FOIA Number: 2018-0764-F

FOIA MARKER

This is not a textual record. This is used as an administrative marker by the William J. Clinton Presidential Library Staff.

Collection/Record Group: Clinton Presidential Records

Subgroup/Office of Origin: National AIDS Policy Office

Series/Staff Member:

Subseries:

OA/ID Number: 21069

FolderID:

Folder Title:
Medical Marijuana [2]

Stack:	Row:	Section:	Shelf:	Position:
S	67	1	2	1

Cannabinoid Biosynthesis

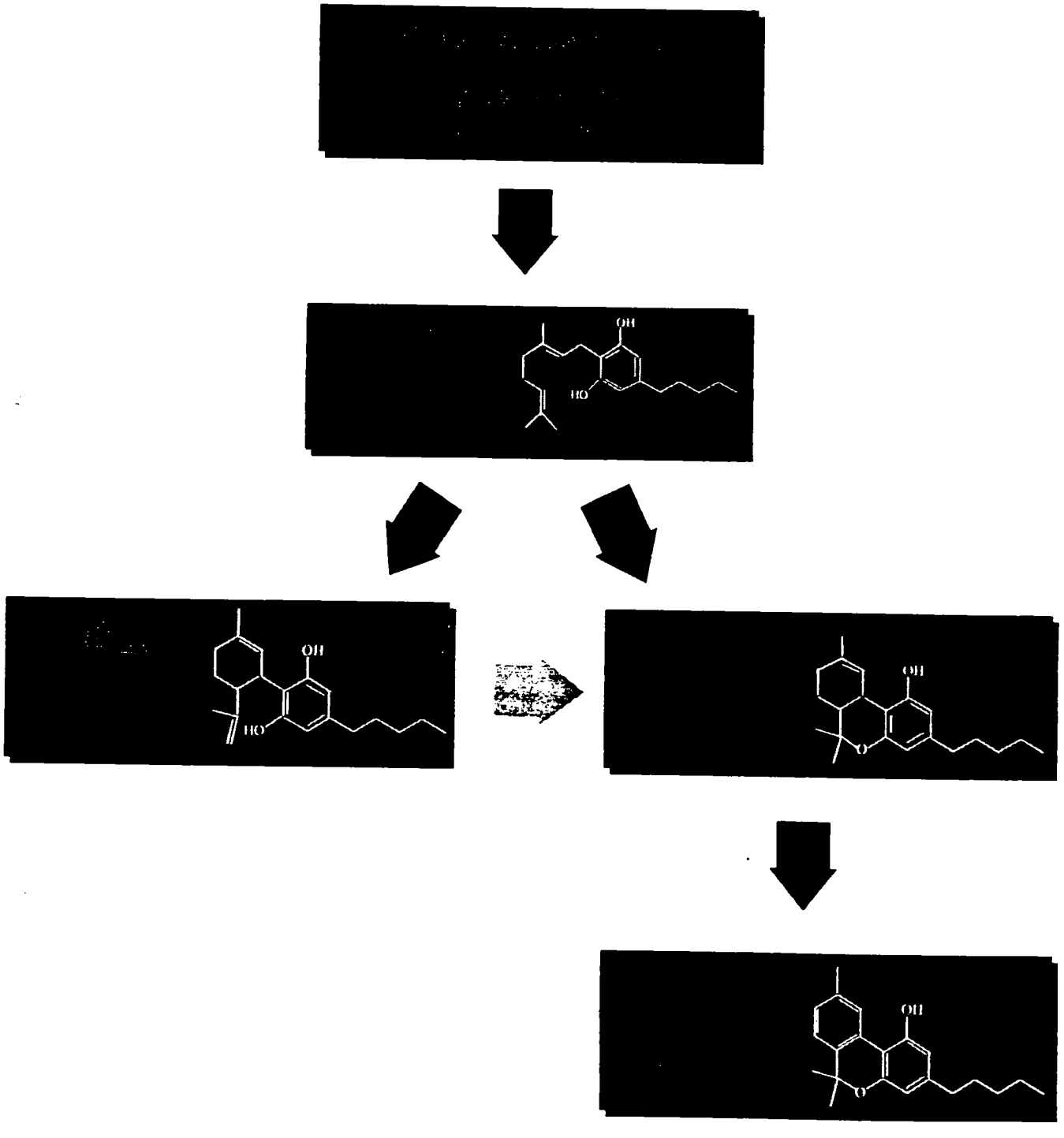


Table 1.5 Cannabinoids Identified in Marijuana

66 Cannabinoids Identified in Marijuana		
Cannabinoid Group	Common Abbreviation	Number of cannabinoid variants known in each group
Δ^9-Tetrahydrocannabinol	Δ^9-THC	9
Δ^8-Tetrahydrocannabinol	Δ^8-THC	2
Cannabichromene	CBC	5
Cannabicyclol	CBL	3
Cannabidiol	CBD	7
Cannabielsoin	CBE	5
Cannabigerol	CBG	6
Cannabinidiol	CBND	2
Cannabinol	CBN	7
Cannabitriol	CBT	9
Miscellaneous types		11

Organization of the Report

Throughout the report, steps that might be taken to fill the gaps in understanding both the potential harms and benefits of marijuana and cannabinoid use will be identified. Those steps include identifying knowledge gaps, promising research directions, and potential therapies based on scientific advances in cannabinoid biology.

Chapter 2 reviews basic cannabinoid biology and provides a foundation to understand the medical value of marijuana or its constituent cannabinoids. In consideration of the physician's first rule, "first, do no harm," the potential harms attributed to the medical use of marijuana are reviewed before the potential medical benefits, chapter 3 reviews the risks posed by marijuana use, with emphasis on medical use.

Chapter 4 analyzes the most credible clinical data relevant to the medical use of marijuana. It reviews what is known about the physiological mechanisms underlying particular conditions (for example, chronic pain, vomiting, anorexia, and muscle spasticity), what is known about the cellular actions of cannabinoids, and the levels of proof needed to show that marijuana is an effective treatment for specific symptoms. It does not analyze the historical literature; history is informative in enumerating uses of marijuana, but it does not provide the sort of information needed for a scientifically sound evaluation of the efficacy and safety of marijuana for clinical use. Because marijuana is advocated primarily as affording relief from the symptoms of disease rather than as a cure, this chapter is organized largely by symptoms as opposed to disease categories. Finally, chapter 4 compares the conclusions of this report with those of other recent reports on the medical use of marijuana.

Chapter 5 describes the process of and analyzes the prospects for cannabinoid drug development.

References

1. Abel EL. 1980. *Marijuana: the first twelve thousand years*. New York: Plenum Press.

2. Angell M, Kassirer JP. 1998. Alternative Medicine - The Risks of Untested and Unregulated Remedies. *The New England Journal of Medicine* 339:839-841.

3. Bonnie RJ, Whitebread II CH. 1974. *The marihuana conviction: A history of marihuana prohibition in the United States*. Charlottesville, VA: University Press of Virginia.

4. Eisenberg DM. 1997. Advising patients who seek alternative medical therapies. *Annals of Internal Medicine* 127:61-69.

5. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kessler RC. 1998. Trends in Alternative Medicine Use in the United States, 1990-1997: Results of a Follow-up National Survey. *Journal of the American Medical Association* 280:1569-1575.

6. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. 1993. Unconventional medicine in the United States: Prevalence, costs, and patterns of use. *New England Journal of Medicine* 328:246-252.

7. Grifo F, Newman D, Fairfield A, Bhattacharya B, Grupenhoff JT. 1997. The Origins of Prescription Drugs. In: Grifo F, Rosenthal J Editors *Biodiversity and Human Health.* Washington, D.C.: Island Press. Pp. 131-163.

8. Herstek J. 1998. Behavioral Health Issue Briefs. *Medical Marijuana.* Washington, D.C.: Health Policy Tracking Service, National Conference of State Legislatures.

9. Kilbourne EM, Philen R M, Kamb M L, Falk H. 1996. Tryptophan produced by Showa Denko and epidemic eosinophilia-myalgia syndrome. *Journal of Rheumatology Supplement* 46:81-88. Comment on: Journal of Rheumatology Supplement 1996 46: 44-58 and 60-72; discussion 58-59.

10. Mathre ML, Editor. 1997. *Cannabis in Medical Practice*. Jefferson, North Carolina: MacFarland and Company, Inc.

11. Mechoulam R. 1986. The pharmacohistory of *Cannabis Sativa*. In: Mechoulam R Editor *Cannabinoids as therapeutic agents.* Boca Raton, FL: CRC Press, Inc. Pp. 1-19.

12. Milburn DS, Myers CW. 1991. Tryptophan toxicity: a pharmacoepidemiologic review of eosinophilia-myalgia syndrome. *DICP* 25:1259-1262.

13. NORML. The Medical Use of Marijuana [WWW Document].URL http://norml.org/medical/index.html (accessed July 9, 1998).

14. Pate DW. 1994. Chemical ecology of cannabis. *Journal of the International Hemp Association* 1:29,32-37.

15. Peterson K. 15 January 1997. Notes: Weighing in on a medical controversy; USA Today's Baby Boomer Panel. *USA Today,* sec. Life, p. 12D.

16. Ross SA, Elsohly MA. 1995. Constituents of Cannabis Sativa L. XXVIII a review of the natural constituents: 1980-1994. *Zagazig Journal for Pharmaceutical Sciences* 4:1-10.

17. Taura F, Morimoto S, Shoyama Y. 1995. First direct evidence for the mechanism of delta1-tetrahydrocannabinolic acid biosysnthesis. *Journal of the American Chemical Society* 117:9766-9767.

18. Turner CE, Elsohly MA, Boeren E.G. 1980. Constituents of Cannabis Sativa L. XVII. A review of the natural constituents. *Journal of Natural Products* 43:169-234.

CHAPTER 2. CANNABINOIDS AND ANIMAL PHYSIOLOGY 2

Chapter 2. Cannabinoids and Animal Physiology

Introduction

Much has been learned since the publication of the 1982 IOM report on *Marijuana and Health.* [•] Although it was clear then that most of the effects of marijuana were due to its actions on the brain, there was little information about how THC acted on brain cells (neurons), which cells were affected by THC, or even what general areas of the brain were most affected by THC. Too little was known about cannabinoid physiology to offer any scientific insights into the harmful or therapeutic effects of marijuana. That is no longer true. During the last 16 years, there have been major advances in what basic science discloses about the potential medical benefits of cannabinoids, the group of compounds related to THC. Many variants are found in the marijuana plant, and other cannabinoids not found in the plant have been chemically synthesized. Sixteen years ago, it was still a matter of debate as to whether THC acted nonspecifically by affecting the fluidity of cell membranes or whether a specific pathway of action was mediated by a receptor that responded selectively to THC (table 2.1).

Basic science is the wellspring for developing new medications and is particularly important for understanding a drug that has as many effects as marijuana. Even committed advocates of the medical use of marijuana do not claim that all the effects of marijuana are desirable for every medical use. But they do claim that the combination of specific effects of marijuana enhances its medical value. An understanding of those specific effects is what basic science can provide. The multiple effects of marijuana can be singled out and studied with the goals of evaluating the medical value of marijuana and cannabinoids in specific medical conditions, as well as minimizing unwanted side effects. An understanding of the basic mechanisms through which cannabinoids affect physiology permits more strategic development of new drugs and designs for clinical trials that are most likely to yield conclusive results.

Research on cannabinoid biology offers new insights into clinical use, especially given the scarcity of clinical studies that adequately evaluate the medical value of marijuana. For example, despite the scarcity of substantive clinical data, basic science has made it clear that cannabinoids can affect pain transmission and specifically that, cannabinoids interact with the brain's endogenous opioid system, an important system for the medical treatment of pain (see chapter 4).

[•] The field of neuroscience has grown substantially since the publication of the 1982 IOM report. The number of members in the Society for Neuroscience provide a rough measure of the growth in research and knowledge about the brain: as of the middle of 1998, there are over 27,000 members, more than triple the number in 1982.

The cellular machinery that underlies the response of the body and brain to cannabinoids involves an intricate interplay of different systems. This chapter reviews the components of that machinery with enough detail to permit the reader to compare what is known about basic biology with specific indications proposed for marijuana. For some readers, that will be too much detail. Those readers who do not wish to read the entire chapter should, nonetheless, be mindful of the following key points in this chapter.

- The most far-reaching of the recent advances in cannabinoid biology are the identification of two types of cannabinoid receptors (CB_1 and CB_2) and of anandamide, a substance naturally produced by the body that acts at the cannabinoid receptor, and has effects similar to those of THC. The CB_1 receptor is found primarily in the brain, and mediates the psychological effects of THC. The CB_2 receptor is associated with the immune system; its role remains unclear.
- The physiological roles of the brain cannabinoid system in humans are the subject of much active research, and not fully known; however, cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
- Animal research has shown that the potential for cannabinoid dependence exists, and cannabinoid withdrawal symptoms can be observed. However, both appear to be mild compared to dependence and withdrawal seen with other drugs.
- Basic research in cannabinoid biology has revealed a variety of cellular pathways through which potentially therapeutic drugs could act on the cannabinoid system. In addition to the known cannabinoids, such drugs might include chemical derivatives of plant-derived cannabinoids or of endogenous cannabinoids such as anandamide, but would also include non-cannabinoid drugs that act on the cannabinoid system.

This chapter summarizes the basics of cannabinoid biology—as known today. It thus provides a scientific basis for interpreting claims founded on anecdotes and for evaluating the clinical studies of marijuana presented in chapter 4.

Table 2.1 Landmark Discoveries Since the 1982 IOM Report

Since the Previous IOM Report on Marijuana in 1982: A Decade of Landmark Discoveries

Year	*Discovery*	*Primary Investigators*
1986	Potent cannabinoid agonists are developed—the key to discovering the receptor	M.R. Johnson and L.S. Melvin[75]
1988	First conclusive evidence of specific cannabinoid receptors	A. Howlett and W. Devane[36]
1990	The cannabinoid brain receptor (CB_1) is cloned, its DNA sequence is identified, and its location in the brain is determined	L. Matsuda et al,[107] and M. Herkenham et al [60]
1992	Anandamide is discovered—a naturally occurring substance in the brain that acts on cannabinoid receptors	R. Mechoulam and W. Devane[37]
1993	A cannabinoid receptor is discovered outside the brain; this receptor (CB_2) is related to the brain receptor but is distinct	S. Munro[112]
1994	The first specific cannabinoid antagonist, SR141716A, is developed	M.Rinaldi-Carmona[132]
1998	The first cannabinoid antagonist, SR144528, that can distinguish between CB_1 and CB_2 receptors discovered.	M. Rinaldi-Carmona[133]

The Value of Animal Studies

Much of the research into the effects of cannabinoids on the brain is based on animal studies. Many speakers in the public workshops associated with this study argued thatanimal studies of marijuana are not relevant to humans. While animal studies are no substitute for clinical trials, they are a necessary complement. Ultimately, every biologically active substance exerts its effects at the cellular and molecular level, and at this level, the evidence has shown remarkable consistency among mammals, even those as different in body and mind as rats and humans. Animal studies typically provide information about how drugs work that would not be obtainable in clinical studies. At the same time, animal studies can never completely inform us about the full range of psychological and physiological effects of marijuana or cannabinoids on humans.

The Active Constituents of Marijuana

Δ^9-THC and Δ^8-THC are the only compounds in the marijuana plant that show all the psychoactive effects of marijuana. Because Δ^9-THC is much more abundant than Δ^8-THC, the psychoactivity of marijuana has been largely attributed to the effects of Δ^9-THC. 11-OH-Δ^9-THC is the primary product of Δ^9-THC metabolism by the liver and is about three times as potent as Δ^9-THC.[128]

There have been considerably fewer experiments with cannabinoids other than Δ^9-THC, although a few studies have been done to examine whether other cannabinoids modulate the effects of THC or mediate the non-psychological effects of marijuana. Cannabidiol (CBD) does not have the same psychoactivity as THC, but it was initially reported to attenuate the psychological response to THC in humans[81, 177] however, later studies reported that CBD did not attenuate the psychological effects of THC.[11, 69] One double-blind study of eight volunteers reported that CBD can block the anxiety induced by high doses of THC (0.5 mg/kg).[177] There are numerous anecdotal reports claiming that marijuana with relatively higher ratios of THC:CBD is less likely to induce anxiety in the user than marijuana with low THC: CBD ratios; but, taken together, the results published thus far are inconclusive.

The most significant effects of cannabidiol (CBD) seem to be its interference with drug metabolism in the liver, including Δ^9-THC metabolism.[14, 114] CBD exerts this effect by inactivating cytochrome P450s, which are the most important class of enzymes that metabolize drugs. Like many P450 inactivators, CBD can also induce P450s after repeated doses.[13] Experiments in which mice were treated with CBD followed by THC showed that CBD treatment was associated with a significant

increase in brain levels of THC and its major metabolites, most likely because of its effects on decreasing the clearance rate of THC from the body.[15]

In mice, THC inhibits the release of luteinizing hormone (LH), the pituitary hormone that triggers the release of testosterone from the testis in males; this effect is increased when THC is given together with cannabinol or CBD.[113]

Cannabinol is considerably less active than THC in the brain, but studies of immune cells have shown that it can modulate immune function (see section on Cannabinoids and the Immune System). In mice, cannabinol lowers body temperature and increases sleep duration.[175]

The Pharmacological Toolbox

A researcher needs certain key tools in order to understand how a drug acts on the brain. To appreciate the importance of these tools, one must first understand some basic principles of drug action. All recent studies have indicated that the behavioral effects of THC are receptor-mediated.[27] Neurons in the brain are activated when a compound binds to its receptor, which is a protein typically located on the cell surface. Thus, THC will exert its effects only after binding to its receptor. In general, a given receptor will accept only particular classes of compounds and will be unaffected by other compounds.

Compounds that activate receptors are called *agonists*. Binding to a receptor triggers an event or a series of events in the cell that results in a change in the cell's activity, its gene regulation, or the signals that it sends to neighboring cells (figure 2.1). This agonist-induced process is called signal transduction.

Another tool for drug research, which only recently became available for cannabinoid research, are the *receptor antagonists*, so-called because they selectively bind to a receptor that would have otherwise been available for binding to some other compound or drug. Antagonists block the effects of agonists and are tools to identify receptor functions by showing what happens when a receptor's normal functions are blocked. Agonists and antagonists are both *ligands*; that is, they bind to receptors. Hormones, neurotransmitters, and drugs can all act as ligands. Morphine and naloxone provide a good example. A large dose of morphine acts as an agonist at opioid receptors in the brain and interferes with, or even arrests, breathing. Naloxone, a powerful opioid antagonist, blocks morphine's effects on opiate receptors, thereby allowing an overdose victim to resume breathing normally. Naloxone itself has no effect on breathing.

Another key tool involves identifying the receptor protein and determining how it works. That makes it possible to locate where a drug activates its receptor in the brain—both the general region of the brain and the cell type where the receptor is. The way to find a receptor for a drug in the brain is to make the receptor "visible" by attaching a radioactive or fluorescent marker to the drug so that it can be detected.

Such markers show where in the brain it binds to the receptor, but this is not necessarily the part of the brain where the drug ultimately has its greatest effects.

Because drugs injected into animals must be dissolved in a water-based solution, it is easier to deliver water-soluble molecules than to deliver fat-soluble (lipophilic) molecules such as THC. THC is so lipophilic that it can stick to glass and plastic syringes used for injection. Because it is lipophilic, it readily enters cell membranes and thus can cross the blood brain barrier easily. (This barrier insulates the brain from many blood-borne substances.) Early cannabinoid research was hindered by the lack of potent cannabinoid ligands (THC binds to its cannabinoid receptors rather weakly) and because they were not readily water-soluble. The synthetic agonist, CP 55,940, which is more water-soluble than THC, became the first useful research tool for studying cannabinoid receptors because of its high potency, and the ability to label it with a radioactive molecule, which enabled researchers to trace its activity.

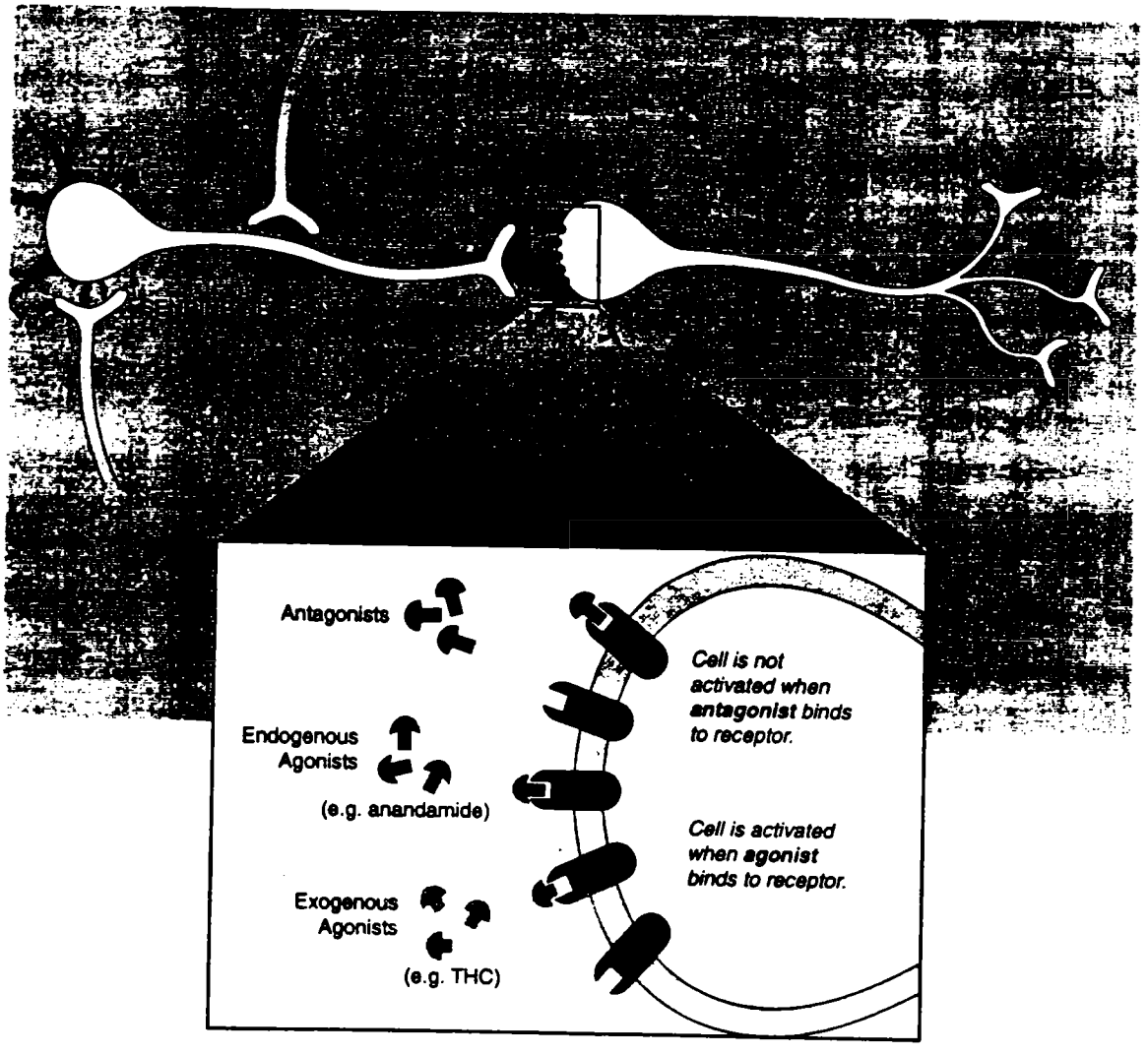
Figure 2.1 Diagram of neuron with synapse

How receptors work: Individual nerve cells, or neurons, both
cellular signals to and from neighboring neurons, but for the purpc
only one activity is indicated for each cell. Neurotransmitter m
black dots) are released from the neuron terminal and move acro
the "sending" and "receiving" neurons. A signal is transmitte
neuron when the neurotransmitters has bound to the receptor o
effects of a transmitted signal include:

- Changing the cell's permeability to ions such as calciun
- Turning a particular gene on or off.
- Sending a signal to another neuron.
- Increasing or decreasing the responsiveness of the ce signals.

Those effects can lead to cognitive, behavioral, or physiological
on which neuronal system is activated.

The expanded view of the synapse illustrates a variety
molecules that bind to receptors. Anandamide is a substance pr
that binds to and activates cannabinoid receptors; it is an *endoge*
can also bind to and activate cannabinoid receptors, but is not na
body; it is an *exogenous agonist*. SR141617A binds to, but
cannabinoid receptors. In this way, it prevents agonists, such
THC, from activating cannabinoid receptors by binding to the
activating them; SR141617A is an *antagonist*, but it is not norma
body. Endogenous antagonists, that is, those normally produced
also exist, but none have been identified.


Antagonists
Endogenous Agonists
(e.g. anandamide)
Exogenous Agonists
(e.g. THC)
Cell is not activated when antagonist binds to receptor.
Cell is activated when agonist binds to receptor.

Cannabinoid Receptors

The cannabinoid receptor is a typical member of the largest known family of receptors: the G-protein-coupled receptors with their distinctive pattern in which the receptor molecule spans the cell membrane seven times (figure 2.2). For excellent recent reviews of cannabionoid receptor biology, see Childers and Breivogel,[27] Abood and Martin,[1] Felder and Glass,[43] and Pertwee.[124] Cannabinoid receptor ligands bind *reversibly* (they bind to the receptor briefly and then dissociate) and *stereoselectively* (when there are molecules that are mirror images of each other, only one version activates the receptor). Thus far, two cannabinoid receptor subtypes (CB_1 and CB_2) have been identified, of which only CB_1 is found in the brain.

The cell responds in a variety of ways when a ligand binds to the cannabinoid receptor (figure 2.3). The first step is activation of G-proteins, the first components of the signal- transduction pathway. That leads to changes in several intercellular components—such as cyclic AMP and calcium and potassium ions—which ultimately produce the changes in cell functions. The final result of cannabinoid receptor stimulation depends on the particular type of cell, the particular ligand, and the other molecules that might be competing for receptor binding sites. Different agonists vary in binding *potency*, which determines the effective dose of the drug, and *efficacy*, which determines the maximal strength of the signal that they transmit to the cell. The potency and efficacy of THC are both relatively lower than those of some synthetic cannabinoids; in fact, synthetic compounds are generally more potent and efficacious than endogenous agonists.

CB_1 receptors are extraordinarily abundant in the brain. They are more abundant than most other G-protein-coupled receptors and ten times more abundant than *mu* opioid receptors, the receptors responsible for the effects of morphine.[148]

Figure 2.2 Cannabinoid receptors

Receptors are proteins, and proteins are made up of strings of amino acids. Each circle in the diagram represents one amino acid. The shaded bar represents the cell membrane, which like all cell membranes in animals, is largely composed of phospholipids. Like many receptors, the cannabinoid receptors span the cell membrane; some sections of the receptor protein are outside the cell membrane (*extracellular*), some are inside (*intracellular*). THC, anandamide, and other known cannabinoid receptor agonists bind to the extracellular portion of the receptor, thereby activating the signal pathway inside the cell.

The CB_1 molecule is larger than CB_2. The receptor molecules are most similar in four of the seven regions where they are embedded in the cell membrane (known as the transmembrane regions). The intracellular loops of the two cannabinoid receptor sub-types are quite different, which might affect the cellular response to the ligand, because these loops are known to mediate G-protein signaling—that is, the next step in the cell signaling pathway after the receptor. Receptor homology between the two receptor sub-types is 44 percent for the full-length protein, and 68 percent within the seven transmembrane regions. The ligand binding sites are typically defined by the extracellular loops and the transmembrane regions.

CB-1 and CB-2 Receptors

CB1 (●) and CB2 (●)

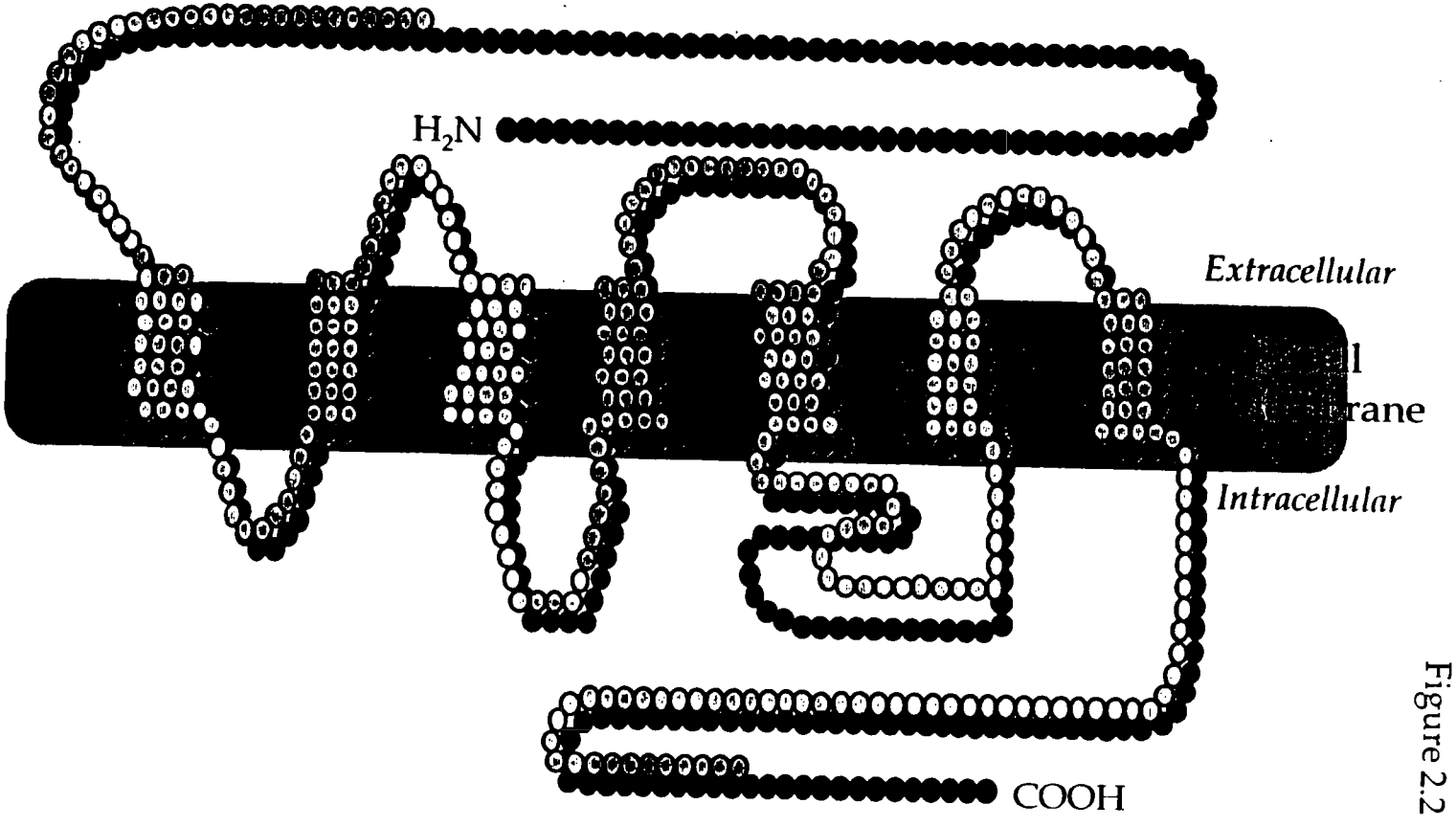
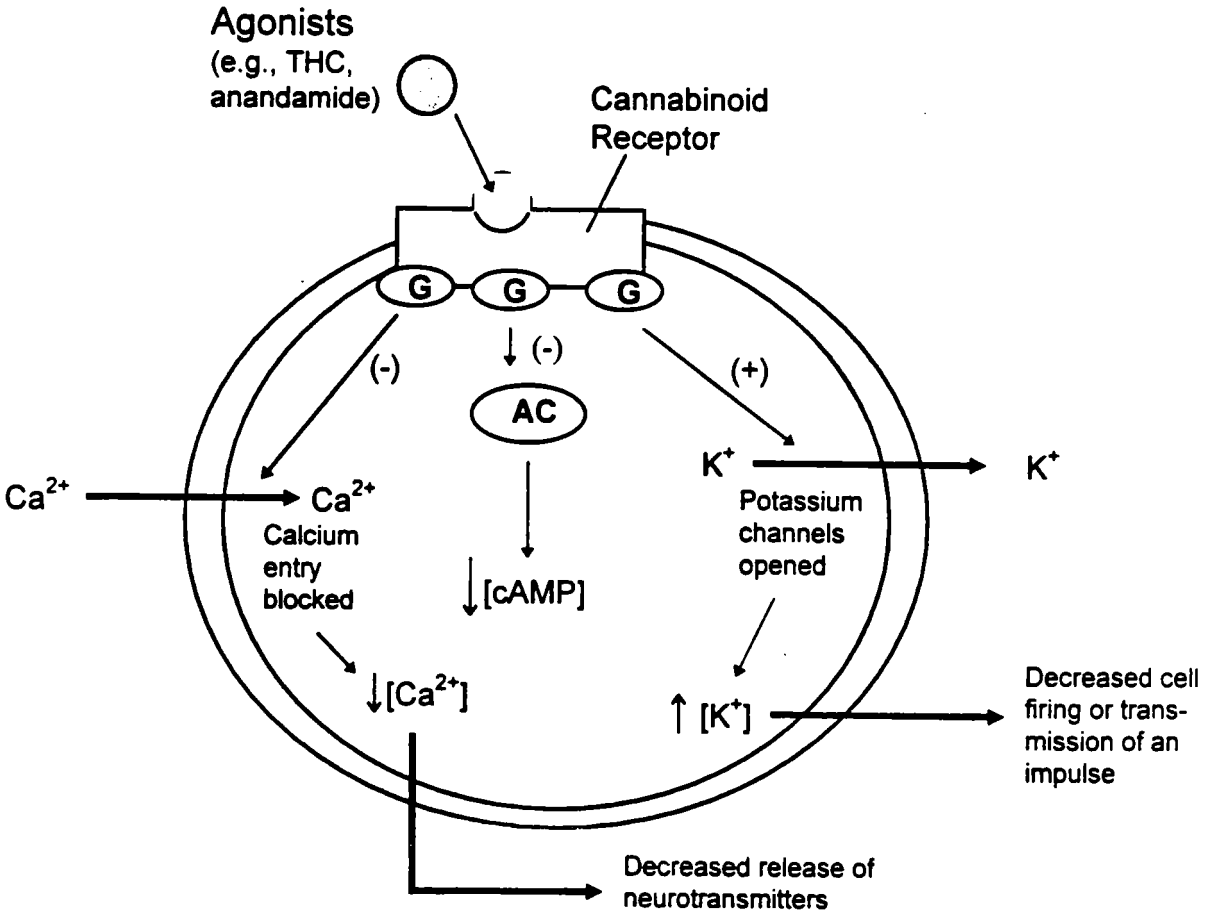


Figure 2.2

Figure 2.3 How cannabinoids affected neuron signals

Figure legend. Intracellular events that happen when cannabinoid agonists bind to receptors. Cannabinoid receptors are embedded in the cell membrane where they are coupled to G-proteins (G) and the enzyme, adenylyl cyclase (AC). Receptors are activated when they bind with ligands such as anandamide or THC in this case. This triggers a variety of reactions including inhibition ((-)) of AC which decreases the production of cAMP and cellular activities dependent on cAMP, opening potassium (K+) channels which decreases cell firing, and closing calcium (Ca^{2+}) channels which decreases the release of neurotransmitters. These changes can influence cellular communication.



The cannabinoid receptor in the brain is a protein referred to as CB_1. The peripheral receptor (outside the nervous system), CB_2, is most abundant on cells of the immune system and is not generally found in the brain.[43, 124] Although no other receptor subtypes have been identified, there is a genetic variant known as CB_1A (such variants are somewhat different proteins that have been produced by the same genes via alternative processing). In some cases, proteins produced via alternative splicing have different effects on cells. It is not yet known whether there are any functional differences between the two, but the structural differences raise the possibility.

CB_1 and CB_2 are similar, but not as similar as members of many other receptor families are to each other. On the basis of a comparison of the sequence of amino acids that make up the receptor protein, the similarity of the CB_1 and CB_2 receptors is 44 percent (figure 2.2). The differences between the two receptors indicate that it should be possible to design therapeutic drugs that would act only on one or the other receptor and thus would activate or attenuate (block) the appropriate cannabinoid receptors. This offers a powerful method for producing biologically selective effects. In spite of the difference between the receptor subtypes, most cannabinoid compounds bind with similar affinity[b] to both CB_1 and CB_2 receptors. One exception is the plant-derived compound, cannabinol, which shows greater binding affinity for CB_2 than for CB_1,[112] although another research group has failed to substantiate that observation.[129] Other exceptions include the synthetic compound, WIN 55,212-2, which shows greater affinity for CB_2 than CB_1, and the endogenous ligands, anandamide and 2-AG, which show greater affinity for CB_1 than CB_2.[43] The search for compounds that bind to only one or the other of the cannabinoid receptor types has been under way for several years and has yielded a number of compounds that are useful research tools and have potential for medical use.

Cannabinoid receptors have been studied most in vertebrates, such as rats and mice. However, they are also found in invertebrates, such as leeches and mollusks.[156] The evolutionary history of vertebrates and invertebrates diverged more than 500 million years ago, so cannabinoid receptors appear to have been conserved throughout evolution at least this long. This suggests that they serve an important and basic function in animal physiology. In general, cannabinoid receptor molecules are similar among different species.[124] Thus, cannabinoid receptors likely fill many similar functions in a broad range of animals, including humans.

---

[b] *Affinity* is a measure of how avidly a drug binds to a receptor. The higher the affinity of a drug, the higher its potency; that is, lower doses are needed to produce its effects.

The Endogenous Cannabinoid System

For any drug for which there is a receptor, the logical question is, "Why does this receptor exist?" The short answer is that there is probably an endogenous agonist (that is, a compound that is naturally produced in the brain) that acts on that receptor. The long answer begins with a search for such compounds in the area of the body that produce the receptors and ends with a determination of the natural function of those compounds. So far, the search has yielded several endogenous compounds that bind selectively to cannabinoid receptors. The best studied of them are anandamide[37] and arachidonyl glycerol (2-AG).[108] However, their physiological roles are not yet known.

Initially, the search for an endogenous cannabinoid was based on the premise that its chemical structure would be similar to that of THC; that was reasonable, in that it was really a search for another "key" that would fit into the cannabinoid receptor "keyhole," thereby activating the cellular message system. One of the intriguing discoveries in cannabinoid biology was how chemically different THC and anandamide are. A similar search for endogenous opioids (endorphins) also revealed that their chemical structure is very different from the plant-derived opioids, opium and morphine.

Further research has uncovered a variety of compounds with quite different chemical structures that can activate cannabinoid receptors (table 2.2 and figure 2.4). It is not yet known exactly how anandamide and THC bind to cannabinoid receptors. Knowing this should permit more precise design of drugs that selectively activate the endogenous cannabinoid systems.

Anandamide

The first endogenous cannabinoid to be discovered was arachidonylethanolamine, named anandamide from the Sanskrit word *ananda*, meaning "bliss."[37] Compared with THC, anandamide has only moderate affinity for CB_1, and is rapidly metabolized by amidases (enzymes that remove amide groups). Despite its short duration of action, anandamide shares most of the pharmacological effects of THC.[37, 152] Rapid degradation of active molecules is a feature of neurotransmitter systems that allows them control of signal timing by regulating the abundance of signaling molecules. It creates problems for interpreting the results of many experiments and might explain why *in vivo* studies with anandamide injected into the brain have yielded conflicting results.

Anandamide appears to have both central (in the brain) and peripheral (in the rest of the body) effects. The precise neuroanatomical localization of anandamide and the enzymes that synthesize it are not yet known. This information will provide

essential clues to the natural role of anandamide and an understanding of the brain circuits in which it is a neurotransmitter. The importance of knowing specific brain circuits that involve anandamide (and other endogenous cannabinoid ligands) is that such circuits are the pivotal elements for regulating specific brain functions, such as mood, memory, and cognition. Anandamide has been found in numerous regions of the human brain: hippocampus (and parahippocampic cortex), striatum, and cerebellum; but it has not been precisely identified with specific neuronal circuits. CB_1 receptors are abundant in these regions, and this further implies a physiological role for endogenous cannabinoids in the brain functions controlled by these areas. But, substantial concentrations of anandamide are also found in the thalamus, an area of the brain that has relatively few CB_1 receptors.[124]

Anandamide has also been found outside the brain. It has been found in spleen, which also has high concentrations of CB_2 receptors; and small amounts have been detected in heart.[44]

In general, the affinity of anandamide for cannabinoid receptors is only one-fourth to one-half that of THC (see table 2.3). The differences depend on the cells or tissue that are tested and on the experimental conditions, such as the binding assay used (reviewed by Pertwee[124]).

The molecular structure of anandamide is relatively simple, and it can be formed from arachidonic acid and ethanolamine. Arachidonic acid is a common precursor of a group of biologically active molecules known as eicosanoids, including prostaglandins.[c] Although anandamide can be synthesized in a variety of ways, the physiologically relevant pathway seems to be through enzymatic cleavage of *N*-arachidonyl-phosphatidyl-ethanolamine (NAPE), which yields anandamide and phosphatidic acid (reviewed by Childers and Breivogel[27]).

Anandamide can be inactivated in the brain via two mechanisms. In one, anandamide is enzymatically cleaved to yield arachidonic acid and ethanolamine—the reverse of what was initially proposed as its primary mode of synthesis. In the other, it is inactivated through neuronal uptake—i.e., by being transported into the neuron, which prevents its continuing activation of neighboring neurons.

[c] Eicosanoids all contain a chain of 20 carbon atoms, and are named after *eikosi*, the Greek word for twenty.

Table 2.2 Compounds that bind to cannabinoid receptors

Compounds That Bind to Cannabinoid Receptors[d]

Compound	Properties
	***Agonists** (Receptor Activators)*
Plant-derived compounds	
Δ^9-THC	Main psychoactive cannabinoid in the marijuana plant; largely responsible for psychological and physiological effects. (Except in discussions of the different forms of THC, THC is used as a synonym for Δ^9-THC.)
Δ^8-THC	Slightly less potent than Δ^9-THC and much less abundant in the marijuana plant, but otherwise similar.
11-0H-Δ^9-THC	Bioactive compound formed when the body breaks down Δ^9-THC. Presumed to be responsible for some of the effects of marijuana.
Cannabinoid agonists found in animals	
anandamide (arachidonyl-ethanolamide)	Found in animals ranging from mollusks to mammals. Appears to be primary endogenous cannabinoid agonist in mammals. Chemical structure very different from plant cannabinoids, and related to prostaglandins.
2-AG (arachidonyl glycerol)	Endogenous agonist. Structurally similar to anandamide. More abundant but less potent than anandamide.
THC analogues	
dronabinol	Synthetic THC. Marketed in the US under the name Marinol® for nausea associated with chemotherapy and for AIDS-related wasting.
nabilone	THC analogue. Marketed in the UK under the name Cesamet® for the same indications as dronabionol.
CP 55,940	Synthetic cannabinoid; *THC analogue*; that is, it is structurally similar to THC
levonantradol	THC analogue.
HU-210	THC analogue, 100-800 fold greater potency than THC.[97]
Chemical structure unlike THC or anandamide	
WIN-55,212	Chemical structure different from known cannabinoids, but binds to both cannabinoid receptors. Chemically related to cyclo-oxygenase inhibitors, which include antiinflammatory drugs.
	***Antagonists** (Receptor Blockers)*
SR 141716A	Synthetic CB_1 antagonist; developed in 1994.[132]
SR 144528	Synthetic CB_2 antagonist; developed in 1997.[133]

[d] *Sources*: Mechoulam et al. 1998[109], Felder and Glass 1998[43]; BMA 1997[17]

Figure 2.4 Chemical structures of cannabinoid agonists

Figure 2.4 Chemical structures of compounds that bind to cannabinoid receptors

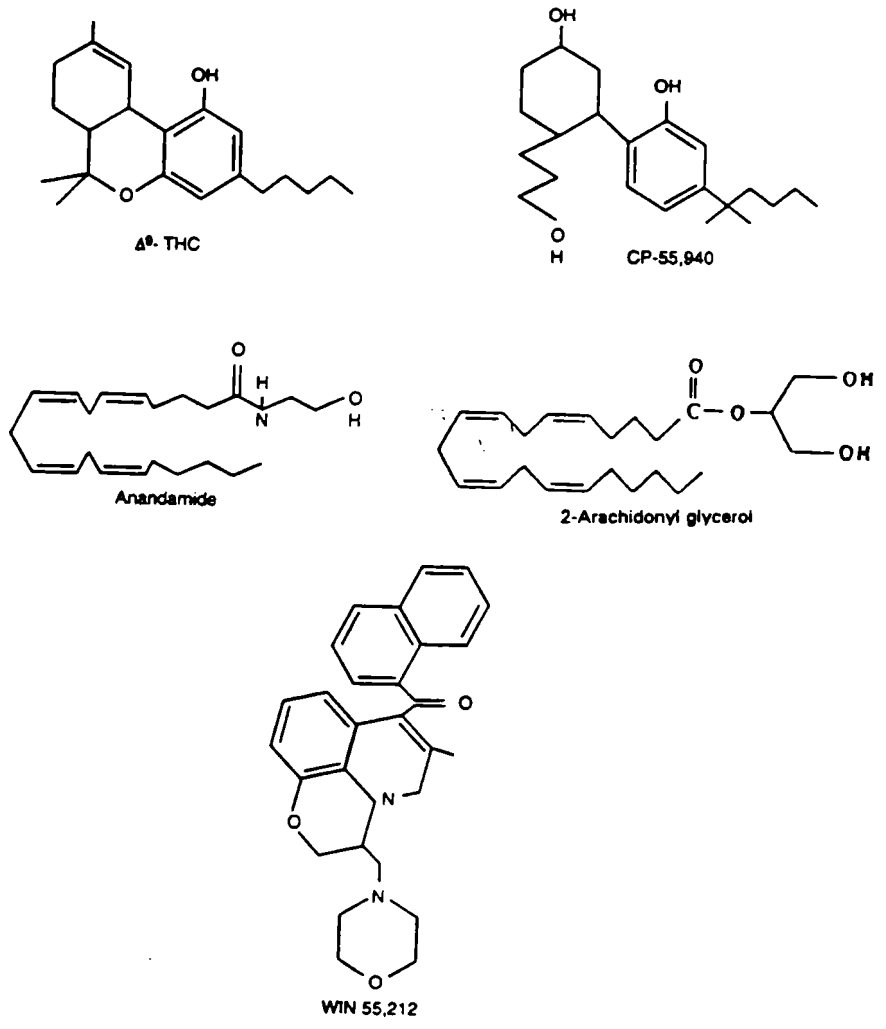


Figure Legend. Selected cannabinoid agonists, or molecules that bind to and activate cannabinoid receptors. **THC** is the primary psychoactive molecule found in marijuana. **CP 55,940** is a THC-analogue; that is, its chemical structure is related to THC. **Anandamide** and **2-arachidonyl glycerol (2-AG)** are endogenous molecules, meaning they are naturally produced in the body. Although the chemical structure of **WIN 55,212** is very different from either THC or anandamide, it is also a cannabinoid agonists.

Table 2.3 Comparison of cannabinoid receptor agonists

Potency can be measured in a variety of ways, from behavioral to physiological to cellular. This table shows potency in terms of receptor binding, which is the most broadly applicable to the many possible actions of cannabinoids. For example, anandamide binds to the cannabinoid receptor only about half as avidly as does THC. Measures of potency might include effects on activity (behavioral) or hypothermia (physiological).

The apparently low potency of 2-AG may, however, be misleading. A study published late in 1998, reports that 2-AG is found with two other, closely related compounds that, by themselves, are biologically inactive; but in the presence of those two compounds, 2-AG is only three times less active than THC.[9] Further, 2-AG is much more abundant than anandamide, although the biological significance of this remains to be determined.

Receptor Binding in Brain Tissue[124]	
Compound	***Potency Relative to THC***
CP 55,940	59
Δ^9-THC	1
Anandamide	0.47
2-AG	0.08

Other endogenous agonists

Several other endogenous compounds that are chemically related to anandamide and that bind to cannabinoid receptors have been discovered, one of which is 2-AG.[108] 2-AG is closely related to anandamide and is even more abundant in the brain. At time of this writing, all known endogenous cannabinoid receptor agonists (including anandamide) are eicosanoids, which are arachidonic acid metabolites. Arachidonic acid (a free fatty acid) is released via hydrolysis of membrane phospholipids.

Other, non-eicosanoid, compounds that bind cannabinoid receptors have recently been isolated from brain tissue, but they have not been identified, and their biological effects are under investigation. This is a fast-moving field of research, and no review over six months old can be fully up-to-date.

The endogenous compounds that bind to cannabinoid receptors probably perform a broad range of natural functions in the brain. This neural signaling system is rich and complex, and has many subtle variations, many of which await discovery. In the next few years, much more will likely by known about these naturally-occurring cannabinoids.

Some effects of cannabinoid agonists are receptor-independent. For example, both THC and CBD can be neuroprotective through their antioxidative activity; that is, they can reduce the toxic forms of oxygen that are released when cells are under stress.[54] Other likely examples of receptor-independent cannabinoid activity are modulation of activation of membrane-bound enzymes (e.g., ATPase), arachidonic acid release, and perturbation of membrane lipids. An important caution in interpreting those reports is that concentrations of THC or CBD used in cellular studies, such as these, are generally much higher than the concentrations of THC or CBD in the body that would likely be achieved by smoking marijuana.

Novel targets for therapeutic drugs

Drugs that alter the natural biology of anandamide, or other endogenous cannabinoids, might have therapeutic uses (table 2.4). For example, drugs that selectively inhibit neuronal uptake of anandamide would increase the brain's own natural cannabinoids and mimic some of the effects of THC. A number of important psychotherapeutic drugs act by inhibiting neurotransmitter uptake. For example, antidepressants like fluoxetine (Prozac®) inhibit serotonin uptake, and are known as selective serotonin reuptake inhibitors, or SSRI's. Another way to alter levels of endogenous cannabinoids would be to develop drugs that act on the enzymes involved in anandamide synthesis. Some anti-hypertensive drugs work by inhibiting

enzymes involved in the synthesis of endogenous hypertensive agents. For example, anti-converting enzyme (ACE) inhibitors are used in hypertensive patients to interfere with the conversion of angiotensin I, which is inactive, to the active hormone, angiotensin II.

Table 2.4. Cellular processes that can be targeted for drug development

TABLE LEGEND. Endogenous cannabinoids are part of a cellular signalling system. This table lists categories of natural processes that regulate such systems, and shows the results of altering those processes.

Cellular Processes That Can Be Targeted for Drug Development

Drug action		*Biological Result*
Block synthesis	Synthesis of bioactive compounds is a continuous process and is one means by which concentrations of that compound are regulated.	**Weaker signal**, due to decreased agonist concentration.
Inhibit degradation	Chemical breakdown is one method the body uses to inactivate endogenous substances.	**Stronger signal**, due to increased agonist concentration increased.
Facilitate neuronal uptake	Neuronal uptake is one of the natural ways in which a receptor agonist is inactivated.	**Stronger signal**, due to increased amount of time during which agonist is present in the synapse where it can stimulate the receptor.

Sites of Action

Cannabinoid receptors are particularly abundant in some areas of the brain. The normal biology and behavior associated with these brain areas are consistent with the behavioral effects produced by cannabinoids (table 2.5 and figure 2.5). The highest receptor density is found in cells of the *basal ganglia* that project locally and to other brain regions. These cells include the *substantia nigra pars reticulata*, *entopeduncular nucleus*, and *globus pallidus*, regions that are generally involved in coordinating body movements. Patients with Parkinson and Huntington disease tend to have impaired functions in these regions.

CB_1 receptors are also abundant in the putamen, part of the relay system within the basal ganglia that regulates body movements; the cerebellum, which coordinates body movements; the hippocampus, which is involved in learning, memory, and response to stress; and the cerebral cortex, which is concerned with the integration of higher cognitive functions.

CB_1 receptors are found on various parts of neurons, including the axon, cell bodies, terminals, and dendrites.[57, 165] Dendrites are generally the "receiving" part of a neuron, and receptors on axons or cell bodies generally modulate other signals. Axon terminals are the "sending" part of the neuron.

Cannabinoids—like the inhibitory neurotransmitter γ-aminobutyric acid (GABA)—tend to inhibit neurotransmission, although the results are somewhat variable. In some cases, cannabinoids diminish the effects of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA);[144] in other cases, cannabinoids can augment the effects of GABA.[120] The effect of activating a receptor depends on where it is found on the neuron: if cannabinoid receptors are presynaptic (on the "sending" side of the synapse) and inhibit the release of GABA, cannabinoids would diminish GABA effects; the net effect would be stimulation. However, if cannabinoid receptors are postsynaptic (on the "receiving" side of the synapse) and on the same cell as GABA receptors, they will probably mimic the effects of GABA; in that case, the net effect would be inhibition.[120, 144, 160]

CB_1 is the predominant brain cannabinoid receptor. CB_2 receptors have not generally been found in the brain, but there is one isolated report suggesting some in mouse cerebellum.[150] CB_2 is found primarily on cells of the immune system. CB_1 receptors are also found in immune cells, but CB_2 is considerably more abundant there (table 2.6) (reviewed by Kaminski[80] in 1998).

As can be appreciated in the next section, the presence of cannabinoid systems in key brain regions is strongly tied to the functions and pathology associated with those regions. The clinical value of cannabinoid systems is best understood in the context of the biology of these brain regions.

Table 2.5 Brain regions in which cannabinoid receptors are abundant[e]

Brain Region	Functions Associated with Region
Brain regions in which cannabinoid receptors are abundant	
Basal ganglia	Movement control
Substantia nigra pars reticulata Entopeduncular nucleus Globus pallidus Putamen	
Cerebellum	Body-movement coordination
Hippocampus	Learning and memory, stress
Cerebral cortex, especially cingulate, frontal, and parietal regions	Higher cognitive functions
Nucleus accumbens	Reward center
Brain regions in which cannabinoid brain receptors are moderately concentrated	
Hypothalamus	Body housekeeping functions (body-temperature regulation, salt and water balance, reproductive function)
Amygdala	Emotional response, fear
Spinal cord	Peripheral sensation, including pain
Brain Stem	Sleep and arousal, temperature regulation, motor control
Central gray	Analgesia
Nucleus of the solitary tract	Visceral sensation, nausea and vomiting

[e] Based on reviews by Pertwee 1997[124] and Herkenham 1995[57]; This table will be accompanied by a figure.

Figure 2.5. Location of brain regions in which cannabinoid receptors are abundant.

See table 2.5 for summary of functions associated with those regions.

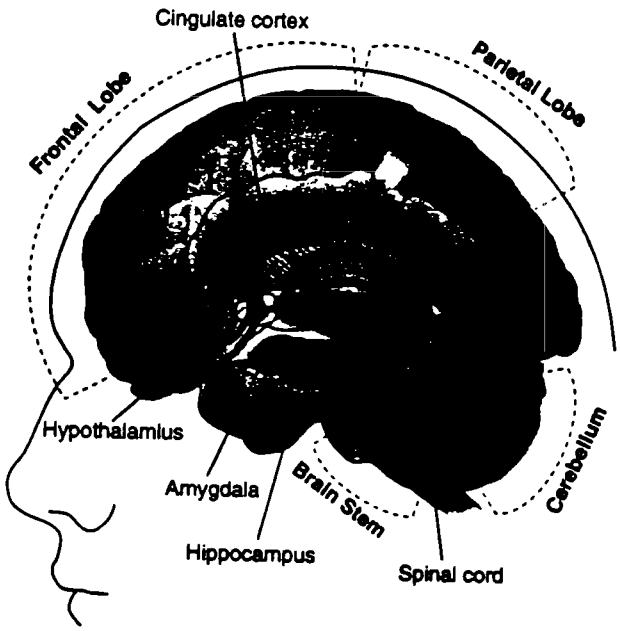


Figure with lobes
Medical Use of Marijuanna

Table 2.6 Summary table of cannabinoid receptors

	CB_1	CB_2
Effects of various cannabinoids		
Δ^9-THC	Agonist	Weak antagonist
Anandamide	Agonist	Agonist
Cannabinol (CBN)	Weak agonist	Agonist; greater affinity for CB_2 than for CB_1
Cannabidiol (CBD)	Does not bind to receptor	Does not bind to receptor
Receptor distribution		
Areas of greatest abundance	Brain	Immune system, especially B cells and natural killer cells

Cannabinoid Receptors and Brain Functions

Motor effects

Marijuana affects psychomotor performance in humans. The effects depend both on the nature of the task and the experience with marijuana. In general, effects are clearest in steadiness (body sway and hand steadiness) and in motor tasks that require attention. The results of testing cannabinoids in rodents are much clearer.

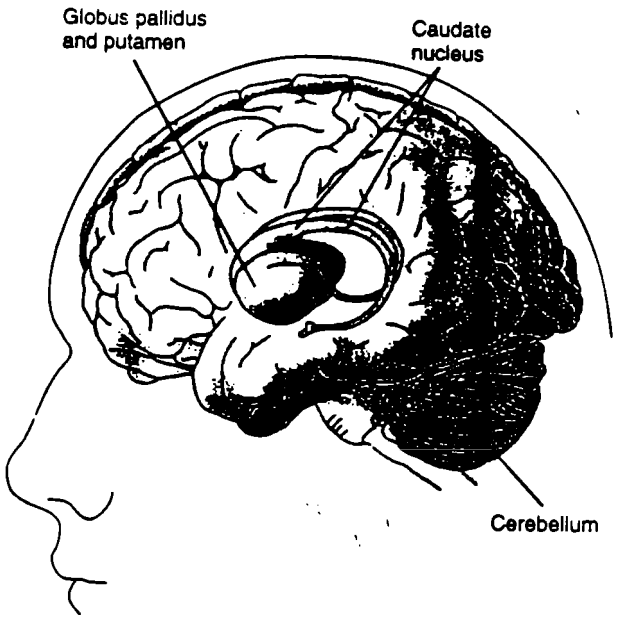
Cannabinoids clearly affect movement in rodents, but the effects depend on the dose: low doses stimulate and higher doses inhibit locomotion.[111, 159] Cannabinoids mainly inhibit the transmission of neural signals, and they inhibit movement through their actions on the basal ganglia and cerebellum, where cannabinoid receptors are particularly abundant (figure 2.6a and 2.6b). Cannabinoid receptors are also found in the neurons that project from the striatum and subthalamic nucleus, which inhibit and stimulate movement, respectively.[58, 101]

Cannabinoids decrease both the inhibitory and stimulatory inputs to the substantia nigra, and therefore might provide dual regulation of movement at this nucleus. In the substantia nigra, cannabinoids decrease transmission from both the striatum and the subthalamic nucleus.[141] The globus pallidus has been implicated in mediating the cataleptic effects of large doses of cannabinoids in rats.[126] (Catalepsy is a condition of diminished responsiveness usually characterized by trancelike states and waxy rigidity of the muscles.) Several other brain regions—the cortex, the cerebellum, and the neural pathway from cortex to striatum—are also involved in the control of movement and contain abundant cannabinoid receptors.[52, 59, 101] They are, therefore, possible additional sites that might underlie the effects of cannabinoids on movement.

Figure 2.6a & b Diagrams showing motor regions of the brain

Figure 2.6. Basal ganglia are a group of three brain regions, or nuclei—**caudate**, **putamen**, and **globus pallidus**. Figure 2.6a is a 3-dimensional view showing the location of those nuclei in the brain. Figure 2.6b shows those structures in a vertical cross-sectional view. The major output pathways of the basal ganglia arise from the globus pallidus and pars reticula of the **substantia nigra**. Their main target is the **thalamus**.

a.



b.

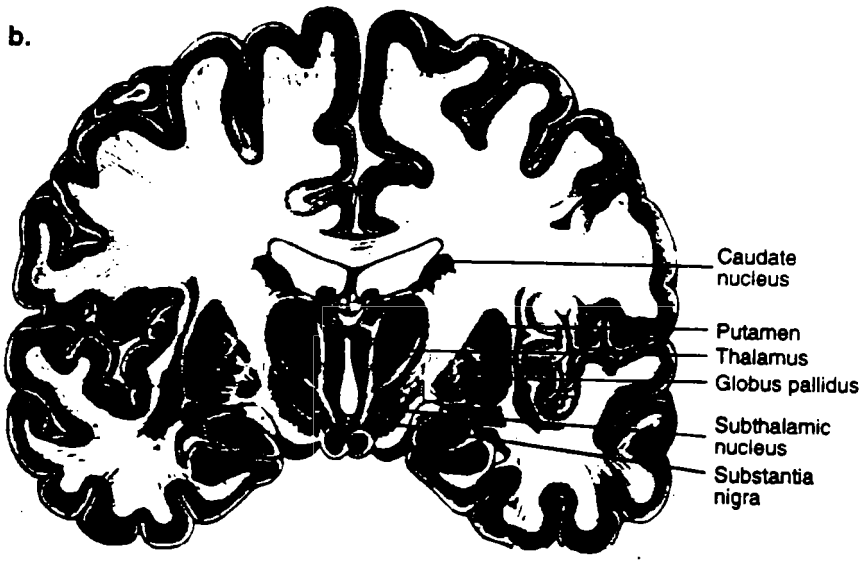


Figure a. and b.

Memory effects

One of the primary effects of marijuana in humans is disruption of short-term memory.[68] That is consistent with the abundance of CB_1 receptors in the hippocampus, the brain region most closely associated with memory. The effects of THC resemble a temporary hippocampal lesion.[63] Deadwyler and colleagues have demonstrated that cannabinoids decrease neuronal activity in the hippocampus and its inputs.[23, 24, 83] *In vitro*, several cannabinoid ligands and endogenous cannabinoids can block the cellular processes associated with memory formation.[29, 30, 116, 157, 163] Furthermore, cannabinoid agonists inhibit release of several neurotransmitters: acetylcholine from the hippocampus,[49, 50, 51] norepinephrine from human and guinea pig (but not rat or mouse) hippocampal slices,[143] and glutamate in cultured hippocampal cells.[144] Cholinergic and noradrenergic neurons project into the hippocampus, but circuits within the hippocampus are glutamatergic.[f] Thus, cannabinoids could block transmission both into and within the hippocampus by blocking presynaptic neurotransmitter release.

Pain

After nausea and vomiting, chronic pain was the condition cited most often to the IOM study team as a medical use for marijuana. Recent research presented below has shown intriguing parallels with anecdotal reports of the modulating effects of cannabinoids on pain—both the effects of cannabinoids acting alone and the effects of their interaction with opioids.

Behavioral Studies

Cannabinoids reduce reactivity to acute painful stimuli in laboratory animals. In rodents, cannabinoids reduced the responsiveness to pain induced through various stimuli, including thermal, mechanical, and chemical stimuli.[12, 19, 46, 72, 96, 154, 174] Cannabinoids were comparable with opiates in potency and efficacy in these experiments.[12, 72]

Cannabinoids are also effective in rodent models of chronic pain. Herzberg and coworkers found that cannabinoids can block allodynia and hyperalgesia

[f] Neurons are often defined by the primary neurotransmitter released at their terminals. Thus, *cholinergic* neurons release acetylcholine, *noradrenergic* neurons release noradrenalin (also known as norepinephrine), and *glutamergic* neurons release glutamate.

associated with neuropathic pain in rats.[117] (Allodynia refers to pain elicited by stimuli that are normally innocuous; hyperalgesia refers to abnormally increased reactivity to pain.) This is an important advance, because chronic pain frequently results in a series of neural changes that increase suffering due to allodynia, hyperalgesia, and spontaneous pain; furthermore, some chronic pain syndromes are not amenable to therapy, even with the most powerful narcotic analgesics.[10]

Pain perception is controlled mainly by neurotransmitter systems within the central nervous system, and cannabinoids clearly play a role in the control of pain in those systems.[45] However, pain-relieving and pain-preventing mechanisms also occur in peripheral tissues, and endogenous cannabinoids appear to play a role in peripheral tissues. Thus, the different cannabinoid receptor subtypes might act synergistically. Experiments in which pain is induced by injecting dilute formalin into a mouse's paw have shown that anandamide and palmitylethanolamide (PEA) can block peripheral pain.[22, 73] [22] Anandamide acts primarily at the CB_1 receptor, whereas PEA has been proposed as a possible CB_2 agonist; in short, there might be a biochemical basis for their independent effects. When injected together, the analgesic effect is stronger than that of either alone. That suggests an important strategy for the development of a new class of analgesic drug: a mixture of CB_1 and CB_2 agonists. Because there are few, if any, CB_2 receptors in the brain, it might be possible to develop drugs that enhance the peripheral analgesic effect while minimizing the psychological effects.

Neural sites of altered responsiveness to painful stimuli

The brain and spinal cord mediate cannabinoid analgesia. A number of brain areas participate in cannabinoid analgesia and support the role of descending pathways (neural pathways that project from the brain to the spinal cord).[103, 105] Although more work is needed to produce a comprehensive map of the sites of cannabinoid analgesia, it is clear that the effects are limited to particular areas, most of which have an established role in pain.

Specific sites where cannabinoids act to affect pain processing include the periaqueductal gray,[104] the rostral ventral medulla,[105, 110] and the thalamic nucleus submedius,[102] the thalamic ventroposterolateral nucleus,[102] dorsal horn of the spinal cord,[64, 65] and peripheral sensory nerves.[64, 65, 66, 131] Those nuclei also participate in opiate analgesia. Although similar to opiate analgesia, cannabinoid analgesia is not mediated by opioid receptors; morphine and cannabinoids sometimes act synergistically, and opioid antagonists generally have no effect on cannabinoid-induced analgesia.[171] However, a *kappa*-receptor antagonist has been shown to attenuate spinal, but not supraspinal, cannabinoid analgesia.[153, 170, 171] (*Kappa* opioid receptors constitute one of the three major types of opioid receptors; the other two types are *mu* and *delta* receptors.)

Neurophysiology and neurochemistry of cannabinoid analgesia

Because of the marked effects of cannabinoids on motor function, behavioral studies in animals alone cannot provide sufficient grounds for the conclusion that cannabinoids depress pain perception. Motor behavior is typically used to measure responses to pain, but this behavior is itself affected by cannabinoids. Thus, experimental results include an unmeasured combination of cannabinoid effects on motor and pain systems. The effects on specific neural systems, however, can be measured at the neurophysiological and neurochemical levels. Cannabinoids decrease the response of immediate-early genes (genes that are activated in the early or immediate stage of response to a broad range of cellular stimuli) to noxious stimuli in spinal cord, decrease response of pain neurons in the spinal cord, and decrease the responsiveness of pain neurons in the ventral posterolateral nucleus of the thalamus.[67, 102] Those changes are mediated by cannabinoid receptors, selective for pain neurons, and unrelated to changes in skin temperature or depth of anesthesia, and they follow the time course of the changes in behavioral responses to painful stimuli, but not the time course of motor changes.[67] Cannabinoids also modulate the responses of on-cells and off-cells in the rostral ventral medulla in a manner that is very similar to that of morphine.[55, 110] These cells control pain transmission at the level of the spinal cord.

Endogenous cannabinoids modulate pain

Endogenous cannabinoids can modulate pain sensitivity, through both central and peripheral mechanisms. For example, animal studies have shown that pain sensitivity can be increased when endogenous cannabinoids are blocked from acting at CB_1 receptors[22, 62, 110, 130, 158] Administration of cannabinoid antagonists in either the spinal cord[130] or paw[22] increase the sensitivity of animals to pain. In addition, there is evidence that cannabinoids also act at the site of injury to reduce peripheral inflammation[131]

Current data suggest the endogenous cannabinoid analgesic system might offer protection against the long-lasting central hyperalgesia and allodynia that sometimes follow skin or nerve injuries[130, 158] These results raise the possibility that therapeutic interventions that alter the levels of endogenous cannabinoids might be useful for managing pain in humans.

Chronic Effects of THC

Most substances of abuse produce tolerance, physical dependence, and withdrawal symptoms. *Tolerance* is the most common response to repetitive use of the same drug (not necessarily a drug of abuse) and is the condition in which, after repeated exposure to a drug, increasing doses are needed to achieve the same effect. *Physical dependence* develops as a result of tolerance (adaptation) produced by a resetting of homeostatic mechanisms in response to repeated drug use. It is important to reiterate that the phenomena of tolerance, dependence, and withdrawal are not associated uniquely with drugs of abuse. Many medications that are not addicting can produce these types of effects; examples of such medications include clonidine, propranolol, and tricyclic antidepressants. The following sections discuss what is known about the biological mechanisms that underlie on tolerance, reward, and dependence; clinical studies about those topics are discussed in chapter 3.

Tolerance

Chronic administration of cannabinoids to animals results in tolerance to many of the acute effects of THC, including memory disruption,[34] decreased locomotion,[2, 119] hypothermia,[42, 125] neuroendocrine effects,[134] and analgesia.[4] Tolerance also develops to the cardiovascular and psychological effects of THC and marijuana in humans (see also discussion in chapter 3).[55, 56, 76]

Tolerance to cannabinoids appears to result from both *pharmacokinetic* (how the drug is absorbed, distributed, metabolized, and excreted) and *pharmacodynamic* (how the drug interacts with target cells) changes. Chronic treatment with the cannabinoid agonist, CP 55,940, increases the activity of the microsomal cytochrome P450 oxidative system.[31] Because this is the system through which drugs are metabolized in the liver, this suggests pharmacokinetic tolerance. Chronic cannabinoid treatments also produce changes in brain cannabinoid receptors and cannabinoid receptor mRNA levels, indicating that pharmacodynamic effects are important, as well.

Most studies have found that brain cannabinoid receptor levels usually decrease after prolonged exposure to agonists,[42, 119, 136, 138] although some studies have reported increases[137] or no changes[2] in receptor binding in brain. Differences among studies may be due to the particular agonist tested, the assay used, brain region examined, or treatment time. For example, the THC analogue, levonantradol, produces a greater desensitization of adenylyl cyclase inhibition than THC in cultured neuroblastoma cells,[40] which may be explained by the efficacy differences between these two agonists.[18, 147] Furthermore, a time course study revealed differences in the rates and magnitudes of receptor down-regulation across brain

regions.[16] These findings suggest that tolerance to different effects of cannabinoids develops at different rates.

Chronic treatment with THC also produces variable effects on cannabinoid-mediated signal transduction systems. Chronic THC treatment produces significant desensitization of cannabinoid-activated G-proteins in a number of rat brain regions.[147] Moreover, the time course of this desensitization varies across brain regions.[16]

It is difficult to extend the findings of these short-term animal studies to human marijuana use. In order to simulate long-term use, the doses used in animal studies are higher than normally achieved by smoking marijuana. For example, the average human will feel "high" after a 0.06 mg/kg injection of THC,[118] compared to 10-20 mg/kg/day used in many chronic studies in rats. At the same time, doses of marijuana needed to observe behavioral changes in rats (usually changes in locomotor behavior) are substantially higher than doses at which people feel "high." In addition, pharmacokinetics of THC distribution in the body are dramatically different between rats and humans, as well as being highly dependent on the THC delivery system—that is, whether it is inhaled, injected, or swallowed. Nevertheless, it is likely that some of the same biochemical adaptations to chronic cannabinoid administration occur in both laboratory animals and humans, but the magnitude of the effects in humans may be smaller in proportion to the respective doses used.

Reward and dependence

Experimental animals that are given the opportunity to self-administer cannabinoids generally do not choose to do so, which has led to the conclusion that they are not reinforcing and rewarding.[38] However, behavioral[95] and brain stimulation[94] studies have shown that THC can be rewarding to animals. The behavioral study used a "place-preference" test, in which an animal is given repeated doses of a drug in one place, and is then given a choice between a place where it did not receive the drug and one where it did; the animals chose the place where they received the THC. These rewarding effects are highly dose-dependent. In all models studied, cannabinoids are only rewarding at mid-range; doses that are too low are not rewarding, doses that are too high can be aversive. Mice will self-administer the cannabinoid agonist, WIN 55,212, but only at low doses.[106] This effect is specifically mediated by CB_1 receptors, and indicates that stimulation of those receptors is rewarding to the mice. Antagonism of cannabinoid receptors is also rewarding in rats; in conditioned place-preference tests, animals show a preference for the place they receive the cannabinoid antagonist, SR141716A, at both low and high doses.[140] Cannabinoids increase dopamine levels in the mesolimbic dopamine system of rats, a pathway associated with reinforcement.[25, 39, 161] However, the

mechanism by which THC increases dopamine levels appears to be different from that of other abused drugs[51] [g] (see chapter 3 for further discussion of reinforcement).

Physical dependence on cannabinoids has only been observed under experimental conditions of "precipitated withdrawal" in which animals are first treated chronically with cannabinoids and then given the CB_1 antagonist, SR141716A.[3, 166] The addition of the antagonist accentuates any withdrawal effect by competing with the agonist at receptor sites; that is, the antagonist helps to clear agonists off and keep them off receptor sites. This suggests that, under normal cannabis use, the long half-life and slow elimination from the body of THC, and the residual bioactivity of its metabolite, 11-OH -THC, may prevent significant abstinence symptoms. The precipitated withdrawal effects produced by SR141716A have some of the characteristics of opiate withdrawal, but are not affected by opioid antagonists and affect motor systems differently. An earlier study with monkeys also suggested that abrupt cessation of chronic THC is associated with withdrawal symptoms.[8] Monkeys in that study were trained to work for food after which they were given THC on a daily basis; when the investigators stopped administering THC, the animals stopped working for food.

A study in rats indicated that the behavioral cannabinoid withdrawal syndrome correlates with stimulation of central amygdaloid corticotropin-releasing hormone release, consistent with the consequences of withdrawal from other abused drugs.[135] However, the withdrawal syndrome for cannabinoids and the corresponding increase in corticotropin-releasing hormone are only observed following administration of the CB_1 antagonist, SR 141716A, to cannabinoid-tolerant animals;[3, 166] The implications of data based on precipitated withdrawal in animals for human cannabinoid abuse have not been established.[166] Furthermore, acute administration of THC also produces increases in corticotropin-releasing hormone and adrenocorticotropin release, both of which are stress-related hormones.[71] This set of withdrawal studies may explain the generally aversive effects of cannabinoids in animals, and may indicate that the increase in corticotropin-releasing hormone is merely a rebound effect. Thus, while cannabinoids appear to be conforming to some of the neurobiological effects of other drugs abused by humans, the underlying mechanisms of these actions and their significance in determining the reinforcement and dependence liability of cannabinoids in humans remain undetermined.

---

[g] These increases in dopamine are due to increases in the firing rate of dopamine cells in the ventral tegmental area by Δ^9-THC[47]. However, these increases in firing rate in the ventral tegmental area could not be explained by increases in the firing of the A10 dopamine cell group, where other abused drugs have been shown to act[51].

Cannabinoids and the Immune System

The human body protects itself from invaders such as bacteria and viruses through the elaborate and dynamic network of organs and cells referred to as the immune system (see box on Cells of the Immune System).

Cannabinoids, especially THC, can modulate the function of immune cells in various ways—in some cases enhancing, and in others diminishing the immune response[85] (summarized in table 2.7). However, the natural function of the cannabinoids in the immune system is not known. Immune cells respond to cannabinoids in a variety of ways, depending upon experimental factors such as drug concentration, timing of drug delivery to leukocytes in relation to antigen stimulation, and the type of cell function analyzed. Although the chronic effects of cannabinoids on the immune system have not been studied, based on acute exposure studies in experimental animals it appears that the concentrations of THC which modulate immunological responses are higher than those required for psychoactivity.

Table 2.7 Effects of Cannabinoids on the Immune System

Drug tested	Cell Types Tested or Type of Animal Experiment	Drug Concentration [a]	Result	Reference
THC 2-AG 11-OH-THC CBN	Lymphocytes and splenocytes in vitro	0.1–30 μM	Higher doses suppress T cell proliferation	Luo, 1992; Pross,1992* Klein, 1985⌖; Specter,1990⚙ Lee, 1995* Herring, 1998
THC 2-AG	Lymphocytes and splenocytes	0.1–25 μM	Lower doses increase T cell proliferation in vitro	Luo,1992; Lee, 1995* Pross, 1992*
Anandamide	Splenocytes in vitro	1–25 μM	Little or no effect on T cell proliferation	Lee, 1995* Devane, 1992
THC, 11-OH-THC AG-2	Splenocytes in vitro	3–30 μM	Decrease B cell proliferation	Klein, 1985⌖ Lee, 1995*
THC CP 55,940 WIN 55,212-2	Lymphocytes in vitro	0.1–100nM [0.0001–0.1 uM]	Increase B cell proliferation	Derocq, 1995
THC	Mice were injected with drug	> 5 mg/kg	Antibody production was suppressed	Baczynsky, 1983 Schatz, 1993
HU-210		> 0.05 mg/kg		Titishov, 1989
THC 11-OH-THC CBD CP55,940 CBN	Splenocytes in vitro	1–30μM	Antibody production was suppressed	Klein, 1990 Baczynsky, 1983 Kaminski, 1994 Kaminski, 1992 Herring, 1998
THC	Rodents were injected with drug	3mg/kg/day for 25days–40mg/kg/day for 2 days	Repeated low doses or a high dose of THC suppress the activity of natural killer cells	Patel, 1985 Klein,1987
THC 11-OH-THC	Natural killer cells in vitro	0.1–32 μM	Doses of ≥10 μM suppress natural killer cell cytolytic activity, doses <10 μM produced no effect	Klein, 1987 Luo,1989
THC	Peritoneal macrophages and monocytes	3–30 μM	Variable doses of THC suppress macophage functions in vitro	Lopez-Cepero, 1986 Specter, 1991 Tang, 1992

THC CBD	Mice injected with drug; in one case, in vitro tests done on spleens	> 5mg/kg for 4 days or 50 mg/kg every 5 days for up to 8 weeks	THC suppresses normal immune response; interferons failed to increase when exposed to cytokine inducer, while CBD had no suppressive effect	Cabral, 1986 Blanchard, 1986
THC CBD	Peripheral blood mononuclear cells in vitro	< 0.1 μM	Increased interferon production	Watzl, 1991
		30 μM	Decreases interferon production	

THC CBD	Splenocytes and T cells in vitro	10 μM	Both THC and CBD suppress IL-2 secretion and the number of IL-2 transcripts	Condie, 1996
THC	Phorbol myristate acetate differentiated macrophage in vitro	10-20 μM	Increase in tumor necrosis factor production and IL-1 supernatant bioactiviy	Shivers, 1994
THC	Endotoxin-activated macrophages in vitro	10-30 μM	Increase processing and release of IL-1 rather than cellular production of the IL-1	Zhu, 1994
THC	Peritoneal macrophages in vitro	10-30 μM	Increased IL-1 bioactivity	Klein, 1990

THC	Mice were injected with drug and either sublethal or lethal dose of *Legionalla pneumophilia*	8mg/kg given before and after bacteria infection	Cytokine-mediated septic shock and death occurs with exposure to sublethal dose of the bacteria	Klein, 1993 and 1994 Newton, 1994
		< 5 mg/kg doses, or one 8 mg/kg or 4 mg/kg dose given before bacteria infection	Survival occurs, but with greater susceptiblity to infection when challenged with bacteria and death when challenged with a lethal dose of bacteria	
THC	Immuno-deficient mice injected with drug and herpes simplex virus	100mg/kg before and after virus infection	Two high doses of THC potentiates the effects of herpes simplex and enhances the progression of death	Specter, 1991
		100 mg/kg before virus infection	A single dose did not promote death	

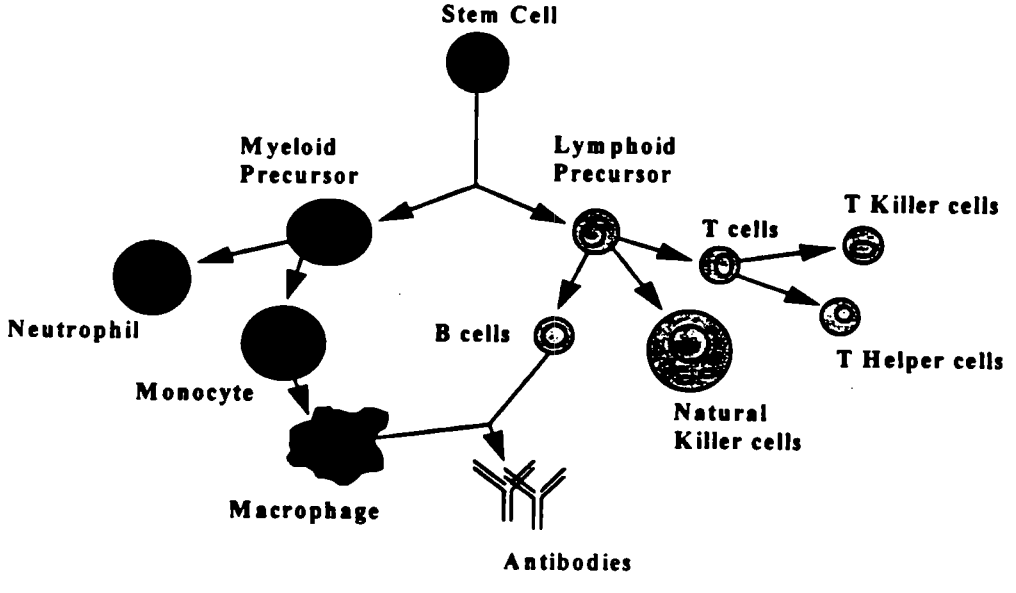
* cell density dependent; * mitogen dependent; ⊕ % serum dependent; ⊕ dependent on timing of drug exposure relative to mitogen exposure.

[a] Drug concentrations are given in the standard format of molarity (M). A one molar solution is the molecular weight of the compound (in grams) dissolved in 1 liter of water or other solvent. The molecular weight of THC is 314 so a 1 molar solution would be 314 grams of THC dissolved in 1 liter of solution, a 10 μM solution would be 3.14 mg THC/liter.

A 1-10 uM concentration will generally elicit a physiologically relevant response in immune cell cultures. Higher doses are often suspected of not being biologically meaningful, because they are a much larger dose than would ever be achieved in the body. The doses listed in this table are, for the most part, very high. See text for further discussion.

Cells of the Immune System

The various organs of the immune system are positioned throughout the body and include bone marrow, thymus, lymph nodes and spleen. The cells of the immune system consist of white blood cells, or leukocytes, which are formed in the bone marrow from stem cells—so-called because a great variety of cells descend from them (see below). There are two kinds of leukocytes: lymphocytes and phagocytes. *Lymphocytes* consist of B cells, T cells,[h] and natural killer cells (NK), and the major phagocytes include monocytes, macrophages and neutrophils. *Phagocytes* have many important roles in the immune response, but most significantly they initiate these responses by engulfing and digesting foreign substances (e.g., bacteria, viruses, foreign proteins), or antigens, that enter the body. Once digested, the antigen is exposed to specialized lymphocytes (i.e., B cells and T cells) so that antibodies and effector T cells can be produced to help destroy any remaining antigens in the body. *Antibodies* are proteins produced by B cells that bind to antigens and promote antigen destruction. Effector T cells include killer T cells which attack and kill antigen laden cells, and helper T cells, which secrete special proteins called cytokines that promote antigen elimination. Natural killer cells are specialized lymphocytes that are also activated by antigen to either kill infected targets or secrete immunoregulatory cytokines.



[h] The B and T refer to where the cells mature, either in the bone marrow (B) or thymus (T).

The CB_2 receptor gene, which is not expressed in the brain, is particularly abundant in immune tissues, with an expression level 10-100 times higher than that of CB_1. In spleen and tonsils, the CB_2 mRNA[i] content is equivalent to that of CB_1 mRNA in the brain.[48] The rank order, from high to low, of CB_2 mRNA levels in immune cells is B-cells > natural killer cells >> monocytes > polymorphonuclear neutrophil cells > T8 cells > T4 cells. In tonsils, the CB_2 receptors appear to be restricted to B-lymphocyte-enriched areas. In contrast, CB_1 receptors are mainly expressed in the central nervous system and, to a lower extent, in several peripheral tissues such as adrenal gland, heart, lung, prostate, uterus, ovary, testis, bone marrow, thymus and tonsils.

Cannabinoid Receptors and Intracellular Action in Immune Cells

CB_2 appears to be the predominant gene expressed in resting leukocytes.[78, 112] The level of CB_1 gene activity is normally low in resting cells but increases with cell activation.[32] Thus the CB_1 receptor might be important only when immune responses are stimulated, but the physiological relevance of this observation remains to be determined. Some of the cannabinoid effects observed in immune systems, especially at high drug concentrations, are likely mediated through non-receptor mechanisms, but these have not yet been identified.[4]

Ligand binding to either the CB_1 or CB_2 receptors inhibits adenylate cyclase, an enzyme that is responsible for cAMP production, and is, thus, an integral aspect of intracellular signal transduction (see figure 2.3).[53, 79, 91, 122, 139, 151, 167] Increases in intracellular cAMP concentrations lead to immune enhancement, while decreases lead to an inhibition of immune responses.[77] Cannabinoids inhibit the rise in intracellular cAMP that normally results from leukocyte activation, and this might be the pathway through which cannabinoids suppress immune cell functions.[28, 74, 167] In addition, cannabinoids activate other molecular pathways such as the nuclear factor-kB pathway and therefore these signals might be modified in drug treated immune cells.[33, 74]

[i] After a gene is transcribed it is often spliced and modified into mRNA, or message RNA. The CB-2 mRNA is the gene "message" that moves from the cell nucleus into the cytoplasm where it will be translated into the receptor protein.

T and B Cells

When stimulated by antigen, lymphocytes (see box on Cells of the Immune System) first proliferate and then mature or differentiate to become potent effector cells, such as B cells that release antibodies or T cells that release cytokines. The normal T cell proliferation that is seen when human lymphocytes and mouse splenocytes (spleen cells) are exposed to antigens and mitogens[j] can be inhibited by THC, 11-OH-THC, cannabinol, and 2-AG, as well as synthetic cannabinoid agonists such as CP 55,940, WIN 55,212 and HU-210[61, 89, 93, 99, 127, 155] In contrast, one study testing anandamide revealed little or no effect on T-cell proliferation.[93]

However, these drug effects are variable, and depend on experimental conditions such as the experimental drug dose used, mitogen used, percent of serum in the culture, and timing of cannabinoid drug exposure. In general, lower doses of cannabinoids increase proliferation while higher doses suppress proliferation. Doses that are effective in suppressing immune function are typically greater than 10 μM in cell culture studies and greater than 5 mg/kg in whole animal studies.[85] By comparison, at 0.05 mg/kg, people will experience the full psychoactive effects of THC; however, because of their high metabolic rates, small rodents frequently require drug doses that are 100-fold higher than doses needed for humans to achieve comparable drug effects. Thus, the immune effects of doses of cannabinoids higher than those ever experienced by humans, should be interpreted with caution.[89, 93, 93, 127, 155] As with T cells, B cell proliferation can be suppressed by various cannabinoids, such as THC, 11-OH-THC and 2-AG, but B cell proliferation is more inhibited at lower drug concentrations than T cell proliferation.[89, 93] Conversely, low doses of THC, CP 55,940 and WIN 55,212-2 *increase* B-cell proliferation in cultured human cells exposed to mitogen.[35] This effect possibly involves the CB_2 receptor, because the effect appears to be the same when the CB_1 receptor was blocked by the antagonist, SR-141716A (which does not block the CB_2 receptor). The reason for the differences in B cell responsiveness to cannabinoids is probably due to differences in cell type and source; for example, B cells collected from mouse spleen might respond to cannabinoids somewhat differently than B cells from human tonsils.

[j] Mitogens are substances that stimulate cell division (mitosis) and cell transformation.

Natural Killer Cells

Repeated injections of relatively low doses of THC (3 mg/kg/day[121] [k]) or two injections of a high dose (40 mg/kg[86]) suppress the ability of natural killer (NK) cells to destroy foreign cells in rats and mice. THC can also suppress natural killer cell cytolytic activity in cell cultures; 11-OH-THC, is even more potent.[86] In contrast, THC doses below 10μM had no effect on natural killer cell activity in mouse cell cultures.[98]

Macrophages

Macrophages perform various functions including phagocytosis (ingestion and destruction of foreign substances), cytolysis, antigen presentation to lymphocytes, and production of a variety of active proteins involved in destroying microorganisms, tissue repair and modulation of immune cells. Those functions can be suppressed by THC doses similar to those capable of modulating lymphocyte functions (see above).[88, 109]

Cytokines

Cytokines are proteins produced by immune cells. When released from the producing cell they can alter the function of other cells they come in contact with. In a sense, they are like hormones. Thus, cannabinoids can either increase or decrease cytokine production depending upon experimental conditions.

Certain cytokines, such as interferon-γ and interleukin-2 (IL-2) are produced by T helper-1 (Th1) cells. These cytokines help to activate cell-mediated immunity and the killer cells that eliminate microbes from the body (see Box on cells of the immune system). When injected into mice, THC suppresses the production of those cytokines that modulate the host response to infection (see below).[115] Cannabinoids also modulate interferons induced by viral infection,[21] as well as other interferon inducers.[85] Furthermore, in human cell cultures, interferon production can be increased by low concentrations, but decreased by high concentrations of either THC or cannabidiol.[168] In addition to Th1 cytokines, cannabinoids also modulate the production of cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and interleukin-6 (IL-6). [145, 176] At 8 mg/kg, THC can increase the *in vivo* mobilization of serum acute phase cytokines including IL-1, TNF, and IL-6.[90] Finally, although these studies suggest that cannabinoids can induce an increase in cytokines, other studies suggest that they can also suppress cytokine production.[85] The different results might be due to different cell culture conditions or because different cell lines were studied.

---

[k] While 3 mg/kg would be a high dose for humans (see table 3.1); in rodents, it is a low dose for immunological effects, and a moderate dose for behavioral effects.

Antibody Production

Antibody production is an important measure of humoral immune function as contrasted with cellular (cell-mediated immunity). Antibody production can be suppressed in mice injected with relatively low doses of THC (>5 mg/kg) or HU210 (>0.05 mg/kg) and in mouse spleen cell cultures exposed to a variety of cannabinoids, including THC, 11-OH-THC, cannabinol, cannabidiol, CP 55,940, or HU-210.[5, 6, 61, 78, 79, 84, 85, 142, 164] However, the inhibition of antibody response by cannabinoids was only observed when antibody-forming cells were exposed to T cell-dependent antigens (the responses require functional T cells and macrophages as accessory cells). Conversely, antibody responses to several T cell-independent antigens were not inhibited by THC, suggesting that the B cell is relatively insensitive to inhibition by cannabinoids.[142]

Resistance To Infection In Animals Exposed To Cannabinoids

Bacterial infections evaluated in mice demonstrated that THC can suppress resistance to infection, although the effect depends upon the dose and timing of drug administration. Mice pre-treated with THC (8 mg/kg) one day prior to infection with a sublethal dose of the pneumonia-causing bacteria, *Legionella pneumophilia*, and then treated again one day after the infection with THC, developed symptoms of cytokine-mediated septic shock and died; control mice that were not pre-treated with THC became immune to repeated infection and survived the bacterial challenge.[90] If only one injection of THC was given or doses less than 5 mg/kg were used, all of the mice survived the initial infection, but failed to survive a subsequent challenge with a lethal dose of the bacteria; hence these mice failed to develop immune memory in response to the initial sublethal infection.[87] Note that these are very high doses, and are considerably higher than doses experienced by marijuana users (see figure 3.1).[115] In rats, doses of 4.0 mg/kg THC are aversive[95]

Few studies have been done to evaluate the effect of THC on viral infections, and this is an area that needs further study.[20] Compared to healthy animals, THC might have greater immunosuppressive effects in animals whose immune systems are severely weakened. For example, a very high dose of THC (100 mg/kg) given twice, two days before and after herpes simplex virus infection, was shown to be a co-factor with herpes simplex virus in enhancing the progression to death in an immunodeficient mouse model infected with a leukemia virus.[85] However, THC given as a single dose (100 mg/kg) two days before herpes simplex virus infection did not promote the progression to death in these animals. Hence, whether THC is immunosuppressive likely depends on the timing of THC exposure relative to an infection.

Anti-inflammatory Effects

As discussed above, cannabinoid drugs can modulate the production of cytokines, which are central to inflammatory processes in the body. In addition, several studies have shown directly that cannabinoids can be anti-inflammatory. For example, in rats with autoimmune encephalomyelitis (an experimental model used to study multiple sclerosis), cannabinoids were shown to attenuate the signs and the symptoms of central nervous system damage.[100, 172] (Some believe that nerve damage associated with multiple sclerosis is caused by an inflammatory reaction.) Likewise, the cannabinoid, HU-211, was shown to suppress brain inflammation that resulted from closed head injury[146] or infectious meningitis[7] in studies on rats. HU-211 is a synthetic cannabinoid that does not bind to cannabinoid receptors, and is not psychoactive;[7] thus, without direct evidence, the effects of marijuana cannot be assumed to include those of HU-211. CT-3, another atypical cannabinoid, suppresses acute and chronic joint inflammation in animals.[178] It is a nonpsychoactive, synthetic derivative of 11-THC-oic acid (a breakdown product of THC), and does not appear to bind to cannabinoid receptors.[129] Cannabichromene, a cannabinoid found in marijuana, has also been reported to have anti-inflammatory properties.[173] No mechanism of action for possible anti-inflammatory effects of cannabinoids has been identified and the effects of these atypical cannabinoids and effects of marijuana are not yet established.

It is interesting to note that two reports of cannabinoid-induced analgesia are based on the ability of the endogenous cannabinoids, anandamide and PEA, to reduce pain associated with local inflammation that was experimentally induced by subcutaneous injections of dilute formalin.[22, 73] Both THC and anandamide can increase serum levels of ACTH and corticosterone in animals.[169] Those hormones are involved in regulating many responses in the body, including those to inflammation. The possible link between experimental cannabinoid-induced analgesia and reported anti-inflammatory effects of cannabinoids is important for potential therapeutic uses of cannabinoid drugs, but has not yet been established.

Conclusions regarding effects on immune system

Based on cell culture and animal studies, cannabinoids have been established as immunomodulators—that is, they increase some immune responses and decrease others. The variable responses depend upon experimental factors such as drug dose, timing of delivery, and type of immune cell examined.

Cannabinoids affect multiple cellular targets within the immune system and a variety of effector functions. Many of the effects noted above appear to occur at

concentrations of > 5 μM *in vitro* and > 5 mg/kg *in vivo*.[1] By comparison, a 5 mg injection of THC into a person (about 0.06 mg/kg) is enough to produce strong psychoactive effects. It should be emphasized, however, that little is known about the effects of chronic low dose exposure to cannabinoids on the immune system.

Another issue in need of further clarification involves the potential usefulness of cannabinoids as therapeutic agents in inflammatory diseases. Glucocorticoids have historically been used for these diseases, but non-psychotropic cannabinoids potentially have fewer side effects and might thus offer an improvement over glucocorticoids in treating inflammatory diseases.

Conclusions and Recommendations

Following the progress of the past fifteen years in understanding the effects of cannabinoids, research over the next decade is likely to reveal even more. It is interesting to compare how little we know about the cannabinoids with how much we know about the opiates (table 2.8). This table, in fact, suggests good reason for optimism about the future of cannabinoid drug development. Now that many of the basic tools of cannabinoid pharmacology and biology have been developed, one can expect to see rapid advances that can begin to match what is known for opiate systems in the brain.

Despite the tremendous progress in understanding the pharmacology and neurobiology of brain cannabinoid systems, this field is still in its early developmental stages. A key focus for future study is the neurobiology of endogenous cannabinoids. Establishing the precise brain localization—i.e., in which cells and where in those cannabinoids are found, cellular storage and release mechanisms, and uptake mechanisms will be crucial in determining the biological role of this system. Technology that will be crucial in establishing the biological significance of these systems will be broad based and include such research tools as the transgenic, or gene knockout mice, as have already been accomplished for various opioid receptor types.[26] In 1997, both CB_1 and CB_2 receptor knockout mice were generated by a team of scientists at NIH, and a group in France has developed another strain of CB_1 receptor knockout mice.[92]

[1] *In vitro* studies are those in which animal cells or tissue are removed and studied outside the animal ; *in vivo* studies are those in which experiments are conducted in the whole animal.

Table 2.8 Historical comparisons between cannabinoids and opiates

Comparisons between cannabinoids and opiates

Pharmacological Discoveries	*Cannabinoids*	*Opiates*
Discovery of receptor existence	1988 (Howlett and Devane)[36, 40]	1973 (Pert and Snyder, Terenius, and Simon)[123, 149, 162]
Identification of receptor antagonist	1994 SR141716A (Rinaldi-Carmona)[132]	pre-1973 Naloxone
Discovery of 1st endogenous ligand	1992 Anandamide (Devane and Mechoulam)[37]	1975 Met- and Leu-enkephalin (Hughes et al)[70]
1st Receptor cloned	1990 (Matsuda)[107]	1992 (Evans et al. and Kieffer et al.)[41, 82]
Natural functions of cannabinoid / opiate systems	Unknown	Pain, reproduction, mood, movement, and others

There are several research tools that will greatly aid such investigations—in particular, a greater selection of agonists and antagonists that permit discrimination between the activation of CB_1 versus CB_2 receptors; hydrophilic agonists (that can be delivered to animals or cells more effectively than hydrophobic compounds). In the area of drug development, future progress should continue to provide more specific agonists and antagonists for CB_1 and CB_2 receptors, with varying potential for therapeutic uses.

There are certain areas that will provide keys to a better understanding of the potential therapeutic value of cannabinoids. For example, basic biology indicates a role for cannabinoids in pain and control of movement, which is consistent with a possible therapeutic role in these areas. The evidence is relatively strong for the treatment of pain, and intriguingly, although less well-established, for movement disorders. The neuroprotective properties of cannabinoids might prove therapeutically useful, although it should be noted that this is a new area and other, better studied, neuroprotective drugs have not yet been shown to be therapeutically useful. Cannabinoid research is clearly relevant not only to drug abuse, but also to

understanding basic human biology. Further, it offers the potential for the discovery and development of new, therapeutically useful drugs.

CONCLUSION: At this point, our knowledge about the biology of marijuana and cannabinoids allows us to make some general conclusions:

- Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
- The natural role of cannabinoids in immune systems is likely multifaceted and remains unclear.
- The brain develops tolerance to cannabinoids.
- Animal research demonstrates the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.
- Withdrawal symptoms can be observed in animals, but appear to be mild compared to opiates or benzodiazepines, such as diazepam (Valium®).

CONCLUSION: The different cannabinoid receptor types found in the body appear to play different roles in normal physiology. In addition, some effects of cannabinoids appear to be independent of those receptors. The variety of mechanisms through which cannabinoids can influence human physiology underlies the variety of potential therapeutic uses for drugs that might act selectively on different cannabinoid systems.

RECOMMENDATION: Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to effects attributable to THC alone.

This chapter has summarized recent progress in understanding the basic biology of cannabinoids, and provides a foundation for the next two chapters which review studies on the potential health risks (chapter 3) and benefits of marijuana use (chapter 4).

References

1. Abood ME, Martin BR. 1996. Molecular neurobiology of the cannabinoid receptor. *International Review of Neurobiology* 39 :197-221.

2. Abood ME, Sauss C, Fan F, Tilton CL, Martin BR. 1993. Development of behavioral tolerance to delta 9-THC without alteration of cannabinoid receptor binding or mRNA levels in whole brain. *Pharmacology, Biochemistry and Behavior* 46:575-9.

3. Aceto MD, Scates SM, Lowe JA, Martin BR. 1995. Cannabinoid precipitated withdrawal by the selective cannabinoid receptor antagonist, SR 141716A. *European Journal of Pharmacology* 282:R1-2.

4. Adams IB, Martin BR. 1996. Cannabis: pharmacology and toxicology in animals and humans. *Addiction* 91:1585-1614.

5. Baczynsky WO, Zimmerman AM. 1983a. Effects of delta-9-tetrahydrocannabinol, cannabinol, and cannabidiol on the immune system in mice: I. In vivo investigation of the primary and secondary immune response. *Pharmocology* 26:1-11.

6. Baczynsky WO, Zimmerman AM. 1983b. Effects of delta 9-tetrahydrocannabinol, cannabinol and cannabidiol on the immune system in mice. II. In vitro investigation using cultured mouse splenocytes. *Pharmacology* 26:12-19.

7. Bass R, Engelhard D, Trembovler V, Shohami E. 1996. A novel nonpsychotropic cannabinoid, HU-211, in the treatment of experimental pneumococcal meningitis. *Journal of Infectious Diseases* 173:735-738.

8. Beardsley PM, Balster RL, Harris LS. 1986. Dependence on tetrahydrocannabinol in rhesus monkeys. *Journal of Pharmacology and Experimental Therapeutics* 239:311-319.

9. Ben-Shabat S, Fride E, Sheskin T, Tamiri T, Rhee MH, Vogel Z, Bisogno T, De Petrocellis L, Di Marzo V, Mechoulam R. 1998. An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity. *European Journal of Pharmacology* 353:23-31.

10. Bennett GJ. 1994. Neuropathic Pain. In: Wall PD, Melzack R Editors *Textbook of Pain.* Edinburgh: Churchill Livingstone.

11. Bird KD, Boleyn T, Chesher GB, Jackson DM, Starmer GA, Teo RKC. 1980. Intercannabinoid and cannabinoid-ethanol interactions and their effects on human performance. *Psychopharmacology* 71:181-188.

12. Bloom AS, Dewey WL, Harris LS, Brosius KK. 1977. 9-nor-9b-hydroxyhexahydrocannabinol, a cannabinoid with potent antinociceptive activity: Comparisons with morphine. *Journal of Pharmacology and Experimental Therapeutics* 200:263-270.

13. Bornheim LM, Everhart ET, Li J, Correia MA. 1994. Induction and genetic regulation of mouse hepatic cytochrome P450 by cannabidiol. *Biochemical Pharmacology (England)* 48:161-171.

14. Bornheim LM, Kim KY, Chen B., Correia MA. 1993. The effect of cannabidiol on mouse hepatic microsomal cytochrome P450-dependent anandamide metabolism. *Biochemical and Biophysical Research Communications (United States)* 197:740-746.

15. Bornheim LM, Kim KY, Li J, Perotti BY, Benet LZ. 1995. Effect of cannabidiol pretreatment on the kinetics of tetrahydrocannabinol metabolites in mouse brain. *Drug Metabolism and Disposition (United States)* 23:825-831.

16. Breivogel CS, Sim LJ, Childers SR. 1997. Regional differences in cannabinoid receptor/G-protein coupling in rat brain. *Journal of Pharmacology and Experimental Therapeutics* 282:1632-1642.

17. British Medical Association. 1997. *Therapeutic uses of cannabis*. Amsterdam, The Netherlands: Harwood Academic Publishers.

18. Burkey TH, Quock RM, Consroe P, Roeske WR, Yamamura HI. 1997. Delta-9-tetrahydrocannabinol is a partial agonist of cannabinoid receptors in mouse brain. *European Journal of Pharmacology* 323:R3-R4.

19. Buxbaum DM. 1972. Analgesic activity of D9-tetrahydrocannabinol in the rat and mouse. *Psychopharmacology* 25:275-280.

20. Cabral G A , Dove Pettit D A. 1998. Drugs and immunity: cannabinoids and their role in decreased resistance to infectious disease. *Journal of Neuroimmunology* 83:116-123.

21. Cabral GA, Lockmuller JC, Mishkin EM. 1986. Delta-9-tetrahydrocannabinol decreases alpha/beta interferon response to herpes simplex virus type 2 in the B6C3F1 mouse. *Proceedings of the Society for Experimental Biology and Medicine* 181:305-311.

22. Calignano A, La Rana G, Giuffrida A, Piomelli D. 1998. Control of pain initiation by endogenous cannabinoids. *Nature* 394:277-281.

23. Campbell KA, Foster TC, Hampson RE, Deadwyler SA. 1986a. Delta-9-tetrahydrocannabinol differentially affects sensory-evoked potentials in the rat dentate gyrus. *Journal of Pharmacology and Experimental Therapeutics* 239:936-940.

24. Campbell KA, Foster TC, Hapson RE, Deadwyler SA. 1986b. Effects of delta-9-tetrahydrocannabinol on sensory-evoked discharges of granule cells in the dentate gyrus of behaving rats. *Journal of Pharmacology and Experimental Therapeutics* 239:941-945.

25. Chen J, Marmur R, Pulles A, Paredes W, Gardner EL. 1993. Ventral tegmental microinjection of delta-9-tetrahydrocannabinol enhances ventral tegmental somatodendritic dopamine levels but not forebrain dopamine levels: evidence for local neural action by marijuana's psychoactive ingredient. *Brain Research* 621:65-70.

26. Childers SR. 1997. Opioid receptors: Pinning down the opiate targets. *Current Biology* 7:R695-R697.

27. Childers SR, Breivogel CS. 1998. Cannabis and endogenous cannabinoid systems. *Drug and Alcohol Dependence* 51:173-187.

28. Coffey RG, Yamamoto Y, Shella E, Pross S. 1996. Tetrahydrocannabinol inhibition of macrophage nitric oxide production. *Biochemical Pharmacology* 52:743-751.

29. Collins DR, Pertwee RG, Davies SN. 1994. The action of synthetic cannabinoids on the induction of long-term potentiation in the rat hippocampal slice. *European Journal of Pharmacology* 259:R7-R8.

30. Collins DR, Pertwee RG, Davies SN. 1995. Prevention by the cannabinoid antagonist, SR141716A, of cannabinoid-mediated blockade of long-term potentiation in the rat hippocampal slice. *British Journal of Pharmacology* 115:869-870.

31. Costa B, Parolaro D, Colleoni M. 1996. Chronic cannabinoid, CP-55,940, administration alters biotransformation in the rat. *European Journal of Pharmacology* 313:17-24.

32. Daaka Y, Friedman H, Klein T. 1996. Cannabinoid receptor proteins are increased in Jurkat, human T-Cell line after mitogen activation. *Journal of Pharmacology and Experimental Therapeutics* 276:776-783.

33. Daaka Y, Zhu W, Friedman H, Klein T. 1997. Induction of interleukin-2 receptor α gene by Δ9-tetrahydrocannabinol is mediated by nuclear factor κB and CB_1 cannabinoid receptor. *DNA and Cell Biology* 16:301-309.

34. Deadwyler SA, Heyser CJ, Hampson RE. 1995. Complete adaptation to the memory disruptive effects of delta-9-THC following 35 days of exposure. *Neuroscience Research Communications* 17:9-18.

35. Derocq JM, Segui M, Marchand J, Le Fur G, Casellas P. 1995. Cannabinoids enhance human B-cell growth at low nanomolar concentrations. *FEBS Letters* 369:177-182.

36. Devane WA, Dysarc FA, Johnson MR, Melvin LS, Howlett AC. 1988. Determination and characterization of a cannabinoid receptor in rat brain. *Molecular Pharmacology* 34:605-613.

37. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffing F, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. 1992. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 258:1946-1949.

38. Dewey WL. 1986. Cannabinoid pharamacology. *Pharmacology Review* 38:151-178.

39. Di Chiara G, Imperato A. 1988. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Science, USA* 85:5274-5278.

40. Dill JA, Howlett AC. 1988. Regulation of adenylate cyclase by chronic exposure to cannabimimetic drugs. *Journal of Pharmacology and Experimental Therapeutics* 244:1157-1163.

41. Evans DJ, Keith DEJ, Morrison H, Magendzo K, Edwards RH. 1992. Cloning of a delta opioid receptor by functional expression. *Science* 258:1952-1955.

42. Fan F, Tao Q, Abood ME, Martin BR. 1996. Cannabinoid receptor down-regulation without alteration of the inhibitory effect of CP 55,940 on adenylyl cyclase in the cerebellum of CP 55,940-tolerant mice. *Brain Research* 706:13-20.

43. Felder CC, Glass M. 1998. Cannabinoid receptors and their endogenous agonists. *Annual Reviews of Pharmacology and Toxicology* 38:179-200.

44. Felder CC, Nielsen A, Briley EM, Palkovits M, Priller J, Axelrod J, Nguyen DN, Richardson JM, Riggin RM, Koppel GA, Paul SM, Becker GW. 1996. Isolation and measurement of the endogenous cannabinoid receptor agonist, anandamide, in brain and peripheral tissues of human and rat. *FEBS Letters* 393:231-5.

45. Fields HL. 1987. *Pain.* New York: McGraw-Hill.

46. Formukong EA, Evans AT, Evans FJ. 1988. Analgesic and antiinflammatory activity of constituents of Cannabis sativa L. *Inflammation* 12:361-371.

47. French ED. 1997. Delta-9-tetrahydrocannabinol excites rat VTA dopamine neurons through activation of cannabinoid CB_1 but not opioid receptors. *Neuroscience Letters* 226:159-162.

48. Galiegue S, Mary S, Marchand J, Dussossoy D, Carriere D, Carayon P, Bouaboula M, Shire D, Le Fur G, Casellas P. 1995. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *European Journal of Biochemistry* 232:54-61.

49. Gessa GL, Mascia MS, Casu MA, Carta G. 1997. Inhibition of hippocampal acetylcholine release by cannabinoids: reversal by SR 141716A. *European Journal of Pharmacology* 327:R1-2.

50. Gifford AN, Ashby Jr CR. 1996. Electrically evoked acetylcholine release from hippocampal slices is inhibited by the cannabinoid receptor agonist, WIN 55212-2, and is potentiated by the cannabinoid antagonist, SR 141716A. *Journal of Pharmacology and Experimental Therapeutics* 277:1431-1436.

51. Gifford AN, Gardner EL, Ashby CRJ. 1997. The effect of intravenous administration of delta-9-tetrahydrocannabinol on the activity of A10 dopamine neurons recorded *in vivo* in anesthetized rats. *Neuropsychobiology* 36:96-99.

52. Glass M, Dragunow M, Faull RLM. 1997. Cannabinoid receptors.in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience* 77:299-318.

53. Hadden JW, Hadden EM, Haddox MK, Goldberg ND. 1972. Guanosine 3':5'-cyclic monophosphates: A possible intracellular mediator of mitogenic influences in lymphocytes. *Proceedings of the National Academy of Sciences* 69:3024-3027.

54. Hampson AJ, Grimaldi M, Axelrod J, Wink D. 1998. Cannabidiol and (-)Delta-9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Science of the United States of America* 95:8268-8273.

55. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. 1999. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology* 141:385-394.

56. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. 1999. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology* 141:395-404.

57. Herkenham M. 1995. Localization of cannabinoid receptors in brain and periphery. In: Pertwee RG ed. *Cannabinoid Receptors.* Academic Press Limited. Pp. 145-166.

58. Herkenham M, Lynn AB, de Costa BR, Richfield EK. 1991a. Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. *Brain Research* 547:267-274.

59. Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC. 1991b. Characterization and localization of cannabinoid receptors in rat brain: a quantative *in vitro* autoradiographic study. *Journal of Neuroscience* 11:563-583.

60. Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, Rice KC. 1990. Cannabinoid receptor localization in the brain. *Proceedings of the National Academy of Sciences of the United States of America* 87:1932-1936.

61. Herring AC, Koh WS, Kaminski NE. 1998. Inhibition of the cyclic AMP signaling cascade and nuclear factor binding to CRE and kappa B elements by cannabinol, a minimally CNS-active cannabinoid. *Biochemical Pharmacology* 55:1013-1023.

62. Herzberg U, Eliav E, Bennett GJ, Kopin IJ. 1997. The analgesic effects of R(+)-WIN 55,212-2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. *Neuroscience Letters* 221:157-60.

63. Heyser CJ, Hampson RE, Deadwyler SA. 1993. Effects of delta-9-tetrahydrocannabinol on delayed match to sample performance in rats: Alterations in short-term memory associated with changes in task specific firing of hippocampal cells. *Journal of Pharmacology and Experimental Therapeutics* 264:294-307.

64. Hohmann AG, Briley E M, Herkenham M. in press (1998). Pre- and postsynaptic distribution of cannabinoid and mu opioid receptors in rat spinal cord. *Brain Research*

65. Hohmann AG, Herkenham M. 1998. Regulation of cannabinoid and mu opioid receptor binding sites following neonatal capsaicin treatment. *Neuroscience Letters* 252:13-16.

66. Hohmann AG, Herkenham M. in press (1998). Localization of central cannabinoid CB1 receptor mRNA in neuronal subpopulations of rat dorsal root ganglia: A double-label *in situ* hybridization study.
. *Neuroscience*

67. Hohmann AG, Martin WJ, Tsou K, Walker JM. 1995. Inhibition of noxious stimulus-evoked activity of spinal cord dorsal horn neurons by the cannabinoid WIN 55,212-2. *Life Sciences* 56:2111-2119.

68. Hollister LE. 1986. Health aspects of cannabis. *Pharmacological Reviews* 38:1-20.

69. Hollister LE, Gillespie BA. 1975. Interactions in man of delta-9-THC. II. Cannabinol and cannabidiol. *Clinical Pharmacology and Therapeutics* 18:80-83.

70. Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR. 1975. Identification of two related pentapeptides from the brain with potent opiate agonists activity. *Nature* 258:577-580.

71. Jackson AL, Murphy LL. 1997. Role of the hypothalamic-pituitary-adrenal axis in the suppression of luteinizing hormone release by delta-9-tetrahydrocannabinol. *Neuroendocrinology* 65:446-452.

72. Jacob J, Ramabadran K, Campos-Medeiros M. 1981. A pharmacological analysis of levonantradol antinociception in mice. *Journal of Clinical Pharmacology* 21:327S-333S.

73. Jaggar SI, Hasnie FS, Sellaturay S, Rice AS. 1998. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB_2 receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. *Pain* 76:189-199.

74. Jeon YJ, Yang K-H, Pulaski JT, Kaminski NE. 1996. Attenuation of inducible nitric oxide synthase gene expression by delta-9-tetrahydrocannabinol is mediated through the inhibition of nuclear factor-kB/Rel activation. *Molecular Pharmacology* 50:334-341.

75. Johnson MR, Melvin LS. 1986. The discovery of non-classical cannabinoid analgesics. In: Mechoulam R editor *Cannabinoids as therapeutic agents*. Boca Raton, FL: CRC Press, Inc. Pp. 121-145.

76. Jones RT, Benowitz NL, Herning RI. 1981. Clinical relevance of cannabis tolerance and dependence. *Journal of Clinical Pharmacology* 21:143S-152S.

77. Kaminski NE. 1996. Immune regulation by cannabinoid compounds through the inhibition of the cyclic AMP signaling cascade and altered gene expression. *Biochemical Pharmacology* 52:1133-1140.

78. Kaminski NE, Abood M E, Kessler F K, Martin B R, Schatz A R. 1992. Identification of a functionally relevant cannabinoid receptor on mouse spleen cells that is involved in cannabinoid-mediated immune modulation. *Molecular Pharmacology* 42:736-742.

79. Kaminski NE, Koh WS, Yang KH, Lee M, Kessler FK. 1994. Suppression of the humoral immune response by cannabinoids is partially mediated through inhibition of adenylate cyclase by a pertussis toxin-sensitive G-protein coupled mechanism. *Biochemical Pharmacology* 48:1899-1908.

80. Kaminski NE. 1998. Regulation of cAMP cascade, gene expression and immune function by cannabinoid receptors. *Journal of Neuroimmunology* 83:124-132.

81. Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA. 1975. Cannabidiol interferes with the effects of delta-9-tetrahydrocannbinol in man. *European Journal of Pharmacology* 28:172-177.

82. Kieffer BL, Befort K, Gaveriaux-Ruff C, Hirth CG. 1992. The dilta-opioid receptor: isolation of a cDNA by expression clining and pharmacological characterization. *Proceedings of the National Academy of Sciences of the United States of America* 89:12048-12052.

83. Kirby MT, Hampson RE, Deadwyler SA. 1995. Cannabinoids selectively decrease paired-pulse perforant path synaptic potentials in the dentate gyrus in vitro. *Brain Research* 688:114-120.

84. Klein TW, Friedman H. 1990. Modulation of murine immune cell function by marijuana components. In: Watson R ed. *Drugs of Abuse and Immune Function.* Boca Raton, FL: CRC Press.

85. Klein TW, Friedman H, Specter SC. 1998. Marijuana, immunity and infection. *Journal of Neuroimmunology* 83:102-115.

86. Klein TW, Newton C, Friedman H. 1987. Inhibition of natural killer cell function by marijuana components. *Journal of Toxicology and Environmental Health* 20:321-332.

87. Klein TW, Newton C, Friedman H. 1994. Resistance to *Legionella pneumophila* suppressed by the marijuana component, tetrahydrocannabinol. *Journal of Infectious Diseases* 169:1177-1179.

88. Klein TW, Newton C, Friedman H. 1998. Cannabinoid receptors and immunity. *Immunology Today* 19:373-381.

89. Klein TW, Newton C, Widen R, Friedman H. 1985. The effect of delta-9-tetrahydrocannabinol and 11-hydroxy-delta-9-tetrahydrocannabinol on T-lymphocyte and B-lymphocyte mitogen responses. *Journal of Immunopharmacology* 7:451-466.

90. Klein TW, Newton C, Widen R, Friedman H. 1993. Delta-9-tetrahydrocannabinol injection induces cytokine-mediated mortality of mice infected with *Legionella pneumophila*. *Journal of Pharmacology and Experimental Therapeutics* 267:635-640.

91. Koh WS, Yang KH, Kaminski NE. 1995. Cyclic AMP is an essential factor in immune responses. *Biochemical and Biophysical Research Communications* 206:703-709.

92. Ledent C , Valverde O , Cossu G , Petitet F , Aubert JF , Beslot F , Bohme GA , Imperato A , Pedrazzini T , Roques BP , Vassart G , Fratta W , Parmentier M. 1999. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. *Science* 283:401-4 .

93. Lee M, Yang KH, Kaminski NE. 1995. Effects of putative cannabinoid receptor ligands, anandamide and 2-arachidonyl-glycerol, on immune function in B6C3F1 mouse splenocytes. *Journal of Pharmacology and Experimental Therapeutics* 275:529-536.

94. Lepore M, Liu X, Savage V, Matalon D, Gardner EL. 1996. Genetic differences in delta 9-tetrahydrocannabinol-induced facilitation of brain stimulation reward as measured by a rate-frequency curve-shift electrical brain stimulation paradigm in three different rat strains. *Life Sciences* 58:365-372.

95. Lepore M, Vorel SR, Lowinson J, Gardner EL. 1995. Conditioned place preference induced by delta 9-tetrahydrocannabinol: Comparison with cocaine, morphine, and food reward. *Life Sciences* 56:2073-2080.

96. Lichtman AH, Martin BR. 1991a. Spinal and supraspinal components of cannabinoid-induced antinociception. *Journal of Pharmacology and Experimental Therapeutics* 258:517-523.

97. Little PJ, Compton DR, Mechoulam R, Martin BR. 1989. Stereochemical effects of 11-OH-delta-8-THC-dimethylheptyl in mice and dogs. *Pharmacology, Biochemistry Behavior* 32:661-666.

98. Lu F, Ou DW. 1989. Cocaine or delta-9-tetrahydrocannabinol does not affect cellular cytotoxicity *in vitro*. *International Journal of Pharmacology* 11:849-852.

99. Luo YD, Patel MK, Wiederhold MD, Ou DW. 1992. Effects of cannabinoids and cocaine on the mitogen-induced transformations of lymphocytes of human and mouse origins. *International Journal of Immunopharmacology* 14:49-56.

100. Lyman WD, Sonett JR, Brosnan CFER, Bornstein MB. 1989. Delta 9-tetrahydrocannabinol: a novel treatment for experimental autoimmune encephalomyelitis. *Journal of Neuroimmunology* 23:73-81.

101. Mailleux P, Vanderhaeghen JJ. 1992. Distribution of neuronal cannabinoid receptor in the adult rat brain: a comparative receptor binding radioautography and *in situ* hybridization histochemistry. *Neuroscience* 48:655-668.

102. Martin WJ, Hohmann AG, Walker JM. 1996. Suppression of noxious stimulus-evoked activity in the ventral posterolateral nucleus of the thalamus by a cannabinoid agonist: Correlation between electrophysiological and antinociceptive effects. *The Journal of Neuroscience* 16:6601-6611.

103. Martin WJ, Patrick SL, Coffin PO, Tsou K, Walker JM. 1995. An examination of the central sites of action of cannabinoid-induced antinociception in the rat. *Life Sciences* 56:2103-2109.

104. Martin W J , Patrick S L, Coffin PO, Tsou K, Walker J M. 1995. An examination of the central sites of action of cannabinoid-induced antinociception in the rat. *Life Sciences* 56:2103-2109.

105. Martin WJ, Tsou K, Walker JM. 1998. Cannabinoid receptor-mediated inhibition of the rat tail-flick reflex after microinjections into the rostral ventromedial medulla. *Neuroscience Letters* 242:33-36.

106. Martoletta MC, Cossu G, Fattore L, Gessa GL, Fratta W. 1998. Self-administration of the cannabinoid receptor agonist WIN 55,212-2 in drug-naive mice. *Neuroscience* 85:327-330.

107. Matsuda L, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. 1990. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 346:561-564.

108. Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NSA, Gopher A, Almog S, Martin BR, Compton D, Pertwee RG, Griffin G, Bayewitch M, Barg J, Vogel Z. 1995. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochemical Pharmacology* 50:83-90.

109. Mechoulam R, Hanus L, Fride E. 1998. Towards cannabinoid drugs--revisited. In: Ellis GP, Luscombe DK, Oxford AW eds. *Progress in Medicinal Chemistry*. v. 35. Amsterdam: Elsevier Science. Pp. 199-243.

110. Meng ID, Manning BH, Martin WJ, Fields HL. 1998. An analgesia circuit activated by cannabinoids. *Nature* 395:381-383.

111. Miller AS, Walker JM. 1996. Electrophysiological effects of a cannabinoid on neural activity in the globus pallidus. *European Journal of Pharmacology* 30:29-35.

112. Munro S, Thomas KL, Abu-Shaar M. 1993. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 365:61-65.

113. Murphy LL, Steger RW, Smith MS, Bartke A. 1990. Effects of delta1-9-tetrahydrocannabinol, cannabinol and cannabidiol, alone and in combinations, on luteinizing hormone and prolactin release and on hypothalamic neurotransmitters in the male rat. *Neuroendocrinology* 52:316-321.

114. Narimatsu S, Watanabe K, Matsunaga T., Yamamoto I, Imaoka S, Funae Y, Yoshimura H. 1993. Suppression of liver microsomal drug-metabolizing enzyme activities in adult female rats pretreated with cannabidiol. *Biological and Pharmaceutical Bulletin (Japan)* 16:428-430.

115. Newton CA, Klein T, Friedman H. 1994. Secondary immunity to Legionella pneumophila and Th1 activity are suppressed by delta-9-tetrahydrocannabinol injection. *Infection and Immunity* 62:4015-4020.

116. Norwicky AV, Teyler TJ, Vardaris RM. 1987. The modulation of long-term potentiation by delta-9-tetrahydrocannabinol in the rat hippocampus, in vitro. *Brain Research Bulletin* 19:663.

117. O'Leary D, Block RI, Flaum M, Boles Ponto LL, Watkins GL, Hichwa RD. 1998. Acute marijuana effects on rCBF and cognition: A PET study. *Abstracts - Society for Neuroscience: 28th Annual Meeting*. Los Angeles, CA, November 7-12, 1998. Washington, DC: Society for Neuroscience.

118. Ohlsson A, Lindgren J-E, Wahlen A, Agurell S, Hollister L E, Gillespie HK. 1980. Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clinical Pharmacology and Therapeutics* 28:409-416.

119. Oviedo A, Glowa J, Herkenham M. 1993. Chronic cannabinoid administration alters cannabinoid receptor binding in rat brain: a quantitative autoradiographic study. *Brain Research* 616:293-302.

120. Pacheco MA, Ward SJ, Childers SR. 1993. Identification of cannabinoid receptors in cultures of rat cerebellar granule cells. *Brain Research* 603:102-110.

121. Patel V, Borysenko M, Kumar MSA, Millard WJ. 1985. Effects of acute and subchronic delta-9-tetrahydrocannabinol administration on the plasma catecholamine, beta-endorphin, and corticosterone levels and splenic natural killer cell activity in rats. *Proceedings of the Society for Experimental Biology and Medicine* 180:400-404.

122. Pepe S, Ruggiero A, Tortora G, Ciaardiello F, Garbi C, Yokozaki H, Cho-Chung YS, Clair T, Skalhegg BS, Bianco AR. 1994. Flow cytometric detection of the RI alpha subunit of type-I cAMP-dependent protein kinase in human cells. *Cytometry* 15:73-79.

123. Pert CB, Snyder SH. 1973. Opiate receptor: demonstration in nervous tissue. *Science* 179:1011-1014.

124. Pertwee RG. 1997b. Pharmacology of cannabinoid CB_1 and CB_2 receptors. *Pharmacology and Therapeutics* 74:129-180.

125. Pertwee RG, Stevenson LA, Griffin G. 1993. Cross-tolerance between delta-9-tetrahydrocannabinol and the cannabimimetic agents, CP 55,940, WIN 55,212-2 and anandamide [published erratum appears in *British Journal of Pharmacology* 1994 Mar;111(3):968]. *British Journal of Pharmacology* 110:1483-90.

126. Pertwee RG, Wickens AP. 1991. Enhancement by chlordiazepoxide of catalepsy induced in rats by intravenous or intrapallidal injections of enantiomeric cannabinoids. *Neuropharmacology* 30:237-244.

127. Pross SH, Nakano Y, Widen R, McHugh S, Newton C, Klein TW, Friedman H. 1992. Differing effects of delta-9-tetrahydrocannabinol (THC) on murine spleen cell populations dependent upon stimulators. *International Journal of Immunopharmacology* 14:1019-1027.

128. Razdan RK. 1986. Structure-activity relationships in cannabinoids. *Pharmacology Review* 38:75-149.

129. Rhee MH, Vogel Z, Barg J, Bayewitch M, Levy R, Hanus L, Breuer A, Mechoulam R. 1997. Cannabinol derivatives: binding to cannabinoid receptors and inhibition of adenylcyclase. *Journal of Medicinal Chemistry* 40:3228-3233.

130. Richardson JD, Aanonsen L, Hargreaves KM. 1998. Hypoactivity of the spinal cannabinoid system results in NMDA-dependent hyperalgesia. *Journal of Neuroscience* 18:451-457.

131. Richardson JD, Kilo S, Hargreaves KM. 1998. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. *Pain* 75:111-119.

132. Rinaldi-Carmona M, Barth F, Heaulme M, Shire D, Calandra B, Congy C, Martinez S, Maruani J, Neliat G, Caput D, Ferrara P, Soubrie P, Breliere JC, Le Fur G. 1994. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Letters* 350:240-244.

133. Rinaldi-Carmona M, Barth F, Millan J, Defrocq J, Casellas P, Congy C, Oustric D, Sarran M, Bouaboula M, Calandra B, Portier M, Shire D, Breliere J, Le Fur G. 1998. SR144528, the first potent and selective antagonist of the CB_2 cannabinoid receptor. *Journal of Pharmacology and Experimental Therapeutics* 284:644-650.

134. Rodríguez de Fonseca F, Fernández-Ruiz JJ, Murphy LL, Eldridge JC, Steger RW, Bartke A. 1991. Effects of delta-9-tetrahydrocannabinol exposure on adrenal medullary function: evidence of an acute effect and development of tolerance in chronic treatments. *Pharmacology, Biochemistry and Behavior* 40:593-598.

135. Rodriguez de Fonseca F, Carrera MRA, Navarro M, Koob G, Weiss F. 1997. Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal [see comments Science 1997. 276:1967-1968]. *Science* 276:2050-2054.

136. Rodriguez de Fonseca F, Gorriti MA, Fernandez-Ruiz JJ, Palomo T, Ramos JA. 1994. Down-regulation of rat brain cannabinoid binding sites after chronic delta-9-tetrahydrocannabinol treatment. *Pharmacology, Biochemistry and Behavior* 47:33-40.

137. Romero J, Garciá L, Fernández-Ruiz JJ, Cebeira M, Ramos JA. 1995. Changes in rat brain cannabinoid binding sites after acute or chronic exposure to their endogenous agonist, anandamide, or to delta-9-tetrahydrocannabinol. *Pharmacology, Biochemistry and Behavior* 51:731-737.

138. Romero J, Garcia-Palomero E, Castro JG, Garcia-Gil L, Ramos JA, Fernandez-Ruiz JJ. 1997. Effects of chronic exposure to delta-9-tetrahydrocannabinol on cannabinoid receptor binding and mRNA levels in several rat brain regions. *Molecular Brain Research* 46:100-8.

139. Russell DH. 1978. Type I cyclic AMP-dependent protein kinase as a positive effector of growth. *Advances in Cyclic Nucleotide Research* 9:493-506.

140. Sanudo-Pena M C, Tsou K, Delay E R , Hohmann AG, Force M, Walker JM. 1997. Endogenous cannabinoids as an aversive or counter-rewarding system in the rat. *Neuroscience Letters* 223:125-128.

141. Sanudo-Pena MC, Walker JM. 1997. Role of the subthalamic nucleus in cannabinoid actions in the substantia nigra of the rat. *Journal of Neurophysiology* 77:1635-1638.

142. Schatz AR, Koh WS, Kaminski NE. 1993. Delta-9-tetrahydrocannabinol selectively inhibits T-cell dependent humoral immune responses through direct inhibition of accessory T-cell function. *Immunopharmacology* 26:129-137.

143. Schlicker E, Timm J, Zenter J, Goethert M. 1997. Cannabinoid CB_1 receptor-mediated inhibition of noradrenaline release in the human and guinea-pig hippocampus. *Naunyn-Schmiedeberg's Archives of Pharmacology* 356:583-589.

144. Shen M, Piser TM, Seybold VS, Thayer SA. 1996. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. *Journal of Neuroscience* 16:4322-4334.

145. Shivers S C, Newton C, Friedman H, Klein TW. 1994. Delta 9-tetrahydrocannabinol (THC) modulates IL-1 bioactivity in human monocyte/macrophage cell lines. *Life Sciences* 54:1281-1289.

146. Shohami E, Galiily R, Mechoulam R, Bass R, Ben-Hur T. 1997. Cytokine production in the brain following closed head injury: dexanabinol (HU-211) is a novel TNF-alpha inhibitor and an effective neuroprotectant. *Journal of Neuroimmunology* 72:169-177.

147. Sim LJ, Hampson RE, Deadwyler SA, Childers SR. 1996. Effects of chronic treatment with delta-9-tetrahydrocannabinol on cannabinoid-stimulated [^{35}S]GTPγS autoradiography in rat brain. *Journal of Neuroscience* 16:8057-8066.

148. Sim LJ, Xiao R, Selley DE, Childers SR. 1996. Differences in G-pr and delta-opioid, and cannabinoid, receptors in rat striatum *Pharmacology* 307:97-105.

149. Simon EJ. 1973. In search of the opiate receptor. *American Journal* 266:160-168.

150. Skaper SD, Buriani A, Dal Toso R, Petrelli L, Romanello S, Facci L ALIAmide palmitoylethanolamide and cannabinoids, but n protective in a delayed postglutamate paradigm of excitoto granule neurons. *Proceedings of the National Academy of States of America* 93:3984-9.

151. Smith JW, Steiner AL, Newberry WM, Parker CW. 1971. Cyclic ad monophosphate in human lymphocytes: Alteration after ph *Journal of Clinical Investigation* 50:432-441.

152. Smith PB, Compton DR, Welch SP, Razdan RK, Mechoulam R, Ma pharmacological activity of anandamide, a putative endoge mice. *Journal of Pharmacology and Experimental Therape*

153. Smith PB, Welch SP, Martin BR. 1994. Interactions between delta 9 and kappa opioids in mice. *Journal of Pharmacology and E Therapeutics* 268:1381-1387.

154. Sofia RD, Nalepa SD, Harakal JJ, Vassar HB. 1973. Anti-edema anc delta-9-tetrahydrocannabinol (THC). *Journal of Pharmaco Therapeutics* 186:646-655.

155. Specter S, Lancz G, Hazelden J. 1990. Marijuana and immunity: tetr mediated inhibition of lymphocyte blastogenesis. *Internatic Immunopharmacology* 12:261-267.

156. Stefano G, Salzet B, Salzet M. 1997. Identification and characterizat cannabinoid receptor: Coupling to nitric oxide release. *Brai* 224.

157. Stella N, Schweitzer P, Piomelli D. 1997. A second endogenous cann long term potentiation. *Nature* 388:773-778.

158. Strangman NM, Patrick SL, Hohmann AG, Tsou K, Walker JM. 199 endogenous cannabinoids in the modulation of acute and to *Brain Research* 813:. 323-328.

159. Sulcova E, Mechoulam R., Fride E. 1998. Biphasic effects of ananda *Biochemistry and Behavior* 59:347-352.

160. Szabo B, Dorner L, Pfreundtner C, Norenberg W, Starke K. 1998. In inhibitory postsynaptic currents by cannabinoids in rat corpu *Neuroscience* 85:395-403.

161. Tanda G, Pontieri FE, Di Chiara G. 1997. Cannabinoid and heroin ac dopamine transmission by a common μ1 opioid receptor me 276:2048-2049.

162. Terenius L. 1973. Characteristics of the "receptor" for narcotic analgesics in synaptic plasma membrane fraction from rat brain. *Acta Pharmacologica Et Toxicologica* 33:377-384.

163. Terranova JP, Michaud JC, Le Fur G, Soubrié P. 1995. Inhibition of long-term potentiation in rat hippocampal slice by anandamide and WIN55212-2: reversal by SR141716 A, a selective antagonist of CB_1 cannabinoid receptors. *Naunyn-Schmiedeberg's Archives of Pharmacology* 352:576-579.

164. Titishov N, Mechoulam R, Zimmerman AM. 1989. Stereospecific effects of (-) and (+)-7-hydroxy-delta-6-tetrahydrocannabinol-dimethylheptyl on the immune system of mice. *Pharmacology* 39:337-349.

165. Tsou K, Brown S, Sanudo-Pena MC, Mackie K, Walker JM. 1998. Immunohistochemical distribution of cannabinoid CB_1 receptors in the rat central nervous system. *Neuroscience* 83:393-411.

166. Tsou K, Patrick SL, Walker JM. 1995. Physical withdrawal in rats tolerant to delta-9-tetrahydrocannabinol precipitated by a cannabinoid receptor antagonist. *European Journal of Pharmacology* 280:R13-R15.

167. Watson PF, Krupinski J, Kempinski A, Frankenfield C. 1994. Molecular cloning and characterization of the type VII isoform of mammalian adenylyl cyclase expressed widely in mouse tissues and in S49 mouse lymphoma cells. *Journal of Biological Chemistry* 269:28893-28898.

168. Watzl B, Scuder P, Watson RR. 1991. Marijuana components stimulate human peripheral blood mononuclear cell secretion of interferon-gamma and suppress interleukin-1 alpha in vitro. *International Journal of Immunopharmology* 13:1091-1097.

169. Weidenfeld J, Feldman S, Mechoulam R. 1994. Effect of the brain constituent anandamide, a cannabinoid receptor agonist, on the hypothalamo-pituitary-adrenal axis in the rat. *Neuroendocrinology* 59:110-112.

170. Welch SP. 1993. Blockade of cannabinoid-induced antinociception by norbinaltorphimine, but not N,N-diallyl-tyrosine-Aib-phenylalanine-leucine, ICI 174,864 or naloxone in mice. *Journal of Pharmacology and Experimental Therapeutics* 265:633-640.

171. Welch SP, Thomas C, Patrick GS. 1995. Modulation of cannabinoid-induced antinociception after intracerebroventricular versus intrathecal administration to mice: Possible mechanisms for interaction with morphine. *Journal of Clinical and Experimental Therapeutics* 272:310-321.

172. Wirguin I, Mechoulam R, Breuer A, Schezen E, Weidenfeld J, Brenner T. 1994. Suppression of experimental autoimmune encephalomyelitis by cannabinoids. *Immunopharmacology* 28:209-214.

173. Wirth PW, Watson ES, ElSohly M, Turner CE, Murphy JC. 1980. Anti-inflammatory properties of cannabichromene. *Life Sciences* 26:1991-1995.

174. Yaksh TL. 1981. The antinociceptive effects of intrathecally administered levonantradol and desacetyl-levonantradol in the rat. *Journal of Clinical Pharmacology* 21:334S-340S.

175. Yoshida H, Usami N, Ohishi Y, Watanabe K, Yamamoto I, Yoshimura H. 1995. Synthesis and pharmacological effects in mice of halogenated cannabinol derivatives. *Chemical and Pharmaceutical Bulletin* 42:335-337.

176. Zhu W, Newton C, Daaka Y, Friedman H, Klein TW. 1994. Delta 9-tetrahydrocannabinol enhances the secretion of interleukin 1 from endotoxin-stimulated macrophages. *Journal of Pharmacology and Experimental Therapeutics* 270:1334-1339.

177. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. 1982. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology (Berl)* 76:245-250.

178. Zurier R.B., Rossetti RG, Lane JH, Goldberg JM, Hunter SA, Burstein SH. 1998. Dimethylheptyl-THC-11 oic acid: A non-psychoactive antiinflammatory agent with a cannabinoid template structure. *Arthritis and Rheumatism* 41:163-170.

CHAPTER 3: FIRST, DO NO HARM: CONSEQUENCES OF MARIJUANA USE AND ABUSE 2

CHAPTER 3: First, Do No Harm: Consequences of Marijuana Use and Abuse

Primum non nocere. This is the physician's first rule: whatever treatment a physician prescribes to a patient—first, that treatment must not harm the patient.

The most contentious aspect of the medical marijuana debate is not whether marijuana can alleviate particular symptoms, but rather the degree of harm associated with its use. This chapter thus explores the negative health consequences of marijuana use, first with respect to drug abuse, then from psychological perspective, and finally from a physiological perspective.

The Marijuana "High"

The most commonly reported effects of smoked marijuana are a sense of well-being or euphoria and increased talkativeness and laughter alternating with periods of introspective dreaminess followed by lethargy and sleepiness (see reviews by Adams and Martin 1996, and Hall 1994 and 1998[1, 58, 59]). A characteristic feature of a marijuana "high" is a distortion in the sense of time associated with deficits in short-term memory and learning. A marijuana smoker typically has a sense of enhanced physical and emotional sensitivity, including a feeling of greater interpersonal closeness. The most obvious behavioral abnormality displayed by someone under the influence of marijuana is difficulty in carrying on an intelligible conversation, perhaps because of an inability to remember what was just said even a few words earlier.

The high associated with marijuana is not generally claimed to be integral to its therapeutic value. But mood enhancement, anxiety reduction, and mild sedation can be desirable qualities in medications—particularly for patients suffering pain and anxiety. Thus, although the psychological effects of marijuana are merely side effects in the treatment of some symptoms, they might contribute directly to relief of other symptoms. They also must be monitored in controlled clinical trials to discern which effect of cannabinoids is beneficial. These possibilities are discussed later under the discussions of specific symptoms in chapter 4.

The effects of various doses and routes of delivery of THC are shown in table 3.1.

Table 3.1 Psychoactive Doses of THC in Humans

THC Delivery System	*THC Dose Administered*	*Resulting Level of THC in Plasma*	*Subjects' Reactions*	*Reference*
One 2.75% THC cigarette smoked	0.32 mg/kg*	50-100 ng/ml	At higher level subjects felt 100% "high" and psychomotor performance is decreased. At 50 ng/ml subjects felt about 50% "high"	Heishman and coworkers 1990
1 gm marijuana cigarette smoked (2% or 3.5% THC)	0.25–0.50 mg/kg*	Not measured	Enough to feel psychological effects of THC	Kelly and coworkers 1993
19 mg THC cigarette smoked (approx 1.9% THC)	Approx. 0.22 mg/kg**	100 ng/ml	Subjects felt "high"	Ohlsson and coworkers 1980
5 mg THC injected i.v.	Approx. 0.06 mg/kg**	100 ng/ml	Subjects felt "high"	
Chocolate chip cookie containing 20 mg THC	Approx. 0.24 mg/kg	8 ng/ml	Subjects rated "high" as only about 40%	
19 mg THC cigarette smoked to "desired high"	12 mg was smoked (7 mg remained in cigarette butt)	85 ng/ml (*after 3 min.*) 35 ng/ml (*after 15 min.*)	Subjects felt "high" after 3 minutes, and maximally high after 10-20 minutes (average self ratings of 5.5 on a 10-point scale)	Lindgren and coworkers 1981
5 mg THC injected i.v.	0.06 mg/kg***	300 ng/ml (*after 3 min.*) 65 ng/ml (*after 15 min.*)	Subjects felt maximally "high" after 10 minutes (average self ratings of 7.5 on a 10-point scale)	

* Subjects' weights and cigarette weights were not given. Calculation based on 85 kg body weight, and 1 g cigarette weight. Note that some THC would have remained in the cigarette butt and some would have been lost in side-stream smoke, so these represent maximal possible doses administered. Actual doses would have been slightly less.

** Based on estimated average weight of 85 kg for 11 men aged 18-35 years.

*** Based on approximately weight of 80 kg (subjects included men and women).

Adverse mood reactions

Although euphoria is the more common reaction to smoking marijuana, adverse mood reactions can occur. Such reactions occur most frequently in inexperienced users after large doses of smoked or oral marijuana. They usually disappear within hours and respond well to reassurance and a supportive environment. Anxiety and paranoia are the most common acute adverse reactions;[58] others include panic, depression, dysphoria, depersonalization, delusions, illusions, and hallucinations.[1, 40, 65, 68] Of regular marijuana smokers, 17% report that they have experienced at least one of the symptoms, usually early in their use of marijuana.[144] Those observations are particularly relevant for the use of medical marijuana in people who have not previously used marijuana.

Drug dynamics

There are many misunderstandings about drug abuse and dependence (see reviews by O'Brien[113] and Goldstein[54]). The terms and concepts used in this report are as defined in the most recent Diagnostic and Statistical Manual of Mental Disorders (DSM-IV[3]), the most influential system in the United States for diagnoses of mental disorders, including substance abuse (see box on definitions). Tolerance, dependence, and withdrawal are often presumed to imply abuse or addiction, but this is not the case. Tolerance and dependence are *normal* physiological adaptations to repeated use of any drug. The correct use of prescribed medications for pain, anxiety, and even hypertension commonly produces tolerance and some measure of physical dependence.

Even a patient who takes a medicine for appropriate medical indications and at the correct dosage can develop tolerance, physical dependence, and withdrawal symptoms if the drug is stopped abruptly rather than gradually. For example, a hypertensive patient receiving a beta-adrenergic receptor blocker, such as propranolol, might have a good therapeutic response; but if the drug is stopped abruptly, there can be a withdrawal syndrome that consists of tachycardia and a rebound increase in blood pressure to a point, temporarily higher than before administration of the medication began.

Because it is an illegal substance, some people consider any use of marijuana as substance abuse. However, this report uses the medical definition; that is, substance abuse is a maladaptive pattern of repeated substance use manifested by recurrent and significant adverse consequences.[3] Substance abuse and dependence are both diagnoses of pathological substance use. Dependence is the more serious diagnosis and implies compulsive drug use that is difficult to stop despite significant substance-related problems (see box on criteria for substance dependence).

Definitions

Addiction. Substance dependence.

Craving refers to the intense desire for a drug and is the most difficult aspect of addiction to overcome.

Physiological dependence is diagnosed when there is evidence of either tolerance or withdrawal; it is sometimes, but not always, manifested in substance dependence.

Reinforcement. A drug—or any other stimulus—is referred to as a reinforcer if exposure to it is followed by an increase in frequency of drug-seeking behavior. The taste of chocolate is a reinforcer for biting into a chocolate bar. Likewise, for many people, the sensation experienced after drinking alcohol or smoking marijuana is a reinforcer.

Substance dependence is a cluster of cognitive, behavioral, and physiological symptoms indicating that a person continues use of the substance despite significant substance-related problems.

Tolerance is the most common response to repetitive use of a drug and can be defined as the reduction in responses to the drug after repeated administrations.

Withdrawal. The collective symptoms that occur when the drug is abruptly withdrawn are known as withdrawal syndrome and are often the only evidence of physical dependence.

DSM-IV Criteria for Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) Tolerance, as defined by either of the following:
   (a) A need for markedly increased amount of the substance to achieve intoxication or desired effect.
   (b) Markedly diminished effect with continued use of the same amount of the substance.

(2) Withdrawal, as defined by either of the following:
   (a) The characteristic withdrawal syndrome for the substance.
   (b) The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.

(3) The substance is often taken in larger amounts or over a longer period than was intended.

(4) There is a persistent desire or unsuccessful efforts to cut down or control substance use.

(5) A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects.

(6) Important social, occupational, or recreational activities are given up or reduced because of substance use.

(7) The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

Substance abuse *with* physiological dependence is diagnosed if there is evidence of tolerance or withdrawal.

Substance abuse *without* physiological dependence is diagnosed if there is no evidence of tolerance or withdrawal.

Reinforcement

Drugs vary in their ability to produce good feelings in the user, and the more strongly reinforcing a drug is, the more likely it will be abused (G. Koob, IOM workshop). Marijuana is indisputably reinforcing for many people. The reinforcing properties of even so mild a stimulant as caffeine are typical of reinforcement by addicting drugs (reviewed by Goldstein[54] in 1994). Caffeine is reinforcing for many people at low doses (100-200 mg, the average amount of caffeine in one to two cups of coffee), and aversive at high doses (600 mg, the average amount of caffeine in six cups of coffee). The reinforcing effects of many drugs are different for different people. For example, caffeine was most reinforcing for test subjects who scored lowest on tests of anxiety but tended not to be reinforcing for the most anxious subjects.

As an argument to dispute the abuse potential of marijuana, some have cited the observation that animals do not willingly self-administer THC, as they will cocaine. Even if that were true, it would not be relevant to human use of marijuana. The value in animal models of drug self-administration is not that they are necessary to show that a drug is reinforcing, but rather that they provide a model in which the effects of a drug can be studied. Furthermore, THC is indeed rewarding to animals at some doses but, like many reinforcing drugs, is aversive at high doses (4.0 mg/kg).[92] Similar effects have been found in experiments conducted in animals outfitted with intravenous catheters that allow them to self-administer WIN 55,212, a drug that mimics the effects of THC.[99]

A specific set of neural pathways has been proposed to be a "reward system" that underlies the reinforcement of drugs of abuse[51] and other pleasurable stimuli.[51] Reinforcing properties of drugs are associated with their ability to increase concentrations of particular neurotransmitters in areas that are part of the proposed brain reward system. The median forebrain bundle and the nucleus accumbens are associated with brain reward pathways.[87] Cocaine, amphetamine, alcohol, opioids, nicotine, and THC[143] all increase extracellular fluid dopamine in the nucleus accumbens region (reviewed by Koob[87] and Nestler[109] in 1997). However, it is important to note that brain reward systems are not strictly "drug reinforcement centers". Rather, their biological role is to respond to a range of positive stimuli, including sweet foods and sexual attraction.

Tolerance

The rate at which tolerance to the various effects of any drug develops is an important consideration for its safety and efficacy. For medical use, tolerance to some effects of cannabinoids might be desirable. Differences in the rates at which tolerance to the multiple effects of a drug develops can be dangerous. For example, tolerance to the euphoric effects of heroin develops faster than tolerance to its

respiratory depressant effects, so heroin users tend to increase their daily doses to reach their desired level of euphoria, thereby putting them at risk for respiratory arrest. Because tolerance to the various effects of cannabinoids might develop at different rates, it is important to evaluate independently their effects on mood, motor performance, memory, and attention, as well as any therapeutic use under investigation.

Tolerance to most of the effects of marijuana can develop rapidly after only a few doses, and it also disappears rapidly. Tolerance to large doses has been found to persist in experimental animals for long periods after cessation of drug use. Performance impairment is less among people who use marijuana heavily than it is among those who use marijuana only occasionally,[29, 103, 123] possibly because of tolerance. Heavy users tend to reach higher plasma concentrations of THC than light users after similar doses of THC, arguing against the possibility that heavy users show less performance impairment because they somehow absorb less THC (perhaps due to differences in smoking behavior).[94]

There appear to be variations in the development of tolerance to the different effects of marijuana and oral THC. For example, a group of daily marijuana smokers participated in a residential laboratory study to compare the development of tolerance to THC pills and to smoked marijuana.[60, 61] One group was given marijuana cigarettes to smoke four times per day for four consecutive days. Another group was given THC pills on the same schedule. During the 4-day period, both groups became tolerant to feeling "high" and what they reported as a "good drug effect." In contrast, neither group became tolerant to the stimulatory effects of marijuana or THC on appetite. Note that tolerance does not mean the drug no longer produced those effects, simply that the effects were less at the end than they were at the beginning of the 4-day period. The marijuana smoking group reported feeling "mellow" after smoking, and did not show tolerance to this effect. Interestingly, the group who took THC pills did not report feeling "mellow," a difference that was also reported by many people who described their experiences to the IOM study team.

The oral and smoked doses were designed to deliver roughly equivalent amounts to THC to the subject. Each smoked marijuana dose consisted of five 10-second puffs of a 3.1% marijuana cigarette; the pills contained 30 mg of THC. Both groups also received placebo drugs during other four-day periods. While the dosing of the two groups was comparable, different routes of administration result in different patterns of drug effect. The peak effect of smoked marijuana is felt within minutes, and declines sharply after 30 minutes,[67, 94] ; the peak effect of oral THC is usually not felt until about an hour and lasts for several hours.[117]

Withdrawal

A distinctive marijuana and THC withdrawal syndrome has been identified, but it is mild and subtle compared to the profound physical syndrome of alcohol or heroin withdrawal.[31, 73] The marijuana withdrawal syndrome includes restlessness, irritability, mild agitation, insomnia, sleep EEG disturbance, nausea, and cramping

(table 3.2). This syndrome, however, has only been reported in a group of adolescents in treatment for substance abuse problems[31] or in a research setting where subjects were given marijuana or THC on a daily basis.[73]

Table 3.2 Drug Withdrawal Symptoms

Nicotine	***Alcohol***	***Marijuana***	***Cocaine***	***Opioids*** *(e.g. heroin)*
Restlessness	Tremor	Restlessness	Dysphoria	Restlessness
Irritability	Irritability	Irritability	Depression	Irritability
Dysphoria	Nausea	Mild agitation	Bradycardia	Increased sensitivity to pain
Impatience, hostility	Sleep disturbance	Sleep EEG disturbance	Sleepiness, fatigue	Dysphoria
Depression	Tachycardia	Insomnia	Cocaine craving	Insomnia, anxiety
Difficulty concentrating	Perceptual distortion	Nausea, cramping		Muscle aches
Anxiety	Hypertension			Nausea, cramps
Decreased heart rate	Sweating			Opioid craving
Increased appetite or weight gain	Seizures			
	Alcohol craving			
	Delirium tremens (severe agitation, confusion, visual hallucinations, fever, profuse sweating, nausea, diarrhea, dilated pupils)			

Table legend. This summary of withdrawal symptoms is from O'Brien's 1996 review.[112] In addition to the established symptoms listed above, two recent studies have reported several more. A group of adolescents under treatment for conduct disorders also reported *fatigue* and *illusions* or *hallucinations* after marijuana abstinence (this study is discussed further under the section on "Prevalence and Predictors of Dependence").[31] In a residential study of daily marijuana users, withdrawal symptoms included *sweating* and *rhinorrhea* (runny nose), in addition to those listed above[61] (this study is discussed further under the section on "Tolerance").[31]

Withdrawal symptoms have been observed in carefully controlled laboratory studies of people following use of both oral THC and smoked marijuana (Haney and coworkers in press). In one study, subjects were given very high doses of oral THC: 180-210 mg per day for 10 to 20 days, roughly equivalent to smoking 9-10 two-percent THC cigarettes per day.[73] During the abstinence period at the end of the study, the study subjects were irritable and showed insomnia, rhinorrhea (runny nose), sweating, and decreased appetite. The withdrawal symptoms, however, were short-lived. After four days they had abated. This time course contrasts with another study in which lower doses of oral THC were used (80-120 mg/day for four days), and withdrawal symptoms were still near maximal after four days (Haney and coworkers, in press).

In animals, simply discontinuing chronic heavy dosing of THC does not reveal withdrawal symptoms[17] However, in animal studies, the "removal" of THC from the brain can be made abrupt by another drug that blocks THC at its receptor when administered at the same time the chronic THC is withdrawn. In this case, the withdrawal syndrome is quite pronounced, and the behavior of the animals becomes hyperactive and disorganized.[152] The half-life of THC in brain is approximately one hour.[16, 24] Although traces of THC can remain in the brain for much longer periods, the amounts are not physiologically significant. Thus, the lack of a withdrawal syndrome seen if THC is abruptly withdrawn without the addition of a receptor-blocking drug is not likely due to a prolonged decline in brain levels.

Craving

Craving, the intense desire for a drug, is the most difficult aspect of addiction to overcome. Research on craving has focused on nicotine, alcohol, cocaine, and opiates, but has not specifically addressed marijuana.[114] Thus, while this section briefly reviews what is known about drug craving, its relevance to marijuana use has not been established.

Most individuals who suffer from addiction relapse within a year of abstinence, and they often attribute their relapse to craving.[57] As addiction develops, craving increases even as maladaptive consequences accumulate. Animal studies indicate that the tendency to relapse is based on changes in brain function that continue for months or years after the last use of the drug.[114] Whether the neurobiology changes during the manifestation of an abstinence syndrome remains an unanswered question in drug abuse research.[87] The "liking" of sweet foods, for example, is mediated by certain opioid forebrain systems and by brain-stem systems, whereas "wanting" seems to be mediated by ascending dopamine neurons that project to the nucleus accumbens.[108]

Anti-craving medications have been developed for nicotine and alcohol. The antidepressant, bupropion, blocks nicotine craving, while naltrexone blocks alcohol craving.[114] Another category of addiction medication includes drugs that block

another drug's effects. Some of these addiction medication drugs also block craving. For example, methadone blocks the euphoria effects of heroin and also reduces craving.

Marijuana Use and Dependence

Prevalence of Use

Millions of Americans have tried marijuana, but most are not regular users. In 1996, 68.6 million people or 32 % of the U.S. population over 12 years old had tried marijuana or hashish at least once in their lifetime, but only 5 % were current users.[131] Marijuana use is most prevalent among 18-25 year olds and declines sharply after age 34 (figure 3.1).[76, 131] Among adolescents, whites are more likely than blacks to use marijuana, although this difference decreases by adulthood. [131]

Most people who have used marijuana did so first during adolescence. Social influences, such as peer pressure and prevalence of use by peers, are highly predictive of initiation into marijuana use.[9] Initiation is not, of course, synonymous with continued or even regular use. A cohort of 456 students who experimented with marijuana during their high school years were surveyed about their reasons for initiating, continuing, and stopping drug use.[9] Students who began as heavy users were excluded from the analysis. Those who did not become regular marijuana users cited two types of reasons for discontinuing. The first was related to their health and well-being; that is, they felt marijuana was bad for their health or their family and work relationships. The second type was based on age-related changes in circumstances, including increased responsibility and less regular contact with other marijuana users. Interestingly, among high school students who quit, parental disapproval was a stronger influence than peer disapproval in discontinuing marijuana use. In the initiation of marijuana use, the reverse was true. The reasons cited by those who continued to use marijuana were to "get in a better mood or feel better." Social factors were not a significant predictor of continued use after initiation. Data on young adults show similar trends. Those who use drugs in response to social influences are more likely to stop using them than those who also use drugs for psychological reasons.[79]

The age distribution of marijuana users among the general population contrasts with that of medical marijuana users. Marijuana use generally declines sharply after age 34, whereas medical marijuana users tend to be over 35 (figure 3.1). This raises the question as to what, if any, relationship exists between abuse and medical use of marijuana; however, there are no studies reported in the scientific literature that address this question.

Figure 3.1 Age distribution of marijuana users among the general population

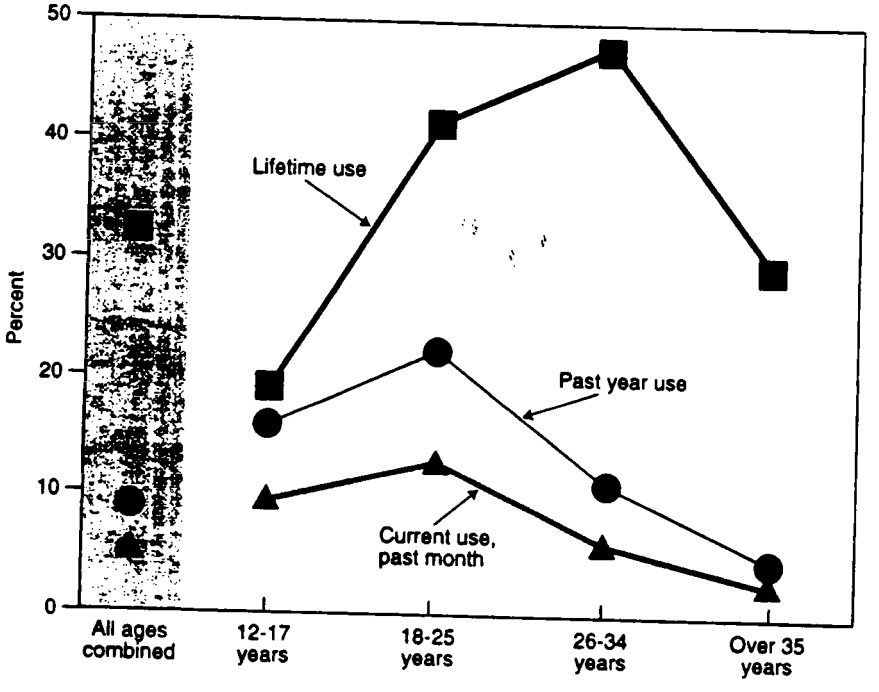


FIG 3.1
Job 11763

Prevalence and Predictors of Drug Dependence

Many factors influence the likelihood that a particular person will become a drug abuser or an addict: the user, the environment, and the drug are all important factors (table 3.3).[113] The first two categories apply to potential abuse of any substance; that is, someone who is vulnerable to drug abuse for individual reasons, and who finds themselves in an environment that encourages drug abuse, is initially likely to abuse the most readily available drug—regardless of its unique set of effects on the brain.

The third category includes drug-specific effects that influence the abuse liability of a particular drug. As discussed earlier in this chapter, the more strongly reinforcing a drug is, the more likely it will be abused. The abuse liability of a drug is enhanced by how quickly its effects are felt, and this is determined by how the drug is delivered. In general, the effects of drugs that are inhaled or injected are felt within minutes, those that are ingested take half an hour or more. The proportion of people who become addicted varies among drugs (table 3.4).

Table 3.3 Factors that are correlated with drug dependence

Individual Factors

- Pharmacological effects of the drug
- Gender
- Age
- Genetic factors
- Individual risk-taking propensities
- History of prior drug use

Environmental Factors

- Availability of the drug
- Acceptance of the use of that drug within society
- Balance of social reinforcements and punishments for use
- Balance of social reinforcements and punishments for abstinence

Source: Crowley and Rhine (1985)[32]

Table legend. Factors that can influence the likelihood that an individual will become dependent on a drug.

Table 3.4 Prevalence of Drug Use and Dependence Among the General Population

Drug Category	*Proportion Who Have Ever Used Different Types of Drugs*	*Proportion Of Users That Ever Became Dependent*
Tobacco	76 %	32 %
Alcohol	92 %	15 %
Marijuana (including hashish)	46 %	9 %
Anxiolytics (including sedatives and hypnotic drugs)	13 %	9 %
Cocaine	16%	17 %
Heroin	2%	23 %

Table legend. The table shows estimates for the proportion of people among the general population who used or became dependent on different types of drugs. The ***proportion of users that ever became dependent*** includes anyone who was ***ever*** dependent—whether it was for a period of weeks or years—and thus includes more than those who are currently dependent. The diagnosis of drug dependence used in this study was based on DSM-III-R criteria.[2] Adapted from table 2 in Anthony and coworkers (1994).[8]

Compared to most other drugs listed in this table, dependence among marijuana users is relatively rare. This might be due to differences in the specific drug effects; in the availability of, or penalties associated with the use of, the different drugs—or, some combination of these possible reasons.

Note that the percent listed are from the Epidemiological Catchment Area study, and (of people who ever used marijuana) (46 %), are higher than that reported by the National Household Survey on Drug abuse (32%). The differences are likely due to different survey methods (for discussion see Kandel 1992 [75]).

Daily use of most illicit drugs is extremely rare in the general population. In 1989 daily use of marijuana among high school seniors was less than that of alcohol (2.9% and 4.2 %, respectively)[75]

Drug dependence is more prevalent in certain sectors of the population than others. Age, gender, and race or ethnic group are all significant factors.[8] Excluding tobacco and alcohol, the following trends of drug dependence are statistically significant:[8] Men are 1.6 times more likely than women to become drug dependent. Non-Hispanic whites are about twice as likely as African-Americans to become drug dependent. (The difference between non-Hispanic and Hispanic whites was not significant.) Lastly, people aged 25-44 years are more than three times as likely as those over 45 years to become drug dependent.

More often than not, drug dependence co-occurs with one or more other psychiatric disorders. The majority of individuals diagnosed with a drug dependence disorder are also diagnosed with another psychiatric disorder (76 % of men, 65 % of women).[75] The most frequent co-occurring disorder is alcohol abuse; 60 % of men and 30 % for women diagnosed as drug dependent also abuse alcohol. For women who are drug dependent, phobic disorders and major depression are almost equally common (29 % and 28 %, respectively). Note that this study distinguished only between alcohol, nicotine and "other drugs," the category that included marijuana. The frequency with which drug dependence and other psychiatric disorders co-occur might not be the same for marijuana and other drugs that were included in that category of "other drugs."

A strong association between drug dependence and antisocial personality or its precursor, conduct disorder, is also widely reported in children and adults (reviewed by Robins[125] in 1998). Although the causes of this association are still uncertain, Robins recently concluded that it is more likely that conduct disorders generally lead to substance abuse than the reverse.[125] Such a trend might, however, depend on the age at which the conduct disorder is manifested.

A longitudinal study by Brooks and coworkers indicated that while childhood conduct disorder may lead to later drug use for older adolescents there is no evidence that depression, anxiety, or conduct disorders precede heavy drug use.[18] Rather, the drug use preceded the psychiatric disorders. In contrast to tobacco and other illicit drugs, moderate (less than once a week, more than once a month) to heavy marijuana use did not predict anxiety or depressive disorders, but was consistent with those other drugs in predicting antisocial personality disorder. The rates of disruptive disorders increased with increased levels of drug use. Thus, heavy drug use among adolescents can be a warning sign for later psychiatric disorders; whether it is an early manifestation of symptoms for those disorders or a causal factor remains to be determined.

Psychiatric disorders are more prevalent among adolescents who use drugs—including alcohol and nicotine.[78] Table 3.5 indicates that daily cigarette smoking among adolescent boys is associated with an approximately tenfold increase in the likelihood of being diagnosed with a psychiatric disorder compared to those who do not smoke. Note, however, that the table does not compare equivalent intensity of use among the different drug classes. Thus, although *daily* cigarette smoking among adolescents is more strongly associated with psychiatric disorders than is any use of illicit substances, it does not follow that this comparison is true for every amount of cigarette smoking.[78]

Table 3.5 Psychiatric disorders associated with drug use among children

Relative prevalence of diagnoses for psychiatric disorders associated with drug use among children

Drug Use	Relative Prevalence Estimates	
	Boys	*Girls*
Weekly alcohol use	6.1	1.6 (n.s.)
Daily cigarette smoking	9.8	2.1 (n.s.)
Any illicit substance use	3.2	5.3

Table legend. The subjects ranged in age from 9-18 years, with an average age of 13 years.

A ratio of one means that the relative prevalence of the disorder is equal among those who do and those who do not use the particular type of drug; that is, there is no measurable association. A ratio greater than one indicates that the factor is associated. Thus boys who smoke daily are as almost ten times more often diagnosed as having a psychiatric disorder (not including substance abuse) as those who smoke less. Substance abuse was excluded from this analysis since the subjects being analyzed were already grouped by their high drug use. Except where noted (n.s.) all values are statistically significant.

Data are from table 4 in Kandel and coworkers 1997[78]

Marijuana Dependence

Few marijuana users become dependent (table 3.4), but those who do encounter problems similar to those associated with dependence on other drugs.[19, 142] The severity of dependence appears to be less among people who use only marijuana than among those who abuse cocaine or abuse marijuana with other drugs (including alcohol).[19, 142]

Data gathered in 1990-1992 from the National Comorbidity Study of over 8,000 persons aged 15-54 years indicate that 4.2 % of the general population were dependent on marijuana at one time in their life.[8] Similar results for the frequency of substance abuse among the general population were obtained from the Epidemiological Catchment Area Program, a survey of over 19,000 people. Based on data collected in the early 1980s for that study, 4.4 % of adults have, at one time, met the criteria for marijuana dependence. For comparison, 13.8 % of adults met the criteria for alcohol-dependence and 36.0 % met them for tobacco. After alcohol and nicotine, marijuana was the substance most frequently associated with a diagnosis of substance dependence.

In a fifteen-year study begun in 1979 of 1,201 adolescents and young adults in suburban New Jersey, 7.3 % of those subjects, at one time, met the criteria for marijuana dependence, indicating that the rate of marijuana dependence might be even higher in some groups of adolescents and young adults than for the general population.[70] Adolescents meet the criteria of drug dependence at lower rates of marijuana use than do adults, suggesting that they are more vulnerable to dependence than adults[25] (see box on Criteria for Substance Abuse).

Youths who are already dependent on other substances are particularly vulnerable to marijuana dependence. For example, Crowley and coworkers[31] interviewed a group of 229 adolescent patients in a residential treatment program for delinquent, substance-involved youth, and found that those patients were dependent on an average of 3.2 different substances. The adolescents in this study had previously been diagnosed as dependent on at least one substance (including nicotine and alcohol) and had three or more conduct disorder symptoms during their life. Among those troubled adolescents, about 83 % of those who had previously used marijuana at least six times went on to develop marijuana dependence. Approximately equal numbers of youths in this study were diagnosed as marijuana-dependent as were diagnosed as alcohol-dependent; fewer were diagnosed as nicotine-dependent. However, comparisons between the dependence potential of different drugs should be made cautiously. The probability that a particular drug will be abused is influenced by many factors, including the specific drug effects and availability of the drug.

Although parents often state that marijuana caused their children to be rebellious, the troubled adolescents in the study by Crowley and coworkers developed conduct disorders *before* marijuana abuse. This is consistent with reports showing that the more symptoms of conduct disorders children have, the younger they begin drug abuse,[126] and that the younger they begin drug use, the more likely it is to be followed by abuse or dependence.[124]

Genetic factors are known to play a role in the likelihood of substance abuse for drugs other than marijuana,[7, 128] and it is not unexpected that genetic factors might play a role in the marijuana experience, including the likelihood of abuse. A study of over 8,000 male twins listed in the Vietnam Era Twin Registry indicated that genes have a significant influence on whether an individual finds the effects of marijuana pleasant.[96] Not surprisingly, individuals who found marijuana to be pleasurable used it more often than those who found it unpleasant. The study suggested that, although social influences play an important role in the initiation of use, individual differences—perhaps associated with the brain's reward system—influence whether an individual will continue using marijuana. Similar results were found in a study of female twins.[85] Family and social environment strongly influenced the likelihood of ever using marijuana, but had little impact on the likelihood of heavy use or abuse. The latter were more influenced by genetic factors. These results are consistent with the finding that the degree to which rats find THC rewarding is genetically based.[91]

In sum, although few marijuana users develop dependence, some do. But, they appear to be less likely to do so than users of other drugs (including alcohol and nicotine), and marijuana dependence appears to be less severe than it is for other drugs. Drug dependence is more prevalent in certain sectors of the population, but no group has been identified as being particularly vulnerable to the drug-specific effects of marijuana. Adolescents, especially troubled adolescents, and people with psychiatric disorders (including substance abuse) appear to more likely than the general population to become dependent on marijuana.

If marijuana or cannabinoid drugs were approved for therapeutic uses, it would be important to consider the possibility of dependence, particularly for patients in high risk groups for substance dependence. Certain controlled substances that are approved medications produce dependence after long term use. This is, however, a normal part of patient management and does not generally present undue risk to the patient.

Progression from Marijuana to Other Drugs

The fear that marijuana use might cause, as opposed to merely precede, the use of drugs that are more harmful is of great concern. Judging from comments submitted to the IOM study team, this appears to be an even greater concern than the harms directly related to marijuana itself. The discussion that marijuana is a "gateway" drug implicitly recognizes that other illicit drugs might inflict greater damage to health or social relations than marijuana. Although the scientific literature generally discusses drug use progression between a variety of drug classes, including alcohol and tobacco, the public discussion has focused on marijuana as a "gateway" drug that leads to abuse of more harmful illicit drugs such as cocaine and heroin.

There are strikingly regular patterns in the progression of drug use from adolescence to adulthood. Because it is the most widely used illicit drug, marijuana is predictably the first illicit drug most people encounter. Not surprisingly, most users of other illicit drugs have used marijuana first.[80, 81] In fact, most drug users do not begin their drug use with marijuana; they begin with alcohol and nicotine—and usually when they are too young to do so legally.[81 89]

The gateway analogy evokes two ideas that are often confused. The first, more often referred to as the 'stepping stone' hypothesis, is the idea that progression from marijuana to other drugs arises from pharmacological properties of marijuana itself.[81] The second interpretation is that marijuana serves as a gateway to the world of illegal drugs in which youths have greater opportunity and are under greater social pressure to try other illegal drugs. This is the interpretation most often used in the scientific literature, and is supported by—although not proven by—the available data.

The stepping stone hypothesis applies to marijuana only in the broadest sense. People who enjoy the effects of marijuana are, logically, more likely to be willing to try other mood-altering drugs than are people who are not willing to try marijuana or who dislike its effects. In other words, many of the factors associated with a willingness to use marijuana are, presumably, the same as those associated with a willingness to use other illicit drugs. Those factors include physiological reactions to the drug effect, which are consistent with the stepping stone hypothesis, but also psychosocial factors that are independent of drug-specific effects. There is no evidence that marijuana serves as a stepping stone on the basis of its particular drug effect. One might argue that marijuana is generally used before other illicit mood-altering drugs, in part, because its effects are milder, but in that case, marijuana is a stepping stone only in the same sense as taking a small dose of a particular drug and then increasing that dose over time is a stepping stone to increased drug use.

Whereas the stepping stone hypothesis presumes a predominantly physiological component to drug progression, the gateway theory is a social theory. The latter does not suggest that the pharmacological qualities of marijuana make it a risk factor for progression to other drug use. Instead it is the legal status of marijuana that makes it a gateway drug.[81]

Psychiatric disorders are associated with substance dependence, and are likely risk factors for progression in drug use. For example, the troubled adolescents studied by Crowley and coworkers[31] were dependent on an average of 3.2 substances, suggesting that their conduct disorders are associated with increased risk of progressing from one drug to another. Substance abuse of a single substance is also a likely risk factor for subsequent multiple drug use. For example, in a longitudinal study that examined drug use and dependence, about 26 % of problem drinkers report they first used marijuana after the onset of alcohol-related problems (R. Pandina, IOM workshop). This study also found that 11 % of marijuana users developed chronic marijuana problems, although most also had alcohol problems.

Intensity of drug use is also an important risk factor in progression. Daily marijuana users are more likely than their peers to be extensive users of other substances (for review see Kandel and Davies[77]). Seventy-five percent of 34-35 year old men who had used marijuana 10-99 times by age 24-25 never used any other illicit drug; 53 % of those who had used it more than 100 times did progress to using other illicit drugs 10 or more times. [77] Comparable proportions for women are 64 % and 50 %.

The factors that best predict illicit drug use other than marijuana are likely the following: age of first alcohol or nicotine use, heavy marijuana use, and psychiatric disorders. However, it is important to keep in mind that progression to illicit drug use is not synonymous with heavy or persistent drug use. Indeed, although the age of onset for licit drug alcohol and nicotine) use predicts later illicit drug use, age of first use of licit drugs does *not* appear to predict persistent or heavy use of those drugs.[89]

Data on the gateway phenomenon are frequently over-interpreted. For example, one study reports that "marijuana's role as a gateway drug appears to have increased" (Golub and Johnson 1994). This was a retrospective study based on interviews of drug abusers who reported smoking crack or injecting heroin on a daily basis. Those data provide no indication of what proportion of marijuana users become serious drug abusers. Rather, they indicate that serious drug abusers usually use marijuana before they smoke crack or inject heroin. Only a small percent of the adult population use crack or heroin on a daily basis; during the five-year period from 1993-1997, an average of three people per 1000 had used crack and about two per 1000 had used heroin in the past month.[131]

Many of the data on which the gateway theory is based do not measure dependence. Instead they measure use, even once-only use. Thus those data show only that, compared to people who never use marijuana, marijuana users are more likely to use those drugs (maybe even only once), not that they become dependent or even frequent users. Note that the authors of these studies are careful to point out that their data should not be used as evidence of an inexorable, *causal* progression. Rather they note that identifying stage-based user groups makes it possible to identify the specific risk factors that predict movement from one stage of drug use to the next—this is the real issue in the gateway discussion.[25]

In the sense that marijuana use typically precedes rather than follows initiation into the use of other illicit drugs, it is indeed a gateway drug. However, it does not appear to be a gateway drug to the extent that it is the most significant predictor or even the cause of heavy drug abuse; that is, care must be taken not to attribute cause to association. The most consistent predictors of heavy drug use appear to be the intensity of marijuana use, and co-occurring psychiatric disorders or a family history of psychopathology including alcoholism).[77, 82]

An important caution is that data on drug use progression pertain to nonmedical drug use. It does not follow from those data that if marijuana were available by prescription for *medical* use, the pattern of drug use would be the same. Kandel and coworkers also studied nonmedical use of prescription psychoactive drugs in their study of drug use progression.[81] In contrast to alcohol, nicotine, and illicit drugs, there was not a clear and consistent sequence of drug use involving the abuse of prescription psychoactive drugs. At present, the data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse among medical marijuana users. It is, admittedly, another question as to whether the medical use of marijuana might encourage drug abuse among the general community—not among medical marijuana users themselves, but among others simply because of the fact that marijuana is used for medical purposes.

The Link Between Medical Use and Drug Abuse

Almost everyone who spoke or wrote to the IOM study team about the potential harms of the medical use of marijuana felt that it would send the wrong message to children and teenagers. They stated that information about the harms of marijuana is undermined by claims that marijuana might have medical value. Yet, many of our powerful medicines are also dangerous medicines. These two facets of medicine—effectiveness and risk—are inextricably linked.

The question here is not whether marijuana can be both harmful and helpful, but whether the perception of its benefits will increase its abuse. For now, any answer to the question remains conjecture. Because marijuana is not an approved medicine, there is little information about the consequences of its medical use in modern society. The following are three examples from which reasonable inferences might be drawn. Opiates such as morphine and codeine are an example of a class of drugs that is both abused to great harm and used to great medical benefit, and it would be useful to examine the relationship between medical use and abuse. Another example is the natural experiment during 1973-1978 in which some states decriminalized marijuana, and others did not. Finally, one can examine the short-term consequences of the publicity surrounding the 1996 medical marijuana campaign in California. Did this have any measurable impact on the marijuana consumption among youth in California? The consequences of this "message" that marijuana might have medical use are examined below.

Medical Use and Abuse of Opiates

Two highly influential papers published in the 1920s and 1950s led to a widespread concern among physicians and medical licensing boards that liberal use of opiates would result in many addicts reviewed by Moulin and coworkers[105] in 1996). Such fears have proven unfounded; it is now recognized that fear of producing addicts through medical treatment resulted in needless suffering among patients with pain, as physicians needlessly limited appropriate doses of medications.[27, 44] Few individuals begin their drug addiction problems by misuse of drugs that have been prescribed for medical use.[113] In general, opiates are carefully regulated in the medical setting and diversion of medically prescribed opiates to the black market is not generally considered to be a major problem.

There is no evidence to suggest that the use of opiates or cocaine for medical purposes has increased the perception that the illicit use of these drugs is safe or acceptable. Clearly, there are risks that patients may abuse marijuana for its psychoactive effects as well as risks of diversion of marijuana from legitimate medical channels into the illicit market. Again, this does not differentiate marijuana from many accepted medications that are abused by some patients or diverted from medical channels for non-medical use. Where this has taken place, medications have been placed in Schedule II of the Controlled Substances Act, which brings the drug under stricter control, including quotas on the amount that can be legally manufactured (see chapter 5 for discussion of the Controlled Substances Act). This scheduling also signals to physicians that the drug has abuse potential and that they should monitor the use of the medication by patients that may be at risk for drug abuse.

Effect of Marijuana Decriminalization

Monitoring the Future, the annual survey of values and life-styles of high school seniors, revealed that high school seniors in decriminalized states reported using no more marijuana than did their counterparts in states where marijuana was not decriminalized.[71] Another study reported somewhat conflicting evidence indicating that decriminalization had increased marijuana use.[104] That study used data from the Drug Awareness Warning Network (DAWN), which has collected data since 1975 on drug-related emergency (ER) room cases. Among states that had decriminalized marijuana in 1975-1976, there was a greater increase from 1975 to 1978 in the proportion of ER patients who had used marijuana than in states that did not decriminalize marijuana (table 3.6). Despite the greater increase among decriminalized states, by 1978, the proportion of marijuana users among ER patients was about equal in states that did and states that did not decriminalize marijuana. This is because the non-decriminalized states had higher rates of marijuana use *before* decriminalization. In contrast to marijuana use, rates of other illicit drug use among ER patients were substantially higher among states that did not decriminalize

marijuana use. Thus, there are different possible reasons for the relatively greater increase in marijuana use in the decriminalized states. On the one hand, decriminalization might have led to an increased use of marijuana (at least among people who seek health care in hospital emergency rooms). On the other hand, the lack of decriminalization might have encouraged greater use of drugs that are even more dangerous than marijuana. Interpretations are ambiguous.

The differences between the results for high school seniors from the Monitoring the Future study and DAWN data are unclear, although the author of the latter study suggests the reasons might lie in limitations inherent in how the DAWN data are collected.[104] In sum, there is not strong evidence that decriminalization causes a significant increase in marijuana use.

In 1976, the Dutch adopted a policy of toleration for possession of up to 30 g of marijuana. There was little change in marijuana use during the seven years following this policy change, suggesting that the policy change itself had little impact; however, in 1984 when Dutch "coffee shops" that sold marijuana commercially spread throughout Amsterdam, marijuana use began to increase.[97] During the 1990s, marijuana use has continued to increase in the Netherlands at the same rate as in the United States and Norway—two countries that strictly forbid marijuana sale and possession. Further, during this period, approximately equal percentages of American and Dutch 18-year olds used marijuana; Norwegian 18-year olds were approximately half as likely to have used marijuana. The authors of this study conclude that there is little evidence that the Dutch marijuana depenalization policy led to increased levels of marijuana use, although they note that commercialization of marijuana might have contributed to its increased use.

In sum, there is little evidence that decriminalization of marijuana use necessarily leads to a substantial increase in marijuana use.

Table 3.6 Decriminalization and Marijuana Use

Effect of Decriminalization on Marijuana Use in ER Cases

		Total Reports of Drug Use per ER	
	Time Period(States the decriminalized did so after 1975 and before 1978	*States that Decriminalized Marijuana*	*States that did not decriminalize marijuana*
Marijuana use	1975	0.8	1.5
	1978	2.7	2.5
Other drug use	1975	47	55
	1978	55	70

Table legend. The values shown indicate the frequency of drug use among ER patients in states that decriminalized marijuana from July 1975- July 1977 and in those that did not. Data are based on patient self-reports. The 1975 values reflect ER marijuana reports before or in the first months of decriminalization, whereas the 1978 values reflect ER reports when decriminalization laws had been in effect at least one year. The 1978 levels are median values for quarters in 1978, and are derived from figures 1 and 2 in Model (1993).[104] The values in the column for states that did not decriminalize represent what might have been seen if the states in the first column had not decriminalized.

Effect of the Medical Marijuana Debate

The most recent National Household Survey on Drug Abuse showed that among youth ages 12-17 the perceived risk of smoking marijuana once or twice a week had decreased significantly between 1996 and 1997.[131] (*Perceived risk* is measured as the percent of survey respondents who report that they "perceive great risk of harm" in using a drug at a specified frequency.) At first glance, this might seem to validate the fear that the medical marijuana debate of 1996—prior to the passage of the California medical marijuana referendum in November 1997—had sent a message that marijuana use is safe. But a closer analysis of the data shows that Californian youth were an exception to the national trend. The perceived risk of marijuana use did not change among California youth between 1996 and 1997.[131] •. In sum, there is no evidence that the medical marijuana debate has altered perceptions among adolescents about the risks of marijuana use.[131]

Psychological Harms

In assessing the relative risks and benefits of the medical use of marijuana, the psychological effects of marijuana may be viewed both as unwanted side effects as well as potentially desirable end points in medical treatment. However, the vast majority of research on the psychological effects of marijuana has been done in the context of assessing the drug's intoxicating effects when used for non-medical purposes. Thus the literature does not directly address what effects will occur when marijuana is taken for medical purposes.

There are some important caveats to consider in attempting to extrapolate from this research to the medical use of marijuana. The circumstances under which psychoactive drugs are taken are an important influence on the psychological effects produced. Further, research protocols to study marijuana's psychological effects in most instances were required to use participants who had prior experience with marijuana. Clearly, people who might have had adverse reactions to marijuana would either choose to not participate in this type of study or would be screened out by the investigator. Therefore, the incidence of adverse reactions to marijuana that might occur in individuals with no marijuana experience cannot be estimated from such studies. A further complicating factor concerns the dose regimen used for laboratory studies. In most instances laboratory research studies have looked at the effects of single doses of marijuana which might be different than that observed when the drug is taken repeatedly for a chronic medical condition.

Nonetheless, laboratory studies are useful in suggesting what psychological functions might be studied when marijuana is evaluated for medical purposes.

• Although Arizona also passed a medical marijuana referendum, it was embedded in a broader referendum concerning prison sentencing. Hence the debate in Arizona did not focus on medical marijuana the way it did in California, and changes in Arizona youth attitudes likely reflect factors peripheral to medical marijuana .)

Laboratory studies indicate that acute and chronic marijuana use has pronounced effects on mood, psychomotor, and cognitive functions. These psychological domains should, therefore, be considered in assessing the relative risks and benefits of the therapeutic use of marijuana or cannabinoids for any medical condition.

Psychiatric disorders

A major question remains as to whether marijuana can produce lasting mood disorders or psychotic disorders such as schizophrenia. Georgotas and Zeidenberg[52] reported that smoking 10-22 marijuana cigarettes per day was associated with a gradual waning of the positive mood and social facilitating effects of marijuana and an increase in irritability, social isolation and paranoid thinking. Considering that smoking *one* cigarette is enough to make a person feel "high" for about one to three hours,[67, 94, 117] the subjects in that study were taking very high doses marijuana. Reports have described the development of apathy, lowered motivation and impaired educational performance in heavy marijuana users who do not appear to be behaviorally impaired in other ways.[120, 121] There are clinical reports of marijuana-induced psychotic-like states (schizophrenia-like; depression and/or mania) lasting for a week or more.[111] Hollister suggests that because of the varied nature of the psychotic states induced by marijuana, there is no specific "marijuana psychosis." Rather, the marijuana experience may trigger latent psychopathology of many types.[65] More recently, Hall and colleagues[59] concluded that "there is reasonable evidence that heavy cannabis use, and perhaps acute use in sensitive individuals, can produce an acute psychosis in which confusion, amnesia, delusions, hallucinations, anxiety, agitation and hypomanic symptoms predominate." Regardless of which of these interpretations is correct, both reports agree that there is little evidence that marijuana alone produces a psychosis that persists after the period of intoxication.

Schizophrenia

The association between marijuana and schizophrenia is not well understood. The scientific literature indicates general agreement that heavy marijuana use can precipitate schizophrenic episodes, but not that marijuana use can cause the underlying psychotic disorder.[58, 95, 150] As noted earlier, drug abuse is common among people with psychiatric disorders. Estimates of the prevalence of marijuana use among schizophrenics vary considerably, but are in general agreement that it is greater than or equal to use among the general population.[133] Interestingly, schizophrenics prefer the effects of marijuana over those of alcohol and cocaine,[35] which they generally use less often than does the general population.[133] The reasons for this are unknown, but it raises the possibility that schizophrenics might obtain some symptomatic relief from moderate marijuana use. But overall, compared with the general population, individuals with schizophrenia or with a family history of

schizophrenia are likely to be at greater risk of suffering adverse psychiatric effects from the use of cannabinoids.

Cognition

As discussed earlier, acutely administered marijuana impairs cognition.[59, 65, 111] PET imaging (positron emission tomography) allows investigators to measure the acute effects of marijuana smoking on active brain function. Human volunteers who perform auditory attention tasks before and after smoking a marijuana cigarette show impaired performance while under the influence of marijuana; this is associated with substantial reduction in blood flow to the temporal lobe of the brain, an area that is sensitive to such tasks. [115, 116] In other brain regions, such as the frontal lobes and lateral cerebellum, marijuana smoking increases blood flow.[100, 154] Earlier studies purporting to show structural changes in the brains of heavy marijuana users[22] (have not been replicated using more sophisticated techniques.[28, 88]

Nevertheless, recent studies[121] [14] have found subtle defects in cognitive tasks in heavy marijuana users after a brief period (19-24 hours) of marijuana abstinence. Longer term cognitive deficits in heavy marijuana users have also been reported.[139] Although these studies have attempted to match heavy marijuana users with subjects with similar cognitive abilities prior to exposure to marijuana use, the adequacy of this matching has been questioned.[132] A consideration of the complex methodological issues facing research in this area is well reviewed in an article by Pope and colleagues.[120] Care must be exercised in this area so that studies are designed to differentiate between changes in brain function caused by the illness for which marijuana is being given and the effects of marijuana. AIDS dementia is an obvious example of this possible confusion. It is also important to determine whether the repeated use of marijuana at therapeutic dosage levels produces any irreversible cognitive effects.

Psychomotor Performance

Marijuana administration has been reported to affect psychomotor performance on a number of different tasks. The review by Chait and Pierri[23] details not only the studies which have been done in this area but also points out the inconsistencies across studies, the methodological shortcomings of many studies, and the large individual differences among the studies attributable to subject, situational and methodological factors. Those factors must be considered when designing studies of psychomotor performance in participants involved in a clinical trial of the efficacy of marijuana. The types of psychomotor functions that have been shown to be disrupted by the acute administration of marijuana include: body sway, hand steadiness, rotary pursuit, driving and flying simulation, divided attention, sustained attention, and the digit-symbol substitution test. A study of experienced airplane pilots showed that, even 24 hours after a single marijuana cigarette, their

When compared to changes produced by either placebo or an active control medication, the magnitude of desirable therapeutic effects produced by marijuana could be determined, as well as the frequency and magnitude of adverse psychological side effects. This would allow a more thorough assessment of the risk:benefit ratio associated with the use of marijuana for a given indication.

CONCLUSION: The psychological effects of cannabinoids, such as anxiety reduction, sedation, and euphoria can influence their potential therapeutic value. Those effects are potentially undesirable for certain patients and situations, and beneficial for others. In addition, psychological effects can complicate the interpretation of other aspects of the drug effect.

RECOMMENDATION: **Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.**

Physiological Harms: Tissue and Organ Damage

Many people who spoke to the IOM study team in favor of the medical use of marijuana cited the absence of marijuana overdoses as evidence that it is safe. Indeed, epidemiological data indicate that—for the general population—marijuana use is not associated with increased mortality.(Sidney 1997a) However, there are other serious health outcomes to consider, and they are discussed below.

It is important to keep in mind that most of the studies that report physiological harms resulting from marijuana use are based on the effects of marijuana smoking. Thus we emphasize that the effects reported cannot be presumed to be caused by THC alone or even in combination with other cannabinoids found in marijuana. It is likely that smoke is a major cause of the reported effects. In most studies, the methods used make it impossible to weigh the relative contributions of smoke versus cannabinoids.

Immune System

The relationship between marijuana and the immune system presents many facets, including potential benefits and suspected harms. This section reviews the evidence on suspected harms to the immune system caused by marijuana use.

Despite the many claims that marijuana suppresses the human immune system, the health impact of marijuana-induced immunomodulation is still unclear. Few studies have been done with animals or humans to assess the effects of marijuana exposure on host resistance to bacteria, viruses or tumors.

performance on flight simulator tests was impaired (Yesavage and coworkers 1985[162]). Before the tests, however, they told the study investigators that they were sure their performance would be unaffected.

Clearly, cognitive impairments associated with acutely administered marijuana limit the activities that individuals being treated with marijuana would be able to do safely or productively. For example, no one under the influence of marijuana or THC should drive a vehicle or operate potentially dangerous equipment.

Amotivational Syndrome

One of the more controversial of the effects claimed for marijuana is the production of an "amotivational syndrome." This syndrome is not a medical diagnosis, but it has been used to describe young people who drop out of social activities and show little interest in school, work, or other goal-directed activity. When heavy marijuana use accompanies these symptoms, the drug is often cited as the cause, but there are no convincing data to demonstrate a causal relationship between marijuana smoking and these behavioral characteristics.[23] It is not enough to observe that a chronic marijuana user lacks motivation. Instead, relevant personality traits and behavior of subjects must be assessed before, as well as, after the subject becomes a heavy marijuana user. Because such research can only be done on subjects who become heavy marijuana users on their own, a large population study—such as the Epidemiological Catchment Area study described earlier in this chapter—would be needed to shed light on the relationship between motivation and marijuana use. Even then, while a causal relationship between the two could, in theory, be dismissed by an epidemiological study, causality not be proven.

Summary on Psychological Effects

Measures of mood, cognition, and psychomotor performance should be incorporated into clinical trials evaluating the efficacy of marijuana or cannabinoid drugs for a given medical condition. Ideally, participants would complete mood assessment questionnaires at various intervals throughout the day for a period prior to and at weekly intervals during treatment, and, where appropriate, after the cessation of marijuana therapy. A full psychological screening of research participants should be conducted to determine whether there is an interaction between the mood altering effects of chronic marijuana use and the psychological characteristics of the individual. Similarly, the cognitive and psychomotor functioning of individuals should be assessed prior to and at regular intervals during the course of a chronic regimen of marijuana or cannabinoid treatment to determine to what extent tolerance develops to the impairing effects of marijuana and to monitor whether new problems develop.

Human studies

Several approaches have been used to determine the effects of marijuana on the human immune system, but each of these has serious limitations which will be discussed below.

Leukocyte assays from marijuana smokers

One of the more common approaches has been to isolate peripheral blood leukocytes from individuals who have smoked marijuana in order to evaluate the immune response of those cells *in vitro*—most often by measuring mitogen-induced cell proliferation, a normal immune response. Almost without exception, this approach has failed to demonstrate any reduction in leukocyte function. The major problem with this approach is that after drawing blood samples from the study subjects, the leukocytes need to be isolated from whole blood before they are tested. This is done by high-speed centrifugation followed by extensive washing of the cells, thus resulting in removal of the cannabinoid; perhaps for that reason no adverse effects have been demonstrated in peripheral blood leukocytes from marijuana smokers.[74, 90, 122, 159]

Leukocyte responses to THC

Another approach is to isolate peripheral blood leukocytes from healthy control individuals who do not smoke marijuana and then to measure the effect of THC on the ability of these cells to proliferate in response to mitogenic stimulation *in vitro*. However, it is notable that one significant difference between leukocytes isolated from a marijuana smoker, as described above, and the *in vitro* studies in which THC has been added directly to leukocyte cell cultures is in the cannabinoid composition. Marijuana smoke contains many distinct cannabinoid compounds of which THC is just one. Moreover, since the immunomodulatory activity of many of the other cannabinoid compounds present in marijuana smoke has never been tested, and because it is now known that at least one of those—cannabinol (CBN)—has greater activity on the immune system than the central nervous system,[63] it is unclear whether the profile of activity observed with THC accurately represents the effects of marijuana smoke on immune competence. Likewise, it is unclear to what extent different cannabinoids in combination exhibit additive, synergistic or antagonistic effects with respect to their immunomodulatory activity. This issue is further complicated by the fact that leukocytes express both types of cannabinoid receptors, CB_1 and CB_2.

One additional factor which may affect the immunomodulatory activity of cannabinoids in leukocytes is metabolism. Since leukocytes have very low levels of

the cytochrome P-450 drug metabolizing enzymes[20] , the metabolism of cannabinoids is probably different between *in vivo* and *in vitro* exposure. This last point is primarily pertinent to investigations of chronic and not acute cannabinoid exposure.

Human-derived cell lines

A third approach for investigating the effects of cannabinoids on human leukocytes has been to study human-derived cell lines.[b] As described above, the cell lines are treated *in vitro* with cannabinoids to test their responses to different stimuli. Although cell lines are a convenient source of human cells, the same problems described above apply. Additionally, the cell lines might not be the same as the original cells. For example, cell lines do not necessarily have the same number of cannabinoid receptors as the original human cells.

Rodent studies

The most widely used approach is to evaluate the effects of cannabinoids in rodents, using rodent-derived cells *in vitro*. The rationale for this approach is based on the fact that the human and rodent immune systems are remarkably similar, and it is assumed that the effects produced by cannabinoids on the rodent immune system will be similar to those produced in humans. Although no significant species differences in immune system sensitivity to cannabinoids have been reported, it is important to consider the possibility.

Summary

The complete effect of marijuana smoking on immune function remains unknown. More importantly, it is not known whether smoking leads to increased rates of infections, tumors, allergies, or autoimmune responses. The problem is how to duplicate the "normal" marijuana smoking pattern while at the same time removing other potential immune modulating life-style factors such as alcohol and tobacco use. Epidemiological studies are needed to determine whether marijuana users have a higher incidence of diseases such as infections, tumors, allergies, and autoimmune disease. Studies on resistance to bacterial and viral infection are clearly needed, and should involve the collaboration of immunologists, infectious disease specialists, oncologists, and pharmacologists.

---

[b] Cell lines are created by removing cells from an organism and then treating them so they are "immortalized," meaning they will continue to divide indefinitely in culture. Cellular processes can then be studied in isolation from their original source.

Marijuana Smoke

Tobacco is the predominant cause of lung diseases such as cancer and emphysema, and marijuana smoke contains many of the same components as tobacco smoke.[7] Thus, it is important to consider the relationship between habitual marijuana smoking and certain lung diseases.

Given a cigarette of comparable weight, as much as four times the amount of tar can be deposited in the lungs of marijuana smokers compared to tobacco smokers.[161] This is primarily due to the differences in filtration and smoking technique between tobacco and marijuana smokers. Marijuana cigarettes usually do not have filters, and marijuana smokers typically develop a larger puff volume, inhale more deeply, and hold their breath several times longer than tobacco smokers.[118] However, a marijuana cigarette smoked recreationally typically is not packed as tightly as a tobacco cigarette, and thus the smokable substance is about half that in a tobacco cigarette. In addition, tobacco smokers generally smoke considerably more cigarettes per day than do marijuana smokers.

Cellular Damage

Lymphocytes: T and B Cells

Human studies of the effect of marijuana smoking on immune agents are not all consistent with cannabinoid cell culture and animal studies. For example, antibody production was decreased in a group of hospitalized patients who smoked marijuana for four days (twelve cigarettes/day), but this decrease was seen in only one subtype of humoral antibody (IgG), while two other subtypes (IgA and IgM) remained normal and one (IgE) was elevated.[107] Additionally, T cell proliferation was normal in the blood of a group of marijuana smokers, although when evaluated more closely, there was an increase in one subset of T cells[160] and a decrease in a different subset (CD8).[156] From these studies it appears that marijuana use is associated with intermittent disturbances in T and B cell function, but the magnitude is small and other measures are frequently normal.[86]

Macrophages

Alveolar macrophages are the principal immune-effector cells in the lung and are primarily responsible for protecting the lung against infectious microorganisms, inhaled foreign substances, and tumor cells. They are increased during tissue inflammation. In a large sample of volunteers, habitual marijuana smokers had twice as many alveolar macrophages as nonsmokers, and smokers of both marijuana and

tobacco had twice as many again.[11] Marijuana smoking also reduced the ability of alveolar macrophages to kill fungus such as *Candida albicans*,[c] pathogenic bacteria such as *Staphylococcus aureus*, and tumor target cells. This reduction in ability to destroy fungal organisms was similar to that seen in tobacco smokers. The inability to kill pathogenic bacteria was not seen in tobacco smokers.[10] Furthermore, marijuana smoking depressed pro-inflammatory cytokine production (such as TNF-α and IL-6), but not immunosuppressive cytokines.[10] Since cytokines are important regulators of macrophage function, this marijuana-related decrease in inflammatory cytokine production might be a mechanism whereby marijuana smokers are less able to destroy fungal and bacterial organisms, as well as tumor cells.

The inability of alveolar macrophages from habitual marijuana smokers without apparent disease to destroy fungus, bacteria, and tumor cells, and to release pro-inflammatory cytokines, suggests that marijuana might be an immunosuppressant with clinically significant effects on host defense. Therefore, the risks of smoking marijuana should be seriously weighed before recommending its use in any patient with pre-existing immune deficits—including AIDS patients, cancer patients, and those receiving immunosuppressive therapies (for example, transplant or cancer patients).

Bronchial-pulmonary Damage

Animal Studies

A number of animal studies have revealed certain respiratory tract changes and diseases associated with marijuana smoking, while others have not. Extensive damage to the smaller airways, which are the major site of chronic obstructive pulmonary disease (COPD),[d] as well as acute and chronic pneumonia have been observed in various species exposed to different doses of marijuana smoke.[41, 42, 127] In contrast, rats exposed to increasing doses of marijuana smoke for one year did not show any signs of COPD, whereas rats exposed to tobacco smoke did.[66]

Chronic Bronchitis and Respiratory Illness

Human studies suggest that there is a greater chance of respiratory illness in individuals who smoke marijuana. In a survey of outpatient medical visits in a large HMO, marijuana users were more likely to seek help for respiratory illnesses than people who smoked neither marijuana nor tobacco.[119] However, the incidence of

---

[c] A yeast infection that is particularly prevalent among people whose immune systems are suppressed, such as in AIDS patients.

[d] A slow progressive obstruction of the airways, loss of their elasticity, and loss of lung volume. Characterized by chronic shortness of breath, chronic bronchitis and reduced oxygenation of blood.

seeking help for respiratory illnesses was not elevated for those who smoked marijuana for 10 years or more when compared to those who smoked for less than 10 years. One explanation for this is that people who experience respiratory symptoms are more likely to quit smoking, and the people who continue to smoke represent a set of survivors who do not develop or are indifferent to such symptoms. A limitation of this study is that no data were available on the use of cocaine, which when used with marijuana could contribute to the observed differences. Another limitation is that the survey relied on self-reporting, and tobacco, alcohol and marijuana use might have been underreported (S. Sidney, IOM workshop).

When marijuana smokers were compared to non-smokers and tobacco-smokers in a group of 446 volunteers, 15-20 % reported symptoms of chronic bronchitis, including chronic cough and phlegm production.[145] Twenty to 25 % of the tobacco smokers also reported symptoms of chronic bronchitis. Despite a marked disparity in the amount of each substance smoked per day (3-4 joints of marijuana versus more than 20 cigarettes of tobacco), the difference in the percent of tobacco-smokers and marijuana-smokers experiencing symptoms of chronic bronchitis was insignificant.[145] Similar findings were reported by Bloom and coworkers,[15] and these investigators noted an additive effect of smoking both marijuana and tobacco.

Bronchial Tissue Changes

Habitual marijuana smoking is associated with changes in the lining of the human respiratory tract. Many marijuana or tobacco smokers have increased redness (erythema) and swelling (edema) of the airway tissues and increased mucus secretions.[43, 55] In marijuana smokers, the number and size of small blood vessels in the bronchial wall are increased, tissue edema is present, and the normal ciliated cells* lining the inner surface of the bronchial wall are largely replaced by mucus-secreting goblet cells.. Moreover, the damage is even greater in people who smoke both marijuana and tobacco.[129] Overproduction of mucus by the increased numbers of mucus-secreting cells in the face of diminished numbers of ciliated cells tends to leave cough as the only major mechanism to remove mucus from the airways. This might explain the relatively high proportion of marijuana smokers who complain of chronic cough and phlegm production.[147]

A 1998 study has shown that, compared to nonsmokers, both marijuana and tobacco smokers have significantly more cellular and molecular abnormalities in bronchial epithelium cells; those changes are associated with increased risk of cancer.[12] The tobacco-only smokers in that study smoked an average of 25 cigarettes per day, whereas the marijuana-only smokers smoked an average of 21 marijuana cigarettes per week. Despite the fact that the marijuana smokers smoked many fewer

* Ciliated cells have hair-like projections that function to transport mucus toward the mouth by rapid wave-like motion.

cigarettes, their cellular abnormalities were equivalent, or greater than, those seen in tobacco smokers. This and earlier studies have shown than such abnormalities are greatest in people who smoke both marijuana and tobacco, suggesting an additive effect of marijuana and tobacco smoke on airway tissue.[12, 43, 55] Tenant and coworkers[149] found similar results in U.S. servicemen who suffered from respiratory symptoms and were heavy hashish smokers. (Hashish is the resin from the marijuana plant).

Chronic Obstructive Pulmonary Disease

In the absence of epidemiological data, indirect evidence, such as nonspecific airway hyperresponsiveness and measures of lung function, offers an indicator of the vulnerability of marijuana smokers to COPD.[153] For example, the methacholine provocative challenge test, used to evaluate airway hyperresponsiveness, showed that tobacco smokers develop more airway hyperresponsiveness. But no such correlation has been shown between marijuana smoking and airway hyperresponsiveness.

There are conflicting results as to whether regular marijuana use harms the small airways of the lungs. Bloom found that an average of one joint smoked per day significantly impaired the function of small airways.[15] On the other hand, Tashkin and coworkers[145] did not observe such damage among heavier marijuana users (3-4 joints per day for at least 10 years), but did note a narrowing of large, central airways. Tashkin's long-term study, which adjusted for age-related decline in lung function (associated with an increased risk for developing COPD), showed an accelerated rate of decline in tobacco smokers, but not in marijuana smokers.[146] Thus the question as to whether usual marijuana smoking habits are enough to cause COPD remains open.

Conclusion

Chronic marijuana smoking might lead to acute and chronic bronchitis and extensive microscopic abnormalities in the cells lining the bronchial passageways, some of which may be pre-malignant. These respiratory symptoms are similar to that of tobacco smokers, and the combination of marijuana and tobacco smoking augments these effects. At the time of this writing, it has not been established whether chronic smoking marijuana causes COPD, but there is probably an association.

HIV/AIDS Patients

The relationship between marijuana smoking and the natural course of AIDS is of particular concern because HIV patients are the largest group who report using

marijuana for medical purposes. Marijuana use has been linked to both increased risk of progression to AIDS in HIV-seropositive patients, and to increased mortality in AIDS patients.

For reasons as yet unknown, marijuana use is associated with increased mortality among men with AIDS, but not among the general population.[137] (The relative risk of AIDS mortality for current marijuana users in this 12-year study was 1.90, indicating that, compared to non-current marijuana users, almost twice as many marijuana users died of AIDS.) Never married men used twice as much marijuana as married men and accounted for 83% of the AIDS deaths in the study. The authors of the study note that, while marital status is insufficient to adjust for lifestyle factors—particularly, homosexual behavior—a substantial proportion of the never married men with AIDS were likely homosexuals or bisexuals. This raises the possibility that the association of marijuana use with AIDS deaths might be related to indirect factors, such as use of other drugs or high risk sexual behavior, both of which increase risks of infection to which AIDS patients are more susceptible. The higher mortality of AIDS patients who were current marijuana users also raises the question as to whether this was because patients increased their use marijuana at the end-stages of the disease to treat their symptoms. However, the association between marijuana use and AIDS deaths was similar even when the subjects who died earliest in the first 5 years of this 12 year study, and who were presumably the most sick, were excluded from the analysis. In sum, it is premature to conclude what the underlying causes of this association might be.

For the general population, the risk of mortality associated with marijuana use was lower than that associated with cigarette smoking, and tobacco smoking was not an independent risk factor in AIDS mortality in this study. Interestingly, the authors of this study concluded that therapeutic use of marijuana did not contribute to the increased mortality among men with AIDS.

Marijuana use has been associated with a higher prevalence of HIV-seropositivity in cross-sectional studies,(Ostrow 1994)[83] but the relationship of marijuana to the progression to AIDS in HIV-seropositive patients is a reasonable question. It remains unclear whether marijuana smoking is an independent risk factor in the progression of AIDS in HIV-seropositive men. Marijuana use did not increase the risk of AIDS in HIV-seropositive men in the Multicenter AIDS Cohort Study, in which 1,795 HIV-seropositive men were studied for 18 months,[83] or in the San Francisco Men's Health Study, in which 451 HIV-seropositive men were studied for 6 years.[34] In contrast, the Sydney AIDS Project in Australia (386 HIV-seropositive men were studied for 12 months)[151] reported that marijuana use was associated with increased risk of progression to AIDS. But the results of the 1988 Sydney study are less reliable than the other two studies described. For one, this was the shortest of the studies; and, second, according to the 1993 definition of

AIDS, many of the subjects probably already had AIDS at the beginning of the study.[f]

The most compelling concerns regarding marijuana smoking in HIV/AIDS patients are the possible effects of marijuana on human immunity.[110] Reports of opportunistic fungal and bacterial pneumonia in patients with AIDS who used marijuana suggest that marijuana smoking either suppresses the immune system,[33] or that it exposes patients to an added burden of pathogens.[21] In sum, patients with pre-existing immune deficits due to AIDS should be expected to be vulnerable to serious harms caused by smoking marijuana. The relative contribution of marijuana smoke versus THC or other cannabinoids is not known.

Carcinogenicity

The gas and tar phases of marijuana and tobacco smoke contain many of the same compounds. Furthermore, the tar phase of marijuana smoke contains higher concentrations of polycyclic aromatic hydrocarbons (PAHs), such as the carcinogen benzopyrene. The higher content of carcinogenic PAHs in marijuana tar and the greater deposition of this tar in the lung might act in conjunction to amplify the exposure of the marijuana smoker to carcinogens. For these reasons the carcinogenicity of marijuana smoke is an important concern.

Compared to studies on tobacco smoke, it is more difficult to collect the epidemiological data necessary to establish or refute the link between marijuana smoke and cancer. Far fewer people smoke only marijuana than who smoke only tobacco, and marijuana smokers are more likely to underreport their smoking.

Case Studies

Several case-series suggest that marijuana might play a role in the development of human respiratory cancer. Those reports indicate an unexpectedly large proportion of marijuana users among cases of lung cancer[140, 148] and cancers of the upper aerodigestive tract—that is, the oral cavity, pharynx, larynx, and esophagus—that occur before age 45 years.[36, 39, 148] Respiratory tract cancers associated with heavy tobacco and alcohol consumption are not usually seen before the age of 60 years,[153] and the occurrence of such cancers in marijuana users younger than 60 years suggests that long-term marijuana smoking potentiates the effects of other risk factors, such as tobacco smoking, and is a more potent risk factor than tobacco and alcohol use in the early development of respiratory cancers. Unfortunately, most studies lack the necessary comparison groups to calculate the isolated effect of marijuana use on cancer risk. Many marijuana smokers also smoke tobacco, so when studies lack information regarding cigarette smoking status, there is no way to separate the effects of marijuana smoke from tobacco smoke.

---

[f] In 1993, the diagnosis of AIDS was expanded to include anyone with a CD4 count less than 200. Prior to 1993, this alone would have been insufficient for a diagnosis of AIDS.

Epidemiological Evidence

As of this writing, Sidney and coworkers[138] have conducted the only epidemiological study to evaluate the association between marijuana use and cancer. The study included a cohort of approximately 65,000 men and women between the ages of 15 and 49 years. Marijuana users were defined as those who had used marijuana on six or more occasions. Among the 1,421 cases of cancer in this cohort, marijuana use was associated only with an increased risk of prostate cancer in men who did not smoke tobacco. In these relatively young HMO clients, no association was found between marijuana use and other cancers, including all tobacco-related cancers, colorectal or melanoma. The major limitation associated with interpreting this study is that the development of lung cancer requires a long exposure to smoking, and most marijuana users quit before this level of exposure is achieved. Additionally, marijuana use has only been widespread in the U.S. since the late 1960s; therefore, despite the large cohort size there might not have been a sufficient number of heavy and/or long-term marijuana smokers to observe an effect.

Cellular and Molecular Studies

In contrast to clinical studies, the evidence from cellular and molecular studies provides strong evidence that marijuana smoke is carcinogenic. Cell culture studies implicate marijuana smoke in the development of cancer. Prolonged exposure of hamster lung cell cultures to marijuana smoke led to malignant transformations,[93] and human lung explants exposed to marijuana smoke resulted in chromosomal and DNA alterations.[153] Additionally, the tar from marijuana smoke induced mutations similar to those produced by tar from the same quantity of tobacco in a common bacterial assay for mutagenicity.[157]

Molecular studies also implicate marijuana smoke as a carcinogen. Proto-oncogenes and tumor suppressor genes are a group of genes that affect cell growth and differentiation. Normally, those genes code for proteins that control cellular proliferation. Once mutated or activated, these genes produce proteins which cause cells to multiply rapidly and out of control, resulting in tumors or cancer.[9] When the production of these proteins was evaluated in tissue biopsies taken from marijuana, tobacco, marijuana plus tobacco smokers, and non-smokers, respectively, two of them (EGFR and Ki-67) were markedly increased in the marijuana smokers compared to non-smokers and tobacco smokers. Moreover, the effects of marijuana and tobacco were additive.[130] Thus, in relatively young smokers of marijuana, and

[9] Some of the genes involved in the development of lung cancer include those that encode for Ki-67 (a nuclear proliferation protein responsible for cell division), the p53 tumor suppressor (a protein that normally suppresses cell growth), and epidermal growth factor receptor (EGFR) (a receptor found on a variety of cell types, especially epithelia, and which promotes cellular growth and proliferation when bound to epidermal growth factor).

particularly in those who smoke both marijuana and tobacco, marijuana is implicated as a risk factor for lung cancer.

DNA alterations are known to be early events in the development of cancer, and have been observed in the lymphocytes of pregnant marijuana smokers, as well as in those of their newborns.[4] This is an important study because the investigators were careful to exclude tobacco smokers—a problem in previous studies that cited mutagenic effects of marijuana smoke.[26, 53, 62, 141] These same investigators found similar effects in previous studies among tobacco smokers,[5, 6] so the effects cannot be attributed solely to THC or other cannabinoids. Although it can only be determined by experiment, it is likely that the smoke contents—other than cannabinoids—are responsible for a large part of the mutagenic effect.

Preliminary findings suggest that marijuana smoke activates cytochrome P4501Al (CYP1Al), the enzyme that converts PAHs, such as benz[α]pyrene, into active carcinogens.[98] Bronchial epithelial cells in tissue biopsies taken from marijuana smokers show more binding to CYP1A1 antibodies than do comparable cells in biopsies from nonsmokers (D.Tashkin, IOM workshop). This suggests that there is more of the carcinogen-producing enzyme, CYP1A1, itself in bronchial cells of marijuana smokers, but different experimental methods will be needed to definitely establish that possibility.

Conclusions

At this time, there is no conclusive evidence that marijuana causes cancer in humans, including cancers usually related to tobacco use. However, cellular, genetic and human studies all suggest that marijuana smoke maybe an important risk factor for the development of respiratory cancer. More definitive evidence that habitual marijuana smoking does or does not lead to respiratory cancer awaits the results of well-designed case-controlled epidemiological studies. It has been 30 years since the initiation of widespread marijuana use among young individuals in our society, and such studies should now be feasible.

The following studies or activities would be useful in providing data that could more precisely define the health risks of smoking marijuana.

1. Case-control studies to determine whether marijuana use is associated with an increased risk of respiratory cancer: Despite the lack of compelling epidemiological evidence to date, findings from the biochemical, cellular, immunologic, genetic, tissue and animal studies cited above strongly suggest that marijuana is a risk factor for human cancer. What is required to address this hypothesis more convincingly is a population-based case-controlled study of sufficiently large numbers of lung cancer cases and cases of upper aerodigestive tumors (cancers of the oral cavity and pharynx, larynx and esophagus), as well as non-cancer controls, to demonstrate a statistically significant association, if one exists. Because of the long time period required for induction of human carcinomas and the infrequent use of marijuana in the general U.S. population prior to 1966, no

epidemiological studies so far have been extensive enough to adequately measure the association between marijuana and cancer. However, epidemiological investigation of this association is probably possible now, since approximately 30 years have elapsed since the start of widespread marijuana use in the U.S. among teenagers and young adults.

2. Molecular markers of respiratory cancer progression in marijuana smokers. If an epidemiological association between marijuana use and risk of respiratory cancer is demonstrated, then studies are warranted to explore the presence of molecular markers that may be predictive of genetically increased risk of carcinogenesis in marijuana users, such as TP53, p16, NATZ and GSTML.

3. Prospective epidemiological studies of populations with HIV-seropositivity or at high risk for HIV infection. Because HIV/AIDS patients are largest group that reports smoking marijuana for medical purposes and they are particularly vulnerable to immunosuppressive effects, there is a pressing need for a better understanding of the relative risk and rewards of smoking marijuana. Such studies should include history of marijuana use in the analysis of potential risk factors for seroconversion and acquisition of opportunistic infections/progression to AIDS.[h] These studies could be carried out in the context of any federally approved clinical trials of medicinal marijuana in immunocompromised patients and should provide a sufficiently long period of follow-up to capture any potential adverse events.

4. Regularized recording of marijuana use by patients. Although marijuana is the most commonly used illicit drug, medical providers often do not question patients about marijuana use and rarely document its use.[101] Among 452 Kaiser-Permanente patients who reported daily or almost daily marijuana use, physicians recorded marijuana use in only 3 % of their medical records (S. Sidney, IOM workshop).

5. Additional cellular, animal and human studies to investigate further the impact of THC and marijuana on immune function, including their effects on proinflammatory versus immunosuppressive cytokines, and on the function of leukocytes that present antigen to T cells.

The question that needs to be addressed is whether THC or marijuana is a risk factor for HIV infection, for progression to more severe stages of AIDS, or for opportunistic infection among HIV-positive patients. Studies are needed to determine the effects of marijuana use on the function of alveolar macrophages. It would be important to compare the HIV infectivity and replication of alveolar macrophages harvested from habitual marijuana users with those harvested from non- or infrequent marijuana users. Cell culture studies could be used to compare the

---

[h] A *prospective study* is one in which a group of subjects is identified and then studied over the course of time. Such a study allows an experimenter to balance different factors that may contribute to the study outcome. For example, age, family history, and smoking are risk factors for lung cancer. In a prospective study these factors can be balanced to measure how much smoking increases the risk of lung cancer. A *retrospective study* is one in which people with a particular disease are identified and their histories are studied. Such studies are easier and less expensive to conduct, but they generally lack the explanatory power of prospective studies.

susceptibility of HIV-infected alveolar macrophages to additional infection with opportunistic pathogens. Similarly, further studies on cell cultures of peripheral blood mononuclear cells could be used to assess the impact of exposure to THC on HIV infectivity and replication.

Cardiovascular System

Marijuana smoke and oral THC can cause tachycardia (elevated heart rate) in humans, usually 20 - 100 % above baseline.[56, 84] The increase in heart rate is greatest in the first 10-20 minutes after smoking, and decreases sharply and steadily; depending on whether smoked marijuana or oral THC are used, these side effects can last 3 or 5 hours, respectively.[67, 94] In some cases, blood pressure can be increased while a person is in a reclining position, but can decrease inordinately on standing, resulting in postural hypotension.[f] In contrast to acute administration of THC, chronic oral ingestion of THC reduces heart rate in humans.[13]

In animals, THC decreases heart rate and blood pressure.[56, 155] However, most such animals studies are conducted in anaesthetized animals, and anesthesia causes hypertension. Thus, those studies should be interpreted as reports on the effects of cannabinoids in hypertensive subjects. The results of the animal and human studies are consistent with the conclusion that cannabinoids are hypotensive at high doses in animals, as well as humans (see 1998 review by Wagner and coworkers).[155]

Tolerance can appear after a few days of frequent daily dosing (2 - 3 times per day) of oral THC or marijuana extract with heart rate slowing, reclining blood pressure falling, and postural hypotension disappearing.[72] Thus, the intensity of these effects depends on the frequency of use, dose, and even body position.

The cardiovascular changes have not been a health problem for healthy, young users of marijuana or THC. However, such changes in heart rate and blood pressure could present a serious problem for older patients, especially those with coronary artery or cerebrovascular disease. Since cardiovascular diseases are the leading causes of death in the United States (coronary heart disease is first, stroke is third), any impact of marijuana use on cardiovascular disease could have a substantial impact on public health (S. Sidney, IOM workshop). The magnitude of this impact remains to be determined as chronic marijuana users from the late 1960s enter the age where coronary artery and cerebrovascular diseases become common. Additionally, smoking marijuana is known to decrease maximal exercise performance. This, along with the increased heart rate, could theoretically induce angina (S. Sidney, IOM workshop). Therefore, this raises the possibility that patients with symptomatic coronary artery disease should be advised not to smoke marijuana, and THC might be contraindicated in patients with restricted cardiovascular function.

---

[f] Decreased blood pressure due to changing posture from a lying or sitting position to a standing position, which can cause dizziness and faintness.

Reproductive System

Animal studies

Marijuana and THC can inhibit many reproductive functions on a short-term basis. In both male and female animals, THC injections suppress reproductive hormones and behavior.[106, 158] Studies have consistently shown that injections of THC result in rapid, dose-dependent suppression of serum luteinizing hormone (LH) levels.[69] (LH is the pituitary hormone that stimulates release of the gonadal hormones, testosterone and estrogen.) Embryo implantation also appears to be inhibited by THC. But it does not necessarily follow from this that marijuana use will interfere with human reproduction. With few exceptions, the animal studies are based on acute (i.e., single injections) or short-term treatments (i.e., THC injections given over a series of days). The results are generally observed for only several hours, or sometimes in females for only one ovulatory cycle.

Acute treatments of cannabinoids, including THC, CBD, and cannabinol, and anandamide can decrease the fertilizing capacity of sea urchin sperm.[134, 135, 136] While the sea urchin is only a distant relative of humans, the cellular processes that regulate fertilization are similar enough that one can expect a similar effect in humans. However, the effect of cannabinoids on the capacity of sperm to fertilize eggs is reversible, and is observed at 6-100 μM concentrations, [135, 136] which are higher than those likely to be experienced by marijuana smokers. At the same time, the presence of cannabinoid receptors in sperm suggests the possibility of a natural role for anandamide in modulating sperm function during fertilization. However, it remains to be determined whether smoked marijuana or oral THC taken in prescribed doses has a clinically significant effect on the fertilizing capacity of human sperm.

Exposure to THC *in utero* can result in long-term changes. Many *in utero* effects interfere with embryo implantation (see review by Wenger and coworkers[158]). Exposure to THC close to the time of, or shortly after, their birth can also result in impaired reproductive behavior in adult mice: females are slower to show sexual receptivity and males are slower to mount.[106]

Although THC can act directly on endocrine tissues, such as the testes or ovaries, it appears to affect reproductive physiology through its actions on the brain, but somewhere other than the pituitary. Some, but not all, of the effects of THC are through its effect on stress hormones such as cortisol.[69]

Human Studies

The few human studies are consistent with the acute animal studies: THC inhibits reproductive functions. However, studies of men and women who use marijuana regularly have yielded conflicting results, and show either depression of

reproductive hormones, no effect, or only a short-term effect. Overall, the results from human studies are consistent with the hypothesis that THC inhibits LH on a short-term basis, but not in long-term marijuana users. In other words, long-term users develop tolerance to the inhibitory effect of THC on LH. The results in women are similar, with the added consideration of the menstrual cycle; the acute effects of THC appear to vary with cycle stage. THC appears to have little effect during the follicular phase (the phase after menses and before ovulation), and to inhibit the LH pulse during the luteal phase (the phase after ovulation and before menses).[102] In brief, although there are no data on fertility per se, marijuana or THC would likely decrease human fertility—at least in the short-term—for both men and women. And it is reasonable to predict that THC can interfere with early pregnancy, particularly implantation of the embryo. Like tobacco, marijuana smoke is highly likely to be harmful to fetal development and should be avoided by pregnant women as well as those who might become pregnant in the near future. Nevertheless, although fertility and fetal development are important concerns for many, they are unlikely to be of much concern to people with seriously debilitating or life-threatening diseases. The well-documented inhibition of reproductive functions by THC is thus not a serious concern for evaluating the short-term medical use of marijuana or specific cannabinoids.

Developmental impact of use during pregnancy

Among the studies that have investigated the relationship between prenatal marijuana exposure and birth outcome, the results have been inconsistent (reviewed by Cornelius and coworkers[30] in 1995). Except for adolescent mothers, there is little evidence that gestation is shorter in mothers who smoke marijuana.[30] Several studies of women who smoked marijuana regularly during pregnancy show that they tend to give birth to lower weight babies.[46, 64] Mothers who smoke tobacco also give birth to lower weight babies, and the relative contributions of smoking versus THC are not known from these studies.

Babies born to mothers who smoked marijuana during pregnancy weighed, on average, 3.4 ounces less than babies born to the study's control group of mothers who did not smoke marijuana; there was no significant difference in either gestational age or frequency of congenital abnormalities.[163] These results were based on women whose urine tests indicated recent marijuana. However, when the analysis was based only on self-reports of marijuana use (without verification by urine tests), there was no difference between the weight of babies born to women who reported themselves as marijuana smokers and those born to women who reported they did not smoke marijuana. This raises an important concern about the methods used to measure the effects of marijuana smoking in any study, and perhaps even more so in studies on the effects of marijuana during pregnancy when subjects might be even less likely to admit to smoking marijuana. (The study was conducted in the last trimester of pregnancy, and there was no information about the extent of marijuana use earlier in the pregnancy).

For most of these studies, much of the harms associated with marijuana use are consistent with those associated with tobacco use, and smoking is a significant

factor so the contribution of cannabinoids cannot be confirmed. However, Jamaican women who use marijuana rarely smoke it, but instead prepare it as tea.[37] In a study of neonates born to Jamaican women who either did or did not ingest marijuana during pregnancy, there was no difference in neurobehavioral assessments made at 3 days after birth and at one month.[38] A limitation of this study is that there was no direct measure of marijuana use. Estimates of marijuana use were based on self-reports, which might be more accurate in Jamaica than in the U.S. since there is less social stigma associated with marijuana use in Jamaica, but are nonetheless less reliable than direct measures

Newborns of mothers who smoke either marijuana or tobacco have significantly higher mutation rates than those of non-smokers.[4, 5]

Since 1978, the Ottawa Prenatal Prospective Study has been measuring the cognitive functions of children born to mothers who smoked marijuana during pregnancy.[47] Children of mothers who smoked either moderately (1-6 marijuana cigarettes per week) or heavily (more than 6 marijuana cigarettes per week) have been studied from age four days to 9-12 years. It is important to keep in mind that studies like this provide important data about the risks associated with marijuana use during pregnancy, but they do not establish the *causes* of any such association.

The children in the different marijuana exposure groups showed no lasting differences in global measures of intelligence such as language development, reading scores, and visual or perceptual tests. Moderate cognitive deficits were detectable among these children when they were four days old and again at four years, but these deficits were no longer apparent at five years.

Prenatal marijuana exposure was not, however, without lasting impact. By comparison, at both ages 5-6 and 9-12, children in the same study who were prenatally exposed to tobacco smoke scored significantly lower on tests of language skills and cognitive functioning.[48] In another study,[49, 50] nine-to-twelve years olds who were exposed to marijuana prenatally scored lower than control subjects on tasks associated with "executive function," a term used by psychologists to describe an individual's ability to plan ahead, anticipate, and suppress behaviors that are incompatible with a current goal.[50] This was reflected in how the mothers described their children. The mothers of the marijuana-exposed children were more likely to describe their offspring as hyperactive or impulsive than did mothers of control children. This alteration in executive function was not seen in children born to tobacco smokers. The underlying causes might be the marijuana exposure, or might be more closely related to the reasons underlying their mothers' use of marijuana during pregnancy.

Mice born to dams injected with the endogenous cannabinoid, anandamide, during the last trimester of pregnancy also showed delayed effects. No effect of anandamide treatment during pregnancy was detected until the mice were adults (40 days of age), at which time they showed behavioral changes that are common to the effects of other psychotropic drugs or prenatal stress.[45] As with the children born to mothers who smoked marijuana, it is not known what aspect of the treatment caused the effect. The dams might have found the dose (20 mg/kg of body weight) of

anandamide aversive, in which case, the effect could have resulted from generalized stress, as opposed to a cannabinoid-specific effect. Either case is possible.

Despite the uncertainty as to the underlying causes of impact of prenatal exposure to cannabinoid drugs, it is, nonetheless, prudent to advise against smoking marijuana during pregnancy.

Summary and Conclusions

This chapter summarizes the harmful effects of marijuana to the individual user and, to a lesser extent, to society. The harmful effects to individuals were considered from the perspective of possible medical use of marijuana, and can be divided into acute and chronic effects. The vast majority of data on harmful effects of marijuana is based on *smoked* marijuana, and except for the psychoactive effects that can be reasonably attributable to THC, it is not possible to distinguish the drug effects from the effects of inhaling smoke of burning plant material.

For most people, the primary adverse effect of *acute* marijuana use is diminished psychomotor performance; it is inadvisable to operate any equipment that might put the user or others in danger (such as driving and operating or monitoring complex equipment under the influence of marijuana). While most people can be expected to show impaired performance of complex tasks, a minority experience dysphoria. Individuals with or at risk of psychiatric disorders (including substance dependence) are particularly vulnerable to developing marijuana dependence and marijuana use would be generally contraindicated in those individuals. The short-term immunosuppressive effects are not well-established and, if they exist at all, are not likely great enough to preclude a legitimate medical use. The acute side effects of marijuana use are within the risks tolerated for many medications.

The *chronic* effects of marijuana are of greater concern for medical use and fall into two categories: the effects of chronic smoking, and the effects of THC. Marijuana smoke is like tobacco smoke in that it is associated with increased risk of cancer, lung damage, and poor pregnancy outcomes. Smoked marijuana is unlikely to be a safe medication for any chronic medical condition. The second category is that associated with dependence on the psychoactive effects of THC. Despite past skepticism, it has been established that, although it is not common, a vulnerable subpopulation of marijuana users can develop dependence. Adolescents, particularly those with conduct disorders, individuals with psychiatric disorders, or problems with substance abuse appear to be at greater risk for marijuana dependence than the general population.

As a cannabinoid drug delivery system, marijuana cigarettes are not ideal since they deliver a variable mixture of cannabinoids, as well as a variety of other biologically-active substances, not all of which are desirable or even known. Unknown substances include possible contaminants such as fungus or bacteria.

Finally, there is the broad social concern that sanctioning the medical use of marijuana might lead to an increase in its use among the general population. At this point there are no convincing data to support this concern. The existing data are

consistent with the idea that this would not be a problem if the medical use of marijuana were as closely regulated as other medications with abuse potential, but we acknowledge that there are no data that directly address this question. Even if there were evidence that the medical use of marijuana would decrease the perception that it can be a harmful substance, this is beyond the scope of laws regulating the approval of therapeutic drugs. Those laws concern scientific data concerning safety and efficacy of drugs for individual use, and do not address perceptions or beliefs of the general population.

Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, except for the harms associated with smoking, the adverse effects of marijuana use are within the range tolerated for other medications. Thus the safety issues associated with marijuana do not preclude certain medical uses. But the question remains: is it effective? This topic is covered here in two chapters: chapter 2 summarizes what has been learned about the biological activity of cannabinoids in the past fifteen years from research in the basic sciences; chapter 4 reviews the clinical data on the effectiveness of marijuana and cannabinoids for the treatment of a variety of medical conditions.

Three factors influence the safety of marijuana or cannabinoid drugs for medical uses: the delivery system, the use of plant material, and the side effects of cannabinoid drugs. (1) Smoking marijuana is clearly harmful, and especially for chronic conditions, and is not an ideal drug delivery system. (2) Plants are of uncertain composition which render their effects equally uncertain, hence an undesirable medication. (3) The side effects of cannabinoid drugs fall within the acceptable risks for approved medications. Indeed, some of the 'side effects', such as anxiety reduction and sedation, might be desirable for certain patients. As with many medications, there are people for whom they would likely be contraindicated.

CONCLUSION: Present data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse. However, this question is beyond the issues normally considered for medical uses of drugs, and should not be a factor in evaluating the therapeutic potential of marijuana or cannabinoids.

CONCLUSION: A distinctive marijuana withdrawal syndrome has been identified, but it is mild and short-lived. The syndrome includes restlessness, irritability, mild agitation, insomnia, sleep EEG disturbance, nausea, and cramping.

CONCLUSION: Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory disease.

RECOMMENDATION: Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.

References

1. Adams IB, Martin BR. 1996. Cannabis: pharmacology and toxicology in animals and humans. *Addiction* 91:1585-1614.

2. American Psychiatric Association. 1987. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R)*. 3rd ed. revised. Washington, D.C.: American Psychiatric Association.

3. American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. Fourth edition. Washington, D.C.: American Psychiatric Association.

4. Ammenheuser MM, Berenson AB, Babiak AE, Singleton CR, Whorton Jr EB. 1998. Frequencies of *hprt* mutant lymphocytes in marijuana-smoking mothers and their newborns. *Mutation Research* 403:55-64.

5. Ammenheuser MM, Berenson NJ, Stiglich EB, Whorton Jr EB, Ward Jr JB. 1994. Elevated frequencies of *hprt* mutant lymphocytes in cigarette-smoking mothers and their newborns. *Mutation Research* 304:285-294.

6. Ammenheuser MM, Hastings DA, Whorton Jr EB, Ward Jr JB. 1997. Frequencies of *hprt* mutant lymphocytes in smokers, non-smokers, and former smokers. *Environmental and Molecular Mutagenesis* 30:131-138.

7. Anthenelli RM, Schuckit MA. 1992. Genetics. In: Lowinson JH, Ruiz P, Millman RB, eds. *Substance abuse: A comprehensive textbook*. 2nd Edition. Baltimore, MD: Williams & Wilkins. Pp. 39-50.

8. Anthony JC, Warner LA, Kessler RC. 1994. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology* 2:244-268.

9. Bailey SL, Flewelling RL, Rachal JV. 1992. Predicting Continued Use of Marijuana Among Adolescents: The Relative Influence of Drug-specific and Social Context Factors. *Journal of Health and Social Behavior* 33:51-66.

10. Baldwin GC, Tashkin DP, Buckely DM, Park AN, Dubinett SM, Roth MD. 1997. Marijuana and cocaine impair alveolar macrophage function and cytokine production. *American Journal of Respiratory and Critical Care Medicine* 156:1606-1613.

11. Barbers RG, Gong HJ, Tashkin DP, Oishi J, Wallace J M. 1987. Differential examination of bronchoalveolar lavage cells in tobacco cigarette and marijuana smokers. *American Review of Respiratory Disease* 135:1271-1275.

12. Barsky SH, Roth MD, Kleerup EC, Simmons M, Tashkin DP. 1998. Histopathologic and Molecular Alterations in Bronchial Epithelium in Habitual Smokers of Marijuana, Cocaine, and/or Tobacco. *Journal of the National Cancer Institute* 90:1198-1205.

13. Benowitz NL, Jones RT. 1975. Cardiovascular effects of prolonged delta-9-tetrahydro-cannabinol ingestion. *Clinical Pharmacology and Therapeutics* 18:287-297.

14. Block RI, Ghoneim MM. 1993. Effects of chronic marijuana use on human cognition. *Psychopharmacology* 110:219-228.

15. Bloom JW, Kaltenborn WT, Paoletti P, Camilli A, Lebowitz MS. 1987. Respiratory effects of non-tobacco cigarettes. *British Medical Journal* 295:516-518.

16. Bornheim LM, Kim KY, Li J, Perotti BY, Benet LZ. 1995. Effect of cannabidiol pretreatment on the kinetics of tetrahydrocannabinol metabolites in mouse brain. *Drug Metabolism and Disposition (United States)* 23:825-831.

17. British Medical Association. 1997. *Therapeutic uses of cannabis*. Amsterdam, The Netherlands: Harwood Academic Publishers.

18. Brook JS, Cohen P, Brook DW. 1998. Longitudinal study of co-occurring psychiatric disorders and substance use. *Journal of the American Academy of Child and Adolescent Psychiatry* 37:322-330.

19. Budney AJ, Radonovich KJ, Higgins ST, Wong CJ. 1998. Adults seeking treatment for marijuana dependence: a comparison with cocaine-dependent treatment seekers. *Experimental and Clinical Psychopharmacology* 6:419-426.

20. Burns LA, Meade BJ, Munson AE. 1996. Toxic Responses of the Immune System. In: Casarett, Doul, *Toxicology: The Basic Science of Poisons*. 5th Edition. New York: McGraw-Hill. Pp. 355-402.

21. Caiaffa WT, Vlahov D, Graham N, Astemborski J, Solomon L, Nelson KE, Muñoz. 1994. Drug smoking, *Pneumocystis carinii* pneumonia, and immunosuppression increase risk of bacterial pneumonia in Human Immunodeficiency Virus-seropositive injection drug users. *American Journal of Respiratory and Critical Care Medicine* 150:1493-1498.

22. Campbell AM, Evans M, Thompson JL, Williams MR. 1971. Cerebral atrophy in young cannabis smokers. *Lancet* 2:1219-1224.

23. Chait LD, Pierri J. 1992. Effects of smoked marijuana on human performance: A critical review. In: L Murphy and A Bartke, Eds *Marijuana/Cannabinoids: Neurobiology and Neurophysiology*. Boca Raton FL: CRC Press. Pp. 387-424.

24. Charalambous A, Marciniak G, Shiue C Y, Dewey SL, Schlyer DJ, Wolf AP, Makriyannis A. 1991. PET studies in the primate brain and biodistribution in mice using (-)- 5'-18F-delta 8-THC. *Pharmacology Biochemistry and Behavior* 40: 503-7.

25. Chen K, Kandel DB, Davies M. 1997. Relationships between frequency and quantity of marijuana use and last year proxy dependence among adolescents and adults in the United States. *Drug and Alcohol Dependence* 46:53-67.

26. Chiesara E, Rizzi R. 1983. Chromosome damage in heroin-marijuana and marijuana addicts. *Archives of Toxicology Supplement* 6:128-130.

27. Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, Pandya KJ. 1994. Pain and its treatment in outpatients with metastatic cancer. *New England Journal of Medicine* 330:592-596.

28. Co BT, Goodwin DW, Gado M, Mikhael M, Hill SY. 1977. Absence of cerebral atrophy in chronic cannabis users by computerized transaxial tomography. *Journal of the American Medical Association* 237:1229-1230.

29. Cohen MJ, Rickles Jr WH. 1974. Performance on a verbal learning task by subjects of heavy past marijuana usage. *Psychopharmacologia* 37:323-330.

30. Cornelius MD, Taylor PM, Geva D, Day NL. 1995. Prenatal tobacco and marijuana use among adolescents: Effects on offspring gestational age, growth, and morphology. *Pediatrics* :738-743.

31. Crowley TJ, Macdonald MJ, Whitmore EA, Mikulich SK. 1998. Cannabis Dependence, Withdrawal, and Reinforcing Effects Among Adolescents with Conduct Symptoms and Substance Use Disorders. *Drug and Alcohol Dependence* 50:27-37.

32. Crowley TJ, Rhine MW. 1985. The Substance Use Disorders. In: Simons RC, Editor *Understanding Human Behavior in Health and Illness.* 3rd Edition. Baltimore, MD: Williams & Wilkins. Pp. 730-746.

33. Denning DW, Follansbee SE, Scolaro M, et al. 1991. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. *New England Journal of Medicine* 324:654-662.

34. Di Franco MJ, Sheppard HW, Hunter DJ, Tosteson TD, Ascher MS. 1996. The lack of association of marijuana and other recreational drugs with progression to AIDS in the San Francisco Men's Health Study. *AEP* 6:283-289.

35. Dixon L, Haas G, Weiden PJ, Sweeney J, Frances AJ. 1991. Drug Abuse In Schizophrenic Patients: Clinical Correlates and Reasons for Use. *Am J Psychiatry* 148:224-230.

36. Donald PJ. 1991. Advanced malignancy in the young marijuana smoker. *Advances in Experimental Medicine and Biology* 288:33-56.

37. Dreher M. 1987. The evolution of a roots daughter. *Journal of Psychoactive Drugs* 19:165-170.

38. Dreher MC, Nugent K, Hudgins R. 1994. Prenatal marijuana exposure and neonatal outcomes in Jamaica: an ethnographic study. *Pediatrics* 93:254-260.

39. Endicott JN, Skipper P, Hernandez L. 1993. Marijuana and head and neck cancer. In: Friedman et al, Editors *Drugs of Abuse, Immunity and AIDS.* New York: Plenum Press. Pp. 107-113.

40. Fehr K, Kalant H. 1981. Cannabis and health hazards. *Proceedings of an ARF/WHO scientific meeting on adverse health and behavioral consequences of cannabis use* ., Editors Fehr K, Kalant H. Toronto, Canada: Addiction Research Foundation.

41. Fleischman RW, Baker JR, Rosenkrantz H. 1979. Pulmonary pathologic changes in rats exposed to marijuana smoke for one year. *Toxicology and Applied Pharmacology* 47:557-566.

42. Fligiel SE, Beals TF, Tashkin DP, Paule MG, Scallet AC, Ali SF, Bailey JR, Slikker WJ. 1991. Marijuana exposure and pulmonary alterations in primates. *Pharmacology, Biochemistry and Behavior* 40:637-642.

43. Fligiel SEG, Roth MD, Kleerup EC, Barsky SH, Simmons M, Tashkin DP. 1997. Tracheobronchial Histopathology in Habitual Smokers of Cocaine, Marijuana, and/or Tobacco. *Chest* 112:319-326.

44. Foley K. 1997. Competent care for the dying instead of physician-assisted suicide. *New England Journal of Medicine* 336:54-58.

45. Fride E, Mechoulam R. 1996. Ontogenetic development of the response to anandamide and delta 9-tetrahydrocannabinol in mice. *Brain Research, Developmental Brain Research* 95:131-134.

46. Fried PA. 1982. Marihuana use by pregnant women and effects on offspring: An update. *Neurobehavioral Toxicology and Teratology* 4:451-454.

47. Fried P A. 1995. The Ottawa Prenatal Prospective Study (OPPS): Methological issues and findings - it's easy to throw the baby out with the bath water. *Life Sciences* 56:2159-2168.

48. Fried PA, O'Connell CM, Watkinson B. 1992. 60- and 72-month follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol: cognitive and language assessment. *Developmental and Behavioral Pediatrics* 13:383-391.

49. Fried PA, Watkinson BSLS. 1997. Reading and language in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicology and Teratology* 19:171-183.

50. Fried PA, Watkinson B, Gray R. 1998. Differential effects on Cognitive Functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicology and Teratology* 20:293-306.

51. Gardner EL. 1992. Brain reward mechanisms. In: Lowinson JH, Ruiz P, Millman RB, Editors *Substance Abuse: A Comprehensive Textbook.* 2nd Edition. Baltimore, MD: Williams and Wilkins. Pp. 70-99.

52. Georgotas A, Zeidenberg P. 1979. Observations on the effects of four weeks of heavy marijuana smoking on group interaction and individual behavior. *Comprehensive Psychiatry* 20:427-432.

53. Gilmore DG, Blood AD, Lele KP, Robbins ES, Maximillian C. 1971. Chromosomal aberrations in users of psychoactive drugs. *Archives of General Psychiatry* 24:268-272.

54. Goldstein A. 1994. Tolerance and Dependence. In: Goldstein A, *Addiction: From Biology to Drug Policy.* New York: W.H. Freeman and Company. Pp. 73-84.

55. Gong HJ, Fligiel S, Tashkin DP, Barbers RG. 1987. Tracheobronchial changes in habitual, heavy smokers of marijuana with and without tobacco. *American Review of Respiratory Disease* 136:142-149.

56. Graham JDP. 1986. The cardiovascular action of cannabinoids. In: Mechoulam R, Editor *Cannabinoids as therapeutic agents.* Boca Raton, FL: CRC Press, Inc. Pp. 159-166.

57. Grant S, London ED, Newlin DB, Villemagne VL, Liu X, Contoreggi C, Phillips RL, Kimes AS, Margolin A. 1996. Activation of memory circuits during cue-elicited cocaine craving. *Proceedings of the National Academy of Sciences* 93:12040-12045.

58. Hall W, Solowij N. 1998. Adverse effects of cannabis. *The Lancet* 352:1611-1616.

59. Hall W, Solowij N, Lemon J. 1994. *The health and psychological consequences of cannabis use.* Department of Human Services and Health, Monograph Series, No. 25. Canberra, Australia: Australian Government Publishing Service.

60. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. 1999. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology* 141:385-394.

61. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. 1999. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology* 141:395-404.

62. Herha J, Obe G. 1974. Chromosomal damage in chronical users of cannabis: in vivo investigation with two-day lymphocyte cultures. *Pharmakopsychiatric* 7:328-337.

63. Herring AC, Koh WS, Kaminski NE. 1998. Inhibition of the cyclic AMP signaling cascade and nuclear factor binding to CRE and kappa B elements by cannabinol, a minimally CNS-active cannabinoid. *Biochemical Pharmacology* 55:1013-1023.

64. Hingson R, Alpert JJ, Day N, Dooling E, Kayn H, Morelock S, Oppenheimer E, Zuckerman B. 1982. Effects of maternal drinking and marihuana use on fetal growth and development. *Pediatrics* 70:539-546.

65. Hollister LE. 1986. Health aspects of cannabis. *Pharmacological Reviews* 38:1-20.

66. Huber GL, Mahajan VK. 1988. The comparative response of the lung to marihuana or tobacco smoke inhalation. In: Chesher G, Consroe P, Musty R, Editors *Marijuana: An International Research Report: Proceedings of Melbourne Symposium on Cannabis 2-4 September, 1987.* National Campaign Against Drug Abuse Monograph Series No 7 Edition. Canberra: Australian Government Publishing Service. Pp. 19-24.

67. Huestis MA, Sampson AH, Holicky BJ, Henningfield JE, Cone EJ. 1992. Characterization of the absorption phase of marijuana smoking. *Clinical Pharmacology and Therapeutics* 52:31-41.

68. IOM (Institute of Medicine). 1982. *Marijuana and Health.* Washington, DC: National Academy Press.

69. Jackson AL, Murphy LL. 1997. Role of the hypothalamic-pituitary-adrenal axis in the suppression of luteinizing hormone release by delta-9-tetrahydrocannabinol. *Neuroendocrinology* 65:446-452.

70. Johnson V. 1995. The relationship between parent and offspring comorbid disorders. *Journal of Substance Abuse* 7:267-280.

71. Johnston LD, O'Malley PM, Bachman JG. 1989. Marijuana decriminalization: the impact on youth, 1975-1980. *Journal of Public Health Policy* 10:456.

72. Jones RT, Benowitz NL, Herning RI. 1981. Clinical relevance of cannabis tolerance and dependence. *Journal of Clinical Pharmacology* 21:143S-152S.

73. Jones RT, Benowitz N, Bachman J. 1976. Clinical studies of tolerance and dependence. *Annals of the New York Academy of Sciences* 282:221-239.

74. Kaklamani E, Trichopoulos D, Koutselinis A, Drouga M, Karalis D. 1978. Hashis smoking and T-lymphocytes. *Archives of Toxicology* 40:97-101.

75. Kandel DB. 1992. Epidemiological Trends and Implications for Understanding the Nature of Addiction. In: O'Brien CP, Jaffe JH, Editors *Addictive Studies.* New York: Raven Press, Ltd. Pp. 23-40.

76. Kandel DB, Chen KWLA, Kessler R, Grant B. 1997. Prevalence and demographic correlates of symptoms of last year dependence on alcohol, nicotine, marijuana and cocaine in the U.S. population. *Drug and Alcohol Dependence* 44:11-29.

77. Kandel DB, Davies M. 1992. Progression to Regular Marijuana Involvement: Phenomenology and Risk Factors for Near-Daily Use. In: Glantz M, Pickens R, Editors *Vulnerability to Drug Abuse.* Washington, D.C.: American Psychological Association. Pp. 211-253.

78. Kandel DB, Johnson JG, Bird HR, Canino G, Goodman SH, Lahey BB, Regier DA, Schwab-Stone M. 1997. Psychiatric Disorders Associated with Substance Use Among Children and Adolescents: Findings from the Methods for the Epidemiology of Child and Adolescent Mental Disorders (MECA) Study. *Journal of Abnormal Child Psychology* 25:121-132.

79. Kandel DB, Raveis VH. 1989. Cessation of Illicit Drug Use in Young Adulthood. *Archives of General Psychiatry* 46:109-116.

80. Kandel DB, Yamaguchi K. 1993. From Beer to Crack: Developmental Patterns of Drug Involvement. *American Journal of Public Health* 83:851-855.

81. Kandel DB, Yamaguchi K, Chen K. 1992. Stages of Progression in Drug Involvement from Adolescence to Adulthood: Further Evidence for the Gateway Theory. *J. Stud Alcohol* 53:447-457.

82. Kaplan H B, Martin S S, Johnson R J, Robbins C A. 1996. Escalation of marijuana use: application of a general theory of deviant behavior. *Journal of Health and Social Behavior* 27:44-61.

83. Kaslow RA, Blackwelder WC, Ostrow DG, et al. 1989. No evidence for a role of alcohol or other psychoactive drugs in accelerating immunodeficiency in HIV-1 positive individuals: a report for the multicenter AIDS cohort study. *Journal of the American Medical Association* 261:3424-3429.

84. Kelly T H, Foltin R W, Fischman M W. 1993. Effects of smoked marijuana on heart rate, drug ratings and task performance by humans. *Behavioural Pharmacology* 4:167-178.

85. Kendler, K. S., C. A. Prescott. 1998. Cannabis Use, Abuse, and Dependence in a Population-Based Sample of Female Twins. *American Journal of Psychiatry* 155:1016.

86. Klein TW, Friedman H, Specter SC. 1998. Marijuana, immunity and infection. *Journal of Neuroimmunology* 83:102-115.

87. Koob GF, Le Moal M. 1997. Drug abuse: Hedonic homeostatic dysregulation. *Science* 278:52-58.

88. Kuehnle J, Mendelson JH, Davis KR, New PF. 1977. Computed tomographic examination of heavy marihuana smokers. *Journal of the American Medical Association* 237:1231-1232.

89. Labouvie E, Bates ME, Pandina RJ. 1997. Age of first use: Its reliability and predictive utility. *Journal of Studies on Alcohol* 58:638-643.

90. Lau RJ, Tubergen DG, Barr MJ, Domino EF, Benowitz N, Jones RT. 1976. Phytohemagglutinin-induced lymphocyte transformation in humans receiving delta-9-tetrahydrocannabinol. *Science* 192:805-807.

91. Lepore M, Liu X, Savage V, Matalon D, Gardner EL. 1996. Genetic differences in delta 9-tetrahydrocannabinol-induced facilitation of brain stimulation reward as measured by a rate-frequency curve-shift electrical brain stimulation paradigm in three different rat strains. *Life Sciences* 58:365-372.

92. Lepore M, Vorel SR, Lowinson J, Gardner EL. 1995. Conditioned place preference induced by delta 9-tetrahydrocannabinol: Comparison with cocaine, morphine, and food reward. *Life Sciences* 56:2073-2080.

93. Leuchtenberger C, Leuchtenberger R. 1976. Cytological and cytochemical studies of the effects of fresh marijuana cigarette smoke on growth and DNA metabolism of animal and human lung cultures. In: Braude MC, Szara S, Editors *The Pharmacology of Marijuana.* New York: Raven Press.

94. Lindgren JE, Ohlsson A, Agurell S, Hollister LE, Gillespie H. 1981. Clinical effects and plasma levels of delta 9-tetrahydrocannabinol (delta 9-THC) in heavy and light users of cannabis. *Psychopharmacology (Berl)* 74:208-12.

95. Linzen DH, Dingemans PM, Lenior ME. 1994. Cannabis abuse and the course of recent-onset schizophrenic disorders. *Archives of General Psychiatry* 51:273-279.

96. Lyons Michael J., Toomey R, Meyer J M, Green AI, Eisen S A, Goldberg J, True W R, Tsuang M T. 1997. How do genes influence marijuana use? The role of subjective effects. *Addiction* 92:409-417.

97. MacCoun R, Reuter P. 1997. Interpreting Dutch cannabis policy: Reasoning by analogy in the legalization debate. *Science* 278:47-52.

98. Marques-Magallanes JA, Tashkin DP, Serafian T, Stegeman J, Roth MD. 1997. *In vivo* and *in vitro* activation of cytochrome P4501A1 by marijuana smoke. *Symposium on the Cannabinoids of the International Cannabinoid Research Society Program and Abstracts*. Stone Mountain, GA, June, 1997.

99. Martellotta MC, Cossu G, Fattore L, Gessa GL, Fratta W. 1998. Self-administration of the cannabinoid receptor agonist WIN 55,212-2 in drug-naive mice. *Neuroscience* 85:327-330.

100. Mathew RJ, Wilson WH, Humphreys DF, Lowe JV, Wiethe KE. 1992. Regional cerebral blood flow after marijuana smoking. *Journal of Cerebral Blood Flow and Metabolism* 12:750-758.

101. Mathre ML. 1998. A Survey on Disclosure of Marijuana Use to Health Care Professionals. *Journal of Psychoactive Drugs* 20:117-120.

102. Mendelson JH, Cristofaro P, Ellingboe J, Benedikt R, Mello NK. 1985. Acute effects of marihuana on luteinizing hormone in menopausal women. *Pharmacology, Biochemistry, and Behavior* 23:765-768.

103. Meyer RE, Pillard RC, Shapiro LM, Mirin SM. 1971. Administration of marijuana to heavy and casual marijuana users. *American Journal of Psychiatry* 128:198-204.

104. Model KE. 1993. The effect of Marijuana decriminalization on hospital emergency room drug episodes: 1975-1978. *Journal of the American Statistical Association* 88:737-747.

105. Moulin DE, Iezzi A, Amireh R, Sharpe WKJ, Boyd D, Merskey H. 1996. Randomised trial of oral morphine for chronic non-cancer pain. *Lancet* 347:143-147.

106. Murphy LL, Gher J, Szary A. 1995. Effects of prenatal exposure to delta-9-tetrahydrocannabinol on reproductive, endocrine and immune parameters of male and female rat offspring. *Endocrine* 3:875-879.

107. Nahas GG, Osserman EF. 1991. Altered serum immunoglobulin concentration in chronic marijuana smokers. *Advances in Experimental Medicine and Biology* 288:25-32.

108. Nesse RM, Berridge KC. 1997. Psychoactive Drug Use in Evolutionary Perspective. *Science* 278:63-66.

109. Nestler EJ, Aghajanian GK. 1997. Molecular and Cellular Basis of Addiction. *Science* 278:58-63.

110. Newell GR, Mansell PW, Wilson MB, Lynch HK, Spitz MR, Hersh EM. 1985. Risk factor analysis among men referred for possible Acquired Immune Deficiency Syndrome. *Preventive Medicine* 14:81-91.

111. NIH (National Institutes of Health). 1997. Workshop on the medical utility of marijuana. *Report to the Director, National Institutes of Health by the ad hoc group experts.* Bethesda, MD, February 19-20, 1997.
Publisher:National Institutes of Health, Bethesda, MD.

112. O'Brien CP. 1996. Drug addiction and drug abuse. In: Harmon JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman A G, Editor *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 9th Edition. New York: McGraw-Hill. Pp. 557-577.

113. O'Brien CP. 1996. Recent developments in the pharmacotherapy of substance abuse. *Journal of Consulting and Clinical Psychology* 64:677-86.

114. O'Brien CP. 1997. A range of research-based pharmacotherapies for addiction. *Science* 278:66-70.

115. O'Leary DS, Andreasen NC, Hurtig RR, Torres IJ, Flashman LA, Kesler ML, Arndt SV, Cizadlo TJ, Ponto LLB, Watkins GL, Hichwa RD. 1997. Auditory and visual attention assessed with PET. *Human Brain Mapping* 5:422-436.

116. O'Leary D, Block RI, Flaum M, Boles Ponto LL, Watkins GL, Hichwa RD. 1998. Acute marijuana effects on rCBF and cognition: A PET study. *Abstracts - Society for Neuroscience: 28th Annual Meeting*. Los Angeles, CA, November 7-12, 1998. Washington, DC: Society for Neuroscience.

117. Ohlsson A, Lindgren J-E, Wahlen A, Agurell S, Hollister L E, Gillespie HK. 1980. Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clinical Pharmacology and Therapeutics* 28:409-416.

118. Peterson RC. 1979. Importance of inhalation patterns in determining effects of marijuana use. *Lancet* 1:727-728.

119. Polen MR, Sidney S, Tekawa IS, Sadler M, Friedman D. 1993. Health care use by frequent marijuana smokers who do not smoke tobacco. *The Western Journal of Medicine* 158:596-601.

120. Pope HG, Gruber AJ, Yurgelun-Todd D. 1995. The residual neuropsychological effects of cannabis: The current status of research. *Drug and Alcohol Dependence* 38:25-34.

121. Pope HG, Yurgelun-Todd D. 1996. The residual cognitive effects of heavy marijuana use in college students. *Journal of the American Medical Association* 275:521-527.

122. Rachelefsky G, Opelz G, Mickey M, Lessin P, Kiuchi M, Silverstein M, Stiehm E. 1976. Intact humoral and cell-mediated immunity in chronic marijuana smoking. *Journal of Allergy and Clinical Immunology* 58:483-490.

123. Rickles Jr WH, Cohen MJ, Whitaker CA, McIntyre KE. 1973. Marijuana induced state-dependent verbal learning. *Psychopharmacologia* 30:349-354.

124. Robins LN. 1980. The natural history of drug abuse. *Acta Psychiatrica Scandinavica Suppl* 284:7-20.

125. Robins. L.N. 1998. The intimate connection between antisocial personality and substance abuse. *Social Psychiatry and Psychiatric Epidemiology* 33:393-399.

126. Robins LN, McEvoy LT. 1990. Conduct problems as predictors of substance abuse. In: Robins L, Rutter M, eds. *Straight and devious pathways from childhood to adulthood.* New York Cambridge: Cambridge University Press. Pp. 182-204.

127. Rosenkrantz H, Fleischman RW. 1979. Effects of cannabis on lung. In: Nahas GG, Payton WDH, Editors *Marijuana: Biological Effects*. Oxford, England: Pergamon Press. Pp. 279-299.

128. Rosenzweig MR, Leiman AL, Breedlove SM. 1996. *Biological Psychology*. Sunderland, MA: Sinauer Associates, Inc.

129. Roth MD, Arora A, Barsky SH, Kleerup EC, Simmons MS, Tashkin DP. 1998. Airway inflammation in young marijuana and tobacco smokers. *American Journal of Respiratory and Critical Care Medicine* 157:1-9.

130. Roth MD, Kleerup EC, Arora A, Barsky SH, Tashkin DP. 1996. Endobronchial injury in young tobacco and marijuana smokers as evaluated by visual, pathologic and molecular criteria. *American Review of Respiratory and Critical Care Medicine* 153 (part 2):100A.

131. SAMHSA (Substance Abuse and Mental Health Services Administration). 1998. *National Household Survey on Drug Abuse: Population Estimates 1997.* DHHS Pub No. (SMA) 98-3250. Rockville, MD: SAMHSA, Office of Applied Studies.

132. Scheier LM, Bovtin GJ. 1996. Cognitive effects of marijuana. *Journal of the American Medical Association* 275:JAMA Letters.

133. Schneier F R, Siris SG. 1987. A review of psychoactive substance use and abuse in schizophrenia: patterns of drug choice. *Journal of Nervous and Mental Disease* 175:641-652.

134. Schuel H, Berkery D, Schuel R, Chang MC, Zimmerman AM, Zimmerman S. 1991. Reduction of the fertilizing capacity of sea urchin sperm by cannabinoids derived from marihuana. I. Inhibition of the acrosome reaction induced by egg jelly. *Molecular Reproduction and Development* 29:51-59.

135. Schuel H, Chang MC, Berkery D, Schuel R, Zimmerman AM, Zimmerman S. 1991. Cannabinoids inhibit fertilization in sea urchins by reducing the fertilizing capacity of sperm. *Pharmacology, Biochemistry, and Behavior* 40:609-615.

136. Schuel H, Goldstein E, Mechoulam R, Zimmerman AM, Zimmerman S. 1994. Anandamide (arachidonylethanolamide), a brain cannabinoid receptor, agonist, reduces sperm fertilizing capacity in sea urchins by inhibiting the acrosome reaction. *Proceedings of the National Academy of Sciences* 91:7678-7682.

137. Sidney S, Beck JE, Tekawa IS, Quesenberry CP, Jr, Friedman GD. 1997a. Marijuana Use and Mortality. *American Journal of Public Health* 87:585-590.

138. Sidney S, Quesenberry CP, Jr, Friedman GD, Tekawa IS. 1997b. Marijuana use and cancer incidence (California, United States). *Cancer Cause and Control* 8:722-728.

139. Solowij N. 1995. Do cognitive impairments recover following cessation of cannabis use? *Life Sciences* 56:2119-2126.

140. Sridhar JS, Raub WA, Weatherby NL, et al. 1994. Possible role of marijuana smoking as a carcinogen in the development of lung cancer at a young age. *Journal of Psychoactive Drugs* 26:285-288.

141. Stenchever MA, Kunysz TJ, Allen MA. 1974. Chromosome breakage in users of marijuana. *American Journal of Gynecology* 118:106-113.

142. Stephens RS, Roffman RA, Simpson EE. 1993. Adult marijuana users seeking treatment. *Journal of Consulting and Clinical Psychology* 61:1100-1104.

143. Tanda G, Pontieri FE, Di Chiara G. 1997. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ1 opioid receptor mechanism. *Science* 276:2048-2049.

144. Tart CT. 1971. *On being stoned: A psychological study of marijuana intoxication.* Palo Alto, CA: Science and Behavior Books.

145. Tashkin DP, Coulson A H, Clark V A, Simmons M, Bourque L B, Duann S, Spivey G H, Gong H. 1987. Respiratory symptoms and lung function in habitual, heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. *American Review of Respiratory Disease* 135:209-216.

146. Tashkin DP, Simmons MS, Sherrill DL, Coulson AH. 1997. Heavy habitual marijuana smoking does not cause an accelerated decline in FEV_1 with age. *American Journal of Respiratory and Critical Care Medicine* 155:141-148.

147. Tashkin E. 1999. Effects of marijuana on the lung and its defenses against infection and cancer. *School Psychology International* 20:23-37.

148. Taylor FM. 1988. Marijuana as a potential respiratory tract carcinogen: A retrospective analysis. *Southern Medical Journal* 81:1213-1216.

149. Tennant FS. 1980. Histopathologic and clinical abnormalities of the respiratory system in chronic hashish smokers. *Substance and Alcohol Actions/Misuse* 1:93-100.

150. Thornicroft G. 1990. Cannabis and psychosis: Is there epidemiological evidence for an association? *British Journal of Psychiatry* 157:25-33.

151. Tindall B, Cooper D, Donovan B, Barnes T, Philpot C, Gold J, Penny R. 1988. The Sydney AIDS Project: Development of Acquired Immunodeficiency Syndrome in a Group of HIV Seropositive Homosexual Men. *Australian and New Zealand Journal of Medicine* 18:8-15.

152. Tsou K, Patrick SL, Walker JM. 1995. Physical withdrawal in rats tolerant to delta-9-tetrahydrocannabinol precipitated by a cannabinoid receptor antagonist. *European Journal of Pharmacology* 280:R13-R15.

153. Van Hoozen BE, Cross CE. 1997. Respiratory tract effects of marijuana. *Clinical Reviews in Allergy and Immunology* 15:243-269.

154. Volkow ND, Gillespie H, Mullani N, Tancredi L, Grant C, Valentine A, Hollister L. 1996. Brain glucose metabolism in chronic marijuana users at baseline and during marijuana intoxication. *Psychiatry Research* 67:29-38.

155. Wagner JA, Varga K, Kunos G. 1998. Cardiovascular actions of cannabinoids and their generation during shock. *Journal of Molecular Medicine* 76:824-836.

156. Wallace JM, Tashkin DP, Oishi JS, Barbers RG. 1988. Peripheral blood lymphocyte subpopulations and mitogen responsiveness in tobacco and marijuana smokers. *Journal of Psychoactive Drugs* 20:9-14.

157. Wehner FC, Van Rensburg SJ, Theil PF. 1980. Mutagenicity of marijuana and Transkei tobacco smoke condensates in the Salmonella/microsome assay. *Mutation Research* 77:135-142.

158. Wenger T, Croix D, Tramu G, Leonardelli J. 1992. Effects of delta9-tetrahydrocannabinol on pregnancy, puberty, and the neuroendocrine system. In: Murphy L, Bartke A, *Marijuana/Cannabinoids: Neurobiology and Neurophysiology.* Boca Raton, FL: CRC Press.

159. White SC, Brin SC, Janicki BW. 1975. Mitogen-induced blastogenic responses of lymphocytes from marijuana smokers. *Science* 188:71-72.

160. Whitfield RM, Bechtel LM, Starich GH. 1997. The impact of ethanol and marinol/marijuana usage on hiv+/aidspatients undergoing azidothymidine, azidothymidine/dideoxycytidine, ordideoxyinosine therapy. *Alcohol Clin Exp Res* 21:122-7.

161. Wu TC, Tashkin DP, Djahed B, Rose JE. 1988. Pulmonary hazards of smoking marijuana as compared with tobacco. *New England Journal of Medicine* 318:347-351.

162. Yesavage JA, Leirer VO, Denari M, Hollister LE. 1985. Carry-over effects of marijuana intoxication on aircraft pilot performance: a preliminary report. *American Journal of Psychiatry* 142:1325-1329.

163. Zuckerman B, Frank DA, Hingson R, Amaro H, Levenson S, Kayne J, Parker S, Vinci R, Aboagye K, Fried L, Cabral J, Timperi R, Bauchner H. 1989. Effects of maternal marijuana and cocaine use on fetal growth. *New England Journal of Medicine* 320:762-768.