

REVIEW ARTICLE

SOME ASPECTS OF DRUG ADDICTION

BY P. O. WOLFF, M.D., PH.D., M.A.

Chief, Addiction-producing Drugs Section, World Health Organisation, Geneva

HABIT

To define drug addiction correctly it is first necessary to make a fundamental distinction between habit and true addiction.

Through the ages, philosophers have applied their minds to the definition of habit. As Confucius said¹: "Men are born pretty much alike, but through their habits they gradually grow further and further apart from each other." Aristotle describes habit (ἕξις) as a quality, a disposition or a form of behaviour of permanent character, as opposed to manifestations which are purely transient. Habit commences with the first deed which has a sequel.

Habit may be defined as an acquired condition produced by frequent repetitions of the same actions in such a way that a certain function or action is accomplished more easily, more accurately and more quickly. Habit is acquired unconsciously and tends to be transformed into automatism. It consists not only of an adaptation, for example of an organ to a function or of a function to a stimulus, but also in an "automatisation" of voluntary acts which tends to show the character of impulses or reflexes, i.e., involuntary actions, in which the consciousness of the active processes has decreased or, at least, partially disappeared. Habit is the result of the repetition of earlier deeds without new reflections or conclusions. On the other hand, the continuation of the acts does not produce habit under every condition. On the contrary, for example repetition of a particular noise may produce such a shock that it finally becomes unbearable.

Hume² makes particular comment on our subject in these terms: "This principle is *custom* or *habit*. For wherever the repetition of any particular act or operation produces a propensity to renew the same act or operation, without being impelled by any reasoning or process of the understanding, we always say that this propensity is the effect of *custom*. By employing that word, we pretend not to have given the ultimate reason of such a propensity. We only point out a principle of human nature, which is universally acknowledged, and which is well known by its effects. . . . All inferences from experience, therefore, are effects of custom, not of reasoning. Custom, then, is the great guide of human life. It is that principle alone which renders our experience useful to us, and makes us expect, for the future, a similar train of events with those which have appeared in the past. Without the influence of custom, we should be entirely ignorant of every matter of

fact beyond what is immediately present to the memory and senses. We should never know how to adjust means to ends, or to employ our natural powers in the production of any effect. There would be an end at once of all action, as well as of the chief part of speculation."

On the moral plane, habit may be good or bad. It is thus that the habit of work, of discipline, of order, of method, constitutes a fundamental requirement of pedagogy. Examples of habit in daily life as well as in medicine are universally known. Thus the application of the term "habit" is certainly not limited to the pharmacological effect of certain drugs liable to produce addiction, and its significance does not correspond exactly to the concept that one has in mind when referring to the substances which are the object of the present study.

The difference between "habit" and "addiction" is evident from the definitions recently established by the Expert Committee on Drugs Liable to Produce Addiction, World Health Organisation³. After long deliberation this Committee arrived at the following definition of "habit forming" in the sense which interests us: "A habit-forming drug is one which is, or may be, taken repeatedly without the production of all the characteristics outlined in the definition of addiction and which is not generally considered to be detrimental to the individual and to society."

This definition therefore covers the non-addiction-producing drugs in the full sense of the word, such as tobacco, coffee and others. In establishing its definition, the Committee of Experts wished to draw a sharp distinction between true addiction and habits of various kinds. The international conventions show an equally distinct tendency to avoid the term "habit" and to replace it by "addiction." Moreover, so that no doubt remains, the Expert Committee was of the opinion that the expression "habit-forming" in the sense of "addiction-producing" should be eliminated from all texts concerning addiction.

For reasons which have been explained elsewhere⁴ the English term "addiction" is much more appropriate than the corresponding expression in the Latin languages (the French "toxicomanie" and analogous words in Spanish and Italian). The Latin "addicere" meaning submission or attachment to a master is therefore quite appropriate in the present case.

ADDICTION

Even more serious are the difficulties in defining the term "drug addiction" in a manner corresponding fully to the properties and effects of various drugs, even just of those which figure in the international documents. These difficulties have a double origin: on the one hand, we know still very imperfectly the fundamental mechanism of drug addiction, in spite of far-reaching scientific research, and on the other hand, there are diverse types, pharmacological as well as clinical, of addiction, as has been recognised since experimental and clinical medicine has dealt with this problem.

SOME ASPECTS OF DRUG ADDICTION

The definitions in the texts of the various authors resemble one another in certain respects, but differ in others; in general, they are not valid for all the drugs which come under the provisions of the international conventions. Moreover, no official definition is to be found in these documents; even the technical committee of the 1931 Conference refused to give one. For all these reasons, in response to requests by the Commission on Narcotic Drugs of the Economic and Social Council of the United Nations, the Expert Committee on Drugs Liable to Produce Addiction has established the following definition:

“Drug addiction is a state of periodic or chronic intoxication, detrimental to the individual and to society, produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include:

(1) an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means;

(2) a tendency to increase the dose;

(3) a psychic (psychological) and sometimes a physical dependence on the effects of the drug.”

This definition applies to all the substances embodied in the various diplomatic instruments and has, for this reason, been drawn up very carefully in order to avoid mentioning a symptom which would not be observed in all the types of addiction. It is to be hoped that the quoted definitions, which have been adopted by the Executive Board of the World Organisation, will soon be admitted and employed by all those who deal scientifically with these questions.

From the general point of view, drug addiction is characterised by euphoria (at a certain stage), by tolerance of the dose absorbed, without, however, the extension of this tolerance to all centres and all effects, and by physical and psychic dependence.*

The physical dependence is characterised by a change in certain normal functions which necessitates continuous administration of the drug. But psychic dependence may be considered the essential feature of drug addiction. The decisive factor which proves the addiction and determines the diagnosis is a psychosomatic syndrome typical of abstinence, comprising psychic and physical phenomena, the latter being due to “deformed” physiological processes. The psychic phenomena are at times more marked than the physical manifestations.

During drug addiction the cellular functions of the individual demand the presence of the drug. There is no certain proof that true addiction can be voluntarily abandoned as with the tobacco habit; the possible cases of withdrawal without medical aid may be counted among the very rare exceptions which always present themselves in the biological

* C. K. Himmelsbach (*Publ. Hlth. Rep.*, 1937, Suppl. 125) has contributed in a remarkable manner to the definition of addiction to opiates. Eddy has given a critical analysis of drug addiction; see Krueger, H., Eddy, N. B., and Sumwalt, M. “The Pharmacology of the Opium Alkaloids,” *Publ. Hlth. Rep.*, 1941, Suppl. 165, 687. Physical dependence is also called “habituation.” This word seems, however, less suitable owing to the risk of confusion with “habit.”

field. However, even then, it is wise not to forget that the withdrawal of the pharmacological effects constitutes only the first stage of the treatment.

THE DISTINCTION BETWEEN ADDICTION AND HABIT

Tobacco is a good example of the distinction between addiction and habit; we employ intentionally the term "habit" in speaking of tobacco. In our opinion, a distinction should be made between the individuality of the subject and, as it were, the individuality of the substance; the two must run together, one might almost say collaborate, in order that addiction in the true sense of the word may develop.

The drugs liable to produce true addiction have the property of creating addiction in all persons who take them long enough in sufficiently large doses; it is thus that anyone who regularly uses morphine over a certain period—even the most healthy subject, physically as well as mentally—cannot avoid experiencing an imperative, not to say tragic, need for recourse to morphine. If, in certain cases, thanks to the healthy mental constitution of the subject, psychic fixation phenomena do not occur, or at least develop to a lesser degree, a physical subjugation is nevertheless established which necessitates the continued taking of the drug until treatment *lege artis* be commenced. When the psychic constituent of addiction is non-existent or nearly so, it is proper to speak of a chronic malady due to morphine and not of an addiction proper, because there is not that manifestation of psychic dependence which is to-day considered the essential feature of addiction. In these cases also marked tolerance may occur, causing an increase in the dose. Here, too, dis-intoxication is necessary, but the prognosis is incomparably more favourable and promises a cure.

Thus, the inherent tendency of the substance to produce addiction is one of the principal characteristics of the drug. However, the period necessary for developing addiction and the degree to which it may attain depend on the personality of the subject. This essential property of producing addiction distinguishes substances from others which are used by "habit," for example, tobacco. The latter does not perforce produce tolerance, or, at least, tolerance is not one of its important characteristic effects. There are many smokers, and even heavy smokers, who are able to deprive themselves at any moment of their pleasure, for the active substances of tobacco do not enter into their cellular metabolism; at least, no observations or proofs exist from which this can be established, whilst the opposite is the case with morphine. If the chronic smoker experiences difficulties in breaking himself of the habit, if he manifests neuropathic symptoms, it is his own individuality which is the cause and not the substance⁵.

Incontestably, if one thinks only of the first experiments of the school-boy, a certain tolerance is also produced with tobacco, and similarly with numerous other substances of non-addictive character; we say "a certain" tolerance because this phenomenon does not correspond to the classical form of true tolerance which automatically necessitates the

SOME ASPECTS OF DRUG ADDICTION

increase of the dose in order to avoid abstinence symptoms. Moreover, experiments on inveterate smokers and non-smokers indicate that neither present any difference as to the intensity and duration of elimination of nicotine, which does not accumulate in the organism. With tobacco, too, variations in individual sensitivity, especially to nicotine and carbon monoxide, arise from the constitution of the individual and not from the nature of the substance.

If tobacco was in reality addiction-producing, each smoker would be, after a comparatively short time, the victim of his petty pleasure, and could no longer be considered as a simple user of tobacco, but as an addict with all the well-known consequences which this term implies: decadence, necessity for treatment, etc. It is important to recognise these fundamental differences between addiction (morphine) and habit (tobacco), if the nature and meaning of drug addiction are to be correctly understood.

TOLERANCE

Tolerance does not necessarily imply an already existing addiction; it signifies only that the reaction of the organism to the same dose of substance, repeatedly administered, has diminished little by little, and that a functional adaptation has taken place so that, to reproduce a similar or equivalent effect, larger and larger doses of the same substance must be administered.

Tolerance starts before true addiction is developed. It may finally become so great that even enormous doses of the substance are unable to reproduce the effect of the initial dose. Thus, tolerance may be the first indication that a substance is liable to produce addiction. It is known that tolerance is not essential to the development of psychic dependence (in cocaine addiction, for example). On the other hand, the development of tolerance varies qualitatively as well as quantitatively according to the various tissues and systems of the organism. A simple tolerance to the analgesic action of opiates may be produced in the majority of animal species, but it is not possible to predict from it that a substance under test will have addiction-producing properties⁶.

Different types of tolerance exist: pharmacological tolerance in respect of certain medicaments which do not produce addiction, for example, organic nitrites; individual tolerance, for example, that of many persons for caffeine; the tolerance of certain animal species in respect of some drugs, for example that of rabbits for belladonna. We recognise also "crossed tolerance," when a subject (experimental animal or human being) which tolerates an addiction-producing substance may equally tolerate another substance having analogous properties; crossed tolerance thus gives a valuable indication of the liability of the second substance to produce addiction. This substitution effect is of a major importance for our subject.

THE RECOGNITION OF ADDICTION-PRODUCING PROPERTIES

Considerable difficulties are encountered in determining at the outset with sufficient rapidity and certainty whether a new analgesic substance

is addiction-producing or not. Observations made on animals have only a limited value, owing to the dissimilar reactions of different species to the analgesic and other central effects, notably the development of dependence. A substance may act on various species of animals in varying degrees and in different proportions and the results obtained may reveal relatively great qualitative differences and even contradictory results, in particular in man. Moreover, the comparison of the action of a substance with that of morphine may reveal different effects according to the species of animals and the organs affected; it is therefore only with much caution and in a limited way that the results obtained with animals can be applied to man.

An important fact is, that in infra-human animals phenomena corresponding to the euphoria so often evoked in man have not been observed. Whilst even after a fairly long administration of pethidine or methadone to the monkey, the desire for these drugs was not noticed, in man euphoria has been clinically well established.

Considering the three principal manifestations of addiction, namely, tolerance, physical dependence and psychic dependence, we may say that small animals could be used to observe the development of tolerance and perhaps also for the study of the mechanism of addiction. For confirmation of the symptoms of abstinence—corresponding to physical dependence—only the dog and the monkey, however, can show phenomena comparable to those produced in man, although not with all the drugs which produce those phenomena. These animals also show individuality, and the reaction of abstinence may, therefore, vary considerably. In addition, the observations made with methadone are contradictory: Scott and his collaborators, after having administered this drug to dogs for several weeks, found no sign whatever of abstinence^{7,8}, whereas Wikler and Frank⁹ observed a characteristic syndrome. In the monkey it has not been possible to observe symptoms of pethidine¹⁰ or methadone abstinence¹¹ (at least the phenomena of the latter have been very limited), while the signs of withdrawal of morphine are particularly well marked¹². Nevertheless, the monkey (Rhesus) is still the most appropriate species for these basic experiments.

The third manifestation of addiction, psychic dependence, is only to be observed in man. Some similar phenomena seen, for example, in the dog are sometimes interpreted as such, but in reality they do not correspond to what is understood by "psychic dependence," not forgetting that some phenomena apparently somatic, such as tachycardia, vomiting and even fever, may be "psychic" in their origin¹³. The result, therefore, is that the distinction between the two aspects "physical" and "psychic" is effaced; the schematic system evolved by man in order to explain the phenomena of nature breaks down; nature remains stronger than we. We must content ourselves, then, with the very modest confirmation that the abstinence picture depends fundamentally on the personality of the addict. This conclusion appears very limited, but it is of primary importance. There is now a tendency to attach greater value to psychic dependence than that often displayed by pharmacologists, and to-day it is more

SOME ASPECTS OF DRUG ADDICTION

evident than ever that only the observation of man can furnish us with the bases of a valid judgment.

On the other hand, in order to determine the liability of a substance to produce addiction, experience of its use in man over several years would be necessary. But the protection of the public and the need for control require that all new substances of this pharmacological group should, firstly, be examined in comparison with other known substances for the production of euphoria in former addicts and for the possibility of substituting it for morphine in morphine addicts. Use is therefore made of the phenomenon of crossed tolerance.

This the Expert Committee has expressly recognised in saying, "The committee wished to emphasise that all available evidence at the present time indicates that any substance which will sustain an established addiction—i.e., will adequately replace the drug which has produced the addiction—must be considered as also capable of producing addiction."

THE LEXINGTON TEST

Starting from this fact, a method of analysis has been created in the United States which we will call "the Lexington Test" because it was in the Research Division, U.S. Public Health Service Hospital, Lexington (Kentucky), that this method was worked out; for the time being it is not applied elsewhere. Briefly, it is as follows¹⁴. From the addicts ordered by the Courts to be sent to this hospital for treatment, volunteers with a poor prognosis for a permanent cure are selected. By "cure" we understand "complete rehabilitation both mentally and physically and permanent relief from the addiction"¹⁵. Generally these persons have already undergone several courses of disintoxication followed by relapses. For the test, one of the following four methods, of which we can only indicate the principles, is applied:

(1) Administration of single doses of the drug to former morphine addicts with a view to discovering euphoria; this is clearly defined by certain characteristic symptoms. In case of non-reaction the injections are repeated with progressively increased doses until the euphoric effect obtained by about 30 mg. of morphine, administered to the same person on earlier occasions, has been reached. If euphoria is not detected, larger and larger doses are administered up to the danger point.

(2) Determination of the effect of single doses on the intensity of morphine abstinence in the case of grave morphine addicts; the effect is evaluated with the aid of the well-known Himmelsbach system ("hourly point score system")¹⁶; this system attributes to each of the abstinence phenomena a certain number of points and the determinations are effected hour by hour, the results obtained being added up. The total indicates, by comparison, the gravity of the symptoms of abstinence in the particular case. The procedure is as follows:—morphine is suddenly and completely withheld and the points are counted; then the substance to be studied is administered and again the count is made; it may then be confirmed whether this last drug abolishes or relieves the abstinence

symptoms due to morphine. If such is the case, it is quite likely that the second drug will give rise to physical dependence.

(3) Substitution of the new drug for morphine in cases strongly addicted to the latter; addicts to whom the minimum dose of morphine for prevention of abstinence has been given, receive instead the drug to be studied. The dosage and frequency of administration of the drug under test are determined by previous pharmacological data. If the new drug maintains physical dependence and if, after withdrawal, abstinence symptoms appear, this substance is regarded as liable to produce physical dependence.

(4) "Direct addiction" is considered to be the best method of determining the addiction-producing property because it gives a complete picture of the different aspects of the addiction. The substance is administered to former morphine addicts after an abstinence of 3 months or more, starting with doses normally used in clinical practice, and raising the dosage according to a carefully established scheme. Before undertaking the experiment the subjects are submitted to a very thorough physical and mental examination. Unfortunately, this method demands an inordinate expenditure of time and labour, since the observations must be extended over periods of 3 to 7 months, and require the full-time services of the hospital personnel.

Incontestably the Lexington Test is the best available at present. From time to time the objection is raised that the subjects for experiment, being former morphine addicts, manifest physical and psychic dependence more easily and more rapidly than would non-addicts. The only reply that can be given is that for ethical reasons voluntary addicts are the only individuals available for such experiments. It has also been objected that the same dangerous substances, when used in medical practice in clinical doses, have not produced addiction, and furthermore that former morphine addicts would tend to have reactions that are not observed in "normal" patients. However, those who make these criticisms forget that the task to fulfil is not only to determine the clinical effect, but also the possibility of abusive use. In this respect, people inclined to addiction offer an advantage because they compare with their previous experience. In any case, the Lexington Test appears much more humane than the attitude which denies the practical danger of certain drugs of this group, until the moment when cases of addiction which could have been avoided occur among patients suffering from other diseases.

A future stage in the analysis would be to perform this same test with non-addicts who would not even be former addicts. One might envisage the use of these drugs with patients who have need of a powerful analgesic over many months, for example, with an inoperable cancer. We will not discuss here the moral aspect of this idea; from the practical point of view this would be without doubt a decisive step forward.

To characterise the tendency to produce or not to produce addiction it is sufficient therefore to observe some "secondary" cases of addiction created by the new substance. According to the facts at present known, the Lexington Test gives trustworthy results. Up to the present

SOME ASPECTS OF DRUG ADDICTION

“primary” cases, that is to say, the development of addiction in persons who have not previously abused other addiction-producing drugs, have never failed to manifest themselves when a substance of this nature has been put on the market.

ADDICTION LIABILITY OF NEWER DRUGS

How many times has a substance been brought forward in the belief that it had morphine-like effects, but did not produce addiction, only to find that the hopes raised were vain? Diacetylmorphine, launched some fifty years ago under the name “heroin,” is a classical example of this. Acedicone is another—happily without great practical consequence—and pethidine is one of the most recent and best known¹⁷. In regard to all these substances, at the time of the first “clinical tests,” their harmlessness was insisted upon. But when they were put on sale, the addicts by incomprehensible means—of telepathy one would say—became aware of their true character long before the physicians and Government authorities. Tragic cases are known where a primary addiction has been unconsciously created because the subject or the physician trusted the publicity surrounding a new analgesic said to have the properties of morphine without its dangerous effects; but other cases are also known where addicts, broken down by the lack of opiates and consequently more or less inclined to submit themselves to treatment, have found in such a drug, on sale without the usual restrictions, the *deus ex machina* which enabled them to continue to satisfy their addiction.

There has no doubt been a certain carelessness on the part of those who, until recent years, launched products of this group without taking the necessary precautions and who even persisted thereafter in affirming their harmless nature, in spite of the experience with dihydrodesoxymorphine-D which had already shown clearly how errors having such serious consequences could be avoided. It will be remembered that it was a well known and reputable North American team who, about twenty years ago, realised the chemical composition of this substance and proceeded to the first tests. Out of a range of approximately 125 morphine derivatives this substance was shown to be the most promising, because of its analgesic properties 5 to 10 times greater than those of morphine. The preliminary animal tests caused a favourable opinion, but later experiments carried out on humans (the Lexington Test) brought out “a high degree of addiction liability.” This substance has been judged “much more dangerous than heroin,” so much so that the U.S. Government preferred to prohibit its manufacture and import^{18,19,20}. Notwithstanding, a well-known pharmaceutical firm in another country launched this compound under another name, but, in spite of its extraordinarily high analgesic power, this drug has not met with great success. No case of addiction has, however, been published, perhaps due to its very limited use.

Methadone (amidone) provides a more recent example. Although the addiction-producing properties of this substance were soon recognised

in the Anglo-Saxon countries, for a long time it was maintained in its country of origin (Germany) that it was inoffensive from that point of view. The clinical administration of such a drug to a small number of patients who suffer from an illness requiring a powerful analgesic does not suffice to determine its addiction liability. Already some cases of addiction to methadone have been described. History therefore repeats itself: a *nihil obstat* is granted on the basis of insufficient observations, then involuntary cases of true addiction are produced. The misinterpretation of the facts goes so far that some pharmacologists have made personal representations to us that methadone should be placed in a privileged category, as the administration of this drug, even during long periods, does not produce tolerance and still less addiction. However, an exceptional status of this kind is not foreseen in the Protocol of 1948 which deals with the new synthetic substances and there is at present no governmental intention to create one. In addition, in the light of the experiments carried out with other substances mentioned in this report, such a decision could be considered only after some years of wide practical use: 5, 10 or 20 years. In any case, medical prescription is not prevented by regular legal and administrative control, as we have explained elsewhere¹⁷. A simple obligatory ruling would not in any case be sufficient until such time as the innocuity, relative or absolute, of the drug could be guaranteed.

Recently, a case was described of a patient who preferred intramuscular injections of methadone to those of pethidine and even eucodal²¹. Two other cases were put forward later; those of two doctors, one a woman, who managed to satisfy their drug addiction with methadone, even orally; one of these cases might possibly be "primary." We must stress the fact that the two doctors—who could be classed as methadone addicts—used this substance without hesitation because its non-addiction-producing character had been "repeatedly insisted upon."

Very recently, new cases of methadone addiction have been published, one of them certainly of primary and another of probable primary addiction²². Furthermore, a whole family has apparently become addicted to methadone. Thus, unfortunately, our expectation that primary cases would appear has been confirmed. Methadone is not, therefore, as safe in practice as has been pretended and we must regretfully confess that history repeats itself once again.

The pethidine-type compound which has caused a sensation among the specialists is ketobemidone, 1-methyl-4-methoxyphenyl-4-propionyl-piperidine. The ten men who voluntarily submitted to "the Lexington Test" have all clearly expressed their preference for it, and some of them were even under the impression that they had received a large dose of diacetylmorphine or dilaudide! In addition, following the sudden withdrawal of the drug after a period varying from 42 to 60 days, "an abstinence syndrome developed very rapidly . . . which was so intense as to be regarded as potentially dangerous to life . . .," so that the medical observers felt compelled to alleviate the state of abstinence by hypodermic, even intravenous, administration of morphine

or methadone. What is more, these last substances have had a much less pronounced effect on the symptoms following the suppression of ketobemidone than would have been the case with a severe morphine abstinence. In short, ketobemidone appears to be "one of the most addictive drugs yet discovered" and its addiction liability "is as great as that of heroin."

Following these findings, the American manufacturers who hold the patent of ketobemidone have voluntarily suspended its production and have refrained from launching it on the market^{23,24}. This attitude is in agreement with the research workers of Lexington Hospital, who state: "the evidence is unequivocal that ketobemidone produces a type of addiction which is very similar to addiction to the drugs of the morphine series and which is so great that the drug should not be used in clinical medicine unless it can be shown to possess great advantage."¹¹

By using ketobemidone prepared by a different synthesis²⁵ and sold under a trade mark by a well-known pharmaceutical firm of another country, its powerful analgesic properties have been confirmed clinically on some 140 patients suffering from painful diseases²⁶. This study did not give very far-reaching results with regard to the addiction liability of ketobemidone, and the report indicates that further observations will be necessary to obtain a definite result. A diminution of the analgesic effect in certain cases of malignant tumour (6 out of a total of 29), which permits of the supposition of an apparent tolerance, is, however, confirmed, and it is thought that this tolerance could be caused by the progress of the morbid process, which thesis has still to be proved.

The producing firm insists on the analgesic effect of its product even against most violent pain and attributes to it an efficacy superior to that of morphine²⁷. It is, however, doubtful whether ketobemidone really possesses the "great advantages" mentioned above to such a degree that they could compensate for the grave danger that this drug presents for actual and former addicts, and for those who, because of their constitution, will become the addicts of the future.

DIACETYLMORPHINE

The past offers us a very similar example in that of diacetylmorphine. In spite of certain good therapeutic results, many doctors and many countries have already given up its use because of the great danger of addiction it presents. It has been claimed as one of the particular advantages, that with diacetylmorphine the therapeutic doses are one fifth to one tenth of those of morphine. This juggling with the posology does not, however, constitute an essential advantage. The idea, although widely spread, that the dose is an important factor rests on an erroneous conception of the dynamism of addiction; for, if the therapeutic dose is less, the average dose necessary to maintain addiction is equally so.

Twenty-four countries have already forbidden the manufacture and sale of diacetylmorphine—in other words, have not legalised its therapeutic use. We do not believe that this restrictive measure has created a gap in the therapeutic armament of these numerous countries, nor

that a single patient has had to suffer from the disappearance of diacetylmorphine from the pharmacy.

Nevertheless, although more than half a century has passed since the introduction of heroin, and although the great danger which it presents is now recognised, world medical opinion is not yet unanimous on the need to dismiss it from the therapeutic arsenal. It must be stated that production of diacetylmorphine "is still on the increase." The Expert Committee "expressed grave concern over this situation, particularly as some important countries continue to maintain that their physicians consider this drug indispensable for certain medical uses." It was of the opinion that "further information is urgently needed as to the reasons governing the continuing use of diacetylmorphine, and particularly with regard to its replacement by less dangerous drugs."³ In consequence, the Executive Board of the World Health Organisation recommended "that the Director-General take steps to secure information on the use or dispensability of diacetylmorphine in the various countries, through Governments"; in accordance with the resolution adopted, the Director-General addressed a circular letter to the member-states of the Organization.

The position is certainly different from that of preceding years; at present physicians dispose of other morphine derivatives and new synthetic substances which have similar effects. They might, therefore, be persuaded more easily to give up the use of a product which is assuredly the most dangerous of the morphine derivatives generally available.

The question of the manufacture and sale of diacetylmorphine should be considered as an *international* matter. There is no doubt that in certain countries physicians, particularly of an older generation, have been familiar with this drug since its introduction and have, so to speak, learnt to handle it. However, the international struggle against the abuse of diacetylmorphine will not be brought to a satisfactory conclusion as long as there is still "legal" diacetylmorphine in the world. Its total suppression would clarify the position for all the authorities entrusted to ensure its control, whether they be national or international. We are sure that the national public health administrations and medical bodies of some countries would give a good example of international co-operation in making such a generous gesture in the interest of all, even if, in their own country, the existence of this drug on the pharmaceutical market does not seem to them to constitute a danger.

THE MORPHINAN DRUGS

Recently synthesised substances of the morphinan type may be mentioned here²⁸. These, in our opinion, should be considered as derivatives of morphine, though other authors do not agree because these compounds are not obtained directly from morphine. The most interesting compound of this group is 3-hydroxy-*N*-methylmorphinan, the structure of which resembles closely that of natural morphine²⁹. In fact, it differs chemically from morphine only in the absence of an oxygen bridge, the

alcoholic hydroxyl in position 6 and a double bond in the aliphatic nucleus, or in other words, it is dihydrodesoxymorphine-D without the oxygen bridge. More recently, Grewe³⁰ has synthesised tetrahydrodesoxycodine and has confirmed its identity with tetrahydrodesoxycodine obtained from natural sources. In this way, he has established for the first time the proof that the morphine formula developed by Robinson 25 years ago, is correct.

3-hydroxy-*N*-methylmorphinan (Nu 2206, Dromoran) not only produced all the qualitative effects of morphine in experimental animals, but was also stronger in action and longer in duration than morphine. It seems to be most significant that this drug is also highly active by the oral route³¹. Its analgesic power is, however, weaker than that of dihydrodesoxymorphine-D, apparently owing to the lack of the ether-oxygen bridge. According to the few clinical observations known up till now, it has a prolonged analgesic action with smaller doses than necessary with morphine³². Its addictive character has been stated³. After withdrawal, signs of abstinence were as intense as those after addiction to equivalent doses of morphine³³.

CODEINE AND METHADONE IN THE TREATMENT OF ADDICTION. ORAL ADMINISTRATION

The advantages—and disadvantages—which the new synthetic substances of the pethidine and methadone type present in their daily clinical application, are too well known to require consideration here. We shall therefore draw attention to only two points.

(1) *The use of methadone during withdrawal.* It has happened from time to time that opiates have been employed during disintoxication in order to relieve the symptoms of abstinence in morphine addicts. The first drug to be used was heroin, of which it was said at the time (1898) that it offered all the advantages of morphine without its drawbacks, notably that of producing addiction. Heroin, was, consequently, considered for a certain time as a substitute product. We know, however, the sad results that followed; that is to say, the development of addiction to morphine plus heroin and to heroin itself. Later, the use of codeine was recommended for the same purpose. For some years the Lexington Hospital has used this substance during rapid withdrawal; apparently there is no reason to fear the creation of codeine addiction following this treatment, for Kolb and Himmelsbach^{34,35} mention no danger whatever of this type. We have, however, expressed certain doubts³⁶. Similar remarks apply to ethylmorphine which has been used for the same purpose, although to a much smaller extent. For obvious reasons there is no question of using dilauidide as a substitute for morphine, as suggested by Lambert³⁷.

However, these "related" palliatives have now been supplanted by methadone for disintoxication. Taking it for granted that methadone creates less severe symptoms of abstinence than morphine, morphine is first replaced by methadone and then the latter is dispensed with in the

ordinary manner. This method of substitution was previously advocated with diacetylmorphine addiction. As diacetylmorphine acts strongly on the central nervous system, and notably on the respiratory centre, it has often been recommended that it should first of all be replaced by morphine or codeine, rather than to stop abruptly the heroin addiction³⁶.

Extensive researches at Lexington Hospital have demonstrated the efficacy of methadone in the treatment of morphine addiction (Isbell, Wickler, Eddy, Wilson and Moran³⁸, more recently confirmed by Schader³⁹). Administered from the beginning in a dose of 1 mg. for 4 mg. of morphine, it suppresses the abstinence symptoms; the proportion may be brought little by little to 1 mg. of methadone for 12 mg. of morphine, after which abrupt withdrawal is tolerated without great inconvenience. The symptoms of abstinence *per se* are much less severe than those caused by morphine; for example, the painful muscular cramp which accompanies the withdrawal of morphine is completely absent. The symptoms of abstinence do not appear during the first two days, which confirms the observations of Sattes⁴⁰, the development of abstinence is therefore slower than with morphine. According to Brown⁴¹, methadone is "the most effective substitutive therapeutic agent yet employed¹¹". It appears to us that methadonisation of the morphine addict as a fundamental factor of physical (pharmacological) disintoxication is a most important step at the beginning of the cure, particularly because this form of softened withdrawal helps to establish that confidence between physician and addict which is of primary importance for the success of the essentially psychotherapeutic treatment which has to be continued for a long time.

For the moment it does not seem that the use of methadone during withdrawal is regarded as a real danger so much as a fear, according to Sattes⁴⁰, that the addict will learn from the physician himself of the existence of a new drug to which he can have recourse in the event of a future "need." Pieck²² also emphasises this danger. It is known that in such cases it is sufficient for a "need" to be created by a small upset, an everyday inconvenience, not even an intense pain, but a headache or a simple indisposition. Thus, owing to the latent danger that methadone presents, national and international control must be established and exercised with the same rigour as for other drugs liable to produce addiction.

(2) *The oral use of the new substances of the methadone type.* These drugs as well as metopon (methyldihydromorphinone), act also in a satisfactory manner when administered orally or rectally. While metopon may only be so used, methadone may also be administered parenterally, but it seems that in general injections should be avoided.

If experience confirmed these observations, there would result a considerable advantage. For a long time now we have insisted on the fact that, if at all possible, the act of injection itself should be avoided, otherwise the "needle addiction" of French authors may subsist even after the withdrawal, if only from force of habit and for pleasure⁴².

SOME ASPECTS OF DRUG ADDICTION

Very often the patient who suffers from a pain associates from the outset the idea of morphine with the injection which is given to him, with all the psychic consequences which may arise therefrom: this is a thing to be avoided.

SPECULATION ON FUTURE DEVELOPMENT

The new synthetic drugs are no doubt most promising analgesics. Those available to-day have already replaced morphine to a certain extent, and it can be expected that other more suitable drugs will appear.

It must not be forgotten that the greater part of the morphine manufactured is converted into codeine because the small proportion of the latter which is found in opium is quite insufficient for the therapeutic requirements. The figures in Table I illustrate this fact⁴³.

TABLE I
ANNUAL FIGURES FOR THE CONVERSION OF MORPHINE INTO CODEINE FOR THERAPEUTIC USE

Year	Quantity of morphine manufactured (in kg.)	Quantity of morphine converted into		Total per cent.
		methyilmorphine (codeine)	ethylmorphine (dionine)	
1936	36·884	23·901	2·828	72·4
1946*	43·799	35·631	3·509	89·3
1947*	53·764	41·286	4·515	85·2
1948*	54·718	43·933	4·390	88·3

* The figures for the years 1946, 1947 and 1948 are incomplete owing to lack of statistical returns from certain countries, but this does not affect the principle of the converted percentages.

It is therefore possible to forecast that once the synthesis of a perfect substitute for codeine has been established, the manufacture of morphine and ultimately even the culture of the opium poppy will become commercially and economically much less interesting. It might be that the pharmaceutical industry and perhaps even national bodies, in particular in the countries not producing opium, would appreciate not being bound by the result of the harvests and market prices, and would prefer an independence unknown until now, thanks to the production of synthetic analgesics in the country itself.

REFERENCES

1. Confucius, *The Wisdom of Aphorisms*, Ed. by Lin Yutang, Modern Library, New York, 1936, 183.
2. Hume, *An Enquiry concerning Human Understanding*, Section V, part I.
3. *Expert Comm. on Drugs Liable to Produce Addiction, World Hlth. Org. Tech. Rep. Ser.*, 1950 (21).
4. Wolff, P. O., *Journées therap.*, 1950, Paris, Dion to be published.
5. Wolff, P. O., *An. Soc. cient. argent.*, 1947, **143**, 25.
6. Seevers, *Ann. N.Y. Acad. Sci.*, 1948, **51**, 98.
7. Scott and Chen, *J. Pharmacol.*, 1946, **87**, 63.
8. Scott, Kohlstaedt, Robbins and Israel, *Fed. Proc.*, 1947, **6**, 370.

P. O. WOLFF

9. Wikler and Frank, *Fed. Proc.*, 1947, **6**, 384.
10. Barlow, *see* Seevers No. 6.
11. Woods, Wyngaarden and Seevers, *Proc. Soc. exp. Biol., N.Y.*, 1947, **65**, 113.
12. Cochin, Gruhzt, Woods and Seevers, *ibid.*, 1948, **69**, 430.
13. Wikler, *Ann. N.Y. Acad. Sci.*, 1948, **51**, 106.
14. Isbell, *Ann. N.Y. Acad. Sci.*, 1948, **51**, 108.
15. Wolff, P. O., *Bull. Hlth. Org. L. of N.*, 1946, **12**, 498.
16. Himmelsbach, *J. Pharmacol.*, 1939, **67**, 239.
17. Wolff, P. O., *Bull. World Hlth. Org.*, 1949, **2**, 193.
18. Eddy and Himmelsbach, *Publ. Hlth. Rep., Wash.*, 1936, Suppl. 118.
19. L. of N. Advisory Comm. on Traffic in Opium and Dangerous Drugs, *Minutes of 21st Session*, 1936, 25.
20. *Ibid.*, *Minutes of 22nd Session*, 1937, 98.
21. Smoler, *Med. Klin.*, 1950, **45**, 277.
22. Pieck, *Med. Klin.*, 1950, **45**, 1429.
23. Eddy, *Off. Rec. World Hlth. Org.*, 1949, (19), 32.
24. Isbell, *J. Pharmacol.*, 1949, **97**, 182.
25. Kägi and Miesher, *Helv. chim. Acta*, 1949, **32**, 2489.
26. Bernstein, *Schweiz. med. Wchschr.*, 1949, **79**, 1159.
27. Gross and Meier, *ibid.*, 1949, **79**, 1154.
28. Grewe, *Angew. Chem.*, 1947, **59**, 194.
29. Schnider and Greessner, *Helv. Chim. Acta*, 1949, **32**, 821.
30. Grewe, Mondon and Nolte, *Liebigs Ann.*, 1949, **564**, 161.
31. Randall and Lehmann, *J. Pharmacol.*, 1950, **99**, 163.
32. Zaager, Sawtelle, Gross, Nagyfy and Tidrick, *J. Lab. clin. Med.*, 1949, **34**, 1530.
33. Isbell and Frazer, *J. Pharmacol.*, 1950, **99**, 361.
34. Kolb and Himmelsbach, *Publ. Hlth. Rep., Wash.*, 1938, Suppl. 128.
35. Kolb and Himmelsbach, *Amer. J. Psychiat.*, 1938, **94**, 759.
36. Wolff, P. O., *Bull. Hlth. Org. L. of N.*, 1946, **12**, 512, 534, 549.
37. Lambert, *New Engl. med. J.*, 1936, **215**, 72.
38. Isbell, Wikler, Eddy, Wilson and Moran, *J. Amer. Med. Ass.*, 1947, **135**, 888.
39. Schader, *Med. Klin.*, 1950, **45**, 1369.
40. Sattes, *Dtsche. med. Wchschr.*, 1950, **75**, 638.
41. Brown, *U.S. Armed Forces med. J.*, 1950, **1**, 328.
42. Wolff, P. O., *Bull. Hlth. Org. L. of N.*, 1946, **12**, 513.
43. *Rep. Permanent Central Opium Board, United Nations, Geneva*, 1949, (11).