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Substance Abuse

A Comprehensive Textbook

FOURTH EDITION

LIPPINCOTT WILLIAMS & WILKINS

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153. Valverde O, Maldonado R, Valjent E, et al. Cannabinoid withdrawal syndrome is reduced in pre-proenkephalin knock-out mice. *J Neurosci* 2000;20: 9284–9289.

CHAPTER 15
Marihuana: Clinical Aspects

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The present generation of young people cannot remember when marihuana was an exotic weed with an aura of mythical power and mysterious danger. Although still illegal, it has become a commonplace part of the American social scene, used regularly by millions and occasionally used by millions more. A realistic view of this drug is now both more important and easier to achieve.

The use of marihuana reached a high point in the late 1970s and early 1980s, declined until the early 1990s, than began to rise slightly. In a 1978 National Institute on Drug Abuse (NIDA) survey, 37% of high school seniors said that they had smoked marihuana in the past 30 days. In 1989, that number fell to 17%, but by 2001, it had risen again to 22% (1). Trends at ages 18 to 25 years are similar. In 1969, 20% of high school seniors had used marihuana at least once; in 1979, 60% had; in 1989, 44%; and in 1994, 38%. Use in the past year reached a low of 22% in 1992 and rose to 30% in 1994. The perceived risk of regular marihuana use has also fallen slightly. In 1978, 35% of high school seniors said it was very risky; in 1986, 71%; in 1992, nearly 80%; in 1994, closer to 60%; and in 2001 it was 53% (2).

HISTORY

The earliest record of human *cannabis* use is a description of the drug in a Chinese compendium of medicines, the *Herbal of Emperor Shen Nung*, dated 2737 B.C. according to some sources, and 400 to 500 B.C. according to others. Marihuana was a subject of controversy even in ancient times. Some warned that the hemp plant lined the road to Hades, whereas others thought it led to paradise. Its intoxicating properties were known in Europe during the nineteenth century, and for a much longer time in South and Central America; thousands of tons of Indian hemp (the common name of the *Cannabis sativa* plant from which the drug is obtained) were produced for its commercially useful long bast fiber beginning in Jamestown, Virginia, in 1611. Nevertheless, during the early American history of *cannabis*, nothing was known of its intoxicating properties.

In 1857, Fitz Hugh Ludlow (3), largely influenced by those members of the French romantic literary movement who belonged to *Le Club des Haschischins,* published *The Hasheesh Eater: Being Passages from the Life of a Pythagorean* and made a number of American literati aware of *cannabis'* euphoriant properties. Unlike his European counterparts, Ludlow did not use hashish but, rather, Tilden's Solution, one of a number of proprietary preparations of *Cannabis indica* (an alcoholic extract of *cannabis*), which he could obtain from his local apothecary. Ludlow established a link in the public mind, albeit a very narrow segment of it, between *cannabis* the medicine and *cannabis* the intoxicating drug. However, in the half-century from the publication of his book to the appearance, across the southern border, of what we now commonly call marihuana, grass, pot, or dope (all names for the dried and chopped flowering pistillate and staminate tops and leaves of the hemp plant), even this limited awareness all but completely vanished.

In any case, throughout history the principal interest in the hemp plant has been in its properties as an agent for achieving euphoria. In this country, it is almost invariably smoked, usually as a cigarette called a "joint" or "doobie"—but elsewhere the drug is often taken in the form of a drink or in foods such as candy. Recently, a new technology of *cannabis* vaporization was developed (4–6) that exploits the property that most of the plant's physiologically active constituents boil at a temperature below that at which the material burns (7). Thus, it becomes practical to administer *cannabis* vapor via the pulmonary route without throat or lung irritation or exposure to potential carcinogens from smoke.

Drug preparations from the hemp plant vary widely in quality and potency, depending on the type (there are possibly three species or, alternatively, various ecotypes of a single species), climate, soil, cultivation, and method of preparation. When the cultivated plant is fully ripe, a sticky, golden yellow resin with a minty fragrance covers its flower clusters and top leaves. The plant's resin contains the active substances, cannabinoids and essential oil terpenoids, which are produced by the plant in glandular trichomes (7). Preparations of the drug come in three grades, identified by Indian names. The cheapest and least potent, called *bhang,* is derived from the cut tops of uncultivated plants and has a low resin content. Much of the marihuana smoked in the United States, particularly a

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few years ago, was of this grade. *Ganja* is obtained from the unfertilized flowering tops and leaves of carefully selected, cultivated plants, and it has a higher quality and quantity of resin. The third and highest grade of the drug, called *charas* in India, is largely made from the resin itself, obtained from the tops of mature plants; only this version of the drug is properly called hashish. Hashish can also be smoked, eaten, or drunk. Recently, more potent and more expensive marihuana from Thailand, Hawaii, British Columbia, and California has become available in the United States. Some California growers have successfully cultivated an unpollinated plant by the early weeding out of male plants; the product is the much sought-after *sinsemilla.* Such new breeding and cultivation techniques have raised the tetrahydrocannabinol content of marihuana smoked in the United States over the last 20 years; although there are some extravagant claims made about the size of this increment, most authorities believe it has been modest (8,9). On average, street *cannabis* is not much more potent than it was in the 1960s.

The chemistry of the *cannabis* drugs is extremely complex and not completely understood. In the 1940s, it was determined that the active constituents are various isomers of tetrahydrocannabinol. The delta-9 form (hereafter called THC) has been synthesized and is believed to be the primary active component of marihuana. However, the drug's effects probably involve other components, such as cannabidiol, other cannabinoids, and terpenoids (7), and also depend on the form in which it is taken. There are more than 60 cannabinoids in marihuana and a number of them are thought to be biologically active. This activity is apparently mediated by the recently discovered receptors in the brain and elsewhere in the body that are stimulated by THC (10). This exciting discovery implied that the body produces its own version of cannabinoids for one or more useful purposes. The first of these cannabinoid-like neurotransmitters was identified in 1992 and named anandamide (*ananda* is the Sanskrit word for bliss) (11). Cannabinoid receptor sites occur not only in the lower brain but also in the cerebral cortex and the hippocampus.

The psychic effects of the drug have been described in a very extensive literature. Hashish long ago acquired a lurid reputation through the writings of literary figures, notably the group of French writers—Baudelaire, Gautier, Dumas père, and others—who formed *Le Club des Haschischins* in Paris in the 1840s. Their reports, written under the influence of large amounts of hashish, must be largely discounted as exaggerations that do not apply to moderate use of the drug. There is a story that hashish was responsible for Baudelaire's psychosis and death; the story overlooks the fact that he had relatively little experience with hashish, was in all probability actually writing about his experience with laudanum, and, moreover, had been an alcoholic and suffered from tertiary syphilis.

Bayard Taylor—the American writer, lecturer, and traveler best known for his translation of Goethe's *Faust*—wrote one of the first accounts of a *cannabis* experience in terms that began to approach a clinical description. He tried the drug in a spirit of inquiry during a visit to Egypt in 1854. His narrative of the effects follows (12):

> The sensations it then produced were... physically of exquisite lightness and airiness—mentally of a wonderfully keen perception of the ludicrous in the most simple and familiar objects. During the half hour in which it lasted, I was at no time so far under its control that I could not, with the clearest perception, study the changes through which I passed. I noted with careful attention the fine sensations which spread throughout the whole tissue of my nervous fibers, each thrill helping to divest my frame of its earthly and material nature, till my substance appeared to me no grosser than the vapors of the atmosphere, and while sitting in the calm of the Egyptian twilight I expected to be lifted up and carried away by the first breeze that should ruffle the Nile. While this process was going on, the objects by which I was surrounded assumed a strange and whimsical expression.... I was provoked into a long fit of laughter.... [The effect] died away as gradually as it came, leaving me overcome with a soft and pleasant drowsiness, from which I sank into a deep, refreshing sleep.

Perhaps a better clinical account is that of Walter Bromberg, a psychiatrist, who described the psychic effects on the basis of his own experience and many observations and talks with people while they were under the influence of marihuana (13):

> The intoxication is initiated by a period of anxiety within 10 to 30 minutes after smoking, in which the user sometimes... develops fears of death and anxieties of vague nature associated with restlessness and hyperactivity. Within a few minutes he begins to feel more calm and soon develops definite euphoria; he becomes talkative... is elated, exhilarated... begins to have... an astounding feeling of lightness of the limbs and body... laughs uncontrollably and explosively... without at times the slightest provocation... has the impression that his conversation is witty, brilliant.... The rapid flow of ideas gives the impression of brilliance of thought and observation... [but] confusion appears on trying to remember what was thought... he may begin to see visual hallucinations... flashes of light or amorphous forms of vivid color which evolve and develop into geometric figures, shapes, human faces, and pictures of great complexity.... After a longer or shorter time, lasting up to two hours, the smoker becomes drowsy, falls into a dreamless sleep and awakens with no physiologic after-effects and with a clear memory of what happened during the intoxication.

Most observers confirm Bromberg's account as a composite, somewhat exaggerated, overinclusive description of marihuana highs. They find that the effects from smoking last from 2 to 4 hours, the effects from ingestion 5 to 12 hours. For a new user, the initial anxiety that sometimes

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occurs is alleviated if supportive friends are present. The intoxication heightens sensitivity to external stimuli, reveals details that would ordinarily be overlooked, makes colors seem brighter and richer, and brings out values in works of art that previously had little or no meaning to the viewer. It is as though the *cannabis*-intoxicated adult perceives the world with some of the newness, wonder, curiosity, and excitement of a child; the person's world becomes more interesting and details that had been taken for granted now attract more attention. The high also enhances the appreciation of music; many jazz and rock musicians have said that they perform better under the influence of marihuana, but this effect has not been objectively confirmed.

The sense of time is distorted: 10 minutes may seem like an hour. Curiously, there is often a splitting of consciousness, so that the smoker, while experiencing the high, is at the same time an objective observer of their own intoxication. The person may, for example, be afflicted with paranoid thoughts, yet at the same time be reasonably objective about them—laughing or scoffing at them and, in a sense, enjoying them. The ability to retain a degree of objectivity may explain why many experienced users of marihuana manage to behave in a perfectly sober fashion in public even when they are highly intoxicated.

Although the intoxication varies with psychological set and social setting, the most common response is a calm, mildly euphoric state in which time slows and sensitivity to sights, sounds, and touch is enhanced. The smoker may feel exhilaration or hilarity and notice a rapid flow of ideas with a reduction in short-term memory. Images sometimes appear before closed eyes; visual perception and body image may undergo subtle changes. It is dangerous to operate complex machinery, including automobiles, under the influence of marihuana, because it slows reaction time and impairs attention and coordination. There is uncertainty as to whether some impairment persists for several hours after the feeling of intoxication has passed (14,15).

Marihuana is sometimes referred to as a hallucinogen. Many of the phenomena associated with lysergic acid diethylamide (LSD) and LSD-type substances can be produced by *cannabis*, but only at very high dosage. As with LSD, the experience often has a wave-like aspect. Other phenomena commonly associated with both types of drugs are distorted perception of various parts of the body, spatial and temporal distortion, depersonalization, increased sensitivity to sound, synesthesia, heightened suggestibility, and a sense of thinking more clearly and having deeper awareness of the meaning of things. Anxiety and paranoid reactions are also sometimes seen as consequences of either drug. However, the agonizingly nightmarish reactions that even the experienced LSD user may endure are quite rare among experienced marihuana smokers, not simply because they are using a far less potent drug, but also because they have much closer and continuing control over the extent and type of reaction they wish to induce. Furthermore, *cannabis* has a tendency to produce sedation, whereas LSD and LSD-type drugs may induce long periods of wakefulness and even restlessness. Unlike LSD, marihuana does not dilate the pupils or materially heighten blood pressure, reflexes, and body temperature. (On the other hand, it does increase the pulse rate, while lowering blood pressure.) Tolerance develops rapidly with LSD-type drugs but little with *cannabis*. Finally, marihuana lacks the potent consciousness-altering qualities of LSD, peyote, mescaline, psilocybin, and other hallucinogens; it is questionable whether in the doses ordinarily used in this country it can produce true hallucinations. These differences, particularly the last, cast considerable doubt on marihuana's credentials for inclusion among the hallucinogens.

HEALTH EFFECTS OF MARIHUANA USE

In recent years, the psychological and physical effects of long-term use have caused most concern. Studies are often conflicting and permit various views of marihuana's possible harmfulness. This complicates the task of presenting an objective statement about the issue.

One of the first questions asked about any drug is whether it is addictive or produces dependence. This question is hard to answer because the terms *addiction* and *dependence* have no agreed-to definitions. Two recognized signs of addiction are tolerance and withdrawal symptoms; these are rarely a serious problem for marihuana users. In the early stages, they actually become more sensitive to the desired effects. After continued heavy use, some tolerance to both physiologic and psychological effects develops, although it seems to vary considerably among individuals. Almost no one reports an urgent need to increase the dose to recapture the original sensation. What is called *behavioral tolerance* may be partly a matter of learning to compensate for the effects of high doses, and may explain why farm workers in some Third World countries are able to do heavy physical labor while smoking a great deal of marihuana (16).

A mild withdrawal reaction also occurs in animal experiments and possibly in some human beings who take high doses for a long time. The rarely reported mild symptoms are anxiety, insomnia, tremors, and chills, lasting for a day or two. It is unclear how common this reaction is; in a Jamaican study, heavy ganja users did not report abstinence symptoms when withdrawn from the drug. In any case, there is little evidence that the withdrawal reaction ordinarily presents serious problems to marihuana users or causes them to go on taking the drug. In a recent comprehensive review, *cannabis* withdrawal was seen as producing symptoms that were low level to nonexistent, with inconsistent onset and offset, with heterogeneous effects claimed with greatest support for transient agitation, appetite change, and sleep disturbance (17). In sum, the concept of *cannabis* withdrawal was considered unproven.

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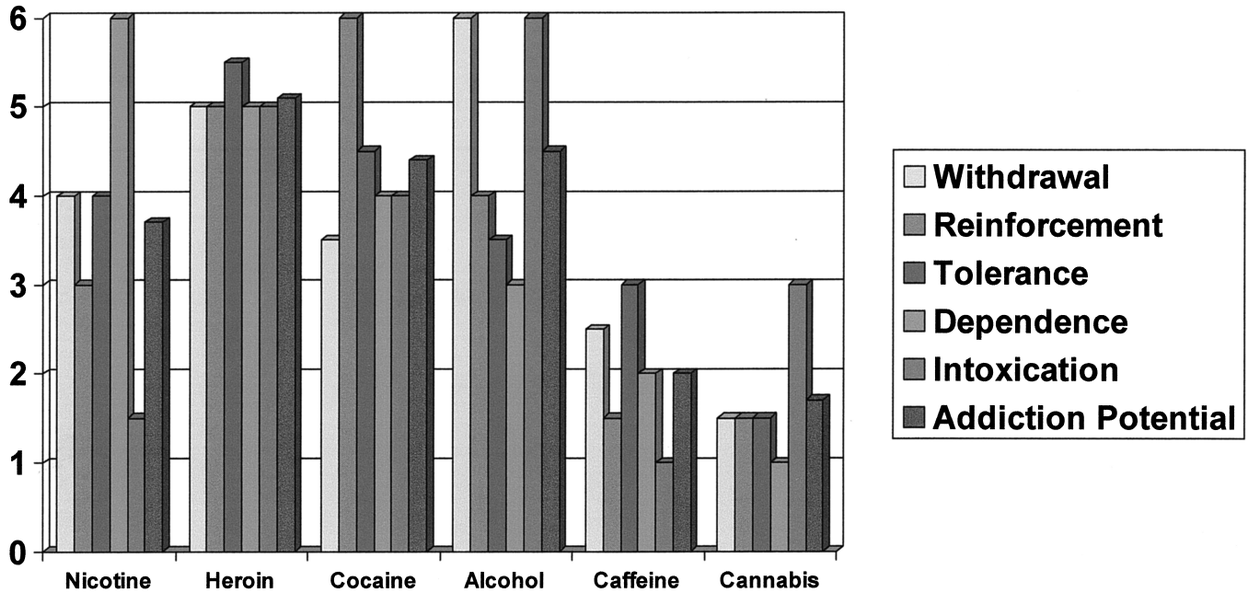

FIG. 15.1. Addiction ratings. From Henningfield, Benowitz. *New York Times* 1994 Aug 2:C3, with permission.

In a more important sense, dependence means an unhealthy and often unwanted preoccupation with a drug to the exclusion of most other things. People suffering from drug dependence find that they are constantly thinking about the drug, or intoxicated, or recovering from its effects. The habit impairs their mental and physical health and hurts their work, family life, and friendships. They often know that they are using too much and repeatedly make unsuccessful attempts to cut down or stop. These problems seem to afflict proportionately fewer marihuana smokers than users of alcohol, tobacco, heroin, or cocaine. Even heavy users in places like Jamaica and Costa Rica do not seem to be dependent in this damaging sense. Marihuana's capacity to lead to psychological dependence is not as strong as that of either tobacco or alcohol. Two experts from the University of California, San Francisco, and the National Institute on Drug Abuse independently compared the dependency potential of *cannabis*, alcohol, nicotine, caffeine, cocaine, and heroin (18,19). Cannabis was considered by both to carry the lowest overall risk (Fig. 15.1).

It is often difficult to distinguish between drug use as a cause of problems and drug use as an effect; this is especially true in the case of marihuana. Most people who develop a dependency on marihuana would also be likely to develop other dependencies because of anxiety, depression, or feelings of inadequacy. The original condition is likely to matter more than the attempt to relieve it by means of the drug. The troubled teenager who smokes *cannabis* throughout the school day certainly has a problem, and excessive use of marihuana may be one of its symptoms.

The idea has persisted that in the long run smoking marihuana causes some sort of mental or emotional deterioration. In three major studies conducted in Jamaica, Costa Rica, and Greece, researchers compared heavy long-term *cannabis* users with nonusers and found no evidence of intellectual or neurologic damage, no changes in personality, and no loss of the will to work or participate in society (20–22). The Costa Rican study showed no difference between heavy users (seven or more marihuana cigarettes a day) and lighter users (six or fewer cigarettes a day). Experiments in the United States show no effects of fairly heavy marihuana use on learning, perception or motivation over periods as long as 1 year (23–26).

On the other side are clinical reports of a personality change called the *amotivational syndrome*. Its symptoms are said to be passivity, aimlessness, apathy, uncommunicativeness, and lack of ambition. Some proposed explanations are hormone changes, brain damage, sedation, and depression. Because the amotivational syndrome does not seem to occur in Greek or Caribbean farm laborers, some writers suggest that it affects only skilled and educated people who need to do more complex thinking (21,22,27). However, there is no credible evidence that what is meant by this syndrome is related to any inherent properties of the drug rather than to different sociocultural adaptations on the part of the users.

The problem of distinguishing causes from symptoms is particularly acute here. Heavy drug users in our society are often bored, depressed, and listless, or alienated, cynical, and rebellious. Sometimes the drugs cause these states of mind, and sometimes they result from personality

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characteristics that lead to drug abuse. Drug abuse can be an excuse for failure, or a form of self-medication. Because of these complications and the absence of confirmation from controlled studies, the existence of an amotivational syndrome caused by *cannabis* use has to be regarded as unproved.

Much attention has also been devoted to the idea that marihuana smoking leads to the use of opiates and other illicit drugs—the stepping stone hypothesis, now commonly referred to as the gateway hypothesis, which was rejected after extensive study by the Institute of Medicine (28) and the Canadian Senate (29). In this country, almost everyone who uses any other illicit drug has smoked marihuana first, just as almost everyone who smokes marihuana has drunk alcohol first. Anyone who uses any given drug is more likely to be interested in others, for some of the same reasons. People who use illicit drugs, in particular, are somewhat more likely to find themselves in company where other illicit drugs are available. None of this proves that using one drug leads to or causes the use of another. Most marihuana smokers do not use heroin or cocaine, just as most alcohol drinkers do not use marihuana. The metaphor of stepping stones suggests that if no one smoked marihuana it would be more difficult for anyone to develop an interest in opiates or cocaine. There is no convincing evidence for or against this. What is clear is that at many times and places marihuana has been used without these drugs, and that these drugs have been used without marihuana.

Only the unsophisticated continue to believe that *cannabis* leads to violence and crime. Indeed, instead of inciting criminal behavior, *cannabis* may tend to suppress it. The intoxication induces a mild lethargy that is not conducive to any physical activity, let alone the commission of crimes. The release of inhibitions results in fantasy and verbal (rather than behavioral) expression. During the high, marihuana users may say and think things they would not ordinarily say and think, but they generally do not do things that are foreign to their nature. If they are not already criminals, they will not commit crimes under the influence of the drug.

Does marihuana induce sexual debauchery? This popular impression may owe its origin partly to writers' fantasies and partly to the fact that users in the Middle East once laced the drug with what they thought were aphrodisiacs. In actuality, there is little evidence that *cannabis* stimulates sexual desire or power. On the other hand, there are those who contend, with equally little substantiation, that marihuana weakens sexual desire. Many marihuana users report that the high enhances the enjoyment of sexual intercourse, and it has been an aid to tantric sexual meditation in India and Tibet since ancient times (30). This appears to be true in the same sense that the enjoyment of art and music is apparently enhanced. It is questionable, however, whether the intoxication breaks down barriers to sexual activity that are not already broken.

Does marihuana lead to physical and mental degeneracy? Reports from many investigators, particularly in Egypt and parts of the Orient, indicate that long-term users of the potent versions of *cannabis* are, indeed, typically passive, nonproductive, slothful, and totally lacking in ambition. This suggests that chronic use of the drug in its stronger forms may have debilitating effects, just as prolonged heavy drinking does. There is a far more likely explanation, however. Many of those who take up *cannabis* in these countries are poverty stricken, hungry, sick, hopeless, or defeated, seeking through this inexpensive drug to soften the impact of an otherwise unbearable reality. This also applies to many of the "potheads" in the United States. In most situations one cannot be certain which came first: the drug, on the one hand, or the depression, anxiety, feelings of inadequacy, or the seemingly intolerable life situation on the other. Numerous chronic use studies have failed to differentiate personality differences between *cannabis* users and nonusers.

There is a substantial body of evidence that moderate use of marihuana does not produce physical or mental deterioration. One of the earliest and most extensive studies of this question was an investigation conducted by the British government in India in the 1890s. The investigating agency, called the Indian Hemp Drugs Commission, interviewed some 800 people—including *cannabis* users and dealers, physicians, superintendents of mental asylums, religious leaders, and a variety of other authorities—and in 1894 published a report of more than 3,000 pages. It concluded that there was no evidence that moderate use of the *cannabis* drugs produced any disease or mental or moral damage, or that it tended to lead to excess any more than did the moderate use of whiskey (31,32).

In the LaGuardia study in New York City, an examination of chronic users who had averaged about seven marihuana cigarettes a day (a comparatively high dosage) over a long period (the mean was 8 years) showed that they had suffered no demonstrable mental or physical decline as a result of their use of the drug (33). The 1972 report of the National Commission on Marihuana and Drug Abuse (34), although it did much to demythologize *cannabis*, cautioned that, of people in the United States who used marihuana, 2% became heavy users and that these abusers were at risk, but it did not make clear exactly what risk was involved. Furthermore, since the publication of this report, several controlled studies of chronic heavy use have been completed that have failed to establish any pharmacologically induced harmfulness, including personality deterioration or the development of the so-called amotivational syndrome (21–26, 35–37). The most recent government-sponsored review of *cannabis*, *Marijuana and Medicine,* conducted by the Institute of Medicine, while cautious in its summary statement, found little documentation for most of the alleged harmfulness of this substance (28).

A common assertion made about *cannabis* is that it may lead to psychosis. The literature on this subject is vast,

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and it divides into all shades of opinion. Many psychiatrists in India, Egypt, Morocco, and Nigeria have declared emphatically that the drug can produce insanity; others insist that it does not. One of the authorities most often quoted in support of the indictment is Benabud of Morocco. He believes that the drug produces a specific syndrome called "*cannabis* psychosis." His description of the identifying symptoms is far from clear, however, and other investigators dispute the existence of such a psychosis. The symptoms said to characterize this syndrome are also common to other acute toxic states, including, particularly in Morocco, those associated with malnutrition and endemic infections. Benabud estimates that the number of kif (marihuana) smokers suffering from all types of psychosis is not more than 5 in 1,000 (38); this rate, however, is lower than the estimated total prevalence of all psychoses in populations of other countries. One would have to assume either (a) that there is a much lower prevalence of psychoses other than *cannabis* psychosis among kif smokers in Morocco or (b) that there is no such thing as a *cannabis* psychosis and the drug is contributing little or nothing to the prevalence rate for psychoses.

Bromberg, in a report of one of his studies, listed 31 patients whose psychoses he attributed to the toxic effects of marihuana. Of these 31, however, 7 patients were already predisposed to functional psychoses that were only precipitated by the drug, 7 others were later found to be schizophrenics, and 1 was later diagnosed as a manic-depressive (39). The Chopras in India, in examinations of 1,238 *cannabis* users, found only 13 users to be psychotic, which is about the usual prevalence of psychosis in the total population in Western countries (40). In the LaGuardia study, 9 of 77 people who were studied intensively had a history of psychosis; however, this high rate could be attributed to the fact that all those studied were patients in hospitals or institutions. Allentuck and Bowman, the psychiatrists who examined this group, concluded that "marihuana will not produce psychosis *de novo* in a well-integrated, stable person" (41).

A 1976 article by Thacore and Shukla revived the concept of the *cannabis* psychosis (42). The authors compared 25 people with what they call a paranoid psychosis precipitated by *cannabis* with an equal number of paranoid schizophrenics. The *cannabis* psychotics were described as patients in whom there had been a clear temporal relation between prolonged abuse of *cannabis* and the development of a psychosis on more than two occasions. All had used *cannabis* heavily for at least 3 years, mainly in the form of bhang, the weakest of the three preparations common in India (it is usually drunk as a tea or eaten in doughy pellets). In comparison with the schizophrenics, the *cannabis* psychotics were described as more panicky, elated, boisterous, and communicative; their behavior was said to be more often violent and bizarre, and their mental processes characterized by rapidity of thought and flight of ideas without schizophrenic thought disorder. The prognosis was said to be good; the symptoms could be easily relieved by phenothiazines and recurrence prevented by a decision not to use *cannabis* again. The syndrome was distinguished from an acute toxic reaction by the absence of clouded sensorium, confusion, and disorientation. Thacore and Shukla did not provide enough information to justify either the identification of their 25 patients' conditions as a single clinical syndrome or the asserted relation to *cannabis* use. They had little to say about the amount of *cannabis* used, except that relatives of the patients regarded it as abnormally large; they did not discuss the question of why the psychosis is associated with bhang rather than the stronger *cannabis* preparations ganja and charas. The meaning of "prolonged abuse on more than two occasions" in the case of men who were constant heavy *cannabis* users was not clarified, and the temporal relation between this situation and psychosis was not specified. Moreover, the *cannabis*-taking habits of the control group of schizophrenics were not discussed—a serious omission where use of bhang is so common. The patients described as *cannabis* psychotics were probably a heterogeneous mixture, with acute schizophrenic breaks, acute manic episodes, severe borderline conditions, and a few symptoms actually related to acute *cannabis* intoxication, mainly anxiety-panic reactions and a few psychoses of the kind that can be precipitated in unstable people by many different experiences of stress or consciousness change (42).

The explanation for such psychoses is that a person maintaining a delicate balance of ego functioning—so that, for instance, the ego is threatened by a severe loss, or a surgical assault, or even an alcoholic debauch—may also be overwhelmed or precipitated into a psychotic reaction by a drug that alters, however mildly, the person's state of consciousness. This concatenation of factors—a person whose ego is already overburdened in its attempts to manage a great deal of anxiety and to prevent distortion of perception and body image, plus the taking of a drug that, in some persons, promotes just these effects—may, indeed, be the last straw in precipitating a schizophrenic break. Of 41 first-break acute schizophrenic patients studied by Dr. Grinspoon at the Massachusetts Mental Health Center, it was possible to elicit a history of marihuana use in 6 (43). In 4 of the 6 patients, it seemed quite improbable that the drug could have had any relation to the development of the acute psychosis, because the psychosis was so remote in time from the drug experience. Careful history taking and attention to details of the drug experiences and changing mental status in the remaining two patients failed either to implicate or exonerate marihuana as a precipitant in their psychoses.

Our own clinical experience and that of others (44) suggests that *cannabis* may precipitate exacerbations in the psychotic processes of some schizophrenic patients at a time when their illnesses are otherwise reasonably well-controlled with antipsychotic drugs. In these patients, it is often difficult to determine whether the use of *cannabis* is simply a precipitant of the psychosis or whether it is

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an attempt to treat symptomatically the earliest perceptions of decompensation; needless to say, the two possibilities are not mutually exclusive. There is little support for the idea that *cannabis* contributes to the etiology of schizophrenia. And in one recently reported case, a 19-year-old schizophrenic woman was more successfully treated with cannabidiol (one of the cannabinoids in marihuana) than she had been with haloperidol (Haldol) (45).

A recent study from Sweden on schizophrenia is most suspect (46). The authors examined Swedish conscripts from 1969. This investigation seems to be an attempt to rehabilitate an extremely criticized study of the same cohort published in 1987 (47), which had been thoroughly criticized (48). In the current study, the authors claim that based on their data, up to 13% of schizophrenia incidence could be attributable to *cannabis*. This is an unsubstantiated allegation, given that only 1.4% of the conscripts that ever smoked *cannabis* wound up schizophrenic. Men of such age are at the critical time in development of the disorder. All of the eventual schizophrenics in the earlier study were recognized to have some psychiatric issue before they entered the service!

Another recent study examined a cohort of young New Zealanders for *cannabis* use versus development of adult psychosis (49). In this brief article, "controls" smoked *cannabis* zero to two times, while "*cannabis* users" took the drug "three times or more" by age 15 years and continued at some unspecified rate of intake by age 18 years. Supposedly smoking *cannabis* increased the incidence of psychosis in adults, and it was more likely the earlier they began. If *cannabis* were truly etiologic in the development of psychosis, it would be reasonable to expect some dose–response effect. That is not evident here in any respect.

Interestingly, *cannabis* may ameliorate certain symptoms of psychosis (50), including activation symptoms and subjective complaints of depression, anxiety, insomnia, and pain. It is noteworthy that levels of anandamide are elevated in the brains of schizophrenics (51).

Although there is little evidence for the existence of a *cannabis* psychosis, it seems clear that the drug may precipitate in susceptible people one of several types of mental dysfunction. The most serious and disturbing of these is the toxic psychosis. This is an acute state that resembles the delirium of a high fever. It is caused by the presence in the brain of toxic substances that interfere with a variety of cerebral functions. Generally speaking, as the toxins disappear, so do the symptoms of toxic psychosis. This type of reaction may be caused by any number of substances taken either as intended or inadvertent overdoses. The syndrome often includes clouding of consciousness, restlessness, confusion, bewilderment, disorientation, dream-like thinking, apprehension, fear, illusions, and hallucinations. It generally requires a rather large ingested dose of *cannabis* to induce a toxic psychosis. Such a reaction is apparently much less likely to occur when *cannabis* is smoked, perhaps because not enough of the active substances can be absorbed sufficiently rapidly, or possibly because the process of smoking modifies in some yet unknown way those cannabinoids that are most likely to precipitate this syndrome.

Some marihuana users suffer what are usually short-lived, acute, anxiety states, sometimes with and sometimes without accompanying paranoid thoughts. The anxiety may reach such proportions as properly to be called panic. Such panic reactions, although uncommon, probably constitute the most frequent adverse reaction to the moderate use of smoked marihuana. During this reaction, the sufferer may believe that the various distortions of bodily perceptions mean that the sufferer is dying or is undergoing some great physical catastrophe, and similarly the individual may interpret the psychological distortions induced by the drug as an indication of the sufferer's loss of sanity. Panic states may, albeit rarely, be so severe as to incapacitate, usually for a relatively short period of time. The anxiety that characterizes the acute panic reaction resembles an attenuated version of the frightening parts of an LSD or other psychedelic experience—the so-called bad trip. Some proponents of the use of LSD in psychotherapy assert that the induced altered state of consciousness involves a lifting of repression. Although the occurrence of a global undermining of repression is questionable, many effects of LSD do suggest important alterations in ego defenses. These alterations presumably make new percepts and insights available to the ego; some, particularly those most directly derived from primary process, may be quite threatening, especially if there is no comfortable and supportive setting to facilitate the integration of the new awareness into the ego organization. Thus, psychedelic experiences may be accompanied by a great deal of anxiety, particularly when the drugs are taken under poor conditions of set and setting; to a much lesser extent, the same can be said of *cannabis*.

These reactions are self-limiting, and simple reassurance is the best method of treatment. Perhaps the main danger to the user is that the user will be diagnosed as having a toxic psychosis. Users with this kind of reaction may be quite distressed, but they are not psychotic. The *sine qua non* of sanity, the ability to test reality, remains intact, and the panicked user is invariably able to relate the discomfort to the drug. There is no disorientation, nor are there true hallucinations. Sometimes this panic reaction is accompanied by paranoid ideation. The user may, for example, believe that the others in the room, especially if they are not well known, have some hostile intentions, or that someone is going to inform on the user, often to the police, for smoking marihuana. Generally speaking, these paranoid ideas are not strongly held, and simple reassurance dispels them. Anxiety reactions and paranoid thoughts are much more likely in someone who is taking the drug for the first time or in an unpleasant or unfamiliar setting, than in an experienced user who is comfortable with the surroundings and companions; the reaction is very rare where marihuana is a casually accepted part of the social scene. The likelihood varies directly with

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the dose and inversely with the user's experience; thus, the most vulnerable person is the inexperienced user who inadvertently (often precisely because the inexperienced user lacks familiarity with the drug) takes a large dose that produces perceptual and somatic changes for which the user is unprepared.

One rather rare reaction to *cannabis* is the flashback, or spontaneous recurrence of drug symptoms while not intoxicated. Although several reports suggest that this may occur in marihuana users even without prior use of any other drug (43), in general, it seems to arise only in those who have used more powerful hallucinogenic or psychedelic drugs. There are also some people who have flashback experiences of psychedelic drug trips while smoking marihuana; this is sometimes regarded as an extreme version of a more general heightening of the marihuana high that occurs after the use of hallucinogens. Many people find flashbacks enjoyable, but to others they are distressing. They usually fade with the passage of time. It is possible that flashbacks are attempts to deal with primary process derivatives and other unconscious material that has breached the ego defenses during the psychedelic or *cannabis* experience.

Rarely, but especially among new users of marihuana, there occurs an acute depressive reaction. It is generally rather mild and transient but may sometimes require psychiatric intervention. This type of reaction is most likely to occur in a user who has some degree of underlying depression; it is as though the drug allows the depression to be felt and experienced as such. Again, set and setting play an important part. Cannabis has been of benefit in mood stabilization in case reports from patients with bipolar disease (52).

Most recent research on the health hazards of marihuana concerns its long-term effects on the body. The main physiologic effects of *cannabis* are increased appetite, a faster heartbeat, and slight reddening of the conjunctiva. Although the increased heart rate could be a problem for people with cardiovascular disease, dangerous physical reactions to marihuana are almost unknown. No human being is known to have died of an overdose. By extrapolation from animal experiments, the ratio of lethal to effective (intoxicating) dose is estimated to be on the order of thousands to one.

Studies have examined the brain, the immune system, the reproductive system, and the lungs. Suggestions of long-term damage come almost exclusively from animal experiments and other laboratory work. Observations of marihuana users and the Caribbean, Greek, and other studies reveal little disease or organic pathology associated with the drug (21,22,27,53).

For example, there are several reports of damaged brain cells and changes in brain-wave readings in monkeys smoking marihuana, but neurologic and neuropsychological tests in Greece, Jamaica, and Costa Rica found no evidence of functional brain damage. A recent study of enrolled patients in the Compassionate Use Investigational New Drug Program in the United States also demonstrated no significant electroencephalograph (EEG) or P300 changes (54). Damage to white blood cells has also been observed in the laboratory, but again, its practical importance is unclear. Whatever temporary changes marihuana may produce in the immune system, they have not been found to increase the danger of infectious disease or cancer. If there were significant damage, we might expect to find a higher rate of these diseases among young people beginning in the 1960s, when marihuana first became popular. There is no evidence of that. Recent studies in human immunodeficiency virus (HIV) (55) and in the Missoula Chronic Use Study (54) also failed to demonstrate deleterious effects on white blood cell or CD4 counts.

The effects of marihuana on the reproductive system are a more complicated issue. In men, a single dose of THC lowers sperm count and the level of testosterone and other hormones. Tolerance to this effect apparently develops; in the Costa Rican study, marihuana smokers and controls had the same testosterone levels. Although the smokers in that study began using marihuana at an average age of 15 years, it had not affected their masculine development. There is no evidence that the changes in sperm count and testosterone produced by marihuana affect sexual performance or fertility.

In animal experiments, THC has also been reported to lower levels of female hormones and to disturb the menstrual cycle. When monkeys, rats, and mice are exposed during pregnancy to amounts of THC equivalent to a heavy human smoker's dose, stillbirths and decreased birth weight are sometimes reported in their offspring. There are also reports of low birth weight, prematurity, and even a condition resembling the fetal alcohol syndrome in some children of women who smoke marihuana heavily during pregnancy. The significance of these reports is unclear because controls are lacking and other circumstances make it hard to attribute causes. No endocrine changes were observed in the Missoula Chronic Use Study (54). To be safe, pregnant and nursing women should follow the standard conservative recommendation to avoid all drugs, including *cannabis*, that are not absolutely necessary. Nonetheless, evidence from a well-controlled study of *cannabis*-only smokers in Jamaica are supportive of a low risk to their children (56).

A well-confirmed danger of long-term, heavy marihuana use is its effect on the lungs. Smoking narrows and inflames air passages and reduces breathing capacity; damage to bronchial cells has been observed in hashish smokers. The possible side effects include bronchitis, emphysema, and lung cancer. Interestingly, one study failed to demonstrate emphysematous degeneration in *cannabis* smokers over time (57). Marihuana smoke contains the same carcinogens as tobacco smoke, usually in somewhat higher concentrations, at least in *cannabis* supplied

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by NIDA. THC may actually interfere with a key biochemical step in carcinogenesis (58). Marihuana is also inhaled more deeply and held in the lungs longer, which increases the danger (59,60). On the other hand, almost no one smokes 20 marihuana cigarettes a day. Marihuana of higher potency may reduce the danger of respiratory damage, because less smoking is required for the desired effect. There is now some experimental evidence demonstrating that high-potency THC cigarettes are smoked less vigorously than those of low potency; the user takes smaller and shorter puffs, inhaling less with each puff (61). Vaporization technology may also reduce risks (62).

It is hard to generalize about abuse or define specific treatments, because the problems associated with marihuana are so vague, and cause and effect so hard to determine. Marihuana smokers may be using the drug as a facet of adolescent exploration, to demonstrate rebelliousness, to cope with anxiety, to medicate themselves for early symptoms of mental illness, or, most commonly, simply for pleasure.

The complexity of the problem is illustrated by a most important long-term study by two Berkeley psychologists (63). Shedler and Block followed the progress of 101 San Francisco children of both sexes from ages 5 to 18 years, and gave them personality tests at 7, 11, and 18 years of age. By the end of the study, 68% had used marihuana and 39% had used it once a week or more; large minorities had also used cocaine, hallucinogens, and prescription stimulants and sedatives. Three main groups could be distinguished: 29 "abstainers" who had used no illicit drugs; 36 "experimenters" who had used marihuana no more than once a month and had tried at most one other drug; and 20 "frequent users" who had smoked marihuana at least once a week and had used at least one other drug. The other 16 fit into none of these categories and were not included in the study.

Striking personality differences among the three groups appeared in childhood, long before any drug use. The frequent users, as early as age 7 years, got along poorly with other children and had few friends. They found it difficult to think ahead and lacked confidence in themselves. They were untrustworthy and seemingly indifferent to moral questions. At age 11 years they were described as inattentive, uncooperative, and vulnerable to stress. At age 18 years, they were insecure, alienated, impulsive, undependable, self-indulgent, inconsiderate, and unpredictable in their moods and behavior; they overreacted to frustration; they felt personally inadequate, as well as victimized and cheated. They had lower high school grades than adolescents in the other two groups.

Abstainers, at age 7 years, were described as inhibited, conventional, obedient, and lacking in creativity. At age 11 years they were shy, neat, and orderly, eager to please, but lacking in humor, liveliness, and expressiveness. The terms that best described them at age 18 years were tense, overcontrolled, moralistic, anxious, and lacking in social ease or personal charm. Their high school grades were average.

The happy mean, statistically, was found in the "experimenters." They were more likely to be warm, responsive, curious, open, active, and cheerful from the age of 7 years on. In the three broad categories of personal happiness, relations with others, and rational self-control, frequent users were doing worst and experimental users best. The authors pointed out that studies comparing moderate drinkers with alcoholics and abstainers have found similar personality differences.

To find some sources of these differences, the authors examined experiments conducted when the children were only 5 years old. Their parents' behavior was observed as they worked with the child on a laboratory task involving blocks and mazes. Mothers of both frequent users and abstainers tended to be cold and unresponsive. They gave their children little encouragement but insisted that they perform well; and the experience seemed unpleasant for both mother and child. Fathers of frequent users did not differ from fathers of experimenters, but abstainers' fathers were impatient, hypercritical, and domineering.

According to the authors, frequent drug users believe that they have nothing to look forward to and are therefore drawn to the immediate gratification provided by drugs. Their alienation and impulsiveness might have roots in their relationship with their mothers. The problems of abstainers are also serious, but they attract less attention, because they are less troublesome for society. Abstainers suppress their impulses to avoid feeling vulnerable, perhaps because they have internalized the attitudes of harsh, authoritarian fathers. Experimental users are the largest and most typical group. At least in the San Francisco area in the 1980s, reasonably inquisitive, open, and independent adolescents experimented with marihuana as part of growing up.

The inverted U-shaped relationship between the degree of drug use and psychological health suggests that the need for therapy would also describe such a curve. The fact that among the abstainers are to be found many individuals who could profit from psychotherapy is not relevant to this discussion of marihuana. The important question concerns the indications for therapy for those who comprise the other two arms of the curve. Given the current prevalence of drug use in our society, the developmentally appropriate propensity of adolescents to explore and experiment, and the relatively benign sequelae of such experimentation with *cannabis*, it is obvious that therapy is not properly indicated for young people who fit the description of the "experimenter."

It is appropriate to consider psychotherapy for the frequent adolescent users of marihuana. The picture that emerges is "one of a troubled adolescent who is interpersonally alienated, emotionally withdrawn, and manifestly unhappy, and who expresses his or her maladjustment through undercontrolled, overtly antisocial behavior"

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(63). They are described as being "overreactive to minor frustrations, likely to think and associate to ideas in unusual ways, having brittle ego-defense systems, self-defeating, concerned about the adequacy of their bodily functioning, concerned about their adequacy as persons, prone to project their feelings and motives onto others, feeling cheated and victimized by life, and having fluctuating moods."

Obviously, psychotherapy is not inappropriate for individuals who exemplify this description. But it should be emphasized that this is not psychotherapy for marihuana abuse; it is therapy for the underlying psychopathology, one of whose symptoms is the abuse of *cannabis*. It is no more appropriate to see marihuana as the cause of the problem here than it is to see repetitive hand-washing as the cause of obsessive-compulsive disorder. The individual may be brought to psychiatric attention because of the hand-washing, but the therapy will address the underlying disorder. Becoming attached to *cannabis* is not so much a function of any inherent psychopharmacologic property of the drug as it is emotionally driven by the underlying psychopathology. Success in curtailing *cannabis* use requires dealing with that pathology.

MEDICINAL USES OF CANNABIS

Cannabis usage as a medicament is ancient, and it has included indications for headache (64,65), other types of pain (66), obstetric and gynecologic conditions (67), and psychiatric disorders (68,69).

The history of *cannabis* as a Western medicine begins in 1839, with a publication by W. B. O'Shaughnessy, a British physician working in Calcutta (70). He reported on the analgesic, anticonvulsant, and muscle relaxant properties of the drug. His paper generated a good deal of interest, and there followed more than 100 other papers in the Western medical literature from 1840 to the turn of the century. In the nineteenth century the drug was widely prescribed in the Western world for various ailments and discomforts, such as coughing, fatigue, rheumatism, asthma, delirium tremens, migraine headache, and painful menstruation. Although its use was already declining somewhat because of the introduction of synthetic hypnotics and analgesics, it remained in the United States Pharmacopoeia until 1941. The difficulties imposed on its use by the Marihuana Tax Act of 1937, as well as quality-control issues with uncertain supplies, completed its medical demise, and, from that time on, physicians allowed themselves to become ignorant about the drug.

The greatest advantage of *cannabis* as a medicine is its unusual safety. The ratio of lethal dose to effective dose is estimated on the basis of extrapolation from animal data to be about 20,000:1. Huge doses have been given to dogs without causing death, and there is no reliable evidence of death caused by *cannabis* in a human being. *Cannabis* also has the advantage of not disturbing any physiologic functions or damaging any body organs when it is used in therapeutic doses. It produces little physical dependence or tolerance; there has never been any evidence that medical use of *cannabis* has led to habitual use as an intoxicant.

Whole *cannabis* preparations have the disadvantages of instability, varying strength, and insolubility in water, which makes it difficult for the drug to enter the bloodstream from the digestive tract. The multitude of ingredients found in *cannabis* is also an opportunity, because it suggests the manufacture of different cannabinoids, synthetic or natural, with properties useful for particular purposes; some of these have now become available (66,71). One that is presently legally available for the treatment of nausea and vomiting of cancer chemotherapy and the acquired immune deficiency syndrome (AIDS) weight loss syndrome is dronabinol (Marinol), a synthetic THC. While it is not as useful medicinally as whole smoked marihuana, it is legally available as a Schedule III drug. Smoking generates quicker and more predictable results because it raises THC concentration in the blood more easily and predictably to the needed level. Also, it may be hard for a nauseated patient in chemotherapy to take oral medicine. But many patients dislike smoking or cannot inhale (69). Alternative-dosing approaches are discussed in several references (4,72–75).

There are many anecdotal reports of marihuana smokers using the drug to reduce postsurgery pain, headache, migraine, menstrual cramps, phantom limbs, and other kinds of pain. It is the case that *cannabis* acts by mechanisms different from those of other analgesics through the endocannabinoid pain mechanisms (66), and that *cannabis* may be more effective than opiates in neuropathic pain states. Again, some new synthetic derivatives might prove useful as an analgesic, but this is not an immediate prospect.

Because of reports that some people use less alcohol when they smoke marihuana, *cannabis* has been proposed as an adjunct to alcoholism treatment, but so far it has not been found useful (76–78). Most alcoholics neither want to substitute marihuana nor find it particularly helpful. But there might be some hope for use of marihuana in combination with disulfiram (Antabuse) (76). Certainly a *cannabis* habit would be preferable to an alcohol habit for anyone who could not avoid dependence on a drug but who was able to substitute one drug for another.

Approximately 20% of epileptic patients do not get much relief from conventional anticonvulsant medications. *Cannabis* has been explored as an alternative, at least since a case was reported in which marihuana smoking, together with the standard anticonvulsants phenobarbital and diphenylhydantoin (Dilantin), was apparently necessary to control seizures in a young epileptic man (79). Recent reports support the role of THC endocannabinoids in modulation of seizure threshold (80,81). Cannabidiol also demonstrates anticonvulsant properties (7,82). In one controlled study, cannabidiol in addition to prescribed anticonvulsants produced improvement in seven patients with grand mal seizures; three showed great improvement.

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Of eight patients who received a placebo instead, only one improved (83).

Marihuana also reduces muscle spasm and tremors in some people who suffer from spastic disorders, including multiple sclerosis (84,85), cerebral palsy, and various causes of hemiplegia and quadriplegia, such as spinal cord injury or disease. Anecdotal reports of the use of *cannabis* for the relief of asthma abound. The antiasthmatic drugs that are available all have drawbacks—limited effectiveness or side effects. Because marihuana dilates the bronchi and reverses bronchial spasm, *cannabis* derivatives have been tested as antiasthmatic drugs. Smoking marihuana would probably not be a good way to treat asthma because of chronic irritation of the bronchial tract by tars and other substances in marihuana smoke, so recent research has sought a better means of administration. THC in the form of an aerosol spray has been investigated extensively (59,60). Other cannabinoids, such as cannabinol and cannabidiol, may be preferable to THC for this purpose. An interesting finding for future research is that cannabinoids may affect the bronchi by means of a different mechanism from that of the familiar antiasthmatic drugs. A promising new medical use for *cannabis* is treatment of glaucoma, the second leading cause of blindness in the United States. About a million Americans suffer from the form of glaucoma (wide angle) treatable with *cannabis*. Marihuana causes a dose-related, clinically significant drop in intraocular pressure that lasts several hours in both normal subjects and in those with the abnormally high ocular tension produced by glaucoma. Oral or intravenous THC has the same effect, which seems to be specific to *cannabis* derivatives rather than simply a result of sedation. *Cannabis* does not cure the disease, but it can retard the progressive loss of sight when conventional medication fails and surgery is too dangerous (86). A recent comprehensive review supports the use of cannabinoids as antioxidant protective agents in the development of vascular retinopathy of glaucoma, a process independent of intraocular pressure (87).

It remains to be seen whether topical use of THC or a synthetic cannabinoid in the form of eyedrops will be preferable to smoking marihuana for this purpose. So far THC eyedrops have not proved effective, and in 1981, the National Eye Institute announced that it would no longer approve human research using these eyedrops (76). Studies continue on certain synthetic *cannabis* derivatives and other natural cannabinoids (87). Smoking marihuana is a better way of titrating the dose than is the taking of an oral cannabinoid, and most patients seem to prefer it. Unfortunately, many patients, especially elderly ones, dislike the psychoactive effects of marihuana.

Cannabis derivatives have several minor or speculative uses in the treatment of cancer, and one major use. As appetite stimulants, marihuana and THC may help to slow weight loss in cancer patients (88), as they have in AIDS patients (55). THC has also retarded the growth of tumor cells in some animal studies, but results are inconclusive, and another *cannabis* derivative, cannabidiol, seems to increase tumor growth (89). Possibly cannabinoids in combination with other drugs will turn out to have some use in preventing tumor growth. THC may promote apoptosis (programmed cell death) in some malignant cells (90). Limonene, a monoterpenoid component of *cannabis* resin, has similar activity on breast tumor cells (91). But the most promising use of *cannabis* in cancer treatment is the prevention of nausea and vomiting in patients undergoing chemotherapy. About half of patients treated with anticancer drugs suffer from severe nausea and vomiting. In 25% to 30% of these cases, the commonly used antiemetics do not work (69). The nausea and vomiting are not only unpleasant, but are a threat to the effectiveness of the therapy. Retching can cause tears of the esophagus and rib fractures, prevent adequate nutrition, and lead to fluid loss.

The antiemetics most commonly used in chemotherapy are prochlorperazine (Compazine) and the newer ondansetron (Zofran) and granisetron (Kytril). The suggestion that *cannabis* might be useful arose in the early 1970s when some young patients receiving cancer chemotherapy found that marihuana smoking, which was, of course, illegal, reduced their nausea and vomiting. In one study of 56 patients who got no relief from standard antiemetic agents, 78% became symptom free when they smoked marihuana (92). Previously unpublished state studies of smoked *cannabis* have demonstrated 70% to 100% relief of vomiting in some 748 chemotherapy patients (93).

Several of the most urgent medical uses of *cannabis* are for the treatment of the nausea and weight loss suffered by many AIDS patients. The nausea is often a symptom of the disease itself and a side effect of some of the medicines (particularly azidothymidine [zidovudine or AZT]). For many AIDS patients the most distressing and threatening symptom is cachexia. Marihuana will retard weight loss in most patients and even helps some regain weight (69).

A committee of the Institute of Medicine of the National Academy of Sciences remarked in a report in 1982 (28, p. 139):

> *Cannabis* shows promise in some of these areas, although the dose necessary to produce the desired effect is often close to one that produces an unacceptable frequency of toxic [undesirable] side effects. What is perhaps more encouraging... is that *cannabis* seems to exert its beneficial effects through mechanisms that differ from those of other available drugs. This raises the possibility that some patients who would not be helped by conventional therapies could be treated with *cannabis*.... It may be possible to reduce side effects by synthesizing related molecules that could have a more favorable ratio of desired to undesired actions; this line of investigation should have a high priority.

The committee recommended further research, especially in the treatment of nausea and vomiting in chemotherapy, asthma, glaucoma, and seizures and spasticity.

Under federal and most state statutes, marihuana is listed as a Schedule I drug: high potential for abuse, no

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currently accepted medical use, and lacking in accepted safety for use under medical supervision. It cannot ordinarily be prescribed and may be used only under research conditions. *Cannabis* was recently legalized for medical use in Canada and Holland, and liberalization of laws is proceeding in the United Kingdom and elsewhere in Western Europe.

The potential of *cannabis* as a medicine is yet to be realized, partly because of its reputation as an intoxicant, ignorance on the part of the medical establishment, and legal difficulties involved in doing the research (94). Recreational use of *cannabis* has affected the opinions of physicians about its medical potential in various ways. When marihuana was regarded as the drug of African Americans, Mexican Americans, and Bohemians, doctors were ready to go along with the Bureau of Narcotics, ignore its medical uses, and urge prohibition. For years the National Organization for the Reform of Marijuana Laws and other groups have been petitioning the government to change this classification. Now that marihuana has become so popular among a broad section of the population, we have been more willing to investigate its therapeutic value. Recreational use now spurs medical interest instead of medical hostility.

It is estimated that more than 70 million Americans have used *cannabis* and more than 10 million use it regularly. They use it not because they are driven by uncontrollable "reefer madness" craving, as some propaganda would lead us to believe, but because they have learned its value from experience. Yet almost all of the research, writing, political activity, and legislation devoted to marihuana has been concerned only with the question of whether it is harmful and how much harm it does. The only exception is the growing resurgence of interest in its usefulness as a medicine. But medicine represents only one category of marihuana use. The rest are sometimes grouped under the general heading of "recreational," but that is hardly an appropriate word to describe the many serious reasons for which people have learned to use *cannabis*. For example, many writers and artists have found that the *cannabis* high can be a catalyst to their creativity (95). Allen Ginsberg, writing while stoned, eloquently put it this way: ". . . the marihuana consciousness is one that, ever so gently, shifts the center of attention from habitual shallow purely verbal guidelines and repetitive secondhand ideological interpretations of experience to more direct, slower, absorbing, occasionally microscopically minute, engagement with sensing phenomena during the high moments or hours after one has smoked" (96). While many artists have learned to use *cannabis* as an aid to their creativity, many other users have discovered its capacity to catalyze the generation of ideas and insights, heighten the appreciation of music and art, or deepen emotional and sexual intimacy. (The reader who wishes to learn more about this is referred to the Uses of Marijuana Web Site [www.marihuana-uses.com], a collection of essays written by marihuana users who have found this drug useful as an enhancer of various capacities and experiences.)

This "enhancement" capacity is often underappreciated—not only by nonusers, but also by some users, especially young people who are primarily interested in promoting sociability and fun. Most of marihuana's powers of enhancement are subtle and not as immediately available as its capacity to lift mood or improve appetite and the taste of food. Many, if not most, people do not achieve a *cannabis* high during their first attempt or attempts because they have yet to learn to recognize the subtle changes in consciousness that comprise the marihuana experience. Similarly, the ability to make use of *cannabis* consciousness as an enhancer of various capacities appears to require both experience in achieving this state and learning how to make use of it.

The potential dangers of marihuana when taken for pleasure and enhancement, and its possible usefulness as a medicine are historically and practically interrelated issues—historically, because the arguments used to justify public and official disapproval of recreational use have had a strong influence on opinions about its medical potential; practically, because the more evidence accumulates that marihuana is relatively safe even when used as an intoxicant, the clearer it becomes that the medical requirement of safety is satisfied. Most recent research is tentative, and initial enthusiasm for drugs is often disappointed after further investigation. But it is not as though *cannabis* were an entirely new agent with unknown properties. Studies done during the past 10 years confirm a centuries-old promise. With the relaxation of restrictions on research and the further chemical manipulation of *cannabis* derivatives, this promise will eventually be realized. The weight of past and contemporary evidence will probably prove *cannabis* to be valuable in a number of ways as a medicine.

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