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Drug Dependence: its Significance and Characteristics

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It has become impossible in practice, and is scientifically unsound, to maintain a single definition for all forms of drug addiction and/or habituation. A feature common to these conditions as well as to drug abuse in general is dependence, psychic or physical or both, of the individual on a chemical agent. Therefore, better understanding should be attained by substitution of the term drug dependence of this or that type, according to the agent or class of agents involved, in discussions of these conditions, especially inter-disciplinary. Short descriptions, followed by concise listings of their characteristics, are formulated for the various types of dependence on at present widely abused major groups of substances.

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INTRODUCTION

Among the functions of the World Health Organization is the taking of decisions on the status of individual drugs under the relevant international treaties for narcotics control. This function has been established by international conventions and depends upon the competence of the WHO Expert Committee on Addiction-Producing Drugs. The conventions specifically direct that, in response to a notification from a government, the Committee come to a finding as to whether or not the substance in question is or is convertible into one with addiction-producing or addiction-sustaining properties similar to those of morphine or cocaine or cannabis. A positive finding by the Committee is followed by a recommendation for appropriate international narcotics control. Pertinent to any conclusion or decision is the consideration of specific therapeutic effects, the liability of substances having such effects to produce drug dependence, and the evaluation of the risk to public health if such substances are used for medical purposes or abused. Obviously, such considerations depend upon the availability of dependable methods and critical evaluation of their application to the determination of both useful therapeutic properties and the kind and degree of dependence that may accompany drug use. WHO

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has already published a series of reports on these requirements (Braenden, Eddy & Halbach, 1955; Eddy, Halbach & Braenden, 1956, 1957; Halbach & Eddy, 1963; WHO Scientific Group on the Evaluation of Dependence-Producing Drugs, 1964).

As a partial guide to its own deliberations and those of others, the WHO Expert Committee on Addiction-Producing Drugs (1952) attempted to formulate a definition of addiction that would be applicable to drugs under international control. A revised definition [1] was proposed by the Committee several years later, in its seventh report (WHO Expert Committee on Addiction-Producing Drugs, 1957).

In its seventh report the Committee sought also to differentiate addiction from habituation and wrote a definition of the latter [2] which, however, failed in practice to make a clear distinction. These definitions gained some acceptance, but confusion in the use of the terms addiction and habituation, and particularly misuse of the former, continue. Both terms are frequently used interchangeably and often inappropriately. It is not uncommon to apply the term addiction to any misuse of drugs outside of medical practice, with a connotation of serious harm to the individual and to society, and often with a demand that something be done about it. Such broad use can only create confusion and misunderstanding when abuse of drugs is discussed from different viewpoints.

The difficulties in terminology become increasingly apparent with the continuous appearance of new agents with various and perhaps unique pharmacological profiles, and with changing patterns of use of drugs already well known. These developments must be considered in their relation to, but may not be adequately characterized by, current definitions of addiction. There is scarcely any agent which can be taken into the body to which some individuals will not get a reaction satisfactory or pleasurable to them, persuading them to continue its use even to the point of abuse—that is, to excessive or persistent use beyond medical need. Probably the only exceptions are agents that have incidental or side effects that prevent such use—for example, cumulative or early toxic effects, to which the individual does not become tolerant.

[1] " Drug addiction is a state of periodic or chronic intoxication 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 generally a physical dependence on the effects of the drug; (4) detrimental effect on the individual and on society."

[2] " Drug habituation (habit) is a condition resulting from the repeated consumption of a drug. Its characteristics include: (1) a desire (but not a compulsion) to continue taking the drug for the sense of improved well-being which it engenders; (2) little or no tendency to increase the dose; (3) some degree of psychic dependence on the effect of the drug, but absence of physical dependence and hence of an abstinence syndrome; (4) detrimental effects, if any, primarily, on the individual."

THE TERM " DRUG DEPENDENCE "

In order to try to clarify this situation, much thought and discussion have been devoted to finding a term that will cover all kinds of drug abuse. The component in common appears to be dependence, whether psychic or physical or both. Hence, use of the term " drug dependence " with a modifying phrase linking it to a particular type of drug in order to differentiate the characteristics associated with one class of drugs or another has been given most careful consideration. In its thirteenth report, the WHO Expert Committee on Addiction-Producing Drugs (1964) has, in fact, recommended substitution of the term " drug dependence " for both of the terms drug addiction and drug habituation. This recommendation has been endorsed by the WHO Scientific Group on Evaluation of Dependence-Producing Drugs (1964) and has been concurred in and supported, *inter alia*, by the Committee on Drug Addiction and Narcotics of the National Academy of Sciences—National Research Council (USA).[3]

Drug dependence is a state of psychic or physical dependence, or both, on a drug, arising in a person following administration of that drug on a periodic or continuous basis. The characteristics of such a state will vary with the agent involved, and these characteristics must always be made clear by designating the particular type of drug dependence in each specific case; for example, drug dependence of morphine type, of barbiturate type, of amphetamine type, etc.

The specification of the type of dependence is essential and should form an integral part of the new terminology, since it is neither possible nor even desirable to delineate or define the term drug dependence independently of the agent involved. It should also be remembered that it was the desire to achieve the impossible and define a complex situation by a single term (" addiction " or " habi-

[3] Twenty-sixth Meeting, Washington, D.C., 1964.

tuation", respectively) which has given rise to confusion in many cases. Therefore, the description of drug dependence as a state is a concept for clarification and not, in any sense, a specific definition.

It must be emphasized that drug dependence is a general term that has been selected for its applicability to all types of drug abuse and thus carries no connotation of the degree of risk to public health or need for any or a particular type of drug control. The agents controlled by international treaties and by national narcotics laws continue to be those that are morphine-like, cocaine-like, or cannabis-like, the use of which may result, respectively, in drug dependence of morphine type, of cocaine type, or of cannabis type. Other types of drug dependence, such as those of the barbiturate and amphetamine types, continue to present problems, and their description under the general term of drug dependence, while it may help to delineate those problems, in no way suggests or affects the measures to be taken to solve them. Use of the general term will help to indicate a relationship by drawing attention to a common feature associated with drug abuse, but at the same time will differentiate, by more exact description, specific characteristics according to the nature of the agent involved.

Further to clarify our meaning, the nature and significance of drug abuse may be considered from two points of view: one relates to the interaction between the drug and the individual, the other to the interaction between drug abuse and society. The first viewpoint is concerned with drug dependence and the interplay between the pharmacodynamic actions of the drug and the psychological status of the individual. The second—the interaction between drug abuse and society—is concerned with the interplay of a wide range of conditions, environmental, sociological, and economic. The Committee tried to encompass both points of view when, in its definition of addiction, it listed characteristics of which some were pharmacodynamic and others psychological and socioeconomic, perhaps thereby compounding some of the existing confusion.

As already noted, individuals may become dependent upon a wide variety of chemical substances that produce central nervous system effects ranging from stimulation to depression. All of these drugs have one effect in common: they are capable of creating, in certain individuals, a particular state of mind that is termed "psychic dependence". In this situation, there is a feeling of satisfaction and a psychic drive that require periodic or continuous administration of the drug to produce pleasure or to avoid discomfort. Indeed, this mental state is the most powerful of all of the factors involved in chronic intoxication with psychotropic drugs, and with certain types of drugs it may be the only factor involved, even in the case of most intense craving and perpetuation of compulsive abuse.

Some drugs also induce physical dependence, which is an adaptive state that manifests itself by intense physical disturbances when the administration of the drug is suspended or when its action is affected by the administration of a specific antagonist. These disturbances, i.e., the withdrawal or abstinence syndromes, are made up of specific arrays of symptoms and signs of psychic and physical nature that are characteristic for each drug type. These conditions are relieved by re-administration of the same drug or of 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. Physical dependence is a powerful factor in reinforcing the influence of psychic dependence upon continuing drug use or relapse to drug use after attempted withdrawal.

To reiterate, psychic dependence can and does develop, especially with stimulant-type drugs, without any evidence of physical dependence and, therefore, without an abstinence syndrome developing after drug withdrawal. Physical dependence, too, can be induced without notable psychic dependence; indeed, physical dependence is an inevitable result of the pharmacological action of some drugs with sufficient amount and time of administration. Psychic dependence, while also related to pharmacological action, is more particularly a manifestation of the individual's reaction to the effects of a specific drug and varies with the individual as well as with the drug.

Many of the drugs that induce dependence, especially those that create physical dependence, also induce tolerance, which is an adaptive state characterized by diminished response to the same quantity of drug or by the fact that a larger dose is required to produce the same degree of pharmacodynamic effect. Both drug dependence and drug abuse may occur without the development of demonstrable tolerance.

Drugs that are capable of inducing dependence may also be associated with psychotoxic effects

that are manifested by profound alterations in behaviour. These effects may occur with a single large dose or during the course of continued administration, or they may be precipitated by withdrawal of the drug following continued administration. The pattern of abnormal behaviour is, within limits, characteristic for 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 significant differences from one generic type to another, a situation that makes it mandatory to establish clearly the pattern for each type of drug dependence. Even though some variations occur among individual members of each generic group, the consistency of the pattern of pharmacodynamic actions and responses is sufficiently uniform to permit, at this time, the delineation of each of the principal types.

CHARACTERISTICS OF DRUG DEPENDENCE

Drug Dependence of Morphine Type

The outstanding and distinctive characteristic of dependence on morphine and morphine-like agents is that the major elements—psychic and physical dependence, as well as tolerance—can be initiated by the repeated administration of small doses and increase in intensity in direct relationship to an increase in dosage. This characteristic implies that dependence on drugs of this generic type may be created within the dosage range generally used for therapeutic purposes, and that its mechanism may be set in motion by the first dose administered.

The characteristics of dependence of the morphine type are:

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

(*b*) An early development of physical dependence which increases in intensity, paralleling increase in dosage. This requires a continuation of administration of the same drug, or an allied one, to maintain a semblance of homeostasis and to prevent the appearance of the symptoms and signs of withdrawal. Withdrawal of the drug or administration of a specific antagonist precipitates a definite, characteristic and self-limited abstinence syndrome.

(*c*) Development of tolerance that requires an increase in dosage to obtain the initial pharmacodynamic effects.

With morphine, the abstinence syndrome appears within a few hours of the last dose, reaches peak intensity in 24 to 48 hours, and subsides spontaneously. The most severe symptoms usually disappear within ten days, although a residuum persists for a much longer period. The time of onset, peak intensity, and duration of abstinence phenomena vary with the degree of dependence on the drug (Andrews & Himmelsbach, 1944) and with the characteristics of the specific agent involved. Administration of a specific antagonist during continuing administration of morphine-like drugs promptly precipitates a more rapid and intense abstinence syndrome that lasts only a few hours.

The unique feature of the morphine abstinence syndrome is that it represents changes in all major areas of nervous activity, including alteration in behaviour, excitation of both divisions of the autonomic system simultaneously, and dysfunction of the somatic nervous system. The complex of symptoms and signs include anxiety, restlessness, generalized body aches, insomnia, yawning, lacrimation, rhinorrhoea, perspiration, mydriasis, piloerection (gooseflesh), hot flushes, nausea, emesis, diarrhoea, elevation of body temperature, of respiratory rate and of systolic blood pressure, abdominal and other muscle cramps, dehydration, anorexia, and loss of body weight (Isbell & White, 1953).

The generic type of morphine-like compounds for which morphine is used as the standard of reference comprises substances with different chemical constitutions but similar pharmacological profiles. They vary in potency from substances with low activity to others that are several thousand times as potent as morphine. These agents are alike in their ability to produce and maintain some degree of physical dependence, to maintain tolerance and physical dependence and to prevent the appearance of abstinence phenomena. These agents are mutually interchangeable by substitution, although not on a milligram-for-milligram basis. Variations exist in the capacity of potent morphine-like substances to induce psychic dependence and to produce psychic satisfaction on substitution for one another.

Within the generic class of agents with pharmacodynamic features similar to those of morphine, making them capable of inducing physical dependence with sufficient dosage, there are some with a

high degree of usefulness which, in therapeutic doses, are generally inadequate substitutes for morphine. Even in higher doses, these compounds are not completely satisfactory in sustaining an established morphine dependence; their effects are not usually sufficiently satisfying subjectively to induce significant psychic dependence. Codeine is generally recognized as a reference standard for this group.

A relationship between dose, pharmacodynamic properties and intensity of physical dependence has been mentioned. Regularity of administration at intervals well within the duration of action of the drug also hastens development of physical dependence. The time from the beginning of administration to the appearance of demonstrable physical dependence also varies with the agent. With morphine, this interval under clinical conditions of administration is two or three weeks; it is shorter for ketobemidone, probably longer for phenazocine and definitely longer for codeine, especially when this is administered orally.

Finally, with drug dependence of the morphine type, harm to the individual is, in the main, indirect, arising from preoccupation with drug-taking; personal neglect, malnutrition and infection are frequent consequences. For society also, the resultant harm is chiefly related to the preoccupation of the individual with drug-taking; disruption of interpersonal relationships, economic loss, and crimes against property are frequent consequences.

Drug Dependence of Barbiturate-Alcohol Type

The signs and symptoms of barbiturate and of alcohol intoxication are similar, as are the signs and symptoms of abstinence from these drugs. Barbiturates will suppress alcohol abstinence phenomena, and alcohol will suppress, at least partially, the symptoms of barbiturate withdrawal. The two drugs are essentially additive and interchangeable in chronic intoxications; these similarities justify the term " dependence of barbiturate-alcohol type ", but there are psychological and sociological differences, so that barbiturate and alcohol dependence will be described separately.

Drug dependence of barbiturate type. While dependence on drugs of the barbiturate type presents certain similarities to dependence on drugs of the morphine type, in detail there is a characteristically different picture both during the course of intoxication and during withdrawal. It is a state arising from repeated administration of a barbiturate on a continuous basis, generally in amounts that exceed the usual therapeutic dose levels. There is a strong desire or need to continue taking the drug, a need that can be satisfied by the drug taken initially or by another with barbiturate-like properties. There is a psychic dependence on the effects of the drug that is related to subjective and individual appreciation of those effects, and there is physical dependence requiring the presence of the drug for the maintenance of homeostatis and resulting in a characteristic and self-limited abstinence syndrome when the drug is withdrawn.

Tolerance to barbiturates does develop and, with relatively low doses, it will become evident within seven days. There is, in contrast with tolerance to morphine-like drugs, a limit to the dose to which a person can become tolerant. This limit is a characteristic of the individual patient and varies widely. Following withdrawal of barbiturates, tolerance is rapidly lost, and some patients may become more sensitive to barbiturates than they had been prior to chronic intoxication with these drugs (Belleville & Fraser, 1957).

During the chronic intoxication of continuing administration, there is some persistence of sedative action, ataxia, etc. through the incomplete development of tolerance, which makes the individual accident-prone. There is also impairment of mental ability, confusion, increased emotional instability, and risk of sudden overdosage through delayed onset of action and perceptional distortion of time. The clinical manifestations of chronic barbiturism are similar to those of chronic alcoholism (Isbell et al., 1950).

The abstinence syndrome is the most characteristic and distinguishing feature of drug dependence of the barbiturate type. It begins to appear within the first 24 hours of cessation of drug-taking, reaches peak intensity in two or three days, and subsides slowly. At present there is no agent which is known to precipitate the barbiturate abstinence syndrome during continuation of drug administration. The complex of symptoms constituting the abstinence syndrome, in approximate order of appearance includes: anxiety, involuntary twitching of muscles, tremor of hands and fingers, progressive weakness, dizziness, distortion in visual preception, nausea, vomiting, insomnia, weight loss, a precipitous drop in blood pressure on standing, convulsions of a grand-mal type, and a delirium resembling alcoholic delirium tremens or a major psychotic episode. Convulsions and delirium do not usually occur at

the same time; generally, a patient may have one or two convulsions during the first 48 hours of withdrawal and then become psychotic during the second or third night. With respect to the psychotic episodes, paranoid reactions, reactions resembling schizophrenia with delusions and hallucinations, withdrawn semi-stuporous state, and disorganized panic have been seen.

One would expect that the mechanism of physical dependence of the barbiturate type, as of that of the morphine type, would be set in motion by the first dose, but there is no evidence that this is the case. There is, indeed, no evidence that physical dependence develops to a detectable degree with continuation of the therapeutic doses usual for the production of sedation or hypnosis; the daily dose must be increased appreciably above the usual therapeutic level before abstinence signs will appear on abrupt withdrawal. Some degree of psychic dependence facilitating continuance of administration may occur with therapeutic doses, but such doses can usually be discontinued without serious subjective disturbance. Factors that may lead to increasing consumption and eventual overt physical dependence include, in addition to tolerance, the incomplete relief of emotional problems and tension, and impairment of judgement, so that larger doses are taken without regard to need.

In drug dependence of the barbiturate type, the detrimental effect on the individual stems in part from his preoccupation with drug-taking, but more particularly from the untoward effects of large doses of the drug: ataxia; dysarthria; impairment of mental function, with confusion, loss of emotional control, poor judgement and, occasionally, a toxic psychosis; coma and death. The harm to society is also related to both the individual's preoccupation with drug-taking and the persistence of the effects of these drugs on motor functioning, emotional stability and interpersonal relationships, with proneness to accidents and to assaults on other persons as frequent consequences. By analogy, all agents which produce barbiturate-like sedation, because of the relief of anxiety, mental stress, etc., should produce some psychic dependence and, for the reasons enumerated for dosage increase, physical dependence when a sufficient concentration in the organism has been attained. This possibility has been confirmed for many sedative agents of different types, including barbiturates and the so-called non-barbiturate sedatives such as glutethimide, methyprylon, meprobamate, chlordiazepoxide, bromisoval, chloral hydrate and paraldehyde, but there may be exceptions.

Drug dependence of alcohol type. Drug dependence of the alcohol type may be said to exist when the consumption of alcohol by an individual exceeds the limits that are accepted by his culture, if he consumes alcohol at times that are deemed inappropriate within that culture, or if his intake of alcohol becomes so great as to injure his health or impair his social relationships. Since the use of alcoholic beverages is a normal, or almost normal, part of the cultures of many countries, dependence on alcohol is usually apparent as an exaggeration of culturally accepted drinking patterns, and the manifestations of dependence vary accordingly in a characteristic fashion with the cultural mode of alcohol use. Thus, in the USA, alcohol is frequently taken in concentrated forms as an aid to social intercourse, so that dependence on alcohol in the USA is usually characterized by heavy consumption of strong spirits during short periods of the day, by a tendency to periodic drinking, and by overt drunkenness. In some other countries, on the other hand, alcohol is customarily consumed in wine, usually with meals. In these countries, dependence on alcohol is characterized by the drinking of wine throughout the day, by a relatively continuous intake of alcohol in this manner, and by relatively little overt drunkenness. A similar pattern applies where beer is the common beverage.

Psychic dependence on alcohol occurs in all degrees. In the mildest grade, alcohol is missed or desired if not available at meals or at social functions. A moderate degree of psychic dependence exists when the individual feels compelled to drink in order to work or to participate socially and takes steps to ensure a supply of alcohol for these purposes. Strong dependence is present if the individual uses alcohol in amounts far exceeding the cultural norm, drinks in situations that culturally do not call for drinking and is obsessed with maintaining a supply of alcohol even to the extent of drinking unusual or poisonous mixtures.

As with other drugs, psychic dependence on alcohol results from an interplay between the pharmacodynamic effects of the drug and the personality problems of the user. The consciously verbalized reasons for the use of alcohol cover a wide gamut and may include a need to stimulate the appetite, to alleviate anxiety or fatigue, to remove boredom or to induce sleep. Other reasons, not consciously verbalized, may include needs to

express masculinity, to remove behavioural controls so that aggressive impulses may be expressed, and to blot out completely a hostile, threatening world.

Tolerance to alcohol does develop. During continuous drinking there is a slight but definite increase in the amount of ingested alcohol required to maintain a given blood level. In addition, some sort of physiological and psychological adaptation occurs so that the alcoholic appears less intoxicated and is less impaired in performance tests at a given concentration of blood alcohol than is a non-alcoholic. Tolerance to alcohol, however, is incomplete and never reaches the degree seen with morphine-like agents.

Physical dependence on alcohol definitely occurs, and the abstinence syndrome resulting when the intake of alcohol is reduced below a critical level is manifested by tremors, sweating, nausea, tachycardia, rise in temperature, hyper-reflexia, postural hypotension and, in severe grades, convulsions and delirium. The last-mentioned condition is characterized by confusion, disorientation, delusions and vivid visual hallucinations. The intensity of the alcohol abstinence syndrome probably varies with the duration and amount of alcohol intake, but as yet little quantitative information on this point is available. The mortality rate, when the alcohol abstinence syndrome is severe, averages at least 8%.

The harm to the individual resulting from dependence on alcohol can be quantitatively greater than that caused by any other type of drug dependence. Alcohol impairs efficiency of thinking and psychomotor co-ordination, leading to deterioration in work performance and to accidents. Judgement deteriorates, leading to all sorts of errors in business and to disturbances of relations with other people. Conscious controls of behaviour are " dissolved ", with resulting exhibitionism, aggressiveness and assaultiveness. In addition, dependence on alcohol predisposes to and causes serious physical disease. The physical damage may be indirect, due to neglect of hygiene or to inadequate dietary intake and utilization, with resultant deficiencies, for example, in vitamins, minerals and proteins. The most common serious complication of protracted alcoholism is fatty portal cirrhosis. Alcoholics are frequently injured because of impaired co-ordination and judgement.

Damage to society is great. The alcoholic squanders his resources to obtain his beverage, his productivity declines, and his family may be neglected to the extent that it has to be supported by society. Alcoholics are frequently involved in accidents, with property damage and injury to others. The economic burden of dependence on alcohol is enormous; even more important is the tremendous amount of human suffering endured by the alcoholic and all who are close to him.

The characteristics of drug dependence of the barbiturate-alcohol type are:

(*a*) Psychic dependence of varying degree that may lead to periodic rather than continuous abuse, especially with alcohol.

(*b*) The definite development of a physical dependence that generally, however, can be detected only after the consumption of amounts considerably above the usual therapeutic or usual socially acceptable levels. Upon the reduction of intake below a critical level, a characteristic self-limited abstinence syndrome ensues, the symptoms of which, in the case of barbiturates, can be suppressed not only by a barbiturate-like agent but also, at least partially, by alcohol. The reverse situation exists in the case of alcohol.

(*c*) The development of tolerance which is irregular and incomplete, so that there is considerable persistence of behavioural disturbance dependent upon the pharmacodynamic effects of the drugs. There is a mutual, but incomplete, cross tolerance of some degree between alcohol and the barbiturates.

(*d*) A frequent consequence of alcoholism is overt pathology in tissues, whereas a similar development with the barbiturates has not been demonstrated.

Drug Dependence of Cocaine Type

Cocaine is the prototype of the stimulant drugs that are capable, in high dosage, of inducing euphoric excitement and hallucinatory experiences. These properties rank it high in the esteem of experienced drug abusers and lead to the highest degree of psychic dependence.

Abuse of cocaine takes several forms. The most common is the centuries-old custom of coca-leaf chewing, which is practised habitually by certain Indians of the high Andes. The leaf, mixed with lime, ostensibly to release the alkaloid, is used almost continuously to reduce sensations of cold, fatigue and hunger. With this form of abuse, release of the alkaloid and its absorption generally are too slow or quantitatively too small to induce mental changes that would lead to abnormal behaviour, as described below.

Despite its vasoconstrictive properties, cocaine is readily absorbed through mucous membranes. At one time, the application of cocaine solutions to oral and nasal lesions was a very popular form of treatment, especially with those patients who appreciated the euphoric stimulation induced by the absorbed drug. Closely allied to such use or abuse is another form of absorption through the mucous membranes that is now less common than it was—namely, the snuffing of cocaine crystals. This is a concentrated form of administration that induces such great psychic effects as to border on those which may be obtained with intravenous administration.

Diminished need for cocaine as a local anaesthetic and control of the world supply has reduced the total illicit use of this drug, but coincidentally there has developed a most dangerous type of abuse—intravenous injection. In the most advanced form, this type of abuse involves administration at frequent intervals, as short as 10 minutes, the user desiring the ecstatic thrills associated with this practice. This type of abuse appeals particularly to persons with psychopathic tendencies, which are often unmasked by the drug. The induced feeling of great muscular and mental strength leads the individual to overestimate his capabilities. This, associated with paranoid delusions and auditory, visual and tactile hallucinations, often makes the user a very dangerous individual, capable of serious antisocial acts. Digestive disorders, nausea, loss of appetite, emaciation, sleeplessness, and occasional convulsions are commonly experienced by cocaine abusers of this type. Long-standing, continuing misuse of cocaine alone at a high level is rare, however. The user reaches such a state of excitement that he voluntarily seeks sedation. A frequent current practice is to antagonize the exciting effects by the alternate administration of morphine or some other depressant drug, or by the injection of the two types of drug in combination, the cocaine-heroin mixture (" speedball ") being particularly popular.

No physical dependence on cocaine develops and, consequently, no characteristic abstinence syndrome is noted on abrupt withdrawal. But severe depression may occur and delusions may persist for some time after withdrawal.

Since cocaine undergoes rapid destruction in the organism, large quantities can be given during a 24-hour period. Indeed, in man as much as 10 gm daily may be used when the drug is administered in relatively small doses at short intervals. This has led to the belief that tolerance to cocaine develops, a conclusion that is warranted neither by the facts nor by analogy with animal experiments. The criteria for tolerance (diminution in objective effects and elevation of the lethal dose) are not observed in animals even though it may be possible to administer several lethal doses within 24 hours, the total quantity varying with the detoxification capacity of the individual species. Although the acute lethal dose for man is unknown, it is clear that, given a constant blood level, no diminution of its subjective or objective effects is noted. These effects, in fact, become enhanced, a sensitization phenomenon that is also seen in animals. It is safe to conclude that man, like animals, does not develop tolerance to cocaine.

In summary, then, the characteristics of drug dependence of the cocaine type are:

(*a*) Strong psychic dependence.

(*b*) No development of physical dependence and, therefore, absence of a characteristic abstinence syndrome when the drug is withdrawn.

(*c*) Absence of tolerance; rather, there is sensitization to the drug's effects in some instances.

(*d*) A strong tendency to continuation of administration, as in coca-leaf chewing, or rapid repetition of the dose, as in the current practice of intravenous administration. Quantitatively, the effects are strikingly different, according to the mode of abuse.

Cocaine is probably the best example of a substance to which neither tolerance nor physical dependence develops and with which psychic dependence can lead to a profound and dangerous type of drug abuse.

Drug Dependence of Cannabis (Marihuana) Type

It is not known with absolute certainty which of the chemical structures that have been isolated from *Cannabis sativa* L. is responsible for the typical cannabis effects, but these can nevertheless be described as constituting an entity that varies in degree according to the concentration of the active principle or principles in the plant and the preparations obtained therefrom, and to the mode of application. These effects are also producible by certain synthetic substances of similar chemical structure.

Among the more prominent subjective effects of cannabis, for which it is taken occasionally, periodically or chronically, are: hilarity, often without apparent motivation; carelessness; loquacious euphoria, with increased sociability as a result; distortion of sensation and perception, especially

of space and time, with the latter reinforcing psychic dependence and being valued under special circumstances; impairment of judgement and memory; distortion of emotional responsiveness; irritability; and confusion. Other effects, which appear especially after repeated administration and as more experience is acquired by the user include: lowering of the sensory threshold, especially for optical and acoustical stimuli, thereby resulting in an intensified appreciation of works of art, paintings and music; hallucinations, illusions, and delusions that predispose to antisocial behaviour; anxiety and aggressiveness as a possible result of the various intellectual and sensory derangements; and sleep disturbances.

In the psychomotor sphere, hypermotility occurs without impairment of co-ordination. Among somatic effects, often persistent, are injection of the ciliary vessels and oropharyngitis, chronic bronchitis and asthma; these conditions and hypoglycaemia, with ensuing bulimia, are symptoms of intoxication, not of withdrawal.

Typically, the abuse of cannabis is periodic but, even during long and continuous administration, no evidence of the development of physical dependence can be detected. There is, in consequence no characteristic abstinence syndrome when use of the drug is discontinued.

Whether administration of the drug is periodic or continuous, tolerance to its subjective and psychomotor effects has not been demonstrated.

Whereas cannabis often attracts the mentally unstable and may precipitate temporary psychoses in predisposed individuals, no unequivocal evidence is available that lasting mental changes are produced.

Drug dependence of the cannabis type is a state arising from chronic or periodic administration of cannabis or cannabis substances (natural or synthetic). Its characteristics are:

(*a*) Moderate to strong psychic dependence on account of the desired subjective effects.

(*b*) Absence of physical dependence, so that there is no characteristic abstinence syndrome when the drug is discontinued.

(*c*) Little tendency to increase the dose and no evidence of tolerance.

For the individual, harm resulting from abuse of cannabis may include inertia, lethargy, self-neglect, feeling of increased capability, with corresponding failure, and precipitation of psychotic episodes. Abuse of cannabis facilitates the association with social groups and sub-cultures involved with more dangerous drugs, such as opiates or barbiturates. Transition to the use of such drugs would be a consequence of this association rather than an inherent effect of cannabis. The harm to society derived from abuse of cannabis rests in the economic consequences of the impairment of the individual's social functions and his enhanced proneness to asocial and antisocial behaviour.

Drug Dependence of Amphetamine Type

The capacity of the amphetamines and drugs with similar pharmacological properties to elevate mood and induce a state of well-being is probably largely the basis for their value and widespread use as stimulants and anorexiants. Since such therapy commonly involves continuous and prolonged administration, the users of these drugs may develop varying degrees of psychic dependence upon them. This fact establishes the basis for abuse, where the dosage may be increased in both quantity and frequency of administration in order to attain a continuing stimulation and state of elation. When carried to an extreme, the psychotoxic effects of large amounts of drugs of the amphetamine type may lead to aggressive and dangerous antisocial behaviour.

The abuse of this class of drugs originates in and is perpetuated by the psychic drive to attain maximum euphoria; no physical dependence is created. Qualitatively, the psychological effects are in many respects similar to those produced by cocaine.

A unique feature of the amphetamines is their capacity to induce tolerance, a quality possessed by few central nervous system stimulants. Although tolerance develops slowly, a progressive increase in dosage permits the eventual ingestion of amounts that are several hundredfold greater than the original therapeutic dose. Apparently, all parts of the central nervous system do not become tolerant at the same rate, so that the user will continue to experience increased nervousness and insomnia as the dose is increased. Although an individual may survive the oral administration of very large quantities, such ingestion may produce profound behavioural changes that are often of a psychotic nature, including hallucinations, delusions, etc. These latter effects are much more likely to occur after intravenous injection than after ingestion. Indeed, the intravenous route is employed for the express purpose of obtaining bizarre mental effects, often associated with sexual functions, even to the

point of orgasm. This type of abuse has been increasingly frequent in recent years with the changing patterns of drug abuse in various countries.

Although the amphetamines do not induce physical dependence, as measured by the criterion of a characteristic and reproducible abstinence syndrome, it would be inaccurate to state that withdrawal from very large dosages is symptomless. The sudden withdrawal of the stimulant drug which has masked chronic fatigue and the need for sleep now permits these conditions to appear in an exaggerated fashion. Thus, the withdrawal period is characteristically a state of depression, both psychic and physical, which probably reinforces the drive to resume the drug. In this regard, it is much less important and does not compare in magnitude with those that occur with morphine, barbiturates, alcohol and other drugs that create physical dependence. Withdrawal of drugs of the amphetamine type is never threatening to life and requires psychological rather than somatic therapy.

The use of amphetamines by self-administration has increased consistently in recent years, ostensibly as anti-fatigue agents in situations in which it is desired to remain mentally alert for long periods without sleep or rest or to permit increased physical performance. The use of amphetamines as stimulants has also increased markedly in persons who abuse alcohol and/or barbiturates; in many such instances there is dependence on more than one drug. In such cases, the prognosis is poor, the relapse rate is high, and continued dependence on one or more drugs is the rule, especially in prepsychotics or individuals with latent schizophrenia.

Thus, the characteristics of drug dependence of the amphetamine type are:

(*a*) A variable psychic dependence.

(*b*) No physical dependence and, consequently, no characteristic abstinence syndrome, though withdrawal will be followed by a state of mental and physical depression as the organism escapes from the persistent stimulation.

(*c*) The slow development of a considerable degree of tolerance to many effects, but not participated in equally by all components of the cerebral system, so that nervousness and sleeplessness persist and psychotoxic effects such as hallucinations and delusions may occur.

Abusers of amphetamines are prone to accidents because of both the excitation produced by these agents and the excessive fatigue which may break through and manifest itself at an inopportune time. Abuse by intravenous administration, with its concomitant bizarre mental effects, may result in serious antisocial behaviour.

Drug Dependence of Khat Type

Khat (*Catha edulis* Forssk.) is cultivated and consumed in circumscribed areas of East Africa and the Arabian peninsula. The common, and quantitatively most profitable, mode of application is by way of chewing the tender parts of the plant in as fresh a state as possible.

The active principle of the khat leaf is chemically and pharmacologically related to the amphetamine group of substances so closely that its effects are to be considered qualitatively identical with those of the latter group and quantitatively equal to their weaker members. These resemblances extend to the somatic as well as to the psychic effects, among which a usually moderate degree of central stimulation, with ensuing elation and removal of fatigue, is the effect most sought for by khat users, besides suppression of hunger and, sometimes, of libido. The quantitative difference between the effects of khat and those of the commonly abused amphetamine substances is enhanced by the limitation of the ingestion and absorption of khat due to its particular mode of application. The naturally limited dose of khat is assumed to prevent the occurrence of tolerance, of rebound phenomena after cessation, and of psychotoxic effects typical of the amphetamines when the latter are administered in pure form and in high dosage. There is no evidence of the development of a physical dependence on khat during chronic use.

Nevertheless, the pleasurable effects afforded by khat are a strong inducement for many to procure by any means the necessary supplies at least once a day or to repeat or prolong the periods of chewing, often at the expense of vital needs such as food. Such behaviour is a manifestation of psychic dependence.

Drug dependence of the khat type is, under the circumstances of its traditional consumption by chewing, characterized by:

(*a*) Moderate but often persistent psychic dependence as long as its maintenance is at all practicable.

(*b*) Lack of physical dependence.

(*c*) Absence of tolerance.

The habitual and, in particular, the exaggerated consumption of khat may also, on account of its

non-amphetamine ingredients (tannins) damage the individual's health. The social and economic consequences of dependence on khat consist, in the main, of the alienation of the user's funds and the erosion of his working capacity and concern both the individual and his environment as well as the community.

Drug Dependence of Hallucinogen (LSD) Type

Drugs of this type include lysergic acid diethylamide (LSD), a semisynthetic derivative of ergonovine; psilocybin, an indole found in a mushroom (" teonanacatl ", *Psilocybe mexicana*); mescaline, the most active alkaloid present in the buttons of a small cactus (" mescal ", " peyote ", *Lophophora williamsii*), and in the seeds of some morning glory varieties (" ololiuqui ", *Rivea corymbosa* L. Hall f.; *Ipomoea violacea* L.), the active principle of which is closely related to LSD. The mushrooms, cactus buttons and the morning glory seeds are used by certain American Indian tribes in religious ceremonies or are employed by medicine men or women of these tribes in treating illness, usually in ritualistic fashion. Such religious and ritualistic use does not seem to lead frequently to drug dependence. The drugs have received wide publicity, however, and they possess a particular attraction for certain psychologically and socially maladjusted persons who have difficulty in conforming to usual social norms. These include " arty " people such as struggling writers, painters and musicians; frustrated non-conformists; and curious thrill-seeking adolescents and young adults. The drugs are taken for thrills (" kicks "), to alter mood, to change and clarify perception, to induce reveries, and to obtain " psychological insight " into the personality problems of the user. Generally, the drugs are taken orally and in the company of other users. Ingestion of a single dose or of several doses over a period of two or three days is the customary pattern; prolonged or continuous use is unusual. Periodic, rather than continuous, use is favoured by difficulty in obtaining the drugs, rapid development and disappearance of tolerance, and lack of physical dependence on these drugs.

Drugs of the LSD type induce a state of excitation of the central nervous system and central autonomic hyperactivity manifested by changes in mood (usually euphoric, sometimes depressive), anxiety, distortion in sensory perception (chiefly visual), visual hallucinations, delusions, depersonalization, dilatation of the pupils, and increases in body temperature and blood pressure.

Psychic dependence on drugs of the LSD type varies greatly, but it usually is not intense. The thrill-seekers and non-conformists may enjoy the effects of these agents and may wish to repeat them, but if such agents are not readily available, these persons will either do without them or substitute another substance. A minority of users may develop such strong psychic dependence on those substances that they wreck their careers by persisting in using the drugs despite strong social condemnation.

No evidence of physical dependence can be detected when the drugs are withdrawn abruptly.

A high degree of tolerance to LSD (Isbell et al., 1956) and to psilocybin (Wolbach, Isbell & Miner, 1962) develops rapidly and disappears rapidly. Tolerance to mescaline develops more slowly. Persons who are tolerant to any of these three drugs are cross-tolerant to the other two (Wolbach, Isbell & Miner, 1962).

The chief dangers to the individual arise from the psychological effects. Impairment of judgement could lead to dangerous decisions or accidents. Occasional persons may become depressed, so that suicide is a possibility in users of these drugs.

RÉSUMÉ

L'élément commun aux différentes formes de la toxicomanie étant un état de dépendance, qu'il soit psychique ou physique ou qu'il ait ce double caractère, le Comité OMS d'experts des Drogues engendrant la Toxicomanie a recommandé de substituer le terme « dépendance » aux termes « toxicomanie » et « accoutumance ».

« Dépendance » est un terme de portée générale, qui a l'avantage d'être applicable à tous les types d'emploi abusif de drogues et de ne préjuger en rien l'ampleur du risque qui résulte de ces abus pour la santé publique, ni la nature du contrôle éventuel à envisager. L'utilisation générale de ce terme contribuera à faire ressortir l'existence d'une relation entre certaines substances, en appelant l'attention sur une caractéristique commune de leur emploi abusif, et elle permet de mieux décrire et de mieux différencier certaines particularités spécifiques des substances en cause.

La dépendance se définit comme un état qui résulte de l'absorption périodiquement ou continuellement répétée d'une certaine drogue. Ses caractéristiques varient

suivant les drogues, ce qui doit être bien précisé par l'indication, dans chaque cas, du type particulier dont il s'agit.

Les descriptions ont été limitées aux aspects médicaux de la dépendance, mais les caractéristiques et répercussions sociales et économiques du phénomène ne doivent pas être perdues de vue. Elles varient suivant le type de drogue et, de même, le préjudice causé à l'individu et à la société diffère selon le type de dépendance.

Dans l'article qui précède, sept types de dépendance ont été décrits, c'est-à-dire la dépendance de type morphinique, barbiturique-alcool, cocaïnique, cannabique, amphétaminique ainsi que des types du khat et des substances hallucinogènes (LSD). Pour les différents types de dépendance, les caractéristiques médicales sont résumées dans une formule brève et précise comme suit:

Caractéristiques de la dépendance de type morphinique:

a) forte dépendance psychique, qui se manifeste par une tendance ou impulsion irrésistible à continuer à prendre la drogue et à se la procurer par tous les moyens, soit pour en obtenir des jouissances, soit pour pallier des sensations désagréables;

b) apparition précoce d'une dépendance physique qui s'accroît parallèlement à l'augmentation des doses. Ce fait oblige à continuer l'administration de la drogue initiale, ou d'une substance ayant des propriétés analogues, afin de maintenir un semblant d'homéostase et de prévenir l'apparition de symptômes et d'indices résultant du sevrage. Celui-ci, de même que l'administration d'un antagoniste, précipite l'apparition d'un syndrome d'abstinence bien défini, caractéristique et limité dans le temps;

c) apparition d'une tolérance, d'où la nécessité d'augmenter les doses pour obtenir les effets pharmacodynamiques initiaux.

Caractéristiques de la dépendance de type barbiturique-alcool:

a) dépendance psychique d'intensité variable qui peut conduire à l'abus périodique plutôt qu'à l'abus continuel, notamment dans le cas de l'alcool;

b) nette apparition d'une dépendance physique qui, cependant, ne peut généralement être décelée qu'après consommation de quantités très supérieures aux normes habituellement admises selon les critères thérapeutiques et sociaux. Si la consommation est abaissée au-dessous d'un seuil critique, on note l'apparition d'un syndrome d'abstinence caractéristique et limité dans le temps. En ce qui concerne les barbituriques, la suppression des symptômes peut être obtenue non seulement par l'administration d'un agent possédant une action analogue, mais également, en partie du moins, par l'administration d'alcool. Pour ce dernier, c'est le phénomène inverse qui se produit;

c) apparition d'une tolérance, dont le caractère inconstant et partiel détermine la persistance, à un degré considérable, d'un trouble du comportement tributaire des effets pharmacodynamiques des drogues. On observe une certaine tolérance croisée et réciproque, mais incomplète, à l'alcool et aux barbituriques;

d) l'alcoolisme entraîne fréquemment des lésions pathologiques évidentes au niveau de certains tissus; une action analogue n'a pu être mise en évidence concernant les barbituriques.

Caractéristiques de la dépendance de type cocaïnique:

a) forte dépendance psychique;

b) absence d'apparition d'une dépendance physique et, par suite, absence d'un syndrome d'abstinence caractéristique lors du sevrage;

c) absence de tolérance; on note plutôt une sensibilisation aux effets de la drogue, dans certains cas.

Caractéristiques de la dépendance de type cannabique:

a) dépendance psychique modérée ou forte, suivant les effets subjectifs recherchés;

b) absence de dépendance physique, de sorte qu'il n'existe pas de syndrome d'abstinence caractéristique lorsque l'administration de la drogue est suspendue;

c) peu de tendance à augmenter les doses; aucune tolérance n'a pu être démontrée.

Caractéristiques de la dépendance de type amphétaminique:

a) dépendance psychique variable;

b) pas de dépendance physique et, par suite, pas de syndrome d'abstinence caractéristique, bien que le sevrage provoque un état de dépression mentale et physique lorsque l'organisme n'est plus soumis à l'excitation permanente de la drogue;

c) développement lent d'une tolérance marquée vis-à-vis de beaucoup des effets de la drogue, mais avec participation inégale des différentes composantes du système cérébral, si bien que l'état d'agitation et l'insomnie persistent et que des phénomènes psychotoxiques, comme des hallucinations ou des illusions, peuvent apparaître.

La dépendance de type khat, dans l'éventualité de la consommation traditionnelle par mastication, *se caractérise par:*

a) une dépendance psychique modérée, mais souvent persistante, pour autant qu'elle puisse être entretenue;

b) l'absence de dépendance physique;

c) l'absence de tolérance.

La dépendance psychique vis-à-vis des *drogues du type des substances hallucinogènes* est très variable, mais généralement peu accentuée.

Aucun indice de dépendance physique n'est observé en cas de sevrage brusque.

Une tolérance marquée à la LSD et à la psilocybine se manifeste rapidement et disparaît également rapidement. La tolérance à la mescaline apparaît plus lentement. Les personnes qui sont tolérantes à l'une de ces trois substances présentent une tolérance croisée aux deux autres.

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