There is an unnecessary aura of uncertainty and confusion in the discussions of the pharmacology of marijuana and its various preparations and constituents. Part of the uncertainty is generated by those who believe that marijuana is a frighteningly dangerous drug in no way comparable to any accepted social drug, and, at the other extreme, by those individuals of increasing number who claim it is a purely beneficent drug in no way comparable to any acceptable social drug. Additional reluctance to summarize the pharmacology of marijuana stems from the assumption that research on its pharmacology is scant, dated, and of poor quality. Certainly much research remains to be done. However, the inability to present a consistent formulation of the pharmacology of marijuana may be due not so much to lack of data as to the failure to apply some unifying concept to the fragmentary information available.

Most drugs can be put into classes or categories. When this is done information derived from the previous study of other drugs in a particular class can be used to predict the effects of the drug under scrutiny. The period of study is shortened and an organizing concept is provided. For example, the study of the latest barbiturate to be synthesized is simplified by the exhaustive studies on the prototypes of its class of drugs.

There is a class of drugs made up of the sedative-hypnotics (alcohol, barbiturates) and the general anesthetics (ether, halothane and other "Freons" including those in hair spray, nitrous oxide, phencyclidine or PCP, the solvents in glue). If the effects of large doses of a sedative—like a dose of barbiturate taken with suicidal intent or an anesthetic dose of Pentothal—are examined, it is apparent that all of the drugs listed have qualitatively similar effects differing mostly in their physical state. Gases and volatile liquids are selected for use as general anesthetics because their transfer across the alveoli of the lungs allows for rapid onset of action, minute-to-minute control of dosage, and rapid recovery. The sedatives are given to achieve a longer less intense effect and, if solids such as barbiturates are selected, they are more easily dispensed.
Having defined one drug class, the sedative-hypnotics, let us examine the following hypothesis: marijuana has all of the properties of a sedative-hypnotic. It seems distinctive from this class mostly because our experience is limited to its use by smoking, which provides for a rapidly appearing effect but also for a rapid decay of the effect as the absorbed drug is redistributed in the body. With the oral use of hashish or synthetic Cannabis equivalents, the apparent distinctiveness from alcohol or barbiturates disappears.

To establish that the hypothesis mentioned above is correct almost beyond question, this paper will list the properties of a sedative-hypnotic (Table 1) and then discuss the observations establishing that the constituents of Cannabis have the same actions.

Throughout the discussion the following cautions should be remembered.

1. Effects are described that aid in the classification of the drug. It does not follow that these effects appear regularly in the ordinary use of marijuana in our culture, where the usual pattern is smoking rather than ingestion and where comparatively weak "grass" is the mode.

2. The assumption is made that hashish, grass, THC, and synthexyl exert qualitatively similar effects. (Synthexyl, or pyrahexyl, differs from the THC, assumed to be the most important active component, by one CH2 group. It has been available in adequate amounts and has been studied far more thoroughly than other natural or synthetic THC's. Studies in humans establish the similarities of effects.) (4)

**Effects of Graded Doses**
Pharmacological Effects of Marijuana

Written by Frederick H Meyers
Saturday, 09 February 2013 00:00

If marijuana is a sedative-hypnotic, the administration of progressively larger doses should lead to a sequence of changes comparable to the stages of general anesthesia. It can be shown in animals that large doses do produce anesthesia and that after huge doses the animal does die from respiratory depression.

The interpretation of the effects of smaller doses, however, appears controversial to some observers because the "high" is assumed to be a manifestation of stimulation by the drug.

To understand the effect of smaller doses of marijuana, one must differentiate between manifest behavior, i.e., excitement or depression, and the underlying pharmacologic effect of stimulation or depression. Marijuana, like alcohol, is a depressant in its effects on the nervous system; the "high" is a result of depression of the higher centers and consequent release of lower centers from chronic inhibitory influences. Increasing the dosage, whether of marijuana, alcohol, or ether, leads to pure depression as the excitement stage is passed. There is other laboratory evidence for the depressant effect of the tetrahydrocannabinols, for example, the ability to prolong the sleep induced by other sedatives.

As marijuana is used in this country, the period of disinhibition or drunkenness is quite brief. Psychomotor ability and probably judgment are impaired during this period. The disinhibition also causes euphoria and relief of anxiety; it also explains the social use and possible misuse of all of the drugs of this class.

An additional area of confusion or controversy is introduced when marijuana is characterized as a "mild hallucinogen." The effect in question is better described as a dreamy state with an increased tendency to fantasize and to accept suggestion. Such a dreamy, hypnagogic state can be induced with almost any one of the sedatives or anesthetics under favorable conditions. The use of nitrous oxide to produce such a state was described by Humphry Davy almost as soon as he isolated the gas. The Pentothal interview and the recent use of PCP (Sernylan®) are additional examples, and a transient "hallucinatory" state has also been described during the therapeutic use of chlordiazepoxide (Librium). (9)

Effects of Continuous Use

1. Physical dependence and withdrawal. Physical dependence as a factor maintaining drug
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misuse has undoubtedly been greatly overemphasized. Alcohol, for example, undoubtedly provides the number 1 drug problem in our culture, but only rarely causes delirium tremens. Nevertheless, if a drug is to be classified as a sedative-hypnotic, it must be demonstrated that the abrupt discontinuance of large doses results in a state of hyperexcitability.

Clinical observations of hashish smokers suggest that withdrawal symptoms are unusual or mild. Experimentally, i.e., for purposes of classification, a withdrawal state can be shown. For example, subjects were given large doses of pyrahexyl orally for 26 to 31 days. On the third day following discontinuation of the drug most patients were restless and slept poorly. One subject experienced agitation progressing to disorientation and the symptoms were abolished within four to five hours by the administration of pyrahexyl. Another passed through a hypomanic state on the fourth day. Under the same experimental conditions subjects were allowed free access to marijuana cigarettes for 39 days. The average patient smoked 17 cigarettes per day but no withdrawal state was demonstrated. (10)

2. Liability for misuse. The question of whether the use of marijuana as a social drug can, like the use of alcohol as a social drug, sometimes lead to the development of a compulsive pattern of use is, of course, an emotionally loaded question. Certainly the hazards of smoking the weak marijuana preparations available in this country are minimal. If one looks outside of our culture to the Muslim world, it appears that a compulsive pattern of use with results comparable to those of chronic alcoholism is indeed possible.

3. Other effects. There are other pharmacologic actions of Cannabis preparations that are useful in classifying the drug but that are of interest primarily to the laboratory investigator. For example, the tetrahydrocannabinols are anticonvulsant and depress polysynaptic transmission within the spinal cord.

None of the preparations of Cannabis has therapeutic applications, and none of the questions associated with its use as a social drug would be altered if it did. The use of synthexyl as an antidepressant is, however, often mentioned. Review of the paper by Stockings (8) usually cited in this regard will establish that he actually used the drug for the relief of anxiety. He clearly characterizes his ambulant patients as neurotic and describes the development after the administration of synthexyl of mild intoxication, euphoria, and dreamy apathy.

MECHANISM OF ACTION

The ability of a sedative or anesthetic to cause loss of consciousness is due to the sensitivity
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of the reticular activating system to their depressant effects. When electrodes are implanted into
the reticular formation and several functionally related areas in the brain, the effect of synhexyl
cannot be distinguished from that of Pentothal. (3)

Conclusion

Thus the effects of marijuana, both operationally and in its mechanism of action, correspond
exactly to those of other sedatives and anesthetics, especially alcohol. The apparent
distinctiveness of marijuana is due mostly to the use of a route of administration that permits the
rapid development of an effect and to properties of the active components that lead to rapid
decrease in the effects. One is driven to the conclusion that the differences between the
dominant attitudes and consequent laws toward marijuana and alcohol are unrelated to the
pharmacologic effects of the drugs but are due to a conflict between the mores of the dominant
and one or more of the subcultures in this country.

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