

A pharmacological classification of drugs of abuse

By G. G. NAHAS

Professor of Anesthesiology, College of Physicians and Surgeons, Columbia University, New York, United States of America

ABSTRACT

This paper questions the validity of the distinction between "psychic" and "physical" dependence in relation to drug addiction. The author describes the action of dependence-producing or addictive drugs on the brain at the neuronal and structural level as well as the alterations of arousal, awareness, impairment of sleep, memory, psychomotor performance and sensory perception which are symptomatic of neuropsychological toxicity. Addictive drugs are consumed for the primary pleasurable reward that they produce as a result of their effects on the pleasure reward mechanisms of the brain. These pleasurable sensations will act as reinforcers for repeated administration when the drug effects have worn off and induce a compulsive drug-oriented behaviour. The tolerance, which develops to addictive drugs and the occurrence of withdrawal symptoms, are added reinforcers. The author therefore proposes a pharmacological classification of the most commonly used addictive drugs based on these foregoing effects which may be quantified to a large extent.

Introduction

From the dawn of history, man has exploited every root, twig, berry, and grain in nature not only for their possible use to satisfy his hunger and thirst and to cure his ailments but also to satisfy another basic need which is to heighten his state of consciousness.

This elevation of mood induced by certain substances was always perceived as a gift of the Gods. Dionysus in Greece was worshipped because of his gift of the grape, Mama Occlo in Peru brought the divine plant coca to the Incas; in Mexico, sacred mushrooms are called the flesh of the Gods. Cannabis, the plant from which marijuana is made, was regarded by the Hindus in the pre-Christian era as a holy plant and it played an important religious role; it is referred to in the Sanskrit literature as "food of the Gods". The ancient Sumerians, who used opium 4,000 years before Christ, identify the poppy from which this drug is extracted with a symbolic lettering meaning "joy". While opium derivatives and cannabis preparations were

used in the East and Far East, in the New World, tobacco and hallucinogenic cacti were used in prehistoric times. These confections were either sniffed or ingested and later inhaled.

In more recent times, the urge to achieve happiness through chemical stimulation has spread to a considerable degree in Western society. In addition to tobacco and alcohol, modern man is being exposed to a large number of other psychoactive drugs which is ever increasing thanks to the ingenuity of the organic chemists.

This series of examples indicates that the urge to elevate one's mood and reach a blissful state with mind-altering drugs is a universal phenomenon; an inherent part of man's nature, and man's brain.

Freud linked the use of intoxicants with their two fundamental properties — the production of pleasure and the dissipation of unpleasant feelings:

"The crudest, but also the most effective among these methods (of averting suffering) is the chemical one — intoxication. I do not think that anyone completely understands its mechanism, but it is a fact that there are foreign substances which, when present in the blood or tissues, directly cause us pleasurable sensations; and they also alter the conditions governing our sensibility that we become incapable of receiving unpleasurable impulses. The two effects not only occur simultaneously, but seem to be intimately bound up with each other" [1].

Freud also postulated that the pleasurable sensations produced by intoxicants might be mediated by natural endogenous mechanisms:

"But there must be substances in the chemistry of our own bodies which have similar effects, for we know at least one pathological state, mania, in which a condition similar to intoxication arises without the administration of any intoxicating drug. Besides this, our normal mental life exhibits oscillations between a comparatively easy liberation of pleasure and a comparatively difficult one, parallel with which there goes a diminished or an increased receptivity to unpleasure. It is greatly to be regretted that this toxic side of mental processes has so far escaped scientific examination" [1].

A similar mechanism of action for the euphoriant effect of cannabis had been postulated much earlier by Moreau in 1845:

"It is really happiness that hashish gives. It is a very curious fact from which one can draw strange conclusions: All joy, all contentment, even though their cause is strictly mental, and our most spiritual, idealistic enjoyments could well be in reality only purely physical sensations, developed in the core of our brain exactly like those produced by hashish" [2].

Therefore, *Homo sapiens* Sapiens in his selection of drugs is in reality *Homo sapiens* Ludens, oriented towards pleasure and fun. However, such playful activity, when it involves drug consumption, has not always been in

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the best interest of his own health and has not benefited society. As Freud put it:

"As is well known, it is precisely this (euphoriant) property of intoxicants which also determines their danger and their injuriousness. They are responsible, in certain circumstances, for the useless waste of a large quota of energy which might have been employed for the improvement of the human lot" [1].

Indeed, it has always been reported that the abuse of euphoriant drugs threatens man's creative activities with damaging results to his community. This fundamental observation has led all societies throughout history to restrict the consumption of those drugs which may be so readily abused.

In primitive societies, religion was the primary regulatory factor in controlling the use of mind-altering drugs. These drugs were jealously controlled by the medicine man or high priest who did not care to share with the common folk the secret of his super-power, and limited their use to very special occasions.

In modern times, secular rulers have attempted to curtail the use of these drugs by laws and edicts which formulated and strengthened social taboos. During this century, these regulations have been channelled through the good offices of the United Nations and its specialized agencies which have singled out "dependence-producing drugs" which I will call addictive drugs, or drugs of abuse.

Drugs of abuse and the United Nations

Over the past 55 years, the League of Nations and the United Nations have played a major role in the series of international conventions which have been concluded in an attempt to limit the use of dependence-producing drugs (addictive drugs) to legitimate scientific and medical needs [3-5]. Under the most recent conventions, the Commission on Narcotic Drugs and the International Narcotics Control Board (an independent control body instituted by the Single Convention) have primary responsibility for monitoring their implementation, while both the Economic and Social Council and the General Assembly have specific duties assigned to them.

The World Health Organization is entrusted by the treaties with the responsibility of formulating recommendations to the Commission on Narcotic Drugs with respect to substances which should be brought under international control or whose system of control under the treaties should be changed. WHO has certain other advisory functions under the conventions, all of which are aimed at protecting the interests of both individual and public health [6].

The World Health Organization expert committees have formulated the following definitions to describe drug dependence.

Drug dependence

"A state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioural and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence. Tolerance may or may not be present. A person may be dependent on more than one drug" [7].

Psychic dependence

A condition in which a drug produces "a feeling of satisfaction and a psychic drive that require periodic or continuous administration of the drug to produce pleasure or to avoid discomfort" [8].

Physical dependence

"An adaptive state that manifests itself by intense physical disturbances when the administration of the drug is suspended. 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" [8].

Table 1
The WHO classification of drugs of abuse

<i>Drug type</i>	<i>Psychic dependence</i>	<i>Physical dependence</i>	<i>Tolerance</i>
Alcohol	Mild to marked	Mild to marked	Some
Barbiturate and certain other sedatives	Mild to marked	Mild to marked	Substantial
Opiate (morphine)	Moderate to marked	Marked	Marked
Cocaine	Mild to marked	None	None
Amphetamine and certain other stimulants	Mild to marked	Little, if any	Marked
Khat	Mild to moderate	Little, if any	Little, if any
Hallucinogen (LSD)	Mild to moderate	None	May be marked with some agents
Cannabis (marijuana)	Mild to moderate	Little, if any	Probably some at higher doses
Volatile solvent (inhalant)	Mild to moderate	Little, if any	Some with certain agents

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By and large, these definitions have been adopted throughout the world and have created some confusion, mostly by introducing the notions of "psychic" and "physical dependence" without the proper biological or pharmacological markers to define these conditions (see table 1).

WHO experts were careful to emphasize that the so-called "psychic" dependence was paramount in drug-seeking behaviour. However, the public has too often associated drug addiction with physical dependence and the occurrence of withdrawal symptoms of the opiate type. This major misconception, which spans most of the popular drug literature, has resulted from the erroneous simplification that opiates are the only truly addictive drugs. Furthermore, many drug experts claim that cocaine, cannabis and tobacco are not addictive because cessation of their use is not accompanied by a full-blown withdrawal syndrome. According to these experts, the use of these drugs may, therefore, be readily interrupted if the user exerts enough "willpower". The clear-cut distinction between "psychic" and "physical" dependence illustrates the old dichotomy between mind and body, which modern neurophysiology and psychopharmacology no longer justify since soma and psyche are inextricably interwoven.

Furthermore, clinical experience and pharmacological research over the past decade indicate that cocaine, cannabis and tobacco, which are claimed to produce according to the old WHO definitions, "mild to marked psychic dependence" and "little if any physical dependence" are in reality addictive if one analyses their overall effects which include biochemical therefore "physical" alterations in the brain, as follows:

Factors which characterize drugs of abuse

Drugs of abuse (addictive drugs):

I. Act primarily on the brain:

- At the neuronal level by interfering with the turnover of neurotransmitters and neuropeptides.
- At the structural level by altering function of the limbic system (primarily the medial forebrain bundle, periventricular system and hypothalamus, and reticular activating system). Cortical receiving and associative areas also affected.

II. Produce reversible symptoms of "neuropsychological toxicity" which may be defined as adverse effects on arousal, awareness, and psychological or psychomotor performances.

III. Produce a primary pleasurable reward, a relief from unpleasant feelings and alteration of sensory perceptions.

IV. Act as "powerful reinforcers" and induce a craving for the drug and compulsive drug-oriented behaviour.

V. Frequent, daily use is associated with tolerance.

VI. Abrupt interruption of their long-term use is associated with an abstinence syndrome which may be mild or severe, depending on the drug.

VII. Frequent, daily use over a long period of time is associated with an increased incidence of physical or mental illness.

We will now attempt to define drug addiction or drug dependence by focusing on pharmacologically measurable factors. It will be seen that an analysis of these factors allows a more precise definition of all drugs of abuse with which we are concerned.

The brain as a target of addictive drugs

Psychoactive drugs act primarily on the brain at the neuronal and structural levels. At the neuronal level these drugs interfere with neurotransmitter turnover. At the structural level they alter the function of key brain structures.

Effect of psychoactive drugs on brain neurotransmitters

The 11 billion neurons of the brain are functionally but not structurally connected to transmit information. Information is carried within a neuron as an electrical impulse, an activity which is little affected by most psychoactive drugs. The functional connection between the neurons is the synapse, the site of production of the neurotransmitters, which process information between one neuron and another. Psychoactive addictive drugs alter the functioning of the brain by modifying the production, release or breakdown of neurotransmitters and of neuropeptides. The type of effect of a given drug will depend on:

- (a) The neurotransmitter (catecholamine, serotonin, acetylcholine) or neuropeptide (endorphin) with which the drug predominantly interacts;
- (b) The nature of this interaction;
- (c) The locus of the interaction in the brain and the function that this area of the brain fulfils.

The turnover of all neurotransmitters and neuropeptides is linked through a network of feedback control mechanisms which normally result in a state of brain equilibrium or brain homeostasis. A drug will, therefore, disrupt this homeostasis which is also dependent on a normal functioning of specialized parts of the brain which we will now briefly describe.

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Effect of addictive drugs on specific brain structures

The brain is made up of certain structures which have specialized functions and these are specifically altered by psychoactive drugs:

The reticular activating system is in the area where the spinal cord connects with the brain. It modulates incoming sensory information and outgoing motor impulses and regulates the degree of alertness and arousal of the cerebral cortex. This structure is predominantly catecholaminergic and will be activated by psycho-stimulants.

The hypothalamus located near the base of the brain serves as an integrator of information from many sources as well as being the control centre for the autonomic nervous system. It acts to adjust the release of hormones from the pituitary or master gland of the body, including the sexual hormones FSH and LH. Because of its rich blood supply, the hypothalamus is exposed to drugs which enter the brain in high concentration. The impairment of reproductive function associated with psychoactive drugs (opiates, marijuana) is mediated by their action on the hypothalamus.

The medial forebrain bundle (MFB) is an area of adrenergic neurons located along both sides of the hypothalamus and was first shown by Robert Heath [9] to be the main locus in man of the "brain reward system" or "endogenous reinforcement system". This area was subsequently mapped and extensively studied in rodents by Olds and his pupils [10]. Olds wrote in 1976, shortly before his untimely death: "Although the evidence is fragmentary, it is fair to suppose that a strong connection may be established between self-stimulation (of the brain reward system) and drug-induced behaviours." Subsequent studies have justified this statement.

The periventricular system groups the cholinergic neurons connecting with those of the MFB which are the substrate for aversion and punishment [11]. Activation of MFB will inhibit this aversion centre.

The basal ganglia are the primary control centres for involuntary movements such as those involved in posture. Impairment of their function by addictive drugs results in unco-ordination.

The areas of the brain which we have described are part of the limbic Papez system. They are entirely covered by the cerebral cortex.

The cerebral cortex, with its 9 billion neurons, is responsible for analysis of incoming information and initiation of voluntary motor behaviour. The cerebral cortex is responsible for final information processing in three of its main areas: receiving areas, output areas and association areas.

The receiving areas of the cortex to which the various senses send information and the output areas are clearly affected by addictive drugs. The sensory cortical areas of the sense organs are so connected that a specific receptor responding to a particular stimulus terminates in the same cortical

neuron. Addictive drugs may affect the activity of the receptor cell, or of the synapses in the pathway from receptor to cortex. Distortion of sensory stimuli (sound, colour) by addictive drugs may be clearly understood by these neuronal effects.

In brief, addictive drugs impair information processing in the brain at two fundamental levels:

- At the neuronal level by interfering with neurotransmitters and neuropeptide turnover.
- At the organizational level, by altering information processing by the limbic system and by the cerebral cortex.

Addictive drugs and "neuropsychological toxicity"

The effects of addictive drugs on the brain neurotransmitters and specialized functions of the limbic structure produce neuropsychological anomalies, which result in behaviour alterations. These are numerous and differ according to the drug. They include:

Alteration of arousal and awareness:

Increased (psychostimulant)

Decreased (opiates, psychodepressants)

Impairment of normal sleep, EEG patterns:

Sleepiness (opiates, barbiturates, cannabis)

Insomnia (amphetamines, cocaine)

Impairment of psychological or psychomotor performance (opiates, psychodepressants, cannabis)

Motor unco-ordination, tremor (alcohol)

Impairment in memory and learning (cannabis)

Distortion of sensory perceptions (hallucinogens, cannabis)

The manifestation of these symptoms is related to the respective biochemical changes induced by the drug at the neuronal or structural level of the brain.

Some addictive drugs such as nicotine or caffeine (in moderate amounts) and alcohol (in small amounts) do not produce any measurable symptoms of neuropsychological toxicity. Some pharmacologists have associated the symptoms of neuropsychological toxicity with behavioural toxicity, which include in addition: suppression of normal anxiety, reduction in motivation and non-purposive or inappropriate behaviour. However, the latter behavioural symptoms do not present "markers" which may be measurable in societies accepting as "normal" a wide range of life styles.

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The primary pleasurable reward of addictive drugs

When addictive drugs are not consumed for medical purposes but for their immediate euphoriant and calming or stimulant effect on the brain, they become drugs of abuse. It follows that these drugs trigger brain mechanisms which are then predisposed to their continued self-administration.

These drugs produce "a primary pleasurable reward" [12] mediated, it is fair to assume, by their action upon brain reward mechanisms [1, 10].

The pleasurable effect of addictive drugs on brain reward mechanisms is associated with their ability to dissipate unpleasant feelings, decrease anxiety and include detachment from the world. The most powerful in this respect are the opiates which through their analgesic properties also relieve the discomfort of pain.

In addition, consumption of these drugs has been associated with changing of sensory perceptions which may be mild or extreme (hallucinations). The latter manifestations reflect profound distortions of brain function, including alterations in the receiving sensory areas of the cerebral cortex.

All of the pleasurable sensations brought about by the addictive drugs are concurrent with their "neuropsychological toxicity" which we have described. They also act as reinforcers for repeated administration when the drug effects have worn off.

The administration of opiates for the relief of pain or of cocaine for topical anaesthesia is associated with a low incidence of addiction among patients treated with these drugs. However, the physician dispenses them with parsimony and their prescription is only associated with the relief of symptomatic ailments. For the physician knows firsthand the potential for abuse of these drugs when taken out of a medical context [13].

Addictive drugs as reinforcers: a compulsive pattern of use

Man's propensity to take drugs of abuse is shared with other mammals [14, 15]. Rhesus monkeys, as well as other laboratory animals, learn to self-administer most of these drugs, when given free access to them, through a system of intravenous injection. The rhesus monkey shows patterns of self-administration that are strikingly similar to those exhibited by human users of the same drug (see table 2). The major psychostimulants are the most profound reinforcers in rhesus monkeys, which will press a lever more than 4,000 times in order to get a single injection of cocaine. When given free access to cocaine or amphetamines, the animals will immediately self-administer high daily doses, resulting in severe toxic effects and death within three weeks. If a saline solution is substituted, there is a rapid burst of lever-pressing for several hours, then all responding suddenly ceases.

Table 2
Self-administration of psychoactive drugs

<i>Drug type</i>	<i>Rhesus monkey</i>	<i>Man^a</i>
Analgesic		
Opiates and derivatives		
Agonists	+	+
Antagonists (Naloxone)	—	—
Mixed agonists antagonists (Buprenorphine)	+	+
Non-narcotic analgesics		
Acetylsalicylic acid	—	
Aminophenazone	—	
Phenylbutazone	—	
Sodium salicylate	—	
Stimulant		
Major		
Cocaine	+	+
Amphetamines	+	+
Minor		
Caffeine	—	
Nicotine	?	+
Khat	?	
Depressant		
Barbiturates	+	+
Methaqualone	+	+
Alcohol	+	+
Benzodiazepines	+	+
THC	+	?
Hallucinogenic		
LSD	—	
Mescaline	—	
STP	—	
Phencyclidine	+	
Antidepressant or antipsychotic		
Amitriptyline	—	
Imipramine	—	
Chlorpromazine	—	
Butyrophenone	—	
Perphenazine	—	

^a In a laboratory setting.

These results obtained with previously untrained monkeys show that injections of a psychomotor stimulant such as cocaine can function as a reinforcer even when personality, pre-existing psychopathology, socioeconomic status and peer pressure are not involved.

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Brief withdrawal of the drug after chronic administration does not result in a clear withdrawal symptom, and cocaine therefore acts as a powerful positive reinforcer of drug-taking behaviour in the absence of withdrawal symptoms of the opiate type.

With opiates, monkeys self-administer the drug by gradually raising the daily dose over a period of weeks until they reach a steady state, which avoids both gross toxicity and withdrawal symptoms. When a saline solution is substituted for morphine, withdrawal symptoms appear, and the animal continues to press the lever at a slow but steady level for some weeks.

All psychodepressants including the benzodiazepines are also self-administered. Self-administration of THC has been reported by one author [16] but not by others [14] which may be due to differences in techniques of administration and of solvents used.

Hallucinogens are not self-administered by non-human primates.

Some drugs used in the treatment of severe mental illness, schizophrenia or endogenous depression are never self-administered. They appear instead to have aversive properties and the monkey learns to avoid manoeuvres that result in small injections of such drugs.

Following these experiments on monkeys, human self-administration of drugs of abuse were performed under controlled conditions in a hospital setting [17, 18]. Results obtained were concurrent, for the same drug, in both species, when the same variables were manipulated: type of drug, dose of drug, response requirement to obtain drug, punishment of self-drug administration. Self-administration of different drugs produces similar effects on the normal behaviour of the drug user. Such a demonstration suggests that "common processes may underlie various aspects of drug self-administration" [17].

Finally, one author concludes these drugs "have as an inherent pharmacological property the capacity to serve as positive reinforcers and that this capacity is directly related to their abuse potential" [18].

In many cases, while the drug itself acts as a primary reinforcer in drug-taking behaviour, there is a more subtle, but important, major secondary reinforcing influence: namely the whole social and cultural context in which drugs are taken. The social environment certainly reinforces the process of drug taking. In addition, WHO lists the more important factors which appear to facilitate drug use, as follows [19]:

- (a) The ready availability of drugs;
- (b) General public acceptance of the use of mood modifiers;
- (c) Increasing mobility, particularly of youths;
- (d) Peer group pressures;
- (e) An abundance of information about drug effects and sources;
- (f) An unstable or broken home.

The fact that addictive drugs act as reinforcers may account for their compulsive use which is characterized by:

- (a) Craving for the drug;
- (b) Major involvement in the securing of its supply;
- (c) A high tendency to relapse after discontinuing use.

The foregoing pattern of compulsive behaviour towards drug use also applies to the minor psychostimulants such as tobacco and caffeine (which do not produce comparable neuropsychological adverse effects).

Tolerance to addictive drugs

Tolerance is described as the necessity to increase the dosage of a drug in order to obtain the initial psychotropic effect [20]. The capacity of the animal or human organism to tolerate elevated doses of drugs of abuse, without displaying acute physical damage, is high, in the order of 1 to 10 for the opiates, alcohol and barbiturates [21]; of 1 to 50 for cocaine [22], and of 1 to 200 for cannabis products [23]. Such a pattern indicates that the lower the acute somatic toxicity of a drug, the greater its tolerance will be.

Furthermore, naturally occurring psychoactive drugs of abuse are as a whole less toxic than synthetic derivatives.

Heroin > Morphine
Amphetamine > Cocaine
DMPH > THC

The mechanism of tolerance is not entirely elucidated. However, it is related to biochemical alterations produced by the drug in the organism, mainly in the liver and the brain. In the liver, the mechanisms of inactivation of the drug for swifter disposal are speeded up (enzymatic induction). This process is designated as metabolic or dispositional tolerance. In the brain, the responses of the target neuronal cells are modified, with a resulting alteration in neurotransmitter turnover: synthesis, release, re-uptake of catecholamines or acetylcholine are modified. Furthermore, neuropeptide turnover, especially of the endorphines which are the major regulators of brain homeostasis, is disturbed. Such alterations have been clearly demonstrated for the opiates and occur also with other drugs of abuse.

The phenomenon of tolerance is a drug-related adaptive process which allows the brain to function in the presence of substances which do not occur naturally in its internal environment (xenobiotics).

Development of tolerance is the major caveat of drugs of abuse, and is closely linked to drug dependence. Before becoming dependent on drugs, the brain biochemical mechanisms have to adjust to their repetitive disrupting effects. Tolerance accentuates the problem of drug supply and the need for

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readministration. It is primarily a symptom of physical dependence and may or may not be accompanied by the syndrome of abstinence once the drug has been discontinued.

Withdrawal or abstinence syndrome

This syndrome is characterized by distressing and painful symptoms resulting from sudden deprivation of the habitual (daily) use of a drug. These symptoms depend upon the nature of the drug used. They may be mild and not always clinically noticeable (cocaine [24], cannabis [25] or marked opiates [26]) and even life-threatening (barbiturates [27] and alcohol [28]).

For the opiates, withdrawal symptoms seem to result mainly from an imbalance or an alteration of the autonomic nervous system, an activity mainly controlled by the hypothalamus [29]. These may linger for weeks as described by Martin [26].

For the barbiturates, withdrawal symptoms are much more severe. In addition to the symptoms of autonomic nervous system imbalance, there are symptoms indicative of an alteration of the basal ganglia such as convulsions which may be life-threatening [30]. Convulsions may also occur following withdrawal from alcohol [28] or the benzodiazepines [21].

It should be noted that abstinence from cocaine or amphetamines, while not accompanied by a withdrawal symptom of the opiate type, produces marked after-effects: prolonged sleep, general fatigue, profound depression. The suppression of REM sleep is accompanied by a rebound increase of the EEG pattern [31]. There is a neuropharmacological basis to include the depressive after-effects of major psychostimulant abstinence among withdrawal symptoms; these symptoms may act as reinforcers in perpetuating drug use and relapse.

Following abrupt withdrawal from heavy THC administration, withdrawal symptoms of the autonomic type have been reported [32] including sweating, salivation, tremors and marked irritability.

Withdrawal symptoms may occur independently of tolerance, and should not be considered as the major reinforcement for continuing drug use. The occurrence of a full-blown withdrawal syndrome of the opiate type is not a prerequisite to the addictive process. It is not pharmacologically correct to equate a withdrawal syndrome with "physical dependence".

Addictive drugs and incidence of mental or physical illness

The long-term use of addictive drugs is associated with an increased incidence of mental or physical illness.

The more potent drugs, especially when administered by the intravenous route, are associated with sudden death, due in general to cardio-respiratory

Table 3
The pharmacological effects of addictive drugs

<i>Drugs</i>	<i>Mood and reward</i>	<i>Neuro-psychological toxicity</i>	<i>Reinforce (self-administered)^a</i>	<i>Tolerance</i>	<i>Withdrawal symptoms</i>	<i>Mental illness^b</i>	<i>Somatic</i>	<i>Lethal overdose</i>
Opiates								
Opium	+	+	+	+	++		+	+
Morphine	+	+	+	+	++		+	+
Heroin	+	+	+	+	++		+	+
Synthetic agonists	+	+	+	+	++		+	+
Major psychostimulants								
Cocaine	+	+	++	++	+	+	+	+
Amphetamines	+	+	++	++	+	++	+	+
Psychodepressants								
Ethyl alcohol (50 ml/day)	+	+	+	+	++	+	+	+
Barbiturates	+	+	+	+	++	+	+	+
Benzodiazepines	+	+	+	+	++	+	+	
Methaqualone	+	+	+	+	++	+	+	+
Cannabis								
Hashish, marijuana-THC	+	+	+	+	+	+	+	
Hallucinogens								
LSD	+	+		+		+		+
Psilocybine	+	+		+				+
Mescaline	+	+		+				+
Phencyclidine	+	+	+	+	+	+	+	+
Solvents								
Benzene	+	+		+			+	+
Toluene	+	+		+			+	+

Solvents						
Benzene	+	+		+		+
Toluene	+	+		+		+
Acetone carbon tetrachloride	+	+		+		+
Trichloroethylene	+	+		+		+
Ether, nitrous oxide, chloroform	+	+		+		+
Minor psychostimulants						
Tobacco (nicotine)	+		?	+	+	+
Cola	+			+		
Khat	+		+	+	+	
Caffeine	+			+		?

^a In non-human primates.

^b After chronic use.

collapse. The long-term effect of other addictive drugs absorbed in non-lethal dose may only be assessed by long-term epidemiological studies similar to those performed on tobacco smokers. Such studies as reported by McLellan [33] indicate that subjects abusing psychostimulants and psychodepressants have a high incidence respectively of psychosis and endogenous depression. Carranza [34] reports also the development of psychosis in chronic marijuana users in the United States. Confirming older reports, the use of opiates does not seem to be associated with increased incidence of psychiatric illness [33].

The long-term damaging physical effects of addictive drugs have been clearly documented only for alcohol and more recently for nicotine [35]. It may, therefore, take several more decades before the pathological long-term effects of other addictive drugs such as cannabis are documented. However, on the basis of experimental studies, these effects will involve besides the brain, the lung, the reproductive function and the immunity system [36]. The effects on reproductive function [37] appear to be mediated mostly through the hypothalamic portion of the brain which controls the pituitary release of gonadotropins.

A pharmacological classification of drugs of abuse

From the foregoing analysis, a pharmacological classification of the most commonly used addictive or dependence-producing drugs is proposed (see table 3).

Conclusion

The simplified concepts of psychic and physical dependence do not properly describe the effects of addictive drugs (or dependence-producing drugs) which all act as primary reinforcers, inducing a compulsive pattern of use.

We have, therefore, proposed to classify addictive drugs on the basis of their effects on brain and behaviour. These effects are primarily mediated through the alteration of brain neurotransmitters in the areas of the limbic system which have been associated with the pleasure reward mechanism of the brain. These mechanisms control motivation and behaviour.

Better knowledge of the mechanism of action of addictive drugs on brain processes has already helped scientists to understand some of the neurochemical regulations which underlie normal thinking and behaviour.

Drugs of abuse produce profound alterations in brain homeostasis: they disrupt the many biochemical regulations and feed-back controls which are essential for the proper processing and integration of the signals constantly

reaching of Clauvations, ' ("The co life"). It greatest c children these dru use [39].

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reaching the brain cells. When speaking of brain homeostasis, I am reminded of Claude Bernard's conclusion of his fundamental physiologic observations, "La constance du milieu intérieur est la condition de la vie libre" ("The constancy of the internal environment is the very condition for a free life"). It is evident that addictive drugs impair this "constancy" [38]. The greatest damaging effects of these drugs are exerted on the growing brains of children and adolescents who are most vulnerable to the adverse effects of these drugs and least prepared to resist the total pressures which foster their use [39].

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