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**EVALUATION OF  
DEPENDENCE-PRODUCING  
DRUGS**

**Report of a WHO Scientific Group**

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WORLD HEALTH ORGANIZATION

GENEVA

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**WHO SCIENTIFIC GROUP  
ON THE EVALUATION OF DEPENDENCE-PRODUCING DRUGS**

*Geneva, 9-14 December 1963*

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# EVALUATION OF DEPENDENCE-PRODUCING DRUGS

## Report of a WHO Scientific Group

The WHO Scientific Group on the Evaluation of Dependence-Producing Drugs met in Geneva from 9 to 14 December 1963. The meeting was opened, on behalf of the Director-General, by Dr O. V. Baroyan, Assistant Director-General. He outlined the motives for holding this meeting which was pertinent to the proper fulfilment of the Organization's functions under certain international treaties for narcotics control as well as to the newly established programme related to safety and efficacy of drugs in general.

Dr N. B. Eddy was elected Chairman, Dr M. H. Seevers Vice-Chairman, and Dr H. F. Fraser Rapporteur.

### 1. INTRODUCTION

One of the statutory functions of WHO is the taking of decisions with respect to the status of individual drugs under the relevant international treaties for narcotics control. Pertinent to this objective is the consideration of specific therapeutic effects, the liability of substances having such effects to produce drug dependence, and the evaluation of risk to public health when such substances are used for medical purposes or are abused. Obviously such considerations depend upon the availability and critical evaluation of the methods used for determining both the useful therapeutic properties and the kind and degree of dependence which may accompany drug use. Formerly, the only means of judgment was general impression gained from prolonged clinical experience. Under these circumstances, a very long time might have elapsed before a reasonably accurate appraisal was attained. More recently, there have been many approaches to the problem through experimental techniques applied to many species of animals as well as to man, while concurrently there has been an increase in diversity of agents potentially open to abuse, creating more complex problems of evaluation.

It is, therefore, appropriate at this juncture to consider the methods available and to appraise critically their applicability or deficiencies in regard to determination of dependence and their value for predicting what is likely to happen if a specific agent becomes available for use or abuse.

Points to be considered specifically are practicability, accuracy, and reproducibility in respect to ability to measure dependence properties.

## 2. TERMINOLOGY: DRUG DEPENDENCE

There are types of new drugs being developed continuously which induce effects that must be considered in connexion with, but are not adequately characterized by, the current definitions of addictiveness. Unfortunately, in practice a clear distinction between addiction and habituation is not always made. The two terms are frequently used interchangeably and often inappropriately. Very commonly, both lay and legal language tends to apply the term addiction to any and every type of misuse of drugs outside medical practice, with the connotation of serious harm to the individual and to society and often with a demand that something be done about it. Addiction can be defined in pharmacological and medical terms, and use of the term should be confined to conditions where such a definition applies. Broader use, such as that just referred to, can only create confusion and misunderstanding when drug abuse is discussed from different viewpoints. A clearly understood general term for drug abuse, medically and scientifically oriented and unrelated to socio-economic factors or need for control, is badly needed. The component in common in drug abuse appears to be dependence, and the term "drug dependence", with a modifying phrase linking it to a particular drug type for differentiation of the characteristics from one class of drugs to another, has been given most careful consideration.

Drug dependence is defined as a state arising from repeated administration of a drug on a periodic or continuous basis. Its characteristics will vary with the agent involved, but it is a general term selected for its applicability to all types of drug abuse and carries no connotation in regard to degree of risk to public health or need for a particular type of control.

The WHO Expert Committee on Addiction-Producing Drugs has recommended substitution of "drug dependence" for the terms "drug addiction" and "drug habituation".<sup>1</sup> The Scientific Group endorsed this recommendation of the Expert Committee. It undertook to outline the characteristics of drug dependence with a view to facilitating the appraisal of procedures for the determination of drug dependence of various types.

The nature and significance of drug abuse may be considered from two points of view: one concerned with the interactions between the individual and the drug and a second with the interaction between drug abuse and society. The first, which is termed drug dependence, is char-

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1964, 273, 9 (section 4).

acterized by the interplay between the pharmacodynamic actions of the drug and the special make-up of the individual. The second, the interaction between drug abuse and society, involves a wide range of conditions which are not considered in this context. The present discussion is limited to the biological foundation of drug dependence which serves *inter alia* as the basis for the evaluation of the sociological and epidemiological implications of drug abuse.

Individuals may become dependent upon a wide variety of chemical substances covering the whole range of pharmacodynamic effects from stimulation to depression. All these drugs have at least one effect in common. They are capable of creating a state of mind in certain individuals which is termed psychic dependence. This is a psychic drive which requires periodic or chronic administration of the drug for pleasure or to avoid discomfort. Indeed, it is the most powerful of all the factors involved in chronic intoxication with psychotropic drugs. With certain types of drugs it may be the only factor involved, even in the most intense type of craving and perpetuation of compulsive abuse.

Some drugs also induce physical dependence, an adaptive state characterized by intense physical disturbances when administration of the drug is suspended or its action is counteracted by a specific antagonist. These disturbances, the withdrawal or abstinence syndrome, display a specific spectrum of symptoms and signs of psychic and physical nature characteristic of each drug type. This condition is relieved by re-administration of the drug or by another drug of similar pharmacological action within the same generic type. No overt manifestation of physical dependence is evident if an adequate dosage is maintained. In certain types of drug dependence, notably in the case of morphine-like substances, physical dependence is a powerful factor in reinforcing psychic dependence.

Many of these drugs also induce tolerance, which is an adaptive state characterized by diminished response to the same quantity of drug or requiring a larger dose to produce the same pharmacodynamic effect. Both drug dependence and drug abuse may occur without the development of tolerance. When tolerance exists, marked increments in dosage may occur without a parallel increase in certain pharmacodynamic responses, thus permitting the rapid development of other adaptive processes especially those associated with the creation of physical dependence.

All drugs capable of inducing dependence may in higher dosage also be associated with psychotoxic effects leading to profound alterations in behaviour. These effects may occur with a large single dose or during the course of chronic drug administration, or they may be precipitated by withdrawal of the drug following chronic administration. The pattern of abnormal behaviour is within certain limits characteristic of each drug type, but wide variation occurs in individual responses depending, among other things, upon the pre-existing mental state of the person involved.

The characteristics of drug dependence show wide variations from one generic type to another, which makes it mandatory to establish clearly the pattern for each type. Even though some variations occur among individual members of each generic group, the consistency of the pattern of pharmacodynamic actions is sufficiently uniform to permit at this time accurate delineation of each of the following generic types: morphine; barbiturate; alcohol; cocaine; amphetamine; hallucinogens; and cannabis.

In order to establish a model for these several generic types the following description of dependence of the morphine type is presented. It is recommended that similar descriptions be prepared for all generic types of drug dependence. This would include dependence on alcohol which has already been considered by WHO.<sup>1</sup>

The outstanding and distinctive characteristics of dependence on morphine are that the three major elements—psychic and physical dependence, and tolerance—can be initiated by the repeated administration even of small doses and that it increases in intensity in direct relationship to an increase in dosage. This implies that dependence on drugs of this generic type may be created with quantities of the drug within the dose range generally used for therapeutic purposes.

The characteristics of dependence of the morphine type include:

(a) strong psychic dependence, which manifests itself as an overpowering drive (compulsion) to continue taking the drug and to obtain it by any means for pleasure or to avoid discomfort;

(b) development of tolerance, which requires an increase in dose to maintain the initial pharmacodynamic effect;

(c) an early development of physical dependence, which increases in intensity, paralleling the increase in dosage. This requires a continuation of drug administration in order to prevent the appearance of the symptoms and signs of withdrawal; withdrawal of the drug, or the administration of a specific antagonist, precipitates a definite, characteristic, and self-limiting abstinence syndrome.

With morphine, the abstinence syndrome appears within a few hours of the last dose, reaches peak intensity in 24-48 hours, and subsides spontaneously, most often within ten days. The time of onset, peak intensity, and the duration vary with the degree of dependence on the drug and the pharmacodynamic characteristics of the specific agent involved. Administration of a specific antagonist precipitates a more intense abstinence syndrome, which occurs explosively and lasts only a few hours.

The unique feature of the abstinence syndrome is that it represents changes in all major areas of nervous activity, including alterations in

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<sup>1</sup> For references see *Wld Hlth Org. techn. Rep. Ser.*, 1955, 94.

behaviour, excitation of both divisions of the autonomic nervous system simultaneously, and somatic dysfunction. The complex of symptoms and signs includes anxiety, restlessness, generalized body aches, and insomnia; yawning, lacrimation, rhinorrhoea, perspiration, mydriasis, pilo-erection, hot flushes, nausea, emesis, diarrhoea; rise in body temperature, in respiratory rate and in systolic blood pressure; abdominal and other muscle cramps; dehydration and loss of body weight.

The generic type of morphine-like compounds for which morphine is used as a standard of reference comprises substances with different chemical constitution varying in potency from those with low activity to others several thousand times as potent as morphine.

Generally speaking all substances in this category possess in varying degree the capacity to induce physical dependence. They are mutually interchangeable in that substitution of one for the other will maintain tolerance and physical dependence and prevent the appearance of abstinence phenomena. Variations exist, however, in the capacity of potent morphine-like compounds to induce psychic dependence.

There are also compounds within this generic class which possess pharmacodynamic features similar in a general way to those of morphine, making them potentially capable of inducing physical dependence when given in sufficient doses. These compounds, although capable of producing low-grade physical dependence in therapeutic dosage, are generally inadequate substitutes for morphine. In contrast to morphine, their effects are not usually sufficiently satisfying subjectively to induce significant psychic dependence. Codeine is generally recognized as a reference standard for this group.

### 3. METHODS OF EVALUATION OF DRUG DEPENDENCE

#### 3.1 Morphine and substances with morphine-like effects<sup>1</sup>

##### 3.1.1 *Tests for tolerance and physical dependence*

Because of the restrictions generally on tests in man, much effort has been spent on devising methods using laboratory animals, preferably one of the smaller species, which would correlate with and have predictive value for events in man. These methods were reviewed by the Group and their principles will be described. As far as possible, an appraisal will be made of their practicability. In all such appraisals, any reference to screening or to predictive value refers, of course, to usefulness at an early stage in the development or comparison of compounds as against eventual tests or

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<sup>1</sup> For a survey of laboratory and clinical methods see: Halbach, H. & Eddy, N. B. (1963) *Bull. Wld Hlth Org.*, **28**, 139.

experience in man. In spite of differences in drug action according to species and the difficulties in using data obtained in one species to predict possible effects in another, animal studies seem, in some instances, to be of predictive value for man.

(a) *Mouse*

It has been observed that for a number of drugs with morphine-like effects there is a significant correlation between rank orders for the "Straub Index" (ratio of lethality to Straub reaction in mice:  $LD_{50}$  divided by  $ED_{50}$ ) and physical dependence liability in man. A similar correlation has been observed for the ratio between lethality and analgesic action ( $LD_{50}$  divided by  $ED_{50}$ ). The scope of drugs surveyed in this way is not nearly wide enough for the method to be considered generally applicable to the prediction of physical dependence liability of new substances. In addition, the Straub index has been found to be very high for apomorphine, which has no physical dependence capacity according to experiments in the monkey and in man.

According to other studies, the development of tolerance and physical dependence in mice seems to be facilitated by continuous administration of morphine (base) in the form of pellets implanted subcutaneously. The nalorphine-induced withdrawal symptoms were not sufficiently consistent, however, to permit the use of this procedure for screening purposes.

(b) *Rat*

Single doses of substances with morphine-like effect have been shown to induce in rats characteristic pharmacodynamic effects, which were reversed by nalorphine or another specific antagonist. Such a response, including the demonstration of characteristic antagonism, might serve as a preliminary screen for the morphine-like character of a substance. Somewhat similar is the significant correlation which has been observed between a drug's activity as tested by the tail-flick method for nociceptive reaction and its capacity to induce physical dependence in man (analgesia) when the potency of the compound is high. On the other hand, for compounds of low potency, or with other methods of measuring "analgesia" such as the hot plate, the correlation is poor.

Many investigators have shown that rats react in a reproducible fashion to chronic administration of drugs with morphine-like effect by developing tolerance and physical dependence. The withdrawal symptoms, whether after abrupt withdrawal or precipitation by a specific antagonist, are sufficient in number and distinctiveness to permit a statement of significant differences when groups of compounds are compared. For optimal results, administration should be at regular intervals without interruption and the dose levels should be such as not to produce significant weight loss in growing rats. It may be that the rat is the preferred small animal species

for initial testing of a series of morphine-like drugs. The Group considered the choice of the rat especially desirable since it would permit the evaluation of analgesic properties and physical dependence liability in the same animal species.

Repeated administration of morphine or substances with morphine-like effects to rats has been shown to bring about a pattern of changes in rectal temperature indicative of the development of tolerance to the drug's effects, with cross-tolerance between different drugs, as well as reversal of the effects (as a sign of physical dependence) when nalorphine was given. For each of 20 compounds examined, a correlation was observed to exist between the temperature response to the drug and its physical dependence capacity in man, a finding that would encourage continuation of this experimental approach.

(c) *Guinea pig*

In experiments with morphine and codeine in guinea pigs, the development of tolerance and physical dependence was similar to that observed in rats. Therefore, the guinea pig might also be used for screening purposes. However, a difficulty might be the relatively high doses required initially in this species to produce an elevation of reaction time (analgesic tests) with morphine-like drugs.

(d) *Dog*

*Single doses* : As in the rat, morphine-like drugs induced characteristic pharmacodynamic effects in the dog and most of these were antagonized by nalorphine. This general picture would constitute presumptive evidence that a compound might produce morphine-like physical dependence.

*Prolonged infusion* : When morphine was infused at a constant rate over several hours, tolerance to its depressant actions developed progressively. If after some hours nalorphine was administered, the animal's behaviour soon came to resemble the abstinence syndrome produced by nalorphine in a chronically morphinized animal. It is questionable whether the symptoms demonstrate an acutely developed physical dependence or represent an unmasking of direct stimulating effects of morphine. In addition, it has not been established that the same phenomena would occur during prolonged infusion with other morphine-like agents.

*Chronic administration tests* : These are of three types. In the intact dog, tolerance and physical dependence developed characteristically and fairly rapidly during chronic administration of morphine once a day or with a smaller total amount given in divided doses. A characteristic abstinence syndrome followed the administration of nalorphine or abrupt withdrawal of morphine. Similar phenomena with many morphine-like agents and a good correlation with results in man have been demonstrated.

In the spinal dog (transection of the cord in the lower cervical or upper thoracic region) characteristic responses to morphine, especially in regard to reflex activity through the severed cord, with tolerance development and an abstinence syndrome were reported. When kept permanently on morphine, the spinal preparation could be used for substitution tests at weekly intervals. The results obtained were satisfactory, but the technical difficulties of preparation and maintenance of the spinal animal are a major obstacle to the more general employment of this technique.

Again, in the intact animal when physical dependence had been developed by administration of progressively increasing doses of morphine, abrupt withdrawal was followed by a significant and reasonably regular increase in motor activity (over-all movements per 24 hours). The number of movements in the second 24-hour period after withdrawal was many times the stabilized level of activity during morphine administration. When a standard dose of morphine was given at the beginning of the second 24-hour period, the number of movements recorded was no greater than before withdrawal. Consequently, a test drug showing similar effects when administered in a similar way would be judged morphine-like.

Records of motor activity and the effect of drugs thereon were not available except for 24-hour periods. Nalorphine was not administered to determine whether its effect was comparable to abrupt withdrawal, as with the other techniques. Few drugs have been compared with morphine for suppression of hyperactivity in the withdrawal phase or for the production of hyperactivity as a withdrawal phenomenon after chronic administration. In addition, any agent that reduces spontaneous activity in the dog might produce what appears to be a morphine-like effect during withdrawal. A further difficulty is the long period required for stabilization before carrying out the test. It should be noted that in this method the recording of motor activity is automatic, that is, completely objective, and on this account the method should be studied further.

(e) *Monkey (Macaca mulatta)*

The principle of the tests used to detect physical dependence in a monkey is similar to that employed in man: morphine-like drugs induce a characteristic pattern of pharmacodynamic effects when administered in single doses to non-tolerant monkeys; they suppress signs of abstinence due to abrupt withdrawal of morphine from dependent monkeys; and when administered chronically in increasing dosage they induce tolerance and characteristic physical dependence, with an abstinence syndrome similar to that seen in man.

*Single-dose administration for morphine-like effects.* When given a single small dose, monkeys showed a response similar to that of man except that the pupil dilated. The outstanding effect was central nervous

system depression characterized by decrease of awareness of, and diminished responsiveness to, environmental stimuli, and a decrease in apprehension. Despite considerable sedation, there was only a moderate degree of ataxia. Respiration was depressed. With this dosage there were no important cardiovascular effects and there was no postural hypotensive response. All the depressive effects could be effectively antagonized by nalorphine. Larger doses of morphine provoked convulsions.

*Determination of physical dependence capacity (single-dose suppression of morphine-like abstinence).* Past experience in animals and man indicates that any substance capable of complete suppression of the specific signs of morphine abstinence would produce physical dependence on chronic administration. In the single-dose test, a state of physical dependence was maintained by the subcutaneous administration of 3 mg/kg of morphine sulfate every six hours without interruption. After a stabilization period of not less than 60 days the monkeys could be utilized at weekly intervals. Drugs, identified by code number only, were administered initially at doses related to effectiveness for other actions (analgesic, anti-tussive, etc.) to two monkeys only. For successive tests (range finding) the dose was increased or decreased until that approximately equivalent to the standard dose of morphine (3 mg/kg) in suppression of abstinence signs was ascertained or toxic reactions which prevented further trial were observed. Drugs effective in the exploratory phase were tested further in cross-over Latin square design employing the standard dose of morphine, a placebo, a dose of the test substance judged to be equivalent to the standard morphine dose, and also one half and twice this dose of test substance. On the day of test, regular morphine injections were withheld for 12 to 14 hours until abstinence signs of intermediate intensity were observed. A single test dose was then administered and the monkey observed for six hours. The intensity of abstinence signs for each medication was plotted and the dose of the test substance equivalent to 3 mg of morphine in suppression of abstinence phenomena was determined by interpolation.

*Direct dependence test.* In certain instances, the test substance was administered chronically to supplement the results with single doses. The drug was administered at regular intervals (usually every 6 hours) without interruption in increasing doses as the development of tolerance permitted. A challenge dose of nalorphine was administered on the 14th and 28th days, and the drug was abruptly withdrawn at the end of the month. Signs of abstinence after nalorphine and after abrupt withdrawal were compared.

Many compounds (over 400) have been evaluated for physical dependence capacity, that is, for single-dose abstinence suppression potency; relatively few have been evaluated by a direct dependence test. The testing has been on a double-blind basis. It has included not only agents shown to be morphine-like in other tests and varying widely in potency, but also

some with other pharmacological actions, and a few for check purposes only.

Qualitatively, estimations of physical dependence capacity in the monkey have agreed consistently with observations in man; quantitatively there have been some divergences. The monkey was unusually sensitive to the effects of pethidine-like substances and, in comparison with man, relatively insensitive to benzomorphans. This difference between the monkey and man has not been too important, since both species have consistently responded positively to a wide range of both pethidine and benzomorphan derivatives. In only one instance (normorphine) has a drug given a negative response in the monkey and a positive response in man when tested for suppression of abstinence signs. Even in this case, signs of physical dependence were demonstrated in the monkey on chronic administration of the compound.

(f) *Man*

*Tests at the Addiction Research Center, Lexington, Ky., USA.* Drugs are referred to the Center by the Committee on Drug Addiction and Narcotics, National Academy of Sciences-National Research Council. They originate principally from pharmaceutical firms throughout the world and are screened by the Committee for their suitability for testing in man. Requisites are that they show clinical efficacy and that a thorough study has been made of their general pharmacology (see Annex).

Four general types of tests are performed: (i) evaluation of single doses by one or more routes of administration; (ii) substitution tests in morphine-dependent patients; (iii) direct dependence studies; and (iv) short-term intravenous preference tests.

The Addiction Research Center studies healthy prisoners with a long history of dependence on narcotics who volunteer for these experiments. They must be at least 26 years old and have a long history of delinquency for offences other than those concerned with narcotics. Most of them have been admitted to the hospital for treatment on several occasions, and all of them have a poor prognosis. They have been withdrawn from drugs for periods varying from several weeks to one or more years prior to beginning the studies and are excluded from the experimental situation eight or more months prior to their discharge from the institution.

(i) *Single-dose administration for morphine-like effects.* Even though the clinically effective dose is known, for reasons of safety a subclinical dose is administered initially to a single subject and he is observed carefully at hourly intervals, using a single-dose questionnaire designed to determine the pattern of subjective effects (subject rating). A parallel questionnaire is completed by an observer to detect overt changes in behaviour (observer rating). If no effect is demonstrated, the dose is

gradually increased in other subjects until a definite response is obtained. These exploratory studies are conducted on a single-blind basis ; that is, only the observer is aware of the nature and general action of the drug, when an attempt is being made to determine the dosage of the new agent equivalent to 20-30 mg of morphine sulfate subcutaneously. Later on, double-blind experiments are conducted, usually at two dose levels of the new drug and a standard drug, morphine, codeine, dextro-propoxyphene or a placebo, selected according to the potency of the drug being studied. These are always cross-over experiments ; the same individual is observed after he has received both the new agent and the standard.

(ii) *Substitution for morphine.* Subjects are given morphine sulfate in increasing doses until after 18 to 20 days a dosage of 240 mg daily, administered in four subcutaneous doses of 60 mg each, is attained. After 6 weeks of stabilization on this dosage, the morphine is abruptly discontinued and during the following 24 hours the unknown drug is substituted, using a dosage schedule compatible with the previously observed potency and length of action. Cross-over trials are used here also, with either a placebo or the same standard as in the single-dose studies serving for comparison. A drug with morphine-like action suppresses all signs of abstinence whereas administration of a placebo is associated with a progressively severe abstinence syndrome. Observations for intensity of abstinence are made at hourly intervals from the 11th up to and including the 24th hour.

(iii) *Direct dependence test.* In this procedure an attempt is made to simulate the conditions of abuse that might arise if the patient were permitted to take a new agent by himself ; that is, administration at the highest tolerated yet safe dosage for a period of one week to several months. Observations are made daily to determine whether the pattern of effect is similar to that with morphine and particularly whether the patient liked the medication and asked for an increase in dosage. The experiment is carried out initially in only one subject to safeguard the dosage. Five or more subjects are employed subsequently in other tests. In short periods of intoxication (7-25 days) cross-over conservations are made with a standard drug, such as morphine, codeine or dextropropoxyphene, again selected according to the potency of the new agent. During the course of the experiment, attempts may be made to precipitate abstinence phenomena by administering nalorphine. Subsequently, the substance is abruptly discontinued and immediately replaced by a placebo in such a way that neither the subject nor the observer is aware of the time of change. Observations for intensity of the abstinence syndrome are then continued for 10 days. Parallel observations are made on the standard drug.

(iv) *Short-term intravenous preference test.* Each one of a small group of subjects (6-8) is given intravenously in random order a sample dose of each of a series of drugs, including a standard such as 30 mg of morphine. The observer but not the subject knows the nature of the drug and the dose is that previously estimated to be the equivalent of the standard. The subjects are asked to rate the drugs in the order of their "liking" for them and to elect to take one or more, or even all of them, in increasing dose intravenously for 7 days. They can also elect not to take any of them or to discontinue a drug at any time during that period. Drugs selected by the subjects are administered in random order. In each instance discontinuance is followed by a withdrawal period of three days and then another drug of the patient's selection is given in similar fashion. At the end of the series, each subject is again asked to rate the drugs in order of preference. Nalorphine or a placebo is administered intravenously on a randomized double-blind basis three hours after the last dose of the experimental drug on the sixth or seventh day of the experiment. This short-term experiment has the advantages that the programme is less rigid in design than in the longer-term direct dependence trials and it allows the subjects the choice of a number of drugs and how long they wish to take an agent before trying another; it also brings out rapidly differences among drugs respecting the quality of the subjective effects and the characteristics of a drug which determine its suitability for intravenous injection. It does not evaluate adequately the relative degree of physical dependence, but it does give valuable information on the subject's immediate like or dislike of a drug by his usually preferred route of administration and, hence, whether or not he would be inclined to use it thus if it were available to him.

Thus far, in all cases where there has been later clinical experience with compounds evaluated, it has confirmed the prediction of dependence liability afforded by the Lexington trials. Difficulties in evaluation arise only with compounds that have a very low potency with respect to production of physical dependence and are not liked by the former addicts, or whose effects differ qualitatively from those of morphine, perhaps not being typically morphine-like.

*Test for tolerance and physical dependence under clinical conditions.* To confirm the satisfactoriness of the Lexington tests for prediction of dependence liability, studies have been designed to evaluate directly the development of tolerance and physical dependence under clinical conditions. The precipitation by nalorphine of signs of abstinence when physical dependence is present has made it possible to monitor the development of the latter. Patients were selected who had chronic pain requiring the continuous administration of a morphine-like agent. They were then

given a test dose of nalorphine to reveal whether or not they were physically dependent on any preceding medication. The administration of morphine or another morphine-like analgesic was then begun and continued as needed for pain relief. The dose initially and throughout was the smallest consistent with reasonable comfort. Throughout the period of administration an increase in the size of the single dose or in the total daily dosage could be indicative of developing tolerance. Periodically (usually every two weeks) the standard test dose of nalorphine was administered two hours after a dose of analgesic and the patient observed for abstinence signs. Their occurrence was taken as evidence of physical dependence.

In the test situation, morphine or the experimental drug was assigned to a patient on a double-blind basis. Then, the comparison between the nature and intensity of abstinence signs precipitated by nalorphine and the time of their appearance after morphine or the experimental drug gave an indication of relative physical dependence liability. This procedure has given results comparable to those seen at Lexington when applied to a number of potent new analgesics administered parenterally.

This method can be carried out wherever there is a sufficiently large group of patients with persistent severe pain—in inoperable malignancies, for example. It is, however, time consuming and requires very close supervision by an interested clinical investigator.

(g) *Other techniques*

*Tissue cultures.* Some thirty years ago, Japanese investigators carried out work on cultures of fibroblasts and epithelium tending to show adaptation (tolerance) to the presence in the medium of morphine or a related substance and structural changes when the drug was removed. Only recently have similar experiments been undertaken with similar results. Extension of the method to a broader survey of drugs would give additional information on tissue adaptation and cross-adaptation, and might afford valuable clues to a mechanism of tolerance and cross-tolerance in the intact animal. However, in view of the present general concept of the relationship of physical dependence to neuronal components, unless neurones can be cultured, it is not likely that the method will throw any light on the mechanism of physical dependence.

*Catecholamines.* In animals, changes in catecholamine metabolism have been shown to occur during the development of tolerance and physical dependence. There is no evidence, however, that tests based on such observations would have significant value in predicting relative dependence qualities of drugs in man. Experiments in man have been very limited and although of some value in interpreting mechanisms of action of morphine, again they are not considered as useful instruments for assessing relative dependence capacity of new agents.

*Corticosteroids.* As noted in the case of catecholamines, the determination of the effects of drugs on the excretion of corticosteroids is of interest relative to the mechanism concerned, but it has not been possible to develop along these lines tests of practical value in assessing dependence capacities of new agents.

### 3.1.2 *Tests for psychic dependence*

#### (a) *Animals*

Several investigators have shown that rats will drink solutions of narcotic analgesics under certain conditions. Some will do so preferentially from the beginning and thus render themselves dependent upon the contained drug ("dependence prone"). Others will do so if they have been made dependent by forced drinking or administration of the drug by another route ("dependence resistant"). If dependence-prone or dependence-resistant animals are inbred, in a high percentage of cases their offspring are dependence prone or dependence resistant, respectively.

A technique has also been developed which enables the rat to self-administer morphine solutions through an indwelling catheter discharging directly into the right heart. This has permitted the determination of the time and amount of drug taken when using different bar-pressing programmes. With this technique also, rats have been shown to vary in susceptibility to initiation of self-administration of narcotic solutions. Work has been started on substitution of one drug for another in self-administration experiments.

Both the above-described techniques have been adapted to experiments in the monkey. Like rats, monkeys showed initial preference for or aversion to morphine solutions, and like rats also, they would maintain themselves on morphine by preferential drinking when dependence had been established. With the intravenous technique in which each dose was given in response to depression of a bar by the animal, administration could be controlled in the following four ways: (i) by the monkey only; (ii) by an automatic timer only; (iii) by the timer if the monkey failed to press the bar for a predetermined period; and (iv) by the monkey, but after each injection the timer blocked the circuit so that the animal was unable to take the next injection before a predetermined time had expired.

Self-administration techniques for rats and monkeys are hardly beyond the developmental stage. Although they are difficult to establish and maintain, they should provide a great deal of information on both physical and psychic dependence.

#### (b) *Man*

In the experiments at the Addiction Research Center, Lexington, a high correlation was found between the ability of former addicts with

wide drug experience to identify new drugs as narcotics (morphine- or heroin-like "dope") and the capacity of the same agents to induce physical dependence. Weak morphine-like agents and agents inducing an atypical pattern of morphine-like subjective effects presented some difficulty. In both cases, chronic administration was usually necessary to confirm the impression obtained with single doses.

In some instances, although a single dose evoked morphine-like effects, a study of the results of chronic administration was not possible. For example, some of the drugs tested provoked side effects, such as nausea and vomiting, nervousness and insomnia, to which the subject did not become tolerant, or excessive sedation which was disliked by the subject who looked for the balance of sedation and stimulation obtained from morphine or heroin. Under these circumstances, the individual could elect voluntarily to discontinue administration of a given morphine-like agent if the whole pattern of its effects was sufficiently disagreeable to him.

Most of these subjective factors have been evaluated at Lexington. They are important in determining the degree of dependence and abuse liability of a particular substance. The limited number of human subjects available has made it desirable to conduct both single-dose and chronic studies on a cross-over basis using the patient as his own control for the comparison of the new drug with a suitable standard (morphine, codeine, dextropropoxyphene or a placebo). It has also been important to realize that the addicts seen at Lexington prefer the intravenous route of administration because it significantly increases the intensity of subjective effects. Morphine, for example, is twice as potent intravenously as intramuscularly, whether the appraisal is made subjectively (extent to which it is identified as "dope") or objectively.

### **3.2 Barbiturates and other sedatives**

#### *3.2.1 Tests for tolerance and physical dependence*

##### *(a) Animals*

Tolerance and withdrawal phenomena with barbiturates and barbiturate-like agents have been studied in male albino mice, using in one method changes in convulsive threshold during chronic intoxication and withdrawal. Convulsions were precipitated either electrically or chemically (intravenous pentetrazol). During chronic intoxication with the sedative, the convulsive threshold was raised. Abrupt withdrawal after 14 days of intoxication was followed by a progressive decrease in the convulsive threshold, the time elapsing between withdrawal and lowering of threshold varying with the agent under study. The interval was, for example, four hours for meprobamate and 12 hours for phenaglycodol; in both instances

the threshold was reduced about 18% below the base-line. Several barbiturate-like drugs were tested; when changes in convulsive threshold were observed, the same agent produced physical dependence in man. The method might be developed as a general screen for physical dependence properties of barbiturates and other sedatives.

In some experiments, rats have proved unsatisfactory for barbiturate physical dependence tests, since they died before a dosage level was reached at which physical dependence could be demonstrated by the appearance of withdrawal signs. However, barbiturate withdrawal convulsions have been described recently in rats susceptible to audiogenic convulsions.

Dogs have been used for testing the physical dependence liability of substances of barbiturate type. They were made tolerant and dependent by prolonged administration and stabilization on sodium barbital, 100 mg/kg/day orally. Mild abstinence signs began to appear approximately 20 hours after the last dose, the intensity progressively increasing to a peak during the 72- to 96-hour period of abstinence and then gradually diminishing. Complete recovery occurred about 10 days after the last dose of sodium barbital. A test drug was shown to possess barbiturate-like physical dependence capacity if: (i) its substitution in single dose for sodium barbital in the 24th hour after abrupt withdrawal suppressed the developing abstinence syndrome; (ii) its substitution in proper dosage for six days prevented the appearance of the typical abstinence syndrome; and (iii) its complete withdrawal after substitution resulted in the appearance of the typical abstinence syndrome.

The barbiturate abstinence signs in the dog are classified as follows:

<i>Mild</i>	<i>Intermediate</i>	<i>Severe</i>
Tachycardia (10-20%)	Anorexia	Hyperthermia (1.5-2.0°C)
Hyperpnoea	Nervousness	Fasciculations
Weight loss (10-15%)	Restlessness	Convulsions
Tremors	Insomnia	Delirium
	Fighting	

Convulsions and delirium are the most dramatic and specific. The other signs can result from a variety of causes, but when they are associated with withdrawal of a drug and are accompanied by convulsions and delirium they too may be considered specific. The lesser signs are most uniform in their appearance in barbiturate withdrawal.

Bromides, chlorpromazine, phenergan and substances with morphine-like effect, when given in tolerated doses failed to act as substitutes for sodium barbital. Sodium phenobarbital (30 mg/kg, q12h), sodium pentobarbital (15 mg/kg, q6h), chloral hydrate (500 mg/kg, q12h) and paraldehyde (1-1.5 ml/kg, q12h) were completely effective substitutes in maintaining physical dependence and thus have the same physical dependence properties as barbital. Other central nervous system depressants are also

satisfactory substitutes for sodium barbital; these include glutethimide, chlordiazepoxide, methyprylon, bromisoval, carisoprodol, and mepro-bamate.

Generally, physical dependence properties measured in the dog correlate well with relative sedative potency and with experience in man. Carisoprodol is an exception. A direct dependence test in man with this agent, using several times the therapeutic dose and an administration period of 20 days, resulted in no signs of abstinence when administration of the drug was abruptly terminated. Patients classified carisoprodol consistently as a placebo and were unaware of its replacement by a placebo. The substitution technique in the dog requires broader trial before a final appraisal of its quantitative and predictive value for drugs of barbiturate type can be made.

The direct dependence technique as described for morphine-like drugs could also be used for those of barbiturate type. It has demonstrated physical dependence to meprobamate and glutethimide as well as to sodium barbital. The method has failed to demonstrate dependence for the short-acting barbiturate amobarbital, and incomplete abstinence patterns developed after secobarbital and pentobarbital at the doses and intervals of administration employed.

(b) *Man*

The principles for evaluating dependence on barbiturate-like depressants in man are similar to those outlined for the morphine group, but there are major differences in symptomatology with respect to both intoxication and withdrawal. The pattern of subjective and objective effects for this class resembles that for alcohol; for example, symptoms of intoxication include ataxia, dysarthria, impairment of mental function, loss of emotional control, confusion, poor judgement and occasionally a toxic psychosis; withdrawal is characterized by an abstinence syndrome which is entirely different from that following withdrawal of morphine. The signs occurring most consistently, in approximate order of appearance, include anxiety, involuntary twitching of muscle, intention tremor of hands and fingers, progressive weakness, dizziness, distortions in visual perception, nausea, vomiting, insomnia, weight loss, and a precipitous drop in blood pressure on standing, or even on sitting. Other symptoms which are hazardous to life may occur: hyperpyrexia, convulsions of a "grand mal" type, and/or delirium resembling alcoholic delirium tremens.

Direct dependence and substitution procedures may be carried out with the barbiturates in man. However, with this class of drugs abrupt withdrawal is hazardous because of the major symptoms referred to and the difficulty in controlling them. In addition, there are no known specific antagonists.

Just as one morphine-like agent may be substituted for another in maintenance of dependence or suppression of abstinence, barbiturates, alcohol and some other sedatives which induce physical dependence may be interchanged with each other. Morphine-like agents are not interchangeable with barbiturates, alcohol and other sedatives.

### 3.2.2 *Tests for psychic dependence*

In man, a limited number of experiments on psychic dependence have been carried out. For example, three different dose levels of pentobarbital were compared with three different dose levels of morphine, both drugs being administered in single doses intramuscularly. The study was conducted with non-tolerant former addicts, and for seven hours after each medication they were questioned respecting their degree of "liking" for each medication. As the dose of morphine was increased, "liking" by the addict developed in proportion to the increase in dosage. On the other hand, although the lower dose levels of pentobarbital were "liked" by the subjects, liking was in this instance negatively correlated with dosage.

The specific sensations and subjective reactions induced in former addicts by barbiturates, as well as by morphine-like agents, have been identified by a questionnaire comprising 500 statements of feeling. The responses of these patients following administration of pentobarbital could be readily and specifically differentiated.

## 3.3 **Amphetamines**

### (a) *Animals*

No comparative tests to measure dependence have been developed for members of the amphetamine group, and the applicability of those described for other agents has not been determined. Chronic intoxication studies of amphetamine in animals generally showed that they developed the following symptoms: anorexia, nervousness, loss of weight, irritability and, with larger doses of the drug, hallucinatory-like behaviour. Tolerance to all of these symptoms developed rapidly and it was necessary to increase the dosage to maintain effectiveness. All the symptoms rapidly subsided when the amphetamine was discontinued, and there was no evidence of a specific abstinence syndrome.

### (b) *Man*

Here again, no comparative tests to measure dependence have been developed. When subjects were chronically intoxicated with dextro-amphetamine they showed the following symptoms: anorexia, nervousness, insomnia, tremor, irritability, loss of weight and, if the dosage was sufficiently high, a psychosis with hallucinatory behaviour. There are some reports in the literature that abrupt cessation of dextro-amphetamine in

patients chronically intoxicated with high doses was followed by a rebound phenomenon characterized primarily by a state of sedation. However, quantitative observations to establish this phenomenon are limited. In one chronic study in which patients were maintained on a dose of dextro-amphetamine which did not cause a significant degree of anorexia, nervousness or insomnia, no signs of abstinences were manifest when dextro-amphetamine was discontinued. Both subjects and observers reported only a return to normal behaviour.

### 3.4 Cocaine

#### (a) *Animals*

Experimental approaches have been limited, but in a number of instances chronic administration of cocaine to dogs and monkeys has resulted in behaviour which indicated liking and strong desire for the drug. For example, when arrangements were made for self-administration by the intravenous route in monkeys and a dilute cocaine solution was provided, once the animals had experienced the effect of the injection, they would compulsively inject themselves by repeated bar-pressing, even to the extent of taking an amount of cocaine sufficient to induce convulsions. Upon recovery from the convulsive state, the animals would immediately resume bar-pressing to maintain self-intoxication.

#### (b) *Man*

Although cocaine has been abused widely, controlled experiments to determine whether chronic intoxication induces physical dependence have been limited. When coca leaves were chewed with lime, the principal symptoms of chronic intoxication were anorexia, weight loss, nervousness and some weakness. Hallucinatory behaviour was seldom seen following such oral administration. When cocaine was taken intermittently by intravenous injection for an occasional debauch ("spree use"), with intravenous injection of morphine or heroin either at the same time or subsequently to counteract excessive stimulatory effects, symptoms associated with acute toxicity of cocaine included primarily sympathomimetic effects, nervousness, hyper-reactive reflexes, sweating, hoarseness, increase in pulse rate and blood pressure and, with the higher doses, a psychosis, the most dangerous aspect of which was its paranoid aspect. During such psychotic episodes the intoxicated person might mistake the identity of individuals, even of friends, around him and interpret their behaviour to mean they were going to harm him. Such observations as have been made indicate that there is no physical dependence on cocaine. There is a psychic dependence and the latter is sufficiently important for many addicts in the USA to rate cocaine in order of preference as second only to heroin,

### 3.5 Hallucinogens : substances resembling lysergic acid diethylamide (LSD)

For this group of compounds, a fair correlation has been described between pyrogenic action in rabbits and hallucinogenic action in man. In another experiment, an open-field test was employed to study behaviour in rats. The principle of the test was that the novel situation evoked a pattern of behaviour characterized by exploration, "emotional defecation" and preening. Eight of 10 psychotomimetic drugs produced changes in behaviour which included a significant decrease in "emotional defecation". Five sedative and three stimulant agents used showed no consistent pattern of behavioural change. These observations have no relevance unless similarity of modification of emotional response can be taken to indicate the possibility of psychic dependence.

In man, drugs of the LSD type have been compared with respect to subjective effects (500-item questionnaire for statements of feeling) and objective effects (rectal temperature, pulse rate, blood pressure, pupil size and knee jerk). Tolerance developed very rapidly and disappeared with equal rapidity. Cross-tolerance between members of the group was also observed. The reports of recent outbreaks of abuse of LSD have not indicated clearly the extent of psychic dependence and there is no evidence of physical dependence.

### 3.6 Cannabis sativa (marihuana)

Cannabis is used in different ways in different parts of the world. It is smoked or ingested in various forms to evoke pleasure and other subjective effects and for alleged enhancement (or distortion) of perception and performance. This may be in large part abuse and associated with a greater or lesser degree of psychic dependence. There is no evidence that cannabis produces physical dependence.

The exact nature of the active principle or principles of cannabis has not yet been established. Methods have been devised which compare certain pharmacological properties of substances which have been derived from cannabis and related products made in the laboratory, but there is no clear quantitative or parallel relationship between the results of these tests and the effects of cannabis or any part of it in man.

## 4. CONCLUDING REMARKS

Many procedures have been developed having as their objectives the determination of morphine-like properties and of the possibility of tolerance and physical dependence. Those employing the smaller animals are of value mainly in identification of the morphine-like character of a new compound. They may in some instances give indication of tolerance and

physical dependence properties. None of them, however, can at present be considered as conclusive in respect to predictive value.

The results of procedures which have been developed in the dog and especially the monkey, when applied to compounds with a potency equal to or greater than that of morphine, have, in the main, shown a good correlation with the results of subsequent tests in man. For substances of such potency, therefore, it has generally been conceded that tests in the monkey are of predictive value for the occurrence of physical dependence in man. When weaker agents are studied or the results are inconclusive, and in all cases when introduction of a substance into clinical medicine is planned, tests in man should be carried out. Such tests as performed at the Addiction Research Center, Lexington, Kentucky, are definitive and their results have been confirmed whenever the agent studied has actually been used in the clinical situation.

Some of the procedures that have been used for the determination of tolerance and physical dependence of morphine-like agents are applicable to the study of similar phenomena occurring with other agents. A good example is chronic administration and withdrawal of barbiturates and other sedatives. In this case, the dog appears at present to be the best experimental animal. However, qualitative and quantitative relationships to results in man are not yet fully established. Tests of barbiturates in man, on an exploratory basis, have also been adapted from tests for dependence properties of morphine.

With the other agents considered (except morphine-like compounds, barbiturates and other sedatives) tolerance may occur, but there is no evidence of any physical dependence. All of them create psychic dependence, which in some instances may be of a compulsive character.

Whatever the agent, the recognition of psychic dependence is for the most part a matter of observation and judgement when it is actually used by man. The experimental approach to the assessment of psychic dependence in both animals and man is just beginning, and no definitive statement regarding techniques or their predictive value can as yet be made.

Need for clarification of the value of certain methods has been pointed out as the methods were discussed. In addition, further exploration of the self-administration techniques and the development of other procedures for assessment or prediction of psychic dependence should be encouraged. Perhaps the greatest lack in the study of dependence is the shortage of clinical facilities for the study of its development under actual clinical conditions. An applicable procedure has been described, and knowledge of safety with respect to risks in clinical practice and for the guidance of the physician would be greatly enhanced if places and personnel for its development could be provided.

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**Annex****A PROCEDURE FOR THE CONTROLLED EVALUATION  
OF A NEW DRUG**

In connexion with the advisory functions of the Committee on Drug Addiction and Narcotics of the National Academy of Sciences-National Research Council, USA, a procedure has been evolved for the examination and evaluation of new agents which may have physical dependence properties.

A producer, having a new agent, especially a new analgesic or antitussive, and desiring information on dependence potentialities, may bring the compound at any stage of its development to the attention of the Committee. He submits a sample to the Secretary of the Committee on a confidential basis, together with data on the nature of the compound, its structure and what is known of its chemical, physical and pharmacological properties. The Secretary arranges for confirmation of potency by laboratory test if the compound is described as an analgesic, and sends a part of the sample under code number only to the Department of Pharmacology at the University of Michigan for evaluation of physical dependence capacity in the monkey. The Department reports the results by code number to the Secretary who transmits the report to the producer. Only then, and with clearance from the producer, are the Michigan investigator and the members of the Committee made aware of the nature of the compound which has been tested.

The procedure at this point varies. If the tests in the monkey are indicative of strong physical dependence capacity and other properties are not outstandingly advantageous, it may be decided to discontinue study of the compound. On the other hand, if the result in the monkey is not so decisive, further study, including testing in man at the Addiction Research Center, Public Health Service Hospital, Lexington, Kentucky, may be requested. The producer goes forward with pharmacological evaluation and at least preliminary clinical trials to provide the background information requested by the Center: general pharmacology of the compound including its toxicity and relative potency; evidence that it has been administered to man and that it may be a useful therapeutic agent; its relative potency in man; and some indication of the side effects which it may produce. The data on general pharmacology should include information on acute and chronic toxicity, on relative potency with respect to analgesic, antitussive and/or constipating action, on whether or not the actions of the drug are antagonized by one of the specific antagonists such as nalorphine, on the rate and extent of dosage increase in chronic

administration in attempted determination of tolerance, whether or not tolerance develops and whether there is cross-tolerance to morphine.

When these data are in hand, the Secretary submits all the information first to the Center for their judgement of its adequacy for initiation by them of clinical trials and then to the members of the Committee. Having reviewed the material and the possibilities of clinical usefulness, the Committee recommends for or against dependence studies in man.

Following the recommendation, the Addiction Research Center carries out such tests as it deems feasible and/or necessary to assess the abuse liability of the new agent<sup>1</sup> and reports to the Committee and the producer through the Secretary. It is now up to the producer to complete the clinical trials and obtain any other information pertinent to licensing for introduction into clinical medicine. The Committee again reviews the situation and may recommend to the Bureau of Narcotics, USA, through the Chairman of the Division of Medical Sciences of the National Research Council, appropriate narcotics control or, in its opinion, the lack of necessity for such control. If control is recommended, provisions for it are initiated at the national level followed by notification through UN to WHO for appropriate international action.

Thus, at all stages, the advantages, potency, and dependence possibilities are determined and checked by an impartial body with whom industry has developed a close relationship and in whom it has confidence. Consequently, prior to the introduction of the drug on the market, adequate information on its usefulness and safety is accumulated for the physician and such control as is indicated in the interests of public health is provided for.

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<sup>1</sup> In addition, the Addiction Research Center evaluates the abuse liability and other properties of new as well as old agents, this research being based on theoretical and other judgements which are not necessarily involved in considerations of the National Research Council Committee on Drug Addiction and Narcotics.

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