number could be quoted as examples, supports the view expressed above that it seems not only advisable, but necessary, to submit—at least provisionally—the whole piperidine group of compounds with pethidine-like structure to the regulations in question.

2. Methadone Series

XIV



6-dimethylamino-4,4-diphenyl-3-heptanone

Methadone (6-dimethylamino-4,4-diphenyl-3-heptanone) is also known under the names amidone, physeptone, dolophine, miadone, AN-148, adanon, butalgin, diadone, etc.

It has previously been explained [24] that the methadone product used in practice is racemic, and produces addiction as a result of its *l*-methadone content. It may be added as evidence of the addicting character of methadone that all former morphine-addicts stated that if opiates were not available they would prefer methadone to pethidine, alcohol, barbiturates or marihuana.[9] It is furthermore noteworthy that no evidence of euphoria was shown in non-addicts or post-addicts with doses of 5 mg. or less, while in former morphine addicts it appeared with 10 mg. Doses of 30 mg., or more, always produced euphoria.[9]

With greater clinical experience, the therapeutic usefulness of methadone becomes clearer. The much greater effect on patients confined to bed has already been stressed. It has recently been stated, however, that toxic symptoms appear in 80% of the ambulatory patients, that this high incidence limits its clinical usefulness,[1] and that methadone is not a satisfactory analgesic. At the same time other authors credit methadone with an analgesic effect equal to that of morphine itself and with no greater incidence of side-effects.

However this may be, methadone will probably become in the future a very attractive product for drug addicts, which is yet another reason for taking every possible precaution regarding its traffic.

It has been stated in an interesting study by Sherrod *et al.*[21] that, from the pharmacological viewpoint, it is hoped that at least five types of methadone derivatives may be synthesized :

(1) a short-acting non-depressant analgesic for use in obstetrics ;

(2) a long-acting orally-effective analgesic to relieve the pain of cancer ;

(3) a potent spasmolytic-analgesic compound ;

(4) a narcotic analgesic with a wide margin of safety for pre-anaesthetic medication ; and

(5) a potent, persistent analgesic which may perhaps, by means of chemical lobotomy, permanently lower the pain threshold in causalgic states.

With these concepts in mind the following compounds are of interest :

	Therapeutic index
(1) Methadone hydrochloride	2.3
(2) Iso-methadone hydrochloride	3.1
(3) N,N-dimethyl-3,3-diphenyl-4-imino-2-methyl-hexylamine hydrochloride	4.0
(4) γ-dimethylamino-α, α-diphenyl-valeric acid hydrochloride	8.0
(5) 1-dimethylamino-2-methyl-3,3-diphenyl-4-acetoxy-heptane hydrochloride	11
(6) 2-dimethylamino-4,4-diphenyl-5-hexylidene acetyl-imine hydrochloride	12
(7) 2-dimethylamino-4,4-diphenyl-5-acetoxyheptane hydrochloride	14
(8) 2-morpholino-4,4-diphenyl-5-acetoxyheptane hydrochloride	40

Compound 4 is unique in this series because of an atropine-like effect on the intestine of the anaesthetized dog. The other derivatives have a spasmogenic effect on the intestine similar to that of methadone. Compounds 5 to 8 are of interest because of their high therapeutic indices and long duration of analgesic action.

The following facts are known concerning the liability to addiction of some of the drugs of the methadone series : [8]

l-*Methadone*. This has already been characterized as the potent component of the racemic compound, a finding which has been confirmed by several authors.[7, 8, 13] It causes a striking diminution in the intensity of abstinence symptoms in former morphine addicts; the relief is greater and longer than that afforded by morphine itself. Upon withdrawal of *l*-methadone, after 14 days substitution for morphine, a definite abstinence syndrome ensued.[7]

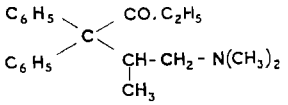
d-*Methadone*. In agreement with earlier observations, this substance shows no detectable effect on the intensity of abstinence in morphine addicts. But according to a recent publication by Scott *et al.*[20] the *d*-form is also analgesic although much less so than the *l*-form; the *l*-form is about 7.5 times stronger in rats, 25 times in dogs, 50 times in man ; practically identical analgesic effects were obtained with 3 mg. of the *l*-form and 160 mg. of the *d*-form. The *l*-form has greater narcotic powers than the *d*-form, when used in doses with equal analgesic effects.

dl-*Methadol*. This substance is the alcoholic analogue of methadone, 6-dimethylamino-4,4-diphenyl-3-heptanol. For mice it is only one-third as toxic as *dl*-methadone, but only one-tenth as active in producing analgesia; it does not produce a Straub reaction. Even in large doses it did not influence the course of abstinence of former morphine addicts. It

has not been stated so far whether methadol is convertible into a habit-forming drug.

dl-iso-*Methadone*. 6-dimethylamino-5-methyl-4,4-diphenyl-3-hexanone, produces irregularly a Straub reaction; in animals it is not a strong analgesic. In former morphine addicts, 60-90 mg. reduced the intensity of

XV

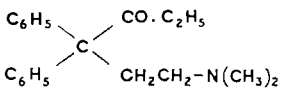


abstinence symptoms as much as 30 mg. of morphine. Consequently even if it is not entirely adequate as a substitute for morphine, it may perhaps have this effect in larger amounts. There exists, furthermore, a direct addiction to *iso*-methadone. The abstinence syndrome develops very rapidly, resembling more that of morphine than that of methadone.[7,8] *Iso*-methadone is thus an addicting drug.

C.B.11, 6-morpholino-4,4-diphenyl-3-heptanone.[b] Apparently C.B.11 is a more effective analgesic than morphine in rats and is of low toxicity. It is more potent than methadone and apparently more active than pethidine. According to Wilson & Hunter,[23] there is no evidence at present that C.B.11 is a drug of addiction, but Hewer & Keele[6] point out that the most important side-effect was euphoria which lasted for several hours after larger doses, and it must be admitted that the importance of euphoria lies in its close relation to the liability to drug addiction.

No. 10582. Another compound, No. 10582, has been the subject of a limited clinical trial. It was rather inefficient in comparison with methadone; side-effects were too frequent.[11]

XVI



Many more derivatives of the methadone group already exist, but, so far as is known, no pharmacological statements regarding their liability to addiction have yet been made. Some of these products have been studied toxicologically, among them a structural isomer of methadone, the 6-dimethylamino-4,4-diphenyl-5-methyl-3-hexanone (Win-1783). It differs from methadone only in the position of the methyl group, but is therapeutically very similar; it is half as active as *dl*-methadone.[13]

[b] Heptalgin

Other derivatives have been tried, but until now without practical results.[19]

Methadone and its derivatives are relatively easy to synthesize and to manufacture. No important chemical plant is needed; therefore, illegal, i.e., uncontrolled, production is possible and must be taken into account. Moreover, other derivatives of the methadone type—still unknown—would also be easy to produce, and it is impossible to foresee whether they would be of an addictive character or not. For all these reasons, it seems legitimate to submit — at least provisionally — all compounds of the methadone type to the usual legal and administrative restrictions.

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