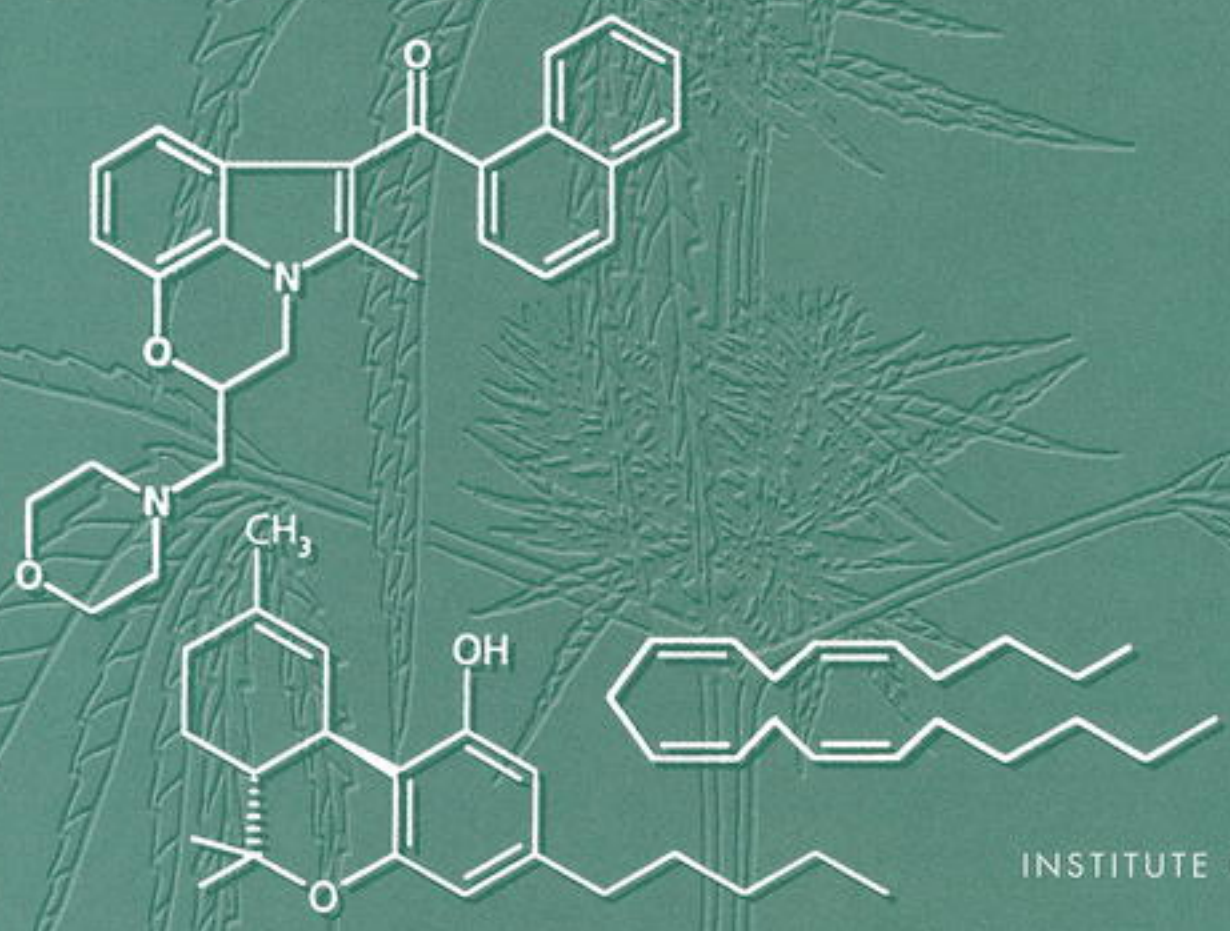
MARIJUANA AND MEDICINE

Assessing the Science Base



INSTITUTE OF MEDICINE

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Assessing the Science Base

Janet E. Joy, Stanley J. Watson, Jr., and
John A. Benson, Jr., *Editors*

Division of Neuroscience and Behavioral Health

INSTITUTE OF MEDICINE

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the Institute of Medicine in making the published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. The committee wishes to thank the following individuals for their participation in the review of this report:

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While the individuals listed above provided constructive comments and suggestions, it must be emphasized that responsibility for the final content of this report rests entirely with the authoring committee and the Institute of Medicine.

Preface

Public opinion on the medical value of marijuana has been sharply divided. Some dismiss medical marijuana as a hoax that exploits our natural compassion for the sick; others claim it is a uniquely soothing medicine that has been withheld from patients through regulations based on false claims. Proponents of both views cite "scientific evidence" to support their views and have expressed those views at the ballot box in recent state elections. In January 1997, the White House Office of National Drug Control Policy (ONDCP) asked the Institute of Medicine to conduct a review of the scientific evidence to assess the potential health benefits and risks of marijuana and its constituent cannabinoids. That review began in August 1997 and culminates with this report.

The ONDCP request came in the wake of state "medical marijuana" initiatives. In November 1996, voters in California and Arizona passed referenda designed to permit the use of marijuana as medicine. Although Arizona's referendum was invalidated five months later, the referenda galvanized a national response. In November 1998, voters in six states (Alaska, Arizona, Colorado, Nevada, Oregon, and Washington) passed ballot initiatives in support of medical marijuana. (The Colorado vote will not count, however, because after the vote was taken a court ruling determined there had not been enough valid signatures to place the initiative on the ballot.)

Information for this study was gathered through scientific workshops, site visits to cannabis buyers' clubs and HIV/AIDS clinics, analysis of the relevant scientific literature, and extensive consultation with biomedical and social scientists. The three 2-day workshops—in Irvine, California; New Orleans, Louisiana; and Washington, D.C.—were open to the public and included scientific presentations and individual reports, mostly from patients and their families, about experiences with and perspectives on the medical use of marijuana. Scientific experts in various fields were selected to talk about the latest research on marijuana, cannabinoids, and related topics. (Cannabinoids are drugs with actions similar to THC, the primary psychoactive ingredient in marijuana.) In addition, advocates for and against the medical use of marijuana were invited to present scientific evidence in support of their positions. Finally, the Institute of Medicine appointed a panel of nine experts to advise the study team on technical issues.

Public outreach included setting up a Web site that provided information about the study and asked for input from the public. The Web site was open for comment from November 1997 until November 1998. Some 130 organizations were invited to participate in the public workshops. Many people in the organizations—particularly those opposed to the medical use of marijuana—felt that a public forum was not conducive to expressing their views; they were invited to communicate their opinions (and reasons for holding them) by mail or telephone. As a result, roughly equal numbers of persons and organizations opposed to and in favor of the medical use of marijuana were heard from.

Advances in cannabinoid science over the past 16 years have given rise to a wealth of new opportunities for the development of medically useful cannabinoid-based drugs. The accumulated data suggest a variety of indications, particularly for pain relief, antiemesis, and appetite stimulation. For patients who suffer simultaneously from severe pain, nausea, and appetite loss, such as those with AIDS or who are undergoing chemotherapy, cannabinoid drugs might offer broad-spectrum relief not found in any other single medication.

Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, the harmful effects to individuals from the perspective of possible medical use of marijuana are not necessarily the same as the harmful physical effects of drug abuse.

Although marijuana smoke delivers THC and other cannabinoids to the body, it also delivers harmful substances, including most of those found in tobacco smoke. In addition, plants contain a variable mixture of biologically active compounds and cannot be expected to provide a pre-

cisely defined drug effect. For those reasons, the report concludes that the future of cannabinoid drugs lies not in smoked marijuana but in chemically defined drugs that act on the cannabinoid systems that are a natural component of human physiology. Until such drugs can be developed and made available for medical use, the report recommends interim solutions.

John A. Benson, Jr.
Stanley J. Watson, Jr.
Co-Principal Investigators

Acknowledgments

This report covers such a broad range of disciplines—neuroscience, pharmacology, immunology, drug abuse, drug laws, and a variety of medical specialties, including neurology, oncology, infectious diseases, and ophthalmology—that it would not have been complete without the generous support of many people. Our goal in preparing this report was to identify the solid ground of scientific consensus and to steer clear of the muddy distractions of opinions that are inconsistent with careful scientific analysis. To this end we consulted extensively with experts in each of the disciplines covered in this report. We are deeply indebted to each of them.

Members of the Advisory Panel, selected because each is recognized as among the most accomplished in their respective disciplines (see page iii), provided guidance to the study team throughout the study—from helping to lay the intellectual framework to reviewing early drafts of the report.

The following people wrote invaluable background papers for the report: Steven R. Childers, Paul Consroe, Howard Fields, Richard J. Gralla, Norbert Kaminski, Paul Kaufman, Thomas Klein, Donald Kotler, Richard Musty, Clara Sanudo-Peña, C. Robert Schuster, Stephen Sidney, Donald P. Tashkin, and J. Michael Walker. Others provided expert technical commentary on draft sections of the report: Richard Bonnie, Keith Green, Frederick Fraunfelder, Andrea Hohmann, John McAnulty, Craig Nichols, John Nutt, and Robert Pandina. Still others responded to many inquiries, provided expert counsel, or shared their unpublished data: Paul Consroe, Geoffrey Levitt, Raphael Mechoulam, Richard Musty, David Pate, Roger

Pertwee, Clara Sanudo-Peña, Carl Soderstrom, J. Michael Walker, and Scott Yarnell. Miriam Davis, consultant to the study team, provided excellent written material for the chapter on cannabinoid drug development.

The reviewers for the report (see page iv) provided extensive, constructive suggestions for improving the report. It was greatly enhanced by their thoughtful attention. Many of these people assisted us through many iterations of the report. All of them made contributions that were essential to the strength of the report. At the same time, it must be emphasized that responsibility for the final content of report rests entirely with the authors and the Institute of Medicine.

We would also like to thank the people who hosted our visits to their organizations. They were unfailingly helpful and generous with their time. Jeffrey Jones and members of the Oakland Cannabis Buyers' Cooperative, Denis Peron of the San Francisco Cannabis Cultivators Club, Scott Imler and staff at the Los Angeles Cannabis Resource Center, Victor Hernandez and members of Californians Helping Alleviate Medical Problems (CHAMPS), Michael Weinstein of the AIDS Health Care Foundation, and Marsha Bennett of the Louisiana State University Medical Center. We also appreciate the many people who spoke at the public workshops or wrote to share their views on the medical use of marijuana (see Appendix A).

Jane Sanville, project officer for the study sponsor, was consistently helpful during the many negotiations and discussion held throughout the study process. Many Institute of Medicine staff members provided greatly appreciated administrative, research, and intellectual support during the study. Robert Cook-Deegan, Marilyn Field, Constance Pechura, Daniel Quinn, and Michael Stoto provided thoughtful and insightful comments on draft sections of the report. Others provided advice and consultation on many other aspects of the study process: Clyde Behney, Susan Fourt, Carolyn Fulco, Carlos Gabriel, Linda Kilroy, Catharyn Liverman, Dev Mani, and Kathleen Stratton. As project assistant throughout the study, Amelia Mathis was tireless, gracious, and reliable.

Deborah Yarnell's contribution as research associate for this study was outstanding. She organized site visits, researched and drafted technical material for the report, and consulted extensively with relevant experts to ensure the technical accuracy of the text. The quality of her contributions throughout this study was exemplary.

Finally, the principal investigators on this study wish to personally thank Janet Joy for her deep commitment to the science and shape of this report. In addition, her help in integrating the entire data gathering and information organization of this report was nothing short of essential. Her knowledge of neurobiology, her sense of quality control, and her unflagging spirit over the 18 months illuminated the subjects and were indispensable to the study's successful completion.

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MARIJUANA AND MEDICINE

Executive Summary

Public opinion on the medical value of marijuana has been sharply divided. Some dismiss medical marijuana as a hoax that exploits our natural compassion for the sick; others claim it is a uniquely soothing medicine that has been withheld from patients through regulations based on false claims. Proponents of both views cite "scientific evidence" to support their views and have expressed those views at the ballot box in recent state elections. In January 1997, the White House Office of National Drug Control Policy (ONDCP) asked the Institute of Medicine (IOM) to conduct a review of the scientific evidence to assess the potential health benefits and risks of marijuana and its constituent cannabinoids (see the Statement of Task on page 9). That review began in August 1997 and culminates with this report.

The ONDCP request came in the wake of state "medical marijuana" initiatives. In November 1996, voters in California and Arizona passed referenda designed to permit the use of marijuana as medicine. Although Arizona's referendum was invalidated five months later, the referenda galvanized a national response. In November 1998, voters in six states (Alaska, Arizona, Colorado, Nevada, Oregon, and Washington) passed ballot initiatives in support of medical marijuana. (The Colorado vote will not count, however, because after the vote was taken a court ruling determined there had not been enough valid signatures to place the initiative on the ballot.)

Can marijuana relieve health problems? Is it safe for medical use?

Those straightforward questions are embedded in a web of social concerns, most of which lie outside the scope of this report. Controversies concerning the nonmedical use of marijuana spill over into the medical marijuana debate and obscure the real state of scientific knowledge. In contrast with the many disagreements bearing on social issues, the study team found substantial consensus among experts in the relevant disciplines on the scientific evidence about potential medical uses of marijuana.

This report summarizes and analyzes what is known about the medical use of marijuana; it emphasizes evidence-based medicine (derived from knowledge and experience informed by rigorous scientific analysis), as opposed to belief-based medicine (derived from judgment, intuition, and beliefs untested by rigorous science).

Throughout this report, *marijuana* refers to unpurified plant substances, including leaves or flower tops whether consumed by ingestion or smoking. References to the "effects of marijuana" should be understood to include the composite effects of its various components; that is, the effects of tetrahydrocannabinol (THC), which is the primary psychoactive ingredient in marijuana, are included among its effects, but not all the effects of marijuana are necessarily due to THC. *Cannabinoids* are the group of compounds related to THC, whether found in the marijuana plant, in animals, or synthesized in chemistry laboratories.

Three focal concerns in evaluating the medical use of marijuana are:

1. Evaluation of the effects of isolated cannabinoids;
2. Evaluation of the risks associated with the medical use of marijuana; and
3. Evaluation of the use of smoked marijuana.

EFFECTS OF ISOLATED CANNABINOIDS

Cannabinoid Biology

Much has been learned since the 1982 IOM report *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. In addition, too little was known about cannabinoid physiology to offer any scientific insights into the harmful or therapeutic effects of marijuana. That all changed with the identification and characterization of cannabinoid receptors in the 1980s and 1990s. During the past 16 years, science has advanced greatly and can tell us much more about the potential medical benefits of cannabinoids.

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 multi-faceted 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 human 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 1: 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.

Efficacy of Cannabinoid Drugs

The accumulated data indicate a potential therapeutic value for cannabinoid drugs, particularly for symptoms such as pain relief, control of nausea and vomiting, and appetite stimulation. The therapeutic effects of cannabinoids are best established for THC, which is generally one of the two most abundant of the cannabinoids in marijuana. (Cannabidiol is generally the other most abundant cannabinoid.)

The effects of cannabinoids on the symptoms studied are generally modest, and in most cases there are more effective medications. However, people vary in their responses to medications, and there will likely always be a subpopulation of patients who do not respond well to other

medications. The combination of cannabinoid drug effects (anxiety reduction, appetite stimulation, nausea reduction, and pain relief) suggests that cannabinoids would be moderately well suited for particular conditions, such as chemotherapy-induced nausea and vomiting and AIDS wasting.

Defined substances, such as purified cannabinoid compounds, are preferable to plant products, which are of variable and uncertain composition. Use of defined cannabinoids permits a more precise evaluation of their effects, whether in combination or alone. Medications that can maximize the desired effects of cannabinoids and minimize the undesired effects can very likely be identified.

Although most scientists who study cannabinoids agree that the pathways to cannabinoid drug development are clearly marked, there is no guarantee that the fruits of scientific research will be made available to the public for medical use. Cannabinoid-based drugs will only become available if public investment in cannabinoid drug research is sustained and if there is enough incentive for private enterprise to develop and market such drugs.

> **Conclusion:** Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances.
>
> **Recommendation 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.**

Influence of Psychological Effects on Therapeutic Effects

The psychological effects of THC and similar cannabinoids pose three issues for the therapeutic use of cannabinoid drugs. First, for some patients—particularly older patients with no previous marijuana experience—the psychological effects are disturbing. Those patients report experiencing unpleasant feelings and disorientation after being treated with THC, generally more severe for oral THC than for smoked marijuana. Second, for conditions such as movement disorders or nausea, in which anxiety exacerbates the symptoms, the antianxiety effects of cannabinoid drugs can influence symptoms indirectly. This can be beneficial or can create false impressions of the drug effect. Third, for cases in which symptoms are multifaceted, the combination of THC effects might provide a form of adjunctive therapy; for example, AIDS wasting patients would likely benefit from a medication that simultaneously reduces anxiety, pain, and nausea while stimulating appetite.

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's effect.

Recommendation 3: Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.

RISKS ASSOCIATED WITH MEDICAL USE OF MARIJUANA

Physiological Risks

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 of effects tolerated for other medications. The harmful effects to individuals from the perspective of possible medical use of marijuana are not necessarily the same as the harmful physical effects of drug abuse. When interpreting studies purporting to show the harmful effects of marijuana, it is important to keep in mind that the majority of those studies are based on *smoked* marijuana, and cannabinoid effects cannot be separated from the effects of inhaling smoke from burning plant material and contaminants.

For most people the primary adverse effect of *acute* marijuana use is diminished psychomotor performance. It is, therefore, inadvisable to operate any vehicle or potentially dangerous equipment while under the influence of marijuana, THC, or any cannabinoid drug with comparable effects. In addition, a minority of marijuana users experience dysphoria, or unpleasant feelings. Finally, the short-term immunosuppressive effects are not well established but, if they exist, are not likely great enough to preclude a legitimate medical use.

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 smoking is associated with abnormalities of cells lining the human respiratory tract. Marijuana smoke, like tobacco smoke, is associated with increased risk of cancer, lung damage, and poor pregnancy outcomes. Although cellular, genetic, and human studies all suggest that marijuana smoke is an important risk factor for the development of respiratory cancer, proof that habitual marijuana smoking does or does not cause cancer awaits the results of well-designed studies.

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

Recommendation 4: Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.

Marijuana Dependence and Withdrawal

A second concern associated with chronic marijuana use is dependence on the psychoactive effects of THC. Although few marijuana users develop dependence, some do. Risk factors for marijuana dependence are similar to those for other forms of substance abuse. In particular, antisocial personality and conduct disorders are closely associated with substance abuse.

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 disturbance, nausea, and cramping.

Marijuana as a "Gateway" Drug

Patterns in progression of drug use from adolescence to adulthood are strikingly regular. 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. In fact, most drug users begin with alcohol and nicotine before marijuana—usually before they are of legal age.

In the sense that marijuana use typically precedes rather than follows initiation of other illicit drug use, it is indeed a "gateway" drug. But because underage smoking and alcohol use typically precede marijuana use, marijuana is not the most common, and is rarely the first, "gateway" to illicit drug use. There is no conclusive evidence that the drug effects of marijuana are causally linked to the subsequent abuse of other illicit drugs. An important caution is that data on drug use progression cannot be assumed to apply to the use of drugs for medical purposes. It does not follow from those data that if marijuana were available by prescription for medical use, the pattern of drug use would remain the same as seen in illicit use.

Finally, there is a broad social concern that sanctioning the medical use of marijuana might increase 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.

> **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.

USE OF SMOKED MARIJUANA

Because of the health risks associated with smoking, smoked marijuana should generally not be recommended for long-term medical use. Nonetheless, for certain patients, such as the terminally ill or those with debilitating symptoms, the long-term risks are not of great concern. Further, despite the legal, social, and health problems associated with smoking marijuana, it is widely used by certain patient groups.

> **Recommendation 5: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.**

The goal of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug but rather to serve as a first step toward the possible development of nonsmoked rapid-onset cannabinoid delivery systems. However, it will likely be many years before a safe and effective cannabinoid delivery system, such as an inhaler, is available for patients. In the meantime there are patients with debilitating symptoms for whom smoked marijuana might provide relief. The use of smoked marijuana for those patients should weigh both the expected efficacy of marijuana and ethical issues in patient care, including providing information about the known and suspected risks of smoked marijuana use.

> **Recommendation 6: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:**

- **failure of all approved medications to provide relief has been documented,**
- **the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,**
- **such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness, and**
- **involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.**

Until a nonsmoked rapid-onset cannabinoid drug delivery system becomes available, we acknowledge that there is no clear alternative for people suffering from *chronic* conditions that might be relieved by smoking marijuana, such as pain or AIDS wasting. One possible approach is to treat patients as *n*-of-1 clinical trials (single-patient trials), in which patients are fully informed of their status as experimental subjects using a harmful drug delivery system and in which their condition is closely monitored and documented under medical supervision, thereby increasing the knowledge base of the risks and benefits of marijuana use under such conditions.

STATEMENT OF TASK

The study will assess what is currently known and not known about the medical use of marijuana. It will include a review of the science base regarding the mechanism of action of marijuana, an examination of the peer-reviewed scientific literature on the efficacy of therapeutic uses of marijuana, and the costs of using various forms of marijuana versus approved drugs for specific medical conditions (e.g., glaucoma, multiple sclerosis, wasting diseases, nausea, and pain).

The study will also include an evaluation of the acute and chronic effects of marijuana on health and behavior; a consideration of the adverse effects of marijuana use compared with approved drugs; an evaluation of the efficacy of different delivery systems for marijuana (e.g., inhalation vs. oral); an analysis of the data concerning marijuana as a gateway drug; and an examination of the possible differences in the effects of marijuana due to age and type of medical condition.

Specific Issues

Specific issues to be addressed fall under three broad categories: science base, therapeutic use, and economics.

Science Base

- Review of the neuroscience related to marijuana, particularly the relevance of new studies on addiction and craving
- Review of the behavioral and social science base of marijuana use, particularly an assessment of the relative risk of progression to other drugs following marijuana use
- Review of the literature determining which chemical components of crude marijuana are responsible for possible therapeutic effects and for side effects

Therapeutic Use

- Evaluation of any conclusions on the medical use of marijuana drawn by other groups
- Efficacy and side effects of various delivery systems for marijuana compared to existing medications for glaucoma, wasting syndrome, pain, nausea, or other symptoms
- Differential effects of various forms of marijuana that relate to age or type of disease

Economics

- Costs of various forms of marijuana compared with costs of existing medications for glaucoma, wasting syndrome, pain, nausea, or other symptoms
- Assessment of differences between marijuana and existing medications in terms of access and availability

RECOMMENDATIONS

RECOMMENDATION 1: 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.

Scientific data indicate the potential therapeutic value of cannabinoid drugs for pain relief, control of nausea and vomiting, and appetite stimulation. This value would be enhanced by a rapid onset of drug effect.

RECOMMENDATION 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.

The psychological effects of cannabinoids are probably important determinants of their potential therapeutic value. They can influence symptoms indirectly which could create false impressions of the drug effect or be beneficial as a form of adjunctive therapy.

RECOMMENDATION 3: Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.

Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory diseases, but the data that could conclusively establish or refute this suspected link have not been collected.

RECOMMENDATION 4: Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.

Because marijuana is a crude THC delivery system that also delivers harmful substances, smoked marijuana should generally not be recom-

mended for medical use. Nonetheless, marijuana is widely used by certain patient groups, which raises both safety and efficacy issues.

RECOMMENDATION 5: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.

If there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives. Isolated cannabinoids will provide more reliable effects than crude plant mixtures. Therefore, the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug but rather to serve as a first step toward the development of nonsmoked rapid-onset cannabinoid delivery systems.

RECOMMENDATION 6: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

- **failure of all approved medications to provide relief has been documented,**
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- **involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.**

1

Introduction

This report summarizes and analyzes what is known about the medical use of marijuana; it emphasizes evidence-based medicine (derived from knowledge and experience informed by rigorous scientific analysis), as opposed to belief-based medicine (derived from judgment, intuition, and beliefs untested by rigorous science).

Scientific data on controversial subjects are commonly misinterpreted, overinterpreted, and misrepresented, and the medical marijuana debate is no exception. We have tried to present the scientific studies in such a way as to reveal their strengths and limitations. One of the goals of this report is to help people to understand the scientific data, including the logic behind the scientific conclusions, so it goes into greater detail than previous reports on the subject. In many cases, we have explained why particular studies are inconclusive and what sort of evidence is needed to support particular claims about the harms or benefits attributed to marijuana. Ideally, this report will enable the thoughtful reader to interpret new information about marijuana that will continue to emerge rapidly well after this report is published.

Can marijuana relieve health problems? Is it safe for medical use? Those straightforward questions are embedded in a web of social concerns, which lie outside the scope of this report. Controversies concerning nonmedical use of marijuana spill over onto the medical marijuana debate and tend to obscure the real state of scientific knowledge. In contrast

with the many disagreements bearing on the social issues, the study team found substantial consensus, among experts in the relevant disciplines, on the scientific evidence bearing on potential medical use. This report analyzes science, not the law. As in any policy debate, the value of scientific analysis is that it can provide a foundation for further discussion. Distilling scientific evidence does not in itself solve a policy problem. What it can do is illuminate the common ground, bringing to light fundamental differences out of the shadows of misunderstanding and misinformation that currently prevail. Scientific analysis cannot be the end of the debate, but it should at least provide the basis for an honest and informed discussion.

Our analysis of the evidence and arguments concerning the medical use of marijuana focuses on the strength of the supporting evidence and does not refer to the motivations of people who put forth the evidence and arguments. That is, it is not relevant to scientific validity whether an argument is put forth by someone who believes that all marijuana use should be legal or by someone who believes that any marijuana use is highly damaging to individual users and to society as a whole. Nor does this report comment on the degree to which scientific analysis is compatible with current regulatory policy. Although many have argued that current drug laws pertaining to marijuana are inconsistent with scientific data, it is important to understand that decisions about drug regulation are based on a variety of moral and social considerations, as well as on medical and scientific ones.

Even when a drug is used only for medical purposes, value judgments affect policy decisions concerning its medical use. For example, the magnitude of a drug's expected medical benefit affects regulatory judgments about the acceptability of risks associated with its use. Also, although a drug is normally approved for medical use only on proof of its "safety and efficacy," patients with life-threatening conditions are sometimes (under protocols for "compassionate use") allowed access to unapproved drugs whose benefits and risks are uncertain. Value judgments play an even more substantial role in regulatory decisions concerning drugs, such as marijuana, that are sought and used for nonmedical purposes. Then policymakers must take into account not only the risks and benefits associated with medical use but also possible interactions between the regulatory arrangements governing medical use and the integrity of the legal controls set up to restrict nonmedical use.

It should be clear that many elements of drug control policy lie outside the realm of biology and medicine. Ultimately, the complex moral and social judgments that underlie drug control policy must be made by the American people and their elected officials. A goal of this report is to

evaluate the biological and medical factors that should be taken into account in making those judgments.

HOW THIS STUDY WAS CONDUCTED

Information was gathered through scientific workshops, site visits, analysis of the relevant scientific literature, and extensive consultation with biomedical and social scientists. The three 2-day workshops—in Irvine, California; New Orleans, Louisiana; and Washington, D.C.—were open to the public and included scientific presentations and reports, mostly from patients and their families, about their experiences with and perspectives on the medical use of marijuana. Scientific experts in various fields were selected to talk about the latest research on marijuana, cannabinoids, and related topics (listed in Appendix B). Selection of the experts was based on recommendations by their peers, who ranked them among the most accomplished scientists and the most knowledgeable about marijuana and cannabinoids in their own fields. In addition, advocates for (John Morgan) and against (Eric A. Voth) the medical use of marijuana were invited to present scientific evidence in support of their positions.

Information presented at the scientific workshops was supplemented by analysis of the scientific literature and evaluating the methods used in various studies and the validity of the authors' conclusions. Different kinds of clinical studies are useful in different ways: results of a controlled double-blind study with adequate sample sizes can be expected to apply to the general population from which study subjects were drawn; an isolated case report can suggest further studies but cannot be presumed to be broadly applicable; and survey data can be highly informative but are generally limited by the need to rely on self-reports of drug use and on unconfirmed medical diagnoses. This report relies mainly on the most relevant and methodologically rigorous studies available and treats the results of more limited studies cautiously. In addition, study results are presented in such a way as to allow thoughtful readers to judge the results themselves.

The Institute of Medicine (IOM) appointed a panel of nine experts to advise the study team on technical issues. These included neurology and the treatment of pain (Howard Fields); regulation of prescription drugs (J. Richard Crout); AIDS wasting and clinical trials (Judith Feinberg); treatment and pathology of multiple sclerosis (Timothy Vollmer); drug dependence among adolescents (Thomas Crowley); varieties of drug dependence (Dorothy Hatsukami); internal medicine, health care delivery, and clinical epidemiology (Eric B. Larson); cannabinoids and marijuana pharmacology (Billy R. Martin); and cannabinoid neuroscience (Steven R. Childers).

Public outreach included setting up a Web site that provided information about the study and asked for input from the public. The Web site was open for comment from November 1997 until November 1998. Some 130 organizations were invited to participate in the public workshops. Many people in the organizations—particularly those opposed to the medical use of marijuana—felt that a public forum was not conducive to expressing their views; they were invited to communicate their opinions (and reasons for holding them) by mail or telephone. As a result, roughly equal numbers of persons and organizations opposed to and in favor of the medical use of marijuana were heard from.

The study team visited four cannabis buyers' clubs in California (the Oakland Cannabis Buyers' Cooperative, the San Francisco Cannabis Cultivators Club, the Los Angeles Cannabis Resource Center, and Californians Helping Alleviate Medical Problems, or CHAMPS) and two HIV/AIDS clinics (AIDS Health Care Foundation in Los Angeles and Louisiana State University Medical Center in New Orleans). We listened to many individual stories from the buyers' clubs about using marijuana to treat a variety of symptoms and heard clinical observations on the use of Marinol to treat AIDS patients. Marinol is the brand name for dronabinol, which is Δ^9-tetrahydrocannabinol (THC) in pill form and is available by prescription for the treatment of nausea associated with chemotherapy and AIDS wasting.

MARIJUANA TODAY

The Changing Legal Landscape

In the 20th century, marijuana has been used more for its euphoric effects than as a medicine. Its psychological and behavioral effects have concerned public officials since the drug first appeared in the southwestern and southern states during the first two decades of the century. By 1931, at least 29 states had prohibited use of the drug for nonmedical purposes.[3] Marijuana was first regulated at the federal level by the Marijuana Tax Act of 1937, which required anyone producing, distributing, or using marijuana for medical purposes to register and pay a tax and which effectively prohibited nonmedical use of the drug. Although the act did not make medical use of marijuana illegal, it did make it expensive and inconvenient. In 1942, marijuana was removed from the U.S. Pharmacopoeia because it was believed to be a harmful and addictive drug that caused psychoses, mental deterioration, and violent behavior.

In the late 1960s and early 1970s, there was a sharp increase in marijuana use among adolescents and young adults. The current legal status of marijuana was established in 1970 with the passage of the Controlled

Medical Marijuana Legislation Among the States

The 1996 California referendum known as Proposition 215 allowed seriously ill Californians to obtain and use marijuana for medical purposes without criminal prosecution or sanction. A physician's recommendation is needed. Under the law, physicians cannot be punished or denied any right or privilege for recommending marijuana to patients who suffer from any illness for which marijuana will provide relief.

The 1996 Arizona referendum known as Proposition 200 was largely about prison reform but also gave physicians the option to prescribe controlled substances, including those in Schedule I (e.g., marijuana), to treat the disease or relieve the suffering of seriously or terminally ill patients. Five months after the referendum was passed, it was stalled whenArizona legislators voted that all prescription medications must be approved by the Food and Drug Administration, and marijuana is not so approved. In November 1998, Arizona voters passed a second referendum designed to allow physician's to prescribe marijuana as medicine, but this is still at odds with federal law.[8]

As of summer 1998, eight states—California, Connecticut, Louisiana, New Hampshire, Ohio, Vermont, Virginia, and Wisconsin—had laws that permit physicians to prescribe marijuana for medical purposes or to allow a medical necessity defense.[8] In November 1998, five states—Arizona, Alaska, Oregon, Nevada, and Washington—passed medical marijuana ballot initiatives. The District of Columbia also voted on a medical marijuana initiative, but was barred from counting the votes because an amendment designed to prohibit them from doing so was added to the federal appropriations bill; however, exit polls suggested that a majority of voters had approved the measure.

Substances Act, which divided drugs into five schedules and placed marijuana in Schedule I, the category for drugs with high potential for abuse and no accepted medical use (see Appendix C, Scheduling Definitions). In 1972, the National Organization for the Reform of Marijuana Legislation (NORML), an organization that supports decriminalization of marijuana, unsuccessfully petitioned the Bureau of Narcotics and Dangerous Drugs to move marijuana from Schedule I to Schedule II. NORML argued that marijuana is therapeutic in numerous serious ailments, less toxic, and in many cases more effective than conventional medicines.[13] Thus, for 25 years the medical marijuana movement has been closely linked with the marijuana decriminalization movement, which has colored the debate. Many people criticized that association in their letters to IOM and during the public workshops of this study. The argument against the medical use

of marijuana presented most often to the IOM study team was that "the medical marijuana movement is a Trojan horse"; that is, it is a deceptive tactic used by advocates of marijuana decriminalization who would exploit the public's sympathy for seriously ill patients.

Since NORML's petition in 1972, there have been a variety of legal decisions concerning marijuana. From 1973 to 1978, 11 states adopted statutes that decriminalized use of marijuana, although some of them recriminalized marijuana use in the 1980s and 1990s. During the 1970s, reports of the medical value of marijuana began to appear, particularly claims that marijuana relieved the nausea associated with chemotherapy. Health departments in six states conducted small studies to investigate the reports. When the AIDS epidemic spread in the 1980s, patients found that marijuana sometimes relieved their symptoms, most dramatically those associated with AIDS wasting. Over this period a number of defendants charged with unlawful possession of marijuana claimed that they were using the drug to treat medical conditions and that violation of the law was therefore justified (the so-called medical necessity defense). Although most courts rejected these claims, some accepted them.[8]

Against that backdrop, voters in California and Arizona in 1996 passed two referenda that attempted to legalize the medical use of marijuana under particular conditions. Public support for patient access to marijuana for medical use appears substantial; public opinion polls taken during 1997 and 1998 generally reported 60–70 percent of respondents in favor of allowing medical uses of marijuana.[15] However, those referenda are at odds with federal laws regulating marijuana, and their implementation raises complex legal questions.

Despite the current level of interest, referenda and public discussions have not been well informed by carefully reasoned scientific debate. Although previous reports have all called for more research, the nature of the research that will be most helpful depends greatly on the specific health conditions to be addressed. And while there have been important recent advances in our understanding of the physiological effects of marijuana, few of the recent investigators have had the time or resources to permit detailed analysis. The results of those advances, only now beginning to be explored, have significant implications for the medical marijuana debate.

Several months after the passage of the California and Arizona medical marijuana referendums, the Office of National Drug Control Policy (ONDCP) asked whether IOM would conduct a scientific review of the medical value of marijuana and its constituent compounds. In August 1997, IOM formally began the study and appointed John A. Benson Jr. and Stanley J. Watson Jr. to serve as principal investigators for the study.

The charge to IOM was to review the medical use of marijuana and the harms and benefits attributed to it (details are given in Appendix D).

MARIJUANA AND MEDICINE

Marijuana plants have been used since antiquity for both herbal medication and intoxication. The current debate over the medical use of marijuana is essentially a debate over the value of its medicinal properties relative to the risk posed by its use.

Marijuana's use as an herbal remedy before the 20th century is well documented.[1,10,11] However, modern medicine adheres to different standards from those used in the past. The question is not whether marijuana can be used as an herbal remedy but rather how well this remedy meets today's standards of efficacy and safety. We understand much more than previous generations about medical risks. Our society generally expects its licensed medications to be safe, reliable, and of proven efficacy; contaminants and inconsistent ingredients in our health treatments are not tolerated. That refers not only to prescription and over-the-counter drugs but also to vitamin supplements and herbal remedies purchased at the grocery store. For example, the essential amino acid *l*-tryptophan was widely sold in health food stores as a natural remedy for insomnia until early 1990 when it became linked to an epidemic of a new and potentially fatal illness (eosinophilia-myalgia syndrome).[9,12] When it was removed from the market shortly thereafter, there was little protest, despite the fact that it was safe for the vast majority of the population. The 1,536 cases and 27 deaths were later traced to contaminants in a batch produced by a single Japanese manufacturer.

Although few herbal medicines meet today's standards, they have provided the foundation for modern Western pharmaceuticals. Most current prescriptions have their roots either directly or indirectly in plant remedies.[7] At the same time, most current prescriptions are synthetic compounds that are only distantly related to the natural compounds that led to their development. Digitalis was discovered in foxglove, morphine in poppies, and taxol in the yew tree. Even aspirin (acetylsalicylic acid) has its counterpart in herbal medicine: for many generations, American Indians relieved headaches by chewing the bark of the willow tree, which is rich in a related form of salicylic acid.

Although plants continue to be valuable resources for medical advances, drug development is likely to be less and less reliant on plants and more reliant on the tools of modern science. Molecular biology, bioinformatics software, and DNA array-based analyses of genes and chemistry are all beginning to yield great advances in drug discovery and development. Until recently, drugs could only be *discovered*; now they can

be *designed*. Even the discovery process has been accelerated through the use of modern drug-screening techniques. It is increasingly possible to identify or isolate the chemical compounds in a plant, determine which compounds are responsible for the plant's effects, and select the most effective and safe compounds—either for use as purified substances or as tools to develop even more effective, safer, or less expensive compounds.

Yet even as the modern pharmacological toolbox becomes more sophisticated and biotechnology yields an ever greater abundance of therapeutic drugs, people increasingly seek alternative, low-technology therapies.[4,5] In 1997, 46 percent of Americans sought nontraditional medicines and spent over 27 billion unreimbursed dollars; the total number of visits to alternative medicine practitioners appears to have exceeded the number of visits to primary care physicians.[5,6] Recent interest in the medical use of marijuana coincides with this trend toward self-help and a search for "natural" therapies. Indeed, several people who spoke at the IOM public hearings in support of the medical use of marijuana said that they generally preferred herbal medicines to standard pharmaceuticals. However, few alternative therapies have been carefully and systematically tested for safety and efficacy, as is required for medications approved by the FDA (Food and Drug Administration).[2]

WHO USES MEDICAL MARIJUANA?

There have been no comprehensive surveys of the demographics and medical conditions of medical marijuana users, but a few reports provide some indication. In each case, survey results should be understood to reflect the situation in which they were conducted and are not necessarily characteristic of medical marijuana users as a whole. Respondents to surveys reported to the IOM study team were all members of "buyers' clubs," organizations that provide their members with marijuana, although not necessarily through direct cash transactions. The atmosphere of the marijuana buyers' clubs ranges from that of the comparatively formal and closely regulated Oakland Cannabis Buyers' Cooperative to that of a "country club for the indigent," as Denis Peron described the San Francisco Cannabis Cultivators Club (SFCCC), which he directed.

John Mendelson, an internist and pharmacologist at the University of California, San Francisco (UCSF) Pain Management Center, surveyed 100 members of the SFCCC who were using marijuana at least weekly. Most of the respondents were unemployed men in their forties. Subjects were paid $50 to participate in the survey; this might have encouraged a greater representation of unemployed subjects. All subjects were tested for drug use. About half tested positive for marijuana only; the other half tested positive for drugs in addition to marijuana (23% for cocaine and 13% for

TABLE 1.1 Self-Reported Disorders Treated with Marijuana by Members of San Francisco Cannabis Cultivators Club

Disorder	No. of Subjects
HIV	60
Musculoskeletal disorders and arthritis	39
Psychiatric disorders (primarily depression)	27
Neurological disorders and nonmusculoskeletal pain syndromes	9
Gastrointestinal disorders (most often nausea)	7
Other disorders	
Glaucoma, allergies, nephrolithiasis, and the skin manifestations of Reiter syndrome	7
Total disorders	149
Total number of respondents	100

amphetamines). The predominant disorder was AIDS, followed by roughly equal numbers of members who reported chronic pain, mood disorders, and musculoskeletal disorders (Table 1.1).

The membership profile of the San Francisco club was similar to that of the Los Angeles Cannabis Resource Center (LACRC), where 83% of the 739 patients were men, 45% were 36–45 years old, and 71% were HIV positive. Table 1.2 shows a distribution of conditions somewhat different from that in SFCCC respondents, probably because of a different membership profile. For example, cancer is generally a disease that occurs late in life; 34 (4.7%) of LACRC members were over 55 years old; only 2% of survey respondents in the SFCCC study were over 55 years old.

Jeffrey Jones, executive director of the Oakland Cannabis Buyers' Cooperative, reported that its largest group of patients is HIV-positive men in their forties. The second-largest group is patients with chronic pain.

Among the 42 people who spoke at the public workshops or wrote to the study team, only six identified themselves as members of marijuana buyers' clubs. Nonetheless, they presented a similar profile: HIV/AIDS was the predominant disorder, followed by chronic pain (Tables 1.3 and 1.4). All HIV/AIDS patients reported that marijuana relieved nausea and vomiting and improved their appetite. About half the patients who reported using marijuana for chronic pain also reported that it reduced nausea and vomiting.

Note that the medical conditions referred to are only those reported to the study team or to interviewers; they cannot be assumed to represent complete or accurate diagnoses. Michael Rowbotham, a neurologist at the UCSF Pain Management Center, noted that many pain patients referred

TABLE 1.2 Self-Reported Disorders Treated with Marijuana by Members of Los Angeles Cannabis Resource Center (LACRC), According to Center Staff[a]

Treated Disorder	No. of Subjects	% of Subjects
HIV[b]	528	71
Cancer	40	5.4
Terminal cancer	10	1.4
Mood disorders (depression)	4	0.5
Musculoskeletal (multiple sclerosis, arthritis)	30	4.1
Chronic pain and back pain	33	4.5
Gastrointestinal	7	2.3
Neurological disorders (epilepsy, Tourette syndrome, brain trauma)	7	0.9
Seizures or migraines[c]	13	1.8
Glaucoma	15	2.0
Miscellaneous	42	5.7
Total number	739	100

[a]Results are based on a review of 739 individual records by LACRC staff members. In contrast with Mendelson's survey of San Francisco Cannabis Cultivators Club (Table 1.1), only the primary disorder is indicated here. Membership in LACRC is contingent on a doctor's letter of acknowledgment, but diagnoses are not independently confirmed.

[b]HIV patients use marijuana to control nausea, increase appetite (to combat wasting), and relieve gastrointestinal distress caused by AIDS medications. These uses are not indicated separately.

[c]As described by LACRC staff, some of these cases might also be neurological disorders.

to that center arrive with incorrect diagnoses or with pain of unknown origin. At that center the patients who report medical benefit from marijuana say that it does not reduce their pain but enables them to cope with it.

Most—not all—people who use marijuana to relieve medical conditions have previously used it recreationally. An estimated 95% of the LACRC members had used marijuana before joining the club. It is important to emphasize the absence of comprehensive information on marijuana use before its use for medical conditions. Frequency of prior use almost certainly depends on many factors, including membership in a buyers' club, membership in a population sector that uses marijuana more often than others (for example, men 20–30 years old), and the medical condition being treated with marijuana (for example, there are probably relatively fewer recreational marijuana users among cancer patients than among AIDS patients).

TABLE 1.3 Summary of Reports to IOM Study Team by 43 Individuals

Symptoms	Dominant Disease	Symptoms	Dominant Disease
Anorexia, nausea, vomiting	AIDS	Pain	Migraine
	AIDS		Injury
	AIDS		Injury
	AIDS		Epilepsy and postpolio syndrome
	AIDS		Trauma and epilepsy
	AIDS		Degenerative disk disease
	AIDS		Rheumatoid arthritis
	AIDS and cancer		Nail-patella syndrome
	Cancer		Reflex sympathetic dystrophy
	Testicular cancer		Gulf War chemical exposure
	Cancer and multiple sclerosis		Multiple congenital cartilaginous exostosis
	Thyroid condition[a]		Histiocytosis X
	Migraine		
	Wilson's disease	Muscle spasticity	Spasticity[a]
			Multiple sclerosis
Mood disorders	Depression		Multiple sclerosis
	Depression		Multiple sclerosis
	Depression and anxiety		Paralysis
	Depression and anxiety		Spinal-cord injury
	Manic depression		Spasmodic torticollis
	Manic depression	Intraocular pressure	Glaucoma
	Posttraumatic stress		
	Premenstrual syndrome		
		Diarrhea	Crohn's disease

[a]Not specified.

NOTE: This table lists the people who reported to the IOM study team during the public workshops, or through letters, that they use marijuana as medicine; it should not be interpreted as a representative sample of the full spectrum of people who use marijuana as medicine. Each dominant disease represents an individual report.

Patients who reported their experience with marijuana at the public workshops said that marijuana provided them with great relief from symptoms associated with disparate diseases and ailments, including AIDS wasting, spasticity from multiple sclerosis, depression, chronic pain, and nausea associated with chemotherapy. Their circumstances and symptoms were varied, and the IOM study team was not in a position to make medical evaluations or confirm diagnoses. Three representative cases presented to the IOM study team are presented in Box 1.1; the stories have been edited for brevity, but each case is presented in the patient's words and with the patient's permission.

TABLE 1.4 Primary Symptoms of 43 Individuals Who Reported to IOM Study Team

	Symptom Frequency		Multiple Symptoms	
Primary Symptom	No. of Reports[a]	% of Total Symptoms Reported	No. Who Reported (primary) Additional Symptoms	% of Those Who Reported Primary Symptoms
Anorexia, nausea, vomiting	21	31	13	62
Diarrhea	4	6	3	75
Intraocular pressure	2	3	1	50
Mood disorders	12	18	7	58
Muscle spasticity	12	18	7	58
Pain	16	24	13	81
Total	67		44	66

[a]Forty-three persons reporting; 20 reported relief from more than one symptom.

The variety of stories presented left the study team with a clear view of people's beliefs about how marijuana had helped them. But this collection of anecdotal data, although useful, is limited. We heard many positive stories but no stories from people who had tried marijuana but found it ineffective. This is a fraction with an unknown denominator. For the numerator we have a sample of positive responses; for the denominator we have no idea of the total number of people who have tried marijuana for medical purposes. Hence, it is impossible to estimate the clinical value of marijuana or cannabinoids in the general population based on anecdotal reports. Marijuana clearly seems to relieve some symptoms for some people—even if only as a placebo effect. But what is the balance of harmful and beneficial effects? That is the essential medical question that can be answered only by careful analysis of data collected under controlled conditions.

CANNABIS AND THE CANNABINOIDS

Marijuana is the common name for *Cannabis sativa*, a hemp plant that grows throughout temperate and tropical climates. The most recent review of the constituents of marijuana lists 66 cannabinoids (Table 1.5).[16] But that does not mean there are 66 different cannabinoid effects or interactions. Most of the cannabinoids are closely related; they fall into only 10

TABLE 1.5 Cannabinoids Identified in Marijuana

Cannabinoid Group	Common Abbreviation	No. of Known Variants 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
Total		66

groups of closely related cannabinoids, many of which differ by only a single chemical moiety and might be midpoints along biochemical pathways—that is, degradation products, precursors, or byproducts.[16,18] Δ^9-tetrahydrocannabinol (Δ^9-THC) is the primary psychoactive ingredient; depending on the particular plant, either THC or cannabidiol is the most abundant cannabinoid in marijuana (Figure 1.1). Throughout this report, THC is used to indicate Δ^9-THC. In the few cases where variants of THC are discussed, the full names are used. All the cannabinoids are lipophilic—they are highly soluble in fatty fluids and tissues but not in water. Indeed, THC is so lipophilic that it is aptly described as "greasy."

Throughout this report, *marijuana* refers to unpurified plant extracts, including leaves and flower tops, regardless of how they are consumed—whether by ingestion or by smoking. References to the effects of marijuana should be understood to include the composite effects of its various components; that is, the effects of THC are included among the effects of marijuana, but not all the effects of marijuana are necessarily due to THC. Discussions concerning *cannabinoids* refer only to those particular compounds and not to the plant extract. This distinction is important; it is often blurred or exaggerated.

Cannabinoids are produced in epidermal glands on the leaves (especially the upper ones), stems, and the bracts that support the flowers of the marijuana plant. Although the flower itself has no epidermal glands, it has the highest cannabinoid content anywhere on the plant, probably because of the accumulation of resin secreted by the supporting bracteole

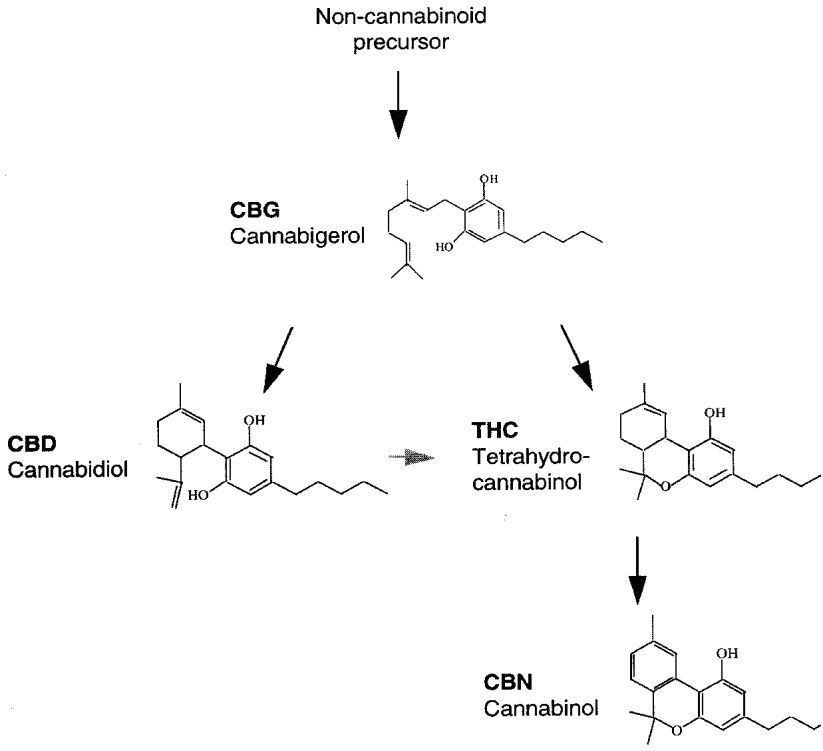

FIGURE 1.1 Cannabinoid biosynthesis. Arrows indicate cannabinoid biosynthesis pathway; dark arrows indicate established pathways; the light gray arrow indicates a probable but not well-established pathway (R. Mechoulam, Hebrew University, personal communication, 1999).[11] The great majority of studies reporting on the effects of cannabinoids refer to THC; most of the rest are about CBD and CBN. Other cannabinoids found in marijuana do not appear to play an important role in the drug's effects.

(the small leaf-like part below the flower). The amounts of cannabinoids and their relative abundance in a marijuana plant vary with growing conditions, including humidity, temperature, and soil nutrients (reviewed in Pate, 1994[14]). The chemical stability of cannabinoids in harvested plant material is also affected by moisture, temperature, sunlight, and storage. They degrade under any storage condition.

BOX 1.1 Selected Cases from the Public Sessions

G.S. spoke at the IOM workshop in Louisiana about his use of marijuana first to combat AIDS wasting syndrome and later for relief from the side effects of AIDS medications.

Skin rashes, dry mouth, foul metallic aftertaste, numbness of the face, swelling of the limbs, fever spikes, headaches, dizziness, anemia, clinical depression, neuropathy so crippling that I could not type, so painful that the bed sheets felt like sandpaper, nausea so severe that I sometimes had to leave the dinner table to vomit, and diarrhea so unpredictable that I dared not leave the house without diapers.

These are some of the horrors that I have endured in the past 10 years during my fight for life against the human immunodeficiency virus. But these ravages were not caused by HIV itself, or by any of the opportunistic infections that mark the steady progression of AIDS. Each of these nightmares was a side effect of one of the hundreds of medications I have taken to fight one infection after another on my way to a seemingly certain early grave.

Had you known me three years ago, you would not recognize me now. After years of final-stage AIDS, I had wasted to 130 lb. The purple Kaposi's sarcoma lesions were spreading. The dark circles under my eyes told of sleepless nights and half-waking days. I encountered passages of time marked by medication schedules, nausea, and diarrhea. I knew that I was dying. Every reflection shimmered with death, my ghost-like pallor in the mirror, the contained terror on the face of a bus passenger beside me, and most of all the resigned sadness in my mother's eyes.

But still I was fortunate because along the way I rediscovered the ancient understanding of marijuana's medicinal benefit. So I smoked pot. Every day. The pot calmed my stomach against handfuls of pills. The pot made me hungry so that I could eat without a tube. The pot eased the pain of crippling neural side effects so that I could dial the phone by myself. The pot calmed my soul and allowed me to accept that I would probably die soon. Because I smoked pot I lived long enough to see the development of the first truly effective HIV therapies. I lived to gain 50 lb., regain my vigor, and celebrate my 35th birthday. I lived to sit on the bus without frightening the passenger beside me.

Even at this stage of my recovery I take a handful of pills almost every day and will probably continue to do so for the rest of my life. While I am grateful for the life-saving protease inhibitor therapies, they bring with them a host of adverse reactions and undesirable side effects. Different patients experience different reactions, of course, but almost all patients experience some. Smoking marijuana relieves many of these side effects.

I am not one of the exceptional eight patients in the United States with

Continued

legal permission to smoke marijuana. Every day I risk arrest, property forfeiture, fines, and imprisonment. But I have no choice, you see, just as I have no choice but to endure the side effects of these toxic medications. So, many patients like me are breaking the law to enjoy relief that no other therapy provides.

I sit here, I believe, as living proof that marijuana can have a beneficial effect in staving off wasting. Every pound was a day. I figured that for every pound of body weight I could maintain, that was another day that I could live in hopes that some effective therapy would emerge.

* * *

B.D. spoke at the IOM workshop in Louisiana. She is one of eight patients who are legally allowed to smoke marijuana under a Compassionate Use Protocol. She uses marijuana to relieve nausea, muscle spasticity, and pain associated with multiple sclerosis.

I was diagnosed with multiple sclerosis in 1988. Prior to that, I was an active person with ballet and swimming. I now have a swimming pool, so I swim each and every day, and I smoke marijuana. The government has given me the marijuana to smoke. Each month I pick up a can filled with the marijuana cigarettes rolled by the government.

At one time I weighed 85 lb. and I now weigh 105. Twenty pounds is quite a bit to put on. I could not walk. I did not have the appetite. I use a scooter now for distance. I can get around the house. I have a standard poodle who is kind of like an assistant dog. She is good at it. She helps me.

When I found out that there was a program to get marijuana from the government, I decided that was the answer. I was not a marijuana smoker before that. In fact, I used to consider the people I knew who smoked the marijuana as undesirables. Now, I myself am an undesirable.

But it works. It takes away the backache. With multiple sclerosis, you can get spasms, and your leg will just go straight out and you cannot stop that leg. You may have danced all of your life and put the leg where you wanted it to be, but the MS takes that from you. So I use the swimming pool, and that helps a lot. The kicks are much less when I have smoked a marijuana cigarette. Since 1991, I've smoked 10 cigarettes a day. I do not take any other drugs. Marijuana seems to have been my helper. At one time, I did not think much of the people who smoke it. But when it comes to your health, it makes a big difference.

* * *

J.H. spoke at the IOM workshop in Washington, D.C. He was seriously injured in an accident, suffers from a form of arthritis associated with abnormal activity of the sympathetic nervous system known as reflex sympathetic dystrophy, and has hepatitis C. He uses marijuana to relieve nausea from liver disease, pain, and muscle spasms.

I am 48 years old, married with two children. I am a veteran who served during the Vietnam war. I was exposed to hepatitis C in 1972 by a blood

transfusion, which I needed because of a motor vehicle accident that broke my back; ruined my right shoulder, my left thumb, and hand; and almost amputated my right leg at the knee. My hepatitis C was not diagnosed until 1997—after the disease had destroyed my pancreas* and I had four heart attacks, one angioplasty, and a minor stroke. In 1989, while at work, I was involved in an accident with a large soil survey auger. My pelvis was crushed, and serious nerve damage was the result. I also have reflex sympathetic dystrophy, which is a neurological disease that has a tremendous amount of pain and muscle spasms.

I have reached what the doctors call end-stage liver disease from the hepatitis C. I have lost 85 lbs. due to the severe bouts of nausea and vomiting. Every time I come home from a hospital stay, my 7 year old asks if I got the liver transplant. I am on a transplant list, but I am not a candidate until I am seven days from death.

In October 1997, after trying four different antinausea medications, four of the doctors that I see told me to go to Europe and see a doctor and try medicinal cannabis. My primary care doctor wrote me a letter to carry with my medical records asking that the doctor help me in any way that he could to alleviate the symptoms of the hepatitis C and the reflex sympathetic dystrophy. Those symptoms are severe nausea and pain from the hepatitis C and pain and muscle spasms from the neurological disease.

I went to Europe in November 1997, where I saw a doctor of internal medicine. He prescribed me cannabis, 1–2 g a day. I got the medicine and a pipe and tried it. Within two minutes of taking two puffs from the pipe, the nausea was gone. I don't think that I felt the high, although I was quite elated. In about 45 min. I was starving. Normally, I have a fear of eating because I vomit almost always after I eat or take a pill. I forgot about that, and I think I ate more that night than I had eaten in months. I did feel a little nauseated after about four hours, but I smoked two more puffs, and in about two hours I went to bed. The next morning I felt hungry. During my nine-day stay in Europe, I was able to stay free of vomiting and the waves of nausea became less frequent.

I had experienced four years of pain control using Tegretol, a drug used by epileptics to control seizures. Now I can't use that medication because of the damage that it causes my cirrhotic liver. When I smoked about 2 g of marijuana a day, the nausea was gone and I was no longer losing weight. The pain was at an acceptable level. Sometimes I still find it necessary to use an opiate painkiller, but only when the pain is at its worst. Surprisingly, I lost an associated high within a few days. I also think the cannabis has an antidepressant effect on me, as I no longer have what I call the "poor me" feelings that I experienced after learning about the hepatitis C.

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*This is an unlikely consequence of hepatitis C; it is more likely that the patient's liver was damaged.

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 are 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. *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, DC: Island Press. Pp. 131–163.
8. Herstek J. 1998. *Behavioral Health Issue Briefs. Medical Marijuana.* Washington, DC: Health Policy Tracking Service, National Conference of State Legislatures.
9. Kilbourne EM, Philen RM, Kamb ML, 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, NC: MacFarland and Co.
11. Mechoulam R. 1986. The pharmacohistory of *Cannabis Sativa*. In: Mechoulam R , Editor. *Cannabinoids as Therapeutic Agents.* Boca Raton, FL: CRC Press. 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,* 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 delta 1-tetrahydrocannabinolic acid biosysnthesis. *Journal of the American Chemical Society* 117:9766–9767.
18. Turner CE, Elsohly MA, Boeren EG. 1980. Constituents of *Cannabis sativa L.* XVII. A review of the natural constituents. *Journal of Natural Products* 43:169–234.

2

Cannabinoids and Animal Physiology

INTRODUCTION

Much has been learned since the publication of the 1982 Institute of Medicine (IOM) report *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 past 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).

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

TABLE 2.1 Landmark Discoveries Since the 1982 IOM Report

Year	Discovery	Primary Investigators
1986	Potent cannabinoid agonists are developed; they are 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[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, SR 141716A, 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]

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 sub-

stantive 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 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 the medical uses 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 are 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 noncannabinoid 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.

The Value of Animal Studies

Much of the research into the effects of cannabinoids on the brain is based on animal studies. Many speakers at the public workshops associated with this study argued that animal studies of marijuana are not relevant to humans. Animal studies are not a substitute for clinical trials, but they are a necessary complement. Ultimately, every biologically active substance exerts its effects at the cellular and molecular levels, and the evidence has shown that this is remarkably consistent 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 inform us completely 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 produce all the psychoactive effects of marijuana. Because Δ^9-THC is much more abundant than Δ^8-THC, the psychoactivity of marijuana has been attributed largely 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 nonpsychological 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 important effect of CBD seems to be its interference with drug metabolism, including Δ^9-THC metabolism in the liver.[14,114] It exerts that 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 substantial increase in brain concentrations of

THC and its major metabolites, most likely because it decreased the rate of clearance of THC from the body.[15]

In mice, THC inhibits the release of luteinizing hormone, the pituitary hormone that triggers the release of testosterone from the testes; this effect is increased when THC is given with cannabinol or CBD.[113]

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

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 set of tools for drug research, which became available only recently 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 the functions of a receptor by showing what happens when its 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 of how agonists and antagonists interact. 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

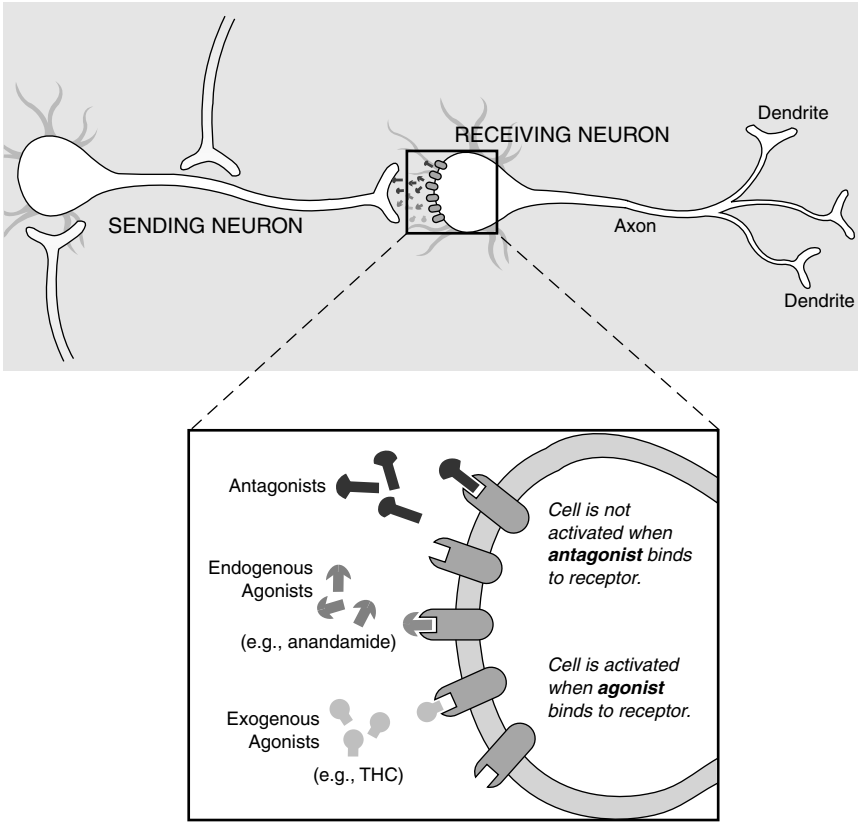

FIGURE 2.1 Diagram of neuron with synapse. Individual nerve cells, or neurons, both send and receive cellular signals to and from neighboring neurons, but for the purposes of this diagram only one activity is indicated for each cell. Neurotransmitter molecules are released from the neuron terminal and move across the gap between the "sending" and "receiving" neurons. A signal is transmitted to the receiving neuron when the neurotransmitters have bound to the receptor on its surface. The effects of a transmitted signal include:

- Changing the cell's permeability to ions, such as calcium and potassium.
- Turning a particular gene on or off.
- Sending a signal to another neuron.
- Increasing or decreasing the responsiveness of the cell to other cellular signals.

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

Continued on bottom of p. 39

the cell type where the receptor is located. 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. Such markers show where in the brain a drug binds to the receptor, although 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, was the first useful research tool for studying cannabinoid receptors because of its high potency and ability to be labeled with a radioactive molecule, which enabled researchers to trace its activity.

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 cannabinoid 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

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The expanded view of the synapse illustrates a variety of *ligands*, that is, molecules that bind to receptors. Anandamide is a substance produced by the body that binds to and activates cannabinoid receptors; it is an *endogenous agonist*. THC can also bind to and activate cannabinoid receptors but is not naturally found in the body; it is an *exogenous agonist*. SR 141716A binds to but does not activate cannabinoid receptors. In this way it prevents agonists, such as anandamide and THC, from activating cannabinoid receptors by binding to the receptors without activating them; SR 141716A is an *antagonist*, but it is not normally produced in the body. Endogenous antagonists, that is, those normally produced in the body, might also exist, but none has been identified.

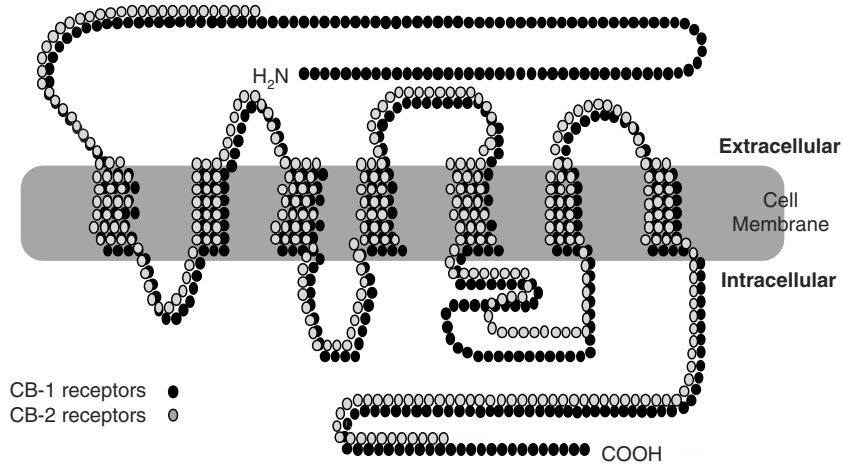

FIGURE 2.2 Cannabinoid receptors. Receptors are proteins, and proteins are made up of strings of amino acids. Each circle in the diagram represents one amino acid. The shaded bar represents the cell membrane, which like all cell membranes in animals is composed largely of phospholipids. Like many receptors, 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 receptor subtypes are quite different, which might affect the cellular response to the ligand because these loops are known to mediate G protein signaling, the next step in the cell signaling pathway after the receptor. Receptor homology between the two receptor subtypes is 44% for the full-length protein and 68% within the seven transmembrane regions. The ligand binding sites are typically defined by the extracellular loops and the transmembrane regions.

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 intracellular 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 de-

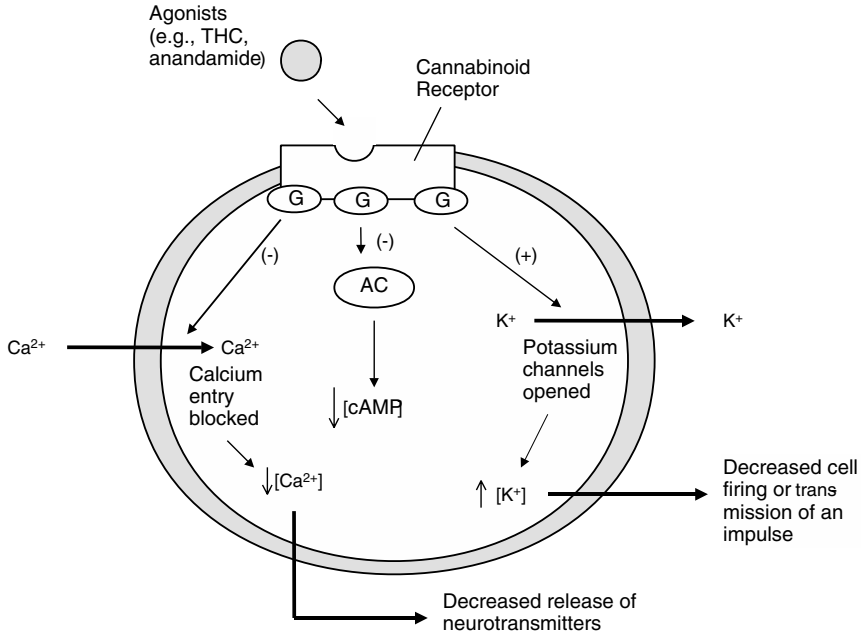

FIGURE 2.3 Cannabinoid agonists trigger a series of reactions within cells. Cannabinoid receptors are embedded in the cell membrane, where they are coupled to G proteins (G) and the enzyme adenylyl cyclase (AC). Receptors are activated when they bind to ligands, such as anandamide or THC in this case. This triggers a variety of reactions, including inhibition (–) of AC, which decreases the production of cAMP and cellular activities dependent on cAMP; opening of potassium (K^+) channels, which decreases cell firing; and closing of calcium (Ca^{2+}) channels, which decreases the release of neurotransmitters. Each of those changes can influence cellular communication.

pends 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 10 times more abundant than *mu* opioid receptors, the receptors responsible for the effects of morphine.[148]

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% (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* to both CB_1 and CB_2 receptors. One exception is the plant-derived compound CBD, which appears to have 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.

**Affinity* is a measure of how avidly a compound binds to a receptor. The higher the affinity of a compound, 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 produces 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 receptor and is rapidly metabolized by amidases (enzymes that remove amide groups). Despite its short duration of action, anand-amide 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 localiza-

TABLE 2.2 Compounds That Bind to Cannabinoid Receptors

Compound	Properties
Agonists (receptor activators)	
Plant-derived compounds	
Δ^9-THC	Main psychoactive cannabinoid in 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 marijuana plant but otherwise similar.
11-OH-Δ^9-THC	Bioactive compound formed when body breaks down Δ^9-THC; presumed to be responsible for some 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 United States as Marinol for nausea associated with chemotherapy and for AIDS-related wasting.
Nabilone	THC analogue; marketed in the United Kingdom as Cesamet for 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- to 800-fold greater potency than THC[97].
Chemical structure unlike THC or anandamide	
WIN-55,212-2	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].

SOURCES: Mechoulam et al., 1998;[109] Felder and Glass, 1998;[43] and British Medical Association.[17]

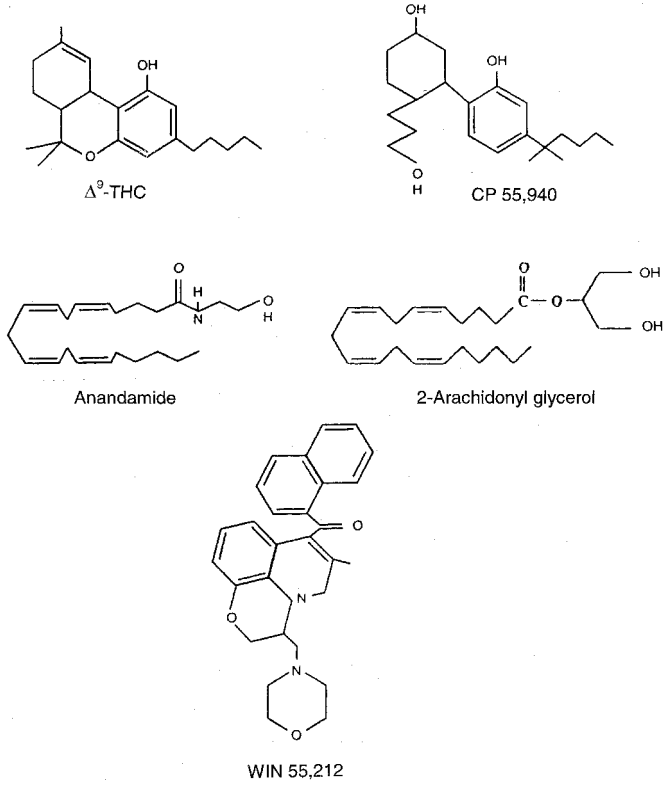

FIGURE 2.4 Chemical structures of selected cannabinoid agonists or molecules that bind to and activate cannabinoid receptors. **THC** is the primary psychoactive molecule found in marijuana. **CP 55,940** is a THC analogue; that is, its chemical structure is related to THC. **Anandamide** and **2-arachidonyl 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 canabinoid agonist.

tion 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

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 (behavior) or hypothermia (physiologic).

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 Δ^9-THC
CP 55,940	59
Δ^9-THC	1
Anandamide	0.47
2-AG	0.08

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 tissue, which also has high concentrations of CB_2 receptors, and small amounts have been detected in heart tissue.[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.* Although anandamide can be synthesized in a variety of ways, the physiologically relevant pathway

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

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 it 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—that is, by being transported into the neuron, which prevents its continuing activation of neighboring neurons.

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 the time of this writing, all known endogenous cannabinoid receptor agonists (including anandamide) were eicosanoids, which are arachidonic acid metabolites. Arachidonic acid (a free fatty acid) is released via hydrolysis of membrane phospholipids.

Other, noneicosanoid, 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 will 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 probably be 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 (such as 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.

TABLE 2.4 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.
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.

NOTE: Endogenous cannabinoids are part of a cellular signaling system. This table lists categories of natural processes that regulate such systems and shows the results of altering those processes.

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, thereby mimicking 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 SSRIs. Another way to alter levels of endogenous cannabinoids would be to develop drugs that act on the enzymes involved in anandamide synthesis. Some antihypertensive 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.

SITES OF ACTION

Cannabinoid receptors are particularly abundant in some areas of the brain. The normal biology and behavior associated with these brain areas

TABLE 2.5 Brain Regions in Which Cannabinoid Receptors Are Abundant

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

SOURCES: Based on reviews by Pertwee (1997b)[124] and Herkenham (1995).[57]

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's or Huntington's 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

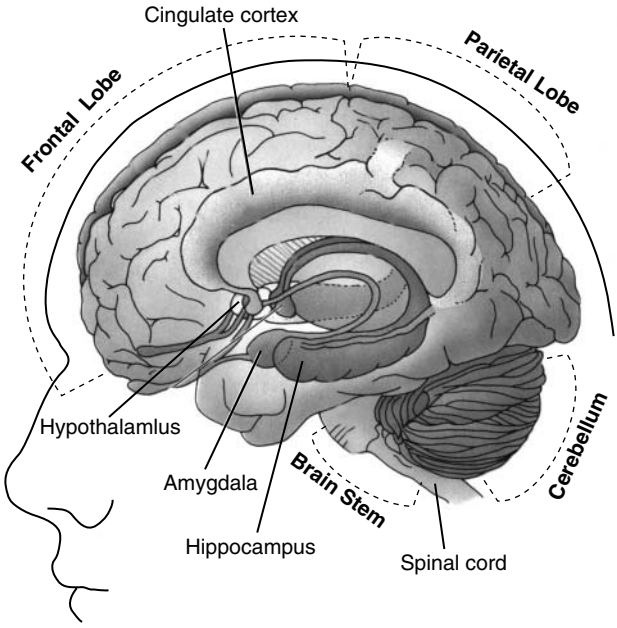

FIGURE 2.5 Locations of brain regions in which cannabinoid receptors are abundant. See Table 2.5 for a summary of functions associated with those regions.

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 tend to inhibit neurotransmission, although the results are somewhat variable. In some cases, cannabinoids diminish the effects of the inhibitory neurotransmitter, g-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

TABLE 2.6 Cannabinoid Receptors

	CB_1	CB_2
Effects of various cannabinoids		
Δ^9-THC	Agonist	Weak antagonist
Anandamide	Agonist	Agonist
Cannabinol	Weak agonist	Agonist; greater affinity for CB_2 than for CB_1
Cannabidiol	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

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.

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 2.6). 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 move-

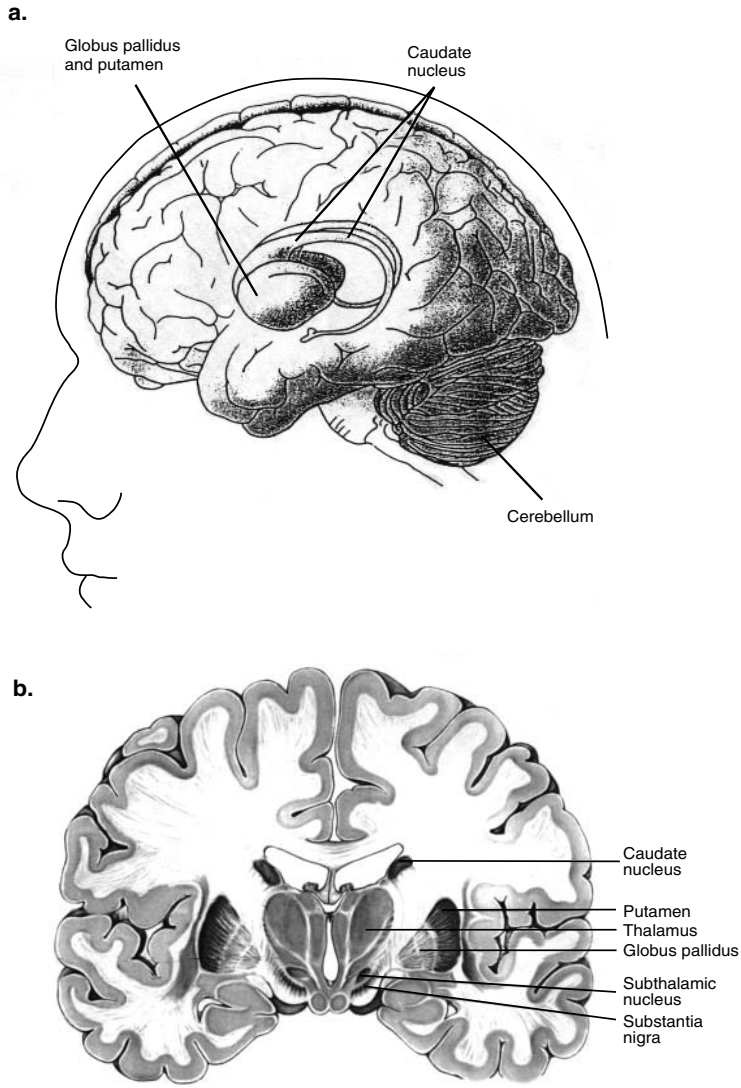

FIGURE 2.6 Diagrams showing motor regions of the brain. Basal ganglia are a group of three brain regions, or nuclei—**caudate**, **putamen**, and **globus pallidus**. Figure 2.6a is a three-dimensional view showing the location of those nuclei in the brain. Figure 2.6b shows those structures in a vertical cross-sectional view. The major output pathways of the basal ganglia arise from the globus pallidus and pars reticulata of the **substantia nigra**. Their main target is the **thalamus**. SOURCE: Figure 2.6a is reprinted from *Principles of Neural Science*, 2nd ed., 1985 (E.R. Kandel and J.H. Schwartz, eds.), with permission from the copyright holder, Appleton and Lange.

ment 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.

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,[49-51] 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.* 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.

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*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.

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 co-workers found that cannabinoids can block allodynia and hyperalgesia associated with neuropathic pain in rats.[62] This is an important advance because chronic pain frequently results in a series of neural changes that increase suffering due to allodynia (pain elicited by stimuli that are normally innocuous), hyperalgesia (abnormally increased reactivity to pain), 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] 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] rostral ventral medulla,[105,110] thalamic nucleus submedius,[102] thalamic ventroposterolateral nucleus,[102] dorsal horn of the spinal cord,[64,65] and peripheral sensory nerves.[64-66,131] 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 the 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, are selective for pain neurons, and are 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] On-cells and off-cells in the rostral ventral medulla control pain transmission at the level of the spinal cord, and cannabinoids also modulate their responses in a manner that is very similar to that of morphine.[110]

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] in-

crease the sensitivity of animals to pain. In addition, there is evidence that cannabinoids act at the site of injury to reduce peripheral inflammation.[131]

Current data suggest that 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 a drug 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 a resetting of homeostatic mechanisms in response to repeated drug use. Tolerance, dependence, and withdrawal are not peculiar to drugs of abuse. Many medicines 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 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* changes (how the drug is absorbed, distributed, metabolized, and excreted) and *pharmacodynamic* changes (how the drug interacts with target cells). Chronic treatment with the cannabinoid agonist, CP 55,940, increases the activity of the microsomal cytochrome P450 oxidative system,[31] the system through which drugs are metabolized in the liver; this suggests pharmacokinetic tolerance. Chronic cannabinoid treatment also produces changes in brain cannabinoid receptors and cannabinoid receptor mRNA concentrations—an indication that pharmacodynamic effects are important as well.

Most studies have found that brain cannabinoid receptor concentra-

tions 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 could be due to the particular agonist tested, the assay used, the brain region examined, or the treatment time. For example, the THC analogue, levonantradol, produces a greater desensitization of adenylyl cyclase inhibition than does THC in cultured neuroblastoma cells.[40] This might be explained by differences in efficacy between these two agonists.[18,147] A time course study revealed differences among brain regins in the rates and magnitudes of receptor down regulation.[16] Those 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. It produces substantial desensitization of cannabinoid-activated G proteins in a number of rat brain regions.[147] The time course of this desensitization varies across brain regions.[16]

It is difficult to extend the findings of short-term animal studies to human marijuana use. To simulate long-term use, higher doses are used in animal studies than are normally achieved by smoking marijuana. For example, the average human will feel "high" after injection of THC at a level of 0.06 mg/kg,[118] compared with the 10–20 mg/kg per day used in many chronic rat studies. 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." The pharmacokinetics of THC distribution in the body are also dramatically different between rats and humans and depend heavily on whether it is inhaled, injected, or swallowed. It is likely that some of the same biochemical adaptations to chronic cannabinoid administration occur in laboratory animals and humans, but the magnitude of the effects in humans might be less than that in animals in proportion to the 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 received the drug and a place where it did not. 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 midrange; doses that are

too low are not rewarding; doses that are too high can be aversive. Mice will self-administer the cannabinoid agonist WIN 55,212-2 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 SR 141716A at both low and high doses.[140] Cannabinoids increase dopamine concentrations in the mesolimbic dopamine system of rats, a pathway associated with reinforcement.[25,39,161] However, the mechanism by which THC increases dopamine concentrations appears to be different from that of other abused drugs[51] (see chapter 3 for further discussion of reinforcement). THC-induced 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]

Physical dependence on cannabinoids has been observed only under experimental conditions of "precipitated withdrawal" in which animals are first treated chronically with cannabinoids and then given the CB_1 antagonist SR 141716A.[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, can prevent substantial abstinence symptoms. The precipitated withdrawal produced by SR 141716A has some of the characteristics of opiate withdrawal, but it is not affected by opioid antagonists, and it affects 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 is consistent with the consequences of withdrawal from other drugs of abuse in that it correlates with the effects of stimulation of central amygdaloid corticotropin-releasing hormone release.[135] However, the withdrawal syndrome for cannabinoids and the corresponding increase in corticotropin-releasing hormone are observed only after 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 are stress-related hormones.[71] This set of withdrawal studies may explain the generally aversive effects of cannabinoids in animals and could indicate that the increase in corticotropin-releasing hormone is merely a rebound effect. Thus, cannabinoids appear to be conforming to some of the neurobiological effects of other drugs abused by humans, but the underlying mechanisms of these actions and their value for determining the reinforcement and dependence liability of cannabinoids in humans remain undetermined.

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. 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 cannabinoids in the immune system is not known. Immune cells respond to cannabinoids in a variety of ways, depending on such factors as drug concentration, timing of drug delivery to leukocytes in relation to antigen stimulation, and type of cell function. 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 THC concentrations that modulate immunological responses are higher than those required for psychoactivity.

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* 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 lesser extent, in several peripheral tissues such as adrenal gland, heart, lung, prostate, uterus, ovary, testis, bone marrow, thymus, and tonsils.

*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.

TABLE 2.7 Effects of Cannabinoids on the Immune System

Drug Tested	Cell Types Tested or Type of Animal Experiment	Drug Concentration*
THC, 2-AG, 11-OH-THC, CBN	Lymphocytes and splenocytes *in vitro*	0.1–30 μM
THC, 2-AG	Lymphocytes and splenocytes	0.1–25 μM
Anandamide	Splenocytes *in vitro*	1–25 μM
THC, 11-OH-THC, 2-AG	Splenocytes *in vitro*	3–30 μM
THC, CP 55,940, WIN 55,212-2	Lymphocytes *in vitro*	0.1–100 nM (0.0001–0.1 μM)
THC	Drug injected into mice	>5 mg/kg
HU-210	Drug injected into mice	>0.05 mg/kg
THC, 11-OH-THC, CBD, CP 55,940, CBN	Splenocytes *in vitro*	1–30 μM
THC	Drug injected into rodents	3 mg/kg per day for 25 days, 40 mg/kg per day for 2 days
THC, 11-OH-THC	Natural killer cells *in vitro*	0.1–32 μM
THC	Peritoneal macrophages and monocytes	3–30 μM
THC, CBD	Drug injected into mice; in one case, *in vitro* tests done on spleens	>5 mg/kg per day for 4 days or 50 mg/kg every 5 days for up to 8 weeks
THC, CBD	Peripheral blood mononuclear cells *in vitro*	<0.1 μM 30 μM
THC, CBD	Splenocytes and T cells *in vitro*	10 μM
THC	Phorbol myristate acetate-differentiated macrophage *in vitro*	10–20 μM
THC	Endotoxin-activated macrophages *in vitro*	10–30 μM
THC	Peritoneal macrophages *in vitro*	10–30 μM

Result	Reference
Higher doses suppressed T cell proliferation	Luo, 1992; Pross, 1992;[b] Klein, 1985;[c] Specter, 1990;[d] Lee, 1995;[a] Herring, 1998
Lower doses increased T cell proliferation *in vitro*	Luo, 1992; Lee, 1995;[a] Pross, 1992[b]
Little or no effect on T cell proliferation	Lee, 1995;[a] Devane, 1992
Decreased B cell proliferation	Klein, 1985;[c] Lee, 1995[a]
Increased B cell proliferation	Derocq, 1995
Antibody production suppressed	Baczynsky, 1983; Schatz, 1993
Antibody production suppressed	Titishov, 1989
Antibody production suppressed	Klein, 1990; Baczynsky, 1983; Kaminski, 1992, 1994; Herring, 1998
Repeated low doses or a high dose of THC suppressed the activity of natural killer cells	Patel, 1985; Klein, 1987
Doses of ≥10 μM suppressed natural killer cell cytolytic activity; doses <10 μM produced no effect	Klein, 1987; Luo, 1989
Variable doses of THC suppressed macophage functions in vitro	Lopez-Cepero, 1986; Specter, 1991; Tang, 1992
THC suppressed normal immune response; interferons failed to increase when exposed to cytokine inducer; CBD had no suppressive effect	Cabral, 1986; Blanchard, 1986
Increased interferon production Decreased interferon production	Watzl, 1991
Both THC and CBD suppressed interleukin-2 secretion and number of interleukin-2 transcripts	Condie, 1996
Increased tumor necrosis factor production and interleukin-1 supernatant bioactivity	Shivers, 1994
Increased processing and release of interleukin-1 rather than cellular production of interleukin-1	Zhu, 1994
Increased interleukin-1 bioactivity	Klein, 1990

Continued

TABLE 2.7 *Continued*

Drug Tested	Cell Types Tested or Type of Animal Experiment	Drug Concentration*
THC	Drug and sublethal or lethal dose of *Legionella pneumophilia* injected in mice	8 mg/kg before and after bacterial infection <5 mg/kg doses or one 8 mg/kg or 4 mg/kg dose before bacteria infection
THC	Drug and herpes simplex virus injected in immunodeficient mice	100 mg/kg before and after viral infection 100 mg/kg before virual infection

[a]Cell density dependent.
[b]Mitogen dependent.
[c]Dependent on serum concentration in cell culture medium.
[d]Dependent on timing of drug exposure relative to mitogen exposure.
*Drug concentrations are given in the standard format of molarity (M). A 1-M solution is the molecular weight of the compound (in grams) in 1 liter (L) of solution. The molecular

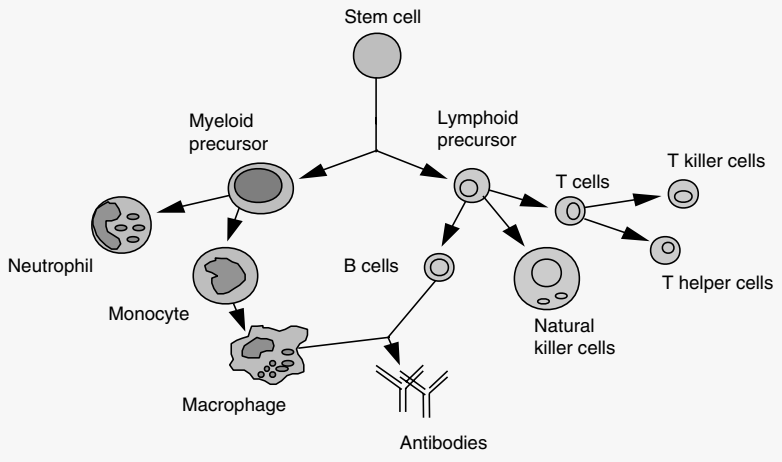
Box 2.1 Cells of the Immune System

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 (B and T refer to where the cells mature, either in the bone marrow [B] or thymus [T]), and natural killer (NK) cells; the major phagocytes are monocytes, macrophages, and neutrophils. *Phagocytes* have many important roles in the immune response; most important is that they initiate the response by engulfing and digesting foreign substances, or antigens (such as bacteria, viruses, and foreign proteins), that enter the body. Once digested, the antigens are exposed to specialized lymphocytes, some of which produce antibodies and effector T cells, which help destroy any antigens remaining 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. NK cells are specialized lymphocytes that are also activated by antigen to either kill infected targets or secrete immunoregulatory cytokines.

Result	Reference
Cytokine-mediated septic shock and death occurred with exposure to sublethal dose of bacteria	Klein, 1993, 1994; Newton, 1994
Survival occurred, but with greater susceptiblity to infection when challenged with bacteria and death when challenged with a lethal dose of bacteria	
Two high doses of THC potentiated the effects of herpes simplex and enhanced the progression of death	Specter, 1991
Single dose did not promote death	

weight of THC is 314, so a 1-M solution would be 314 g of THC in 1 L of solution, and a 10-μM solution would be 3.14 mg THC/L.

A 1- to 10-μM 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 much larger 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.



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 nonreceptor mechanisms, but these have not yet been identified.[4]

Ligand binding to either CB_1 or CB_2 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, and decreases lead to an inhibition of the immune response.[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]

T and B Cells

When stimulated by antigen, lymphocytes (see Box 2.1) 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* can be inhibited by THC, 11-OH-THC, cannabinol, and 2-AG, as well as synthetic cannabinoid agonists such as CP 55,940; WIN 55,212-2; 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, the mitogen used, the percentage of serum in the culture, and the timing of cannabinoid drug exposure. In general, lower doses of cannabinoids increase proliferation and 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

*Mitogens are substances that stimulate cell division (mitosis) and cell transformation.

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.[93]

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.

Natural Killer Cells

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

*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.

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.

Some 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 microorganisms from the body (see Box 2.1). 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 CBD.[168] In addition to Th1 cytokines, cannabinoids 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.

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 HU-210 (>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; this suggests that B cells are relatively insensitive to inhibition by cannabinoids.[142]

Resistance to Infection in Animals Exposed to Cannabinoids

Evaluation of bacterial infections in mice that received injections of

THC can suppress resistance to infection, although the effect depends on the dose and timing of drug administration. Mice pretreated with THC (8 mg/kg) one day before 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 pretreated 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 the mice survived the initial infection but failed to survive later 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 subject 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 two days before and after herpes simplex virus infection was shown to be a cofactor with the virus in advancing 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. Hence, whether THC is immunosuppressive probably depends on the timing of THC exposure relative to an infection.

Antiinflammatory 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 antiinflammatory. 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 deriva-

tive 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 antiinflammatory properties.[173] No mechanism of action for possible antiinflammatory 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 antiinflammatory effects of cannabinoids is important for potential therapeutic uses of cannabinoid drugs but has not yet been established.

Conclusions Regarding Effects on the Immune System

Cell culture and animal studies have established cannabinoids as immunomodulators—that is, they increase some immune responses and decrease others. The variable responses depend on such experimental factors as drug dose, timing of delivery, and type of immune cell examined. Cannabinoids affect multiple cellular targets in the immune system and a variety of effector functions. Many of the effects noted above appear to occur at concentrations over 5 μM *in vitro* and over 5 μg/kg *in vivo*.* 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 immune effects of chronic low-dose exposure to cannabinoids.

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 nonpsychotropic cannabinoids potentially have fewer side effects and might thus offer an improvement over glucocorticoids in treating inflammatory diseases.

**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

Pharmacological Discoveries	Cannabinoids	Opiates
Discovery of receptor existence	**1988** (Devane et al. and Dill and Howlett)[36,40]	**1973** (Pert and Snyder, Simon, and Terenius)[123,149,162]
Identification of receptor antagonist	**1994** SR 141716A (Rinaldi-Carmona et al.)[132]	Before 1973: naloxone
Discovery of first endogenous ligand	**1992** anandamide (Devane et al.)[37]	**1975** met- and leu-enkephalin (Hughes et al.)[70]
First receptor cloned	**1990** (Matsuda et al.)[107]	**1992** (Evans et al. and Kieffer et al.)[41,82]
Natural functions	Unknown	Pain, reproduction, mood, movement, and others

CONCLUSIONS AND RECOMMENDATIONS

Given the progress of the past 15 years in understanding the effects of cannabinoids, research in the next decade is likely to reveal even more. It is interesting to compare how little we know about cannabinoids with how much we know about opiates. Table 2.8 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 of 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 (in which cells and where) of cannabinoids, cellular storage and release mechanisms, and uptake mechanisms will be crucial in determining the biological role of this system. Technology needed to establish the biological significance of these systems will be broad based and include such research tools as the transgenic or gene knockout mice, as has already been accomplished for various opioid-receptor types.[26] In 1997, both CB_1 and CB_2 knockout mice were generated by a team of scientists at the National Institutes of Health, and a group in France has developed another strain of CB_1 knockout mice.[92]

Several research tools will greatly aid such investigations, in particular a greater selection of agonists and antagonists that permit discrimination in activation between CB_1 and CB_2 and 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, intriguing 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 multi-faceted and remains unclear.
- The brain develops tolerance to cannabinoids.
- Animal research has demonstrated 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 mild compared with those of withdrawal from 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* 46:575–579.
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–R2.
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 Δ^9-tetrahydrocannabinol in the rat and mouse. *Psychopharmacology* 25:275–280.
20. Cabral GA , Dove Pettit DA. 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 Sciences, 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* 393:231–235.
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–R2.
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, USA* 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 Sciences, USA* 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, Editor, *Cannabinoid Receptors.* New York: Academic Press. 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, USA* 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* 221:157–160.
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 EM, Herkenham M. 1999. Pre- and postsynaptic distribution of cannabinoid and mu opioid receptors in rat spinal cord. *Brain Research* 822:17–25.
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. 1999. Localization of central cannabinoid CB1 receptor mRNA in neuronal subpopulations of rat dorsal root ganglia: A double-label *in situ* hybridization study. *Neuroscience* 90:923–931.
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 ME, Kessler FK, Martin BR, Schatz AR. 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 delta-opioid receptor: Isolation of a cDNA by expression cloning and pharmacological characterization. *Proceedings of the National Academy of Sciences, USA* 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, Editor, *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* 283:401–404.
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 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.
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, Editors, *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* 304:29–35.
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 delta-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, November 7–12, 1998. Washington, DC: Society for Neuroscience.

118. Ohlsson A, Lindgren J-E, Wahlen A, Agurell S, Hollister LE, 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, 111(3):968]. *British Journal of Pharmacology* 110:1483–1490.
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 adenyl-cyclase. *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* 46:100–108.
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 MC, Tsou K, Delay ER, 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 SC, 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, Gallily 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-protein activation by mu- and delta-opioid, and cannabinoid, receptors in rat striatum. *European Journal of Pharmacology* 307:97–105.
149. Simon EJ. 1973. In search of the opiate receptor. *American Journal of Medical Sciences* 266:160–168.

150. Skaper SD, Buriani A, Dal Toso R, Petrelli L, Romanello S, Facci L, Leon A. 1996. The ALIAmide palmitoylethanolamide and cannabinoids, but not anandamide, are protective in a delayed postglutamate paradigm of excitotoxic death in cerebellar granule neurons. *Proceedings of the National Academy of Sciences, USA* 93:3984–3989.
151. Smith JW, Steiner AL, Newberry WM, Parker CW. 1971. Cyclic adenosine 3',5'-monophosphate in human lymphocytes: Alteration after phytohemagglutinin. *Journal of Clinical Investigation* 50:432–441.
152. Smith PB, Compton DR, Welch SP, Razdan RK, Mechoulam R, Martin BR. 1994. The pharmacological activity of anandamide, a putative endogenous cannabinoid, in mice. *Journal of Pharmacology and Experimental Therapeutics* 270:219–227.
153. Smith PB, Welch SP, Martin BR. 1994. Interactions between delta 9-tetrahydrocannabinol and kappa opioids in mice. *Journal of Pharmacology and Experimental Therapeutics* 268: 1381–1387.
154. Sofia RD, Nalepa SD, Harakal JJ, Vassar HB. 1973. Anti-edema and analgesic properties of delta-9-tetrahydrocannabinol (THC). *Journal of Pharmacology and Experimental Therapeutics* 186:646–655.
155. Specter S, Lancz G, Hazelden J. 1990. Marijuana and immunity: Tetrahydrocannabinol mediated inhibition of lymphocyte blastogenesis. *International Journal of Immunophar-macology* 12:261–267.
156. Stefano G, Salzet B, Salzet M. 1997. Identification and characterization of the leech CNS cannabinoid receptor: Coupling to nitric oxide release. *Brain Research* 753:219–224.
157. Stella N, Schweitzer P, Piomelli D. 1997. A second endogenous cannabinoid that modulates long term potentiation. *Nature* 388:773–778.
158. Strangman NM, Patrick SL, Hohmann AG, Tsou K, Walker JM. 1998. Evidence for a role of endogenous cannabinoids in the modulation of acute and tonic pain sensitivity. *Brain Research* 813:323–328.
159. Sulcova E, Mechoulam R, Fride E. 1998. Biphasic effects of anandamide. *Pharmacology, Biochemistry and Behavior* 59:347–352.
160. Szabo B, Dorner L, Pfreundtner C, Norenberg W, Starke K. 1998. Inhibition of GABAergic inhibitory postsynaptic currents by cannabinoids in rat corpus striatum. *Neuroscience* 85:395–403.
161. 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.
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. *Immunopharma-cology* 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 RB, 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.

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 explores the negative health consequences of marijuana use, first with respect to drug abuse, then from a 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,[1] Hall and Solowij,[59] and Hall et al. [60]). 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 intelli-

gible 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.

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;[59] others include panic, depression, dysphoria, depersonalization, delusions, illusions, and hallucinations.[1,40,66,69] Of regular marijuana smokers, 17% report that they have experienced at least one of the symptoms, usually early in their use of marijuana.[145] 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[114] 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 3.1). 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 physiological dependence.

Even a patient who takes a medicine for appropriate medical indications and at the correct dosage can develop tolerance, physical depen-

TABLE 3.1 Psychoactive Doses of THC in Humans

Investigators	THC Delivery System	THC Dose Administered	Resulting Plasma Concentrations of THC	Subjects' Reactions
Heishman and co-workers (1990)[62a]	One 2.75% THC cigarette smoked	0.32 mg/kg[a]	50–100 ng/ml	At higher level, subjects felt 100% "high" and psychomotor performance was decreased; at 50 ng/ml, subjects felt about 50% "high"
Kelly and co-workers (1993)[85]	1-g marijuana cigarette smoked (2% or 3.5% THC)	0.25–0.50 mg/kg[a]	Not measured	Enough to feel psychological effects of THC
Ohlsson and co-workers (1980)[118]	19-mg THC cigarette smoked (about 1.9% THC)	About 0.22 mg/kg[b]	100 ng/ml	Subjects felt "high"
	5 mg of THC injected intravenously	About 0.06 mg/kg[b]	100 ng/ml	Subjects felt "high"
	Chocolate chip cookie containing 20 mg of THC	About 0.24 mg/kg	8 ng/ml	Subjects rated "high" as only about 40%
Lindgren and co-workers (1981)[95]	19-mg THC cigarette smoked to "desired high"	12 mg smoked (7 mg remained in cigarette butt)	85 ng/ml after 3 min., 35 ng/ml after 15 min.	Subjects felt "high" after 3 min., and maximally high after 10–20 min. (average self-ratings of 5.5 on 10-point scale)
	5 mg of THC injected intravenously	0.06 mg/kg[c]	300 ng/ml after 3 min., 65 ng/ml after 15 min.	Subjects felt maximally "high" after 10 min. (average self ratings of 7.5 on a 10-point scale)

[a]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 sidestream smoke, so these represent maximal possible doses. Actual doses would have been slightly less.
[b]Based on estimated average 85-kg weight of 11 men 18–35 years old.
[c]Based on approximate 80-kg weight of subjects (including men and women).

Box 3.1
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 a drug is abruptly withdrawn are known as withdrawal syndrome and are often the only evidence of physical dependence.

dence, 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 that is 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 3.2).

Box 3.2
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), to use the substance (e.g., chain-smoking), or to 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 users, and the more strongly reinforcing a drug is, the more likely it will be abused (G. Koob, Institute of Medicine (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 is 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).[93] 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.[100]

A specific set of neural pathways has been proposed to be a "reward system" that underlies the reinforcement of drugs of abuse 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.[88] Cocaine, amphetamine, alcohol, opioids, nicotine, and THC[144] all increase extracellular fluid dopamine in the nucleus accumbens region (reviewed by Koob and Le Moal[88] and Nestler and Aghajanian[110] 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 themselves 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,[29,104,124] 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).[95]

There appear to be variations in the development of tolerance to the different effects of marijuana and oral THC. For example, daily marijuana smokers participated in a residential laboratory study to compare the development of tolerance to THC pills and to smoked marijuana.[61,62] 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 four-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. "Tolerance" does not mean that the drug no longer produced the effects but simply that the effects were less at the end than at the beginning of the four-day period. The marijuana smoking group reported feeling "mellow" after smoking and did not show tolerance to this effect; the group that took THC pills did not report feeling "mellow." The difference 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 of THC to a subject. Each smoked marijuana dose consisted of five 10-second puffs of a marijuana cigarette containing 3.1% THC; the pills contained 30 mg of THC. Both groups also received placebo drugs during other four-day periods. Although the dosing of the two groups was comparable, different routes of administration resulted in different patterns of drug effect. The peak effect of smoked marijuana is usually felt within minutes and declines sharply after 30 minutes[68,95]; the peak effect of oral THC is usually not felt until about an hour and lasts for several hours.[118]

Withdrawal

A distinctive marijuana and THC withdrawal syndrome has been

identified, but it is mild and subtle compared with the profound physical syndrome of alcohol or heroin withdrawal.[31,74] The symptoms of marijuana withdrawal include restlessness, irritability, mild agitation, insomnia, sleep EEG disturbance, nausea, and cramping (Table 3.2). In addition to those symptoms, two recent studies noted 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 in the section on "Prevalence and Predictors of Dependence on Marijuana and Other Drugs").[31] In a residential study of daily

TABLE 3.2 Drug Withdrawal Symptoms

Nicotine	Alcohol	Marijuana	Cocaine	Opioids (e.g., heroin or morphine)
Restlessness		Restlessness		Restlessness
Irritability	Irritability	Irritability		Irritability
Impatience, hostility		Mild agitation		
Dysphoria			Dysphoria	Dysphoria
Depression			Depression	
Anxiety				Anxiety
Difficulty concentrating				
	Sleep disturbance	Insomnia	Sleepiness, fatigue	Insomnia
		Sleep EEG disturbance		
	Nausea	Nausea		Nausea
		Cramping		Cramping
Decreased heart rate	Tachycardia, hypertension		Bradycardia	
	Sweating			Muscle aches
	Seizures			Increased sensitivity to pain
	Alcohol craving		Cocaine craving	Opioid craving
Increased appetite or weight gain	Delirium tremens[a]			
	Tremor			
	Perceptual distortion			

[a]Severe agitation, confusion, visual hallucinations, fever, profuse sweating, nausea, diarrhea, dilated pupils.
SOURCE: O'Brien (1996).[113]

marijuana users, withdrawal symptoms included sweating and runny nose, in addition to those listed above.[62] A marijuana withdrawal syndrome, however, has been reported only in a group of adolescents in treatment for substance abuse problems[31] and in a research setting where subjects were given marijuana or THC daily.[62,74]

Withdrawal symptoms have been observed in carefully controlled laboratory studies of people after use of both oral THC and smoked marijuana.[61,62] In one study, subjects were given very high doses of oral THC: 180–210 mg per day for 10–20 days, roughly equivalent to smoking 9–10 2% THC cigarettes per day.[74] During the abstinence period at the end of the study, the study subjects were irritable and showed insomnia, runny nose, sweating, and decreased appetite. The withdrawal symptoms, however, were short lived. In four days they had abated. The time course contrasts with that in 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.[61,62]

In animals, simply discontinuing chronic heavy dosing of THC does not reveal withdrawal symptoms, but the "removal" of THC from the brain can be made abrupt by another drug that blocks THC at its receptor if administered when the chronic THC is withdrawn. The withdrawal syndrome is pronounced, and the behavior of the animals becomes hyperactive and disorganized.[153] The half-life of THC in brain is about an 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 when THC is abruptly withdrawn without administration of a receptor-blocking drug is probably not due to a prolonged decline in brain concentrations.

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.[115] Thus, while this section briefly reviews what is known about drug craving, its relevance to marijuana use has not been established.

Most people who suffer from addiction relapse within a year of abstinence, and they often attribute their relapse to craving.[58] 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.[115] Whether neurobiological conditions change during the manifestation of an abstinence syndrome remains an unanswered question in drug abuse research.[88] The "liking" of sweet foods, for example, is

mediated by opioid forebrain systems and by brain stem systems, whereas "wanting" seems to be mediated by ascending dopamine neurons that project to the nucleus accumbens.[109]

Anticraving medications have been developed for nicotine and alcohol. The antidepressant, bupropion, blocks nicotine craving, while naltrexone blocks alcohol craving.[115] Another category of addiction medication includes drugs that block other drugs' effects. Some of those drugs also block craving. For example, methadone blocks the euphoric 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—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.[132] Marijuana use is most prevalent among 18- to 25-year-olds and declines sharply after the age of 34 (Figure 3.1).[77,132] Whites are more likely than blacks to use marijuana in adolescence, although the difference decreases by adulthood.[132]

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 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 their marijuana 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 health and well-being; that is, they felt that marijuana was bad for their health or for their family and work relationships. The second type was based on age-related changes in circumstances, including increased responsibility and decreased regular contact with other marijuana users. 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. 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 them for psychological reasons.[80]

The age distribution of marijuana users among the general popula-

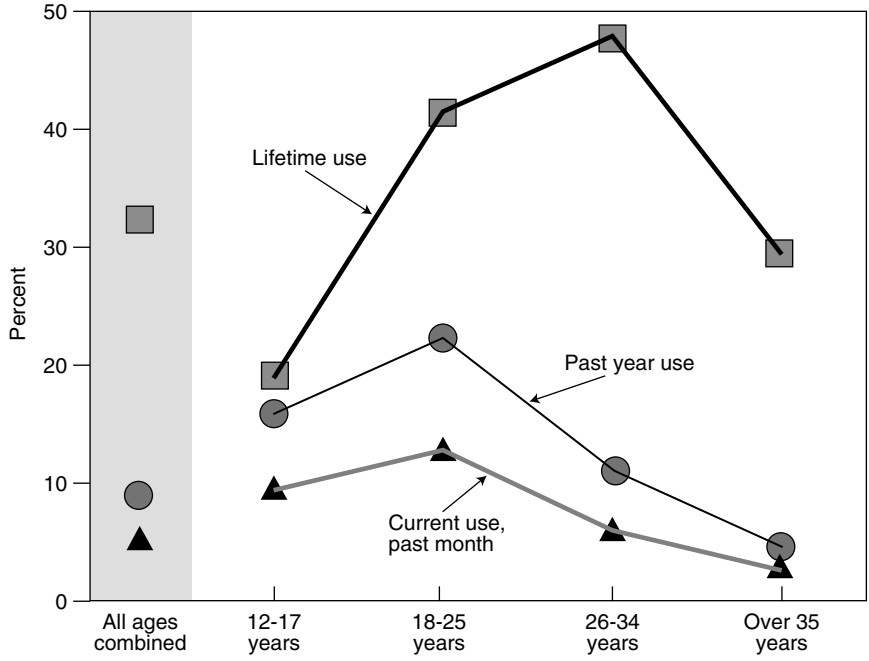


FIGURE 3.1 Age distribution of marijuana users among the general population.

tion contrasts with that of medical marijuana users. Marijuana use generally declines sharply after the age of 34 years, whereas medical marijuana users tend to be over 35. That raises the question of what, if any, relationship exists between abuse and medical use of marijuana; however, no studies reported in the scientific literature have addressed this question.

Prevalence and Predictors of Dependence on Marijuana and Other Drugs

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).[114] The first two categories apply to potential abuse of any substance; that is, people who are vulnerable to drug abuse for individual reasons and who find themselves in an environment that encourages drug abuse are 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

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
- Prior drug use

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

SOURCE: Crowley and Rhine (1985).[32]

liability of a particular drug. As discussed earlier in this chapter, the more strongly reinforcing a drug is, the more likely that 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, and the effects of drugs that are ingested take a half hour or more.

The proportion of people who become addicted varies among drugs. Table 3.4 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. Compared to most other drugs listed in this table, dependence among marijuana users is relatively rare. This might be due to differences in specific drug effects, the availability of or penalties associated with the use of the different drugs, or some combination.

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).[76]

Drug dependence is more prevalent in some sectors of the population than in others. Age, gender, and race or ethnic group are all important.[8] Excluding tobacco and alcohol, the following trends of drug dependence are statistically significant:[8] Men are 1.6 times as likely than women to become drug dependent, non-Hispanic whites are about twice as likely as blacks to become drug dependent (the difference between non-Hispanic

TABLE 3.4 Prevalence of Drug Use and Dependence[a] in the General Population

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

[a]Diagnosis of drug dependence used in this study based on DSM-III-R criteria.[2]
[b]The percentage of people who ever used marijuana is higher than that reported by the National Household Survey on Drug Abuse (32%), probably due to different survey methods (for discussion, see Kandel, 1992[76]).
SOURCE: Adapted from Table 2 in Anthony and co-workers (1994).[8]

and Hispanic whites was not significant), and people 25–44 years old are more than three times as likely as those over 45 years old to become drug dependent.

More often than not, drug dependence co-occurs with other psychiatric disorders. Most people with a diagnosis of drug dependence disorder also have a diagnosis of a another psychiatric disorder (76% of men and 65% of women).[76] The most frequent co-occurring disorder is alcohol abuse; 60% of men and 30% of women with a diagnosis of drug dependence also abuse alcohol. In 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"; marijuana was grouped among "other drugs." 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.

A strong association between drug dependence and antisocial personality or its precursor, conduct disorder, is also widely reported in children and adults (reviewed in 1998 by Robins[126]). Although the causes of the association are uncertain, Robins recently concluded that it is more likely that conduct disorders generally lead to substance abuse than the reverse.[126] Such a trend might, however, depend on the age at which the conduct disorder is manifested.

A longitudinal study by Brooks and co-workers noted a significant relationship between adolescent drug use and disruptive disorders in young adulthood; except for earlier psychopathology, such as childhood conduct disorder, the drug use preceded the psychiatric disorders.[18] In contrast with use of other illicit drugs and tobacco, moderate (less than once a week and more than once a month) to heavy marijuana use did not predict anxiety or depressive disorders; but it was similar to those other drugs in predicting antisocial personality disorder. The rates of disruptive disorders increased with increased drug use. Thus, heavy drug use among adolescents can be a warning sign for later psychiatric disorders; whether it is an early manifestation of or a cause of those disorders remains to be determined.

Psychiatric disorders are more prevalent among adolescents who use drugs—including alcohol and nicotine—than among those who do not.[79] Table 3.5 indicates that adolescent boys who smoke cigarettes daily are about 10 times as likely to have a psychiatric disorder diagnosis as those who do not smoke. However, the table does not compare intensity of use among the different drug classes. Thus, although *daily* cigarette smoking among adolescent boys 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.[79]

Few marijuana users become dependent on it (Table 3.4), but those who do encounter problems similar to those associated with dependence on other drugs.[19,143] Dependence appears to be less severe among people

TABLE 3.5 Relative Prevalence of Diagnoses of Psychiatric Disorders Associated with Drug Use Among Children[a]

	Relative Prevalence Estimates[b]	
Drug Use	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

[a]Subjects were from 9 to 18 years old (average, 13 years old).

[b]An estimate of 1 means that the relative prevalence of the disorder is equal in those who do and those who do not use the particular type of drug; that is, there is no measurable association. An estimate greater than 1 indicates that the factor is associated. Substance abuse was excluded because the subjects were already grouped by high drug use. Except where noted (n.s.), all values are statistically significant.

SOURCE: Data from Table 4 in Kandel and co-workers (1997).[79]

who use only marijuana than among those who abuse cocaine or those who abuse marijuana with other drugs (including alcohol).[19,143]

Data gathered in 1990–1992 from the National Comorbidity Study of over 8,000 persons 15–54 years old indicate that 4.2% of the general population were dependent on marijuana at some time.[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. According to data collected in the early 1980s for that study, 4.4% of adults have, at one time, met the criteria for marijuana dependence. In comparison, 13.8% of adults met the criteria for alcohol dependence and 36.0% for tobacco dependence. After alcohol and nicotine, marijuana was the substance most frequently associated with a diagnosis of substance dependence.

In a 15-year study begun in 1979, 7.3% of 1,201 adolescents and young adults in suburban New Jersey at some time met the criteria for marijuana dependence; this indicates that the rate of marijuana dependence might be even higher in some groups of adolescents and young adults than in the general population.[71] Adolescents meet the criteria for drug dependence at lower rates of marijuana use than do adults, and this suggests that they are more vulnerable to dependence than adults[25] (see Box 3.2).

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 substances. The adolescents 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. About 83% of those who had used marijuana at least six times went on to develop marijuana dependence. About equal numbers of youths in the study had a diagnosis of marijuana dependence and a diagnosis of alcohol dependence; fewer were nicotine dependent. Comparisons of dependence potential between 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. That is consistent with reports that the more symptoms of conduct disorders children have, the younger they begin drug abuse,[127] and that the earlier they begin drug use, the more likely it is to be followed by abuse or dependence.[125]

Genetic factors are known to play a role in the likelihood of abuse for

drugs other than marijuana,[7,129] and it is not unexpected that genetic factors 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 statistically significant influence on whether a person finds the effects of marijuana pleasant.[97] Not surprisingly, people 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 a person will continue using marijuana. Similar results were found in a study of female twins.[86] Family and social environment strongly influenced the likelihood of ever using marijuana but had little effect on the likelihood of heavy use or abuse. The latter were more influenced by genetic factors. Those results are consistent with the finding that the degree to which rats find THC rewarding is genetically based.[92]

In summary, 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 dependence on other drugs. Drug dependence is more prevalent in some sectors of the population than others, but no group has been identified as particularly vulnerable to the drug-specific effects of marijuana. Adolescents, especially troubled ones, and people with psychiatric disorders (including substance abuse) appear to be 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 at high risk for substance dependence. Some controlled substances that are approved medications produce dependence after long-term use; this, however, is 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. To judge from comments submitted to the IOM study team, it appears to be of 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 that most people encounter. Not surprisingly, most users of other illicit drugs used marijuana first.[81,82] In fact, most drug users do not begin their drug use with marijuana—they begin with alcohol and nicotine, usually when they are too young to do so legally.[82,90]

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.[82] The second 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. The latter interpretation is most often used in the scientific literature, and it is supported, 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, which are independent of drug-specific effects. There is no evidence that marijuana serves as a stepping stone on the basis of its particular physiological effect. One might argue that marijuana is generally used before other illicit mood-altering drugs, in part, because its effects are milder; 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 of 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, the legal status of marijuana makes it a gateway drug.[82]

Psychiatric disorders are associated with substance dependence and are probably risk factors for progression in drug use. For example, the troubled adolescents studied by Crowley and co-workers[31] were dependent on an average of 3.2 substances, and this suggests that their conduct disorders were associated with increased risk of progressing from one drug to another. Abuse of a single substance is probably also a risk factor

for later multiple drug use. For example, in a longitudinal study that examined drug use and dependence, about 26% of problem drinkers reported that they first used marijuana after the onset of alcohol-related problems (R. Pandina, IOM workshop). The study also found that 11% of marijuana users developed chronic marijuana problems; most also had alcohol problems.

Intensity of drug use is 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[78]). Of 34- to 35-year-old men who had used marijuana 10–99 times by the age 24–25, 75% 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. [78] Comparable proportions for women are 64% and 50%.

The factors that best predict use of illicit drugs other than marijuana are probably the following: age of first alcohol or nicotine use, heavy marijuana use, and psychiatric disorders. However, progression to illicit drug use is not synonymous with heavy or persistent drug use. Indeed, although the age of onset of use of licit drugs (alcohol and nicotine) predicts later illicit drug use, it does *not* appear to predict persistent or heavy use of illicit drugs.[90]

Data on the gateway phenomenon are often overinterpreted. For example, one study reports that "marijuana's role as a gateway drug appears to have increased."[55] It was a retrospective study based on interviews of drug abusers who reported smoking crack or injecting heroin daily. The data from the study 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 percentage of the adult population uses crack or heroin daily; during the five-year period from 1993 to 1997, an average of three people per 1,000 used crack and about two per 1,000 used heroin in the preceding month.[132]

Many of the data on which the gateway theory is based do not measure dependence; instead, they measure use—even once-only use. Thus, they show only that marijuana users are more likely to use other illicit drugs (even if only once) than are people who never use marijuana, not that they become dependent or even frequent users. 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—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 *cause* or even that it is the most significant predictor of serious drug abuse; that is, care must be taken not to attribute cause to association. The most consistent predictors of serious drug use appear to be the intensity of marijuana use and co-occurring psychiatric disorders or a family history of psychopathology (including alcoholism).[78,83]

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 co-workers also included nonmedical use of prescription psychoactive drugs in their study of drug use progression.[82] In contrast with the use of alcohol, nicotine, and illicit drugs, there was not a clear and consistent sequence of drug use involving the abuse of prescription psychoactive drugs. The current data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse among medical marijuana users. 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 would be used for medical purposes—is another question.

LINK BETWEEN MEDICAL USE AND DRUG ABUSE

Almost everyone who spoke or wrote to the IOM study team about the potential harms posed by the medical use of marijuana felt that it would send the wrong message to children and teenagers. They stated that information about the harms caused by 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. Reasonable inferences might be drawn from some examples. 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 their medical use and their abuse. In a "natural experiment" during 1973–1978 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 and ask whether it had any measurable impact on marijuana con-

sumption among youth in California; the consequences of "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 widespread concern among physicians and medical licensing boards that liberal use of opiates would result in many addicts (reviewed by Moulin and co-workers[106] 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 people begin their drug addiction problems with misuse of drugs that have been prescribed for medical use.[114] 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.

No evidence suggests that the use of opiates or cocaine for medical purposes has increased the perception that their illicit use is safe or acceptable. Clearly, there are risks that patients will abuse marijuana for its psychoactive effects and some likelihood of diversion of marijuana from legitimate medical channels into the illicit market. But those risks do not differentiate marijuana from many accepted medications that are abused by some patients or diverted from medical channels for nonmedical use. Medications with abuse potential are placed in Schedule II of the Controlled Substances Act, which brings them under stricter control, including quotas on the amount that can be legally manufactured (see chapter 5 for discussion of the Controlled Substances Act). That scheduling also signals to physicians that a drug has abuse potential and that they should monitor its use by patients who could be at risk for drug abuse.

Marijuana Decriminalization

Monitoring the Future, the annual survey of values and lifestyles 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.[72] Another study reported somewhat conflicting evidence indicating that decriminalization had increased marijuana use.[105] That study used data from the Drug Awareness Warning Network (DAWN), which has collected data on drug-related emergency room (ER) cases since 1975. There was a greater increase from 1975 to 1978 in the proportion of ER patients who had used marijuana in states that had decriminalized marijuana in 1975–1976 than in states that had not decriminalized it (Table 3.6). Despite the greater

TABLE 3.6 Effect of Decriminalization on Marijuana Use in Emergency Room (ER) Cases

		Total Reports of Drug Use per ER[a]	
	Period[b]	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

[a]Data are based on patient self-reports.

[b]States that decriminalized marijuana did so after 1975 and before 1978. The 1975 values reflect ER marijuana reports before or in the first months of decriminalization, whereas 1978 values reflect ER reports when decriminalization laws had been in effect at least a year. The 1978 levels are median values for quarters in 1978 and are derived from Figures 1 and 2 in Model (1993).[105]

SOURCE: Adapted from Figures 1 and 2 in Model (1993).[105]

increase among decriminalized states, the proportion of marijuana users among ER patients by 1978 was about equal in states that had and states that had not decriminalized marijuana. That is because the non-decriminalized states had higher rates of marijuana use *before* decriminalization. In contrast with marijuana use, rates of other illicit drug use among ER patients were substantially higher in states that did not decriminalize marijuana use. Thus, there are different possible reasons for the 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 sought health care in hospital ERs). On the other hand, the lack of decriminalization might have encouraged greater use of drugs that are even more dangerous than marijuana.

The differences between the results for high school seniors from the Monitoring the Future study and the DAWN data are unclear, although the author of the latter study suggests that the reasons might lie in limitations inherent in how the DAWN data are collected.[105]

In 1976, the Netherlands 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 after the policy change, which suggests that the change itself had little effect; however, in 1984, when Dutch "coffee shops" that sold marijuana commercially spread throughout Amsterdam, marijuana

use began to increase.[98] 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. Furthermore, during this period, approximately equal percentages of American and Dutch 18 year olds used marijuana; Norwegian 18 year olds were about 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 marijuana use, although they note that commercialization of marijuana might have contributed to its increased use. Thus, there is little evidence that decriminalization of marijuana use necessarily leads to a substantial increase in marijuana use.

The Medical Marijuana Debate

The most recent National Household Survey on Drug Abuse showed that among people 12–17 years old the perceived risk associated with smoking marijuana once or twice a week had decreased significantly between 1996 and 1997.[132] (Perceived risk is measured as the percentage of survey respondents who report that they "perceive great risk of harm" in using a drug at a specified frequency.) At first glance, that might seem to validate the fear that the medical marijuana debate of 1996—before 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. In contrast to the national trend, the perceived risk of marijuana use did not change among California youth between 1996 and 1997.[132]* In summary, there is no evidence that the medical marijuana debate has altered adolescents' perceptions of the risks associated with marijuana use.[132]

PSYCHOLOGICAL HARMS

In assessing the relative risks and benefits related to the medical use of marijuana, the psychological effects of marijuana can be viewed both as unwanted side effects and as potentially desirable end points in medical treatment. However, the vast majority of research on the psychological effects of marijuana has been in the context of assessing the drug's intoxicating effects when it is used for nonmedical purposes. Thus, the litera-

*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 youths' attitudes likely reflect factors peripheral to medical marijuana.

ture does not directly address the effects of marijuana taken for medical purposes.

There are some important caveats to consider in attempting to extrapolate from the research mentioned above to the medical use of marijuana. The circumstances under which psychoactive drugs are taken are an important influence on their psychological effects. Furthermore, research protocols to study marijuana's psychological effects in most instances were required to use participants who already had experience with marijuana. People who might have had adverse reactions to marijuana either would choose not to 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 people 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 from those 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. Results of 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 therapeutic benefits related to 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. Inasmuch as smoking *one* cigarette is enough to make a person feel "high" for about 1–3 hours,[68,95,118] the subjects in that study were taking very high doses of 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.[121,122] There are clinical reports of marijuana-induced psychosis-like states (schizophrenia-like, depression, and/or mania) lasting for a week or more.[112] 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 might trigger latent psychopathology of many types.[66]

More recently, Hall and colleagues[60] 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 those interpretations is correct, the two 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.[59,96,151] 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 at least as great as that among the general population.[134] Schizophrenics prefer the effects of marijuana to those of alcohol and cocaine,[35] which they seem to use less often than does the general population.[134] 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, people with schizophrenia or with a family history of schizophrenia are likely to be at greater risk for adverse psychiatric effects from the use of cannabinoids.

Cognition

As discussed earlier, acutely administered marijuana impairs cognition.[60,66,112] Positron emission tomography (PET) imaging 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.[116,117] Marijuana smoking increases blood flow in other brain regions, such as the frontal lobes and lateral cerebellum.[101,155] Earlier studies purporting to show structural changes in the brains of heavy marijuana users[22] have not been replicated with more sophisticated techniques.[28,89]

Nevertheless, recent studies[14,122] 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.[140] Although these studies have attempted to match heavy marijuana users with subjects of similar cognitive abilities before exposure to marijuana use, the adequacy of this matching has been questioned.[133] The complex methodological issues facing research in this area are well reviewed in an article by Pope and colleagues.[121] Care must be exercised so that studies are designed to differentiate between changes in brain function caused the effects of marijuana and by the illness for which marijuana is being given. AIDS dementia is an obvious example of this possible confusion. It is also important to determine whether repeated use of marijuana at therapeutic dosages produces any irreversible cognitive effects.

Psychomotor Performance

Marijuana administration has been reported to affect psychomotor performance on a number of tasks. The review by Chait and Pierri[23] not only details the studies that have been done but also points out the inconsistencies among 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 in studies of psychomotor performance when participants are 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 performance on flight simulator tests was impaired.[163] Before the tests, however, they told the study investigators that they were sure their performance would be unaffected.

Cognitive impairments associated with acutely administered marijuana limit the activities that people 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 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 no convincing data demon-

strate 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 and 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, although a causal relationship between the two could, in theory, be dismissed by an epidemiological study, causality could not be proven.

Summary

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 before; every week during; and, where appropriate, after 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 subjects. Similarly, the cognitive and psychomotor functioning should be assessed before and regularly during the course of a chronic regimen of marijuana or cannabinoid treatment to determine the extent to which tolerance to the impairing effects of marijuana develops and to monitor whether new problems develop.

When compared with changes produced by either placebo or an active control medication, the magnitude of desirable therapeutic effects and the frequency and magnitude of adverse psychological side effects of marijuana could be determined. That 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 in some patients and situations and beneficial in others. In addition, psychological effects can complicate the interpretation of other aspects of the drug's 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 in the general population marijuana use is not associated with increased mortality.[138] However, other serious health outcomes should be considered, and they are discussed below.

It is important to keep in mind that most of the studies that report physiological harm 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 effects of marijuana-induced immunomodulation are 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.

Human Studies

Several approaches have been used to determine the effects of marijuana on the human immune system. Each has serious limitations, which are discussed below.

Assays of Leukocytes from Marijuana Smokers. One of the more common approaches has been to isolate peripheral blood leukocytes from people 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 the approach is that after blood samples are drawn from the study subjects the leukocytes must be isolated from whole blood before they are tested. That is done by high-speed centrifugation followed by extensive washing of the cells, which removes the cannabinoid; perhaps for this reason no adverse effects have been demonstrated in peripheral blood leukocytes from marijuana smokers.[75,91,123,160]

Leukocyte Responses to THC. Another approach is to isolate peripheral blood leukocytes from healthy control subjects 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*. One important difference between leukocytes isolated from a marijuana smoker, as described above, and leukocyte cell cultures to which THC has been added directly is in the cannabinoid composition. Marijuana smoke contains many distinct cannabinoid compounds of which THC is just one. Moreover, the immunomodulatory activity of many of the other cannabinoid compounds has never been tested, and it is now known that at least one of those—cannabinol (CBN)—has greater activity on the immune system than on the central nervous system,[64] so it is unclear whether the profile of activity observed with THC accurately represents the effects of marijuana smoke on immune competence. Likewise, the extent to which different cannabinoids in combination exhibit additive, synergistic, or antagonistic effects with respect to immunomodulatory activity is unclear. The issue is complicated by the fact that leukocytes express both types of cannabinoid receptors: CB_1 and CB_2.

An additional factor that might affect the immunomodulatory activity of cannabinoids in leukocytes is metabolism. Leukocytes have very low levels of the cytochrome P-450 drug-metabolizing enzymes,[20] so the metabolism of cannabinoids is probably different between *in vivo* and *in vitro* exposure. That last point is pertinent primarily to investigations of chronic, 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.* As described above, the cell lines are treated *in vitro* with cannabinoids to test their responses to different stimuli. Although cell lines

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

are a convenient source of human cells, the problems described above apply here as well. In addition, 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 is 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 substantial species differences in immune system sensitivity to cannabinoids have been reported, the possibility should be considered.

Summary

The complete effect of marijuana smoking on immune function remains unknown. More important, 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 removing other potential immunomodulating lifestyle factors, such as alcohol and tobacco use. Epidemiological studies are needed to determine whether marijuana users have a higher incidence of such diseases, as infections, tumors, allergies, and autoimmune diseases. Studies on resistance to bacterial and viral infection are clearly needed and should involve the collaboration of immunologists, infectious disease specialists, oncologists, and pharmacologists.

Marijuana Smoke

Tobacco is the predominant cause of such lung diseases as cancer and emphysema, and marijuana smoke contains many of the components of tobacco smoke.[69] Thus, it is important to consider the relationship between habitual marijuana smoking and some 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 as in the lungs of tobacco smokers.[162] The difference is due primarily 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.[119] However, a marijuana cigarette smoked recreationally typically is not packed

as tightly as a tobacco cigarette, and 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 cell function 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 (12 cigarettes/day), but the decrease was seen in only one subtype of humoral antibody (IgG), whereas two other subtypes (IgA and IgM) remained normal and one (IgE) was increased.[108] In addition, T cell proliferation was normal in the blood of a group of marijuana smokers, although closer evaluation showed an increase in one subset of T cells[161] and a decrease in a different subset (CD8).[157] 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 often normal.[87]

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 fungi, such as *Candida albicans*;* pathogenic bacteria, such as *Staphylococcus aureus*; and tumor target cells. The 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 production of proinflammatory cytokines, such as TNF-I and IL-6, but not of immunosuppressive cytokines.[10] Cytokines are important regulators of macrophage function, so 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 fungi, bacteria, and tumor cells

**Candida albicans* is a yeast infection that is particularly prevalent among people whose immune systems are suppressed, such as in AIDS patients.

and to release proinflammatory 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 preexisting immune deficits—including AIDS patients, cancer patients, and those receiving immunosuppressive therapies (for example, transplant or cancer patients).

Bronchial and Pulmonary Damage

Animal Studies. A number of animal studies have revealed respiratory tract changes and diseases associated with marijuana smoking, but others have not. Extensive damage to the smaller airways, which are the major site of chronic obstructive pulmonary disease (COPD),* and acute and chronic pneumonia have been observed in various species exposed to different doses of marijuana smoke.[41,42,128] 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.[67]

Chronic Bronchitis and Respiratory Illness. Results of human studies suggest that there is a greater chance of respiratory illness in people who smoke marijuana. In a survey of outpatient medical visits at a large health maintenance organization (HMO), marijuana users were more likely to seek help for respiratory illnesses than people who smoked neither marijuana or tobacco.[120] However, the incidence of seeking help for respiratory illnesses was not higher in those who smoked marijuana for 10 years or more than in 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 that people who continue to smoke constitute a set of survivors who do not develop or are indifferent to such symptoms. One 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; tobacco, alcohol, and marijuana use might have been underreported (S. Sidney, IOM workshop).

When marijuana smokers were compared with nonsmokers and tobacco smokers in a group of 446 volunteers, 15–20% of the marijuana smokers reported symptoms of chronic bronchitis, including chronic

*COPD is 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.

cough and phlegm production,[146] and 20–25% of the tobacco smokers reported symptoms of chronic bronchitis. Despite a marked disparity in the amount of each substance smoked per day (three or four joints of marijuana versus more than 20 cigarettes of tobacco), the difference in the percentages of tobacco smokers and marijuana smokers experiencing symptoms of chronic bronchitis was statistically insignificant.[146] Similar findings were reported by Bloom and co-workers,[15] who 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 mucous secretions.[43,56] 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 mucous-secreting goblet cells. The damage is greater in people who smoke both marijuana and tobacco.[130] Overproduction of mucus by the increased numbers of mucous-secreting cells in the presence of decreased numbers of ciliated cells tends to leave coughing 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.[148]

A 1998 study has shown that both marijuana and tobacco smokers have significantly more cellular and molecular abnormalities in bronchial epithelium cells than nonsmokers; these 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. Although the marijuana smokers smoked far fewer cigarettes, their cellular abnormalities were equivalent to or greater than those seen in tobacco smokers. This and earlier studies have shown that such abnormalities are greatest in people who smoke both marijuana and tobacco; hence, marijuana and tobacco smoke might have additive effects on airway tissue.[12,43,56] Tenant[150] 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 hyperrespon-

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

siveness and measures of lung function, offers an indicator of the vulnerability of marijuana smokers to COPD.[154] 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 is conflicting evidence on whether regular marijuana use harms the small airways of the lungs. Bloom and co-workers found that an average of one joint smoked per day significantly impaired the function of small airways.[15] But Tashkin and co-workers[146] did not observe such damage among heavier marijuana users (three to four joints per day for at least 10 years), although they noted a narrowing of large central airways. Tashkin and co-workers' 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.[147] Thus, the question of 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 premalignant. These respiratory symptoms are similar to those of tobacco smokers, and the combination of marijuana and tobacco smoking augments these effects. At the time of this writing, it had 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 both to increased risk of progression to AIDS in HIV-seropositive patients and to increased mortality in AIDS patients.

For unknown reasons, marijuana use is associated with increased mortality among men with AIDS but not among the general population.[138] (The relative risk of AIDS mortality for current marijuana users in this 12-year study was 1.90, indicating that almost twice as many marijuana users died of AIDS as did noncurrent marijuana users.) 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 probably homosexuals or bisexuals. That raises the pos-

sibility 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 of whether this was because patients increased their use of marijuana at the endstages 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 five years of this 12-year study, and who were presumably the most sick, were excluded from the analysis. In summary, it is premature to conclude what the underlying causes of this association might be.

For the general population, the 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. The authors of the study described above 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,[84] 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,[84] or in the San Francisco Men's Health Study, in which 451 HIV-seropositive men were studied for six years.[34] In contrast, the Sydney AIDS Project in Australia, in which 386 HIV-seropositive men were studied for 12 months,[152] reported that marijuana use was associated with increased risk of progression to AIDS. The results of the Sydney study are less reliable than those of the other two studies noted; it was the shortest of the studies and, according to the 1993 definition of AIDS, many of the subjects probably already had AIDS at the beginning of the study.*

The most compelling concerns regarding marijuana smoking in HIV/AIDS patients are the possible effects of marijuana on immunity.[111] Reports of opportunistic fungal and bacterial pneumonia in AIDS patients who used marijuana suggest that marijuana smoking either suppresses the immune system[33] or exposes patients to an added burden of patho-

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

gens.[21] In summary, patients with preexisting immune deficits due to AIDS should be expected to be vulnerable to serious harm 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 a marijuana smoker to carcinogens. For those reasons the carcinogenicity of marijuana smoke is an important concern.

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

Case Studies. Results of several case series suggest that marijuana might play a role in the development of human respiratory cancer. Reports indicate an unexpectedly large proportion of marijuana users among people with lung cancer[141,149] and cancers of the upper aerodigestive tract—that is, the oral cavity, pharynx, larynx, and esophagus—that occur before the age of 45.[36,39,149] Respiratory tract cancers associated with heavy tobacco and alcohol consumption are not usually seen before the age of 60,[154] and the occurrence of such cancers in marijuana users younger than 60 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. 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 and tobacco smoke.

Epidemiological Evidence. As of this writing, Sidney and co-workers[139] had conducted the only epidemiological study to evaluate the association between marijuana use and cancer. The study included a cohort of about 65,000 men and women 15–49 years old. 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 cancer, and 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. In addition, marijuana use has been widespread in the United States only since the late 1960s; therefore, despite the large cohort size there might not have been a sufficient number of heavy or long-term marijuana smokers to reveal an effect.

Cellular and Molecular Studies. In contrast with clinical studies, cellular and molecular studies have provided 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,[94] and exposure of human lung explants to marijuana smoke resulted in chromosomal and DNA alterations.[154] The tar from marijuana smoke also induced mutations similar to those produced by tar from the same quantity of tobacco in a common bacterial assay for mutagenicity.[158]

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, they code for proteins that control cellular proliferation. Once mutated or activated, they produce proteins that cause cells to multiply rapidly and out of control, and this results in tumors or cancer.* When the production of these proteins was evaluated in tissue biopsies taken from marijuana, tobacco, and marijuana plus tobacco smokers, and nonsmokers, two of them (EGFR and Ki-67) were markedly higher in the marijuana smokers than in the nonsmokers and the tobacco smokers. Moreover, the effects of marijuana and tobacco were additive.[131] Thus, in relatively young smokers of marijuana, particularly 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 and in those of their newborns.[4] This is an important study

*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 epithelial cells, that promotes cellular growth and proliferation when bound to epidermal growth factor).

because the investigators were careful to exclude tobacco smokers—a problem in previous studies that cited mutagenic effects of marijuana smoke.[26,53,63,142] The 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 be determined only 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.[99] 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). That suggests that there is more of CYP1A1 itself in the bronchial cells of marijuana smokers, but different experimental methods will be needed to establish that possibility.

Conclusions

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 is an important risk factor for the development of respiratory cancer. More definitive evidence that habitual marijuana smoking leads or does not lead to respiratory cancer awaits the results of well-designed case control epidemiological studies. It has been 30 years since the initiation of widespread marijuana use among young people 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, findings from the biochemical, cellular, immunological, genetic, tissue, and animal studies cited above strongly suggest that marijuana is a risk factor for human cancer. What is required to address that hypothesis more convincingly is a population-based case control study of sufficiently large numbers of people with lung cancer and upper aerodigestive tumors (cancers of the oral cavity and pharynx, larynx, and esophagus), as well as noncancer controls, to demonstrate a statistically significant association, if one exists. Because of the long period required for induction of human carcinomas and the infrequent use of marijuana in the general U.S. population before 1966, no epidemiological studies so far have been extensive enough to measure the

association between marijuana and cancer adequately. However, epidemiological investigation of this association is probably possible now in that some 30 years have elapsed since the start of widespread marijuana use in the United States 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, studies would be warranted to explore the presence of molecular markers—such as TP53, p16, NATZ, and GSTML—that could be predictive of genetically increased risk of carcinogenesis in marijuana users.

3. **Prospective epidemiological studies of populations with HIV seropositivity or at high risk for HIV infection.*** Because HIV/AIDS patients constitute the 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 posed by and the 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 or progression to AIDS. The studies could be carried out in the context of any federally approved clinical trials of medical marijuana in immunocompromised patients and should provide a follow-up period long enough to capture 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.[102] 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 the effects of THC and marijuana on immune function.** The effects studied should include 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

*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.

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 nonusers or infrequent marijuana users. Cell culture studies could be used to compare the 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 effects of exposure to THC on HIV infectivity and replication.

Cardiovascular System

Marijuana smoke and oral THC can cause tachycardia (rapid heart beat) in humans, 20–100% above baseline.[57,85] 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 is used, this can last three or five hours, respectively.[68,95] In some cases, blood pressure increases while a person is in a reclining position but decreases inordinately on standing, resulting in postural hypotension (decreased blood pressure due to changing posture from a lying or sitting position to a standing position, which can cause dizziness and faintness). In contrast with acute administration of THC, chronic oral ingestion of THC reduces heart rate in humans.[13]

In animals, THC decreases heart rate and blood pressure.[57,156] However, most of the animal studies have been conducted in anesthetized 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.[156]

Tolerance can appear after a few days of frequent daily administration (two or three doses per day) of oral THC or marijuana extract, with heart rate decreasing, reclining blood pressure falling, and postural hypotension disappearing.[73] Thus, the intensity of the effects depends on frequency of use, dose, and even body position.

The cardiovascular changes have not posed 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 arterial or cerebrovascular disease. Cardiovascular diseases are the leading causes of death in the United States (coronary heart disease is first; stroke is third), so any effect of mari-

juana use on cardiovascular disease could have a substantial impact on public health (S. Sidney, IOM workshop). The magnitude of the impact remains to be determined as chronic marijuana users from the late 1960s enter the age when coronary arterial and cerebrovascular diseases become common. Smoking marijuana is also known to decrease maximal exercise performance. That, with the increased heart rate, could theoretically induce angina (S. Sidney, IOM workshop), so, 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.

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.[107,159] Studies have consistently shown that injections of THC result in rapid, dose-dependent suppression of serum luteinizing hormone (LH).[70] (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 that marijuana use will interfere with human reproduction. With few exceptions, the animal studies are based on acute treatments (single injections) or short-term treatments (THC injections given over a series of days). The results are generally observed for only several hours or in females sometimes for only one ovulatory cycle.

Acute treatments with cannabinoids—including THC, CBD, cannabinol, and anandamide—can decrease the fertilizing capacity of sea urchin sperm.[135-137] The sea urchin is only a distant relative of humans, but 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 concentrations of 6–100 μM,[136,137] which are higher than those likely to be experienced by marijuana smokers. 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 co-workers[159]). Exposure to THC shortly before or after birth can result in impaired reproductive behavior in mice when they reach adult-

hood: females are slower to show sexual receptivity, and males are slower to mount.[107]

Although THC can act directly on endocrine tissues, such as the testes and ovaries, it appears to affect reproductive physiology through its actions on the brain, somewhere other than the pituitary. Some of the effects of THC are exerted through its action on stress hormones, such as cortisol.[70]

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 of 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 men and women are similar, with the added consideration of the menstrual cycle in women; 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).[103] In brief, although there are no data on fertility itself, marijuana or THC would probably 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 with implantation of the embryo. Like tobacco smoke, marijuana smoke is highly likely to be harmful to fetal development and should be avoided by pregnant women and 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.

The results of studies of the relationship between prenatal marijuana exposure and birth outcome have been inconsistent (reviewed in 1995 by Cornelius and co-workers[30]). 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.[46,65] Mothers who smoke tobacco also give birth to lower weight babies, and the relative contributions of smoking and THC are not known from these studies.

Babies born to mothers who smoked marijuana during pregnancy

weighed an average of 3.4 ounces less than babies born to a control group of mothers who did not smoke marijuana; there was no statistically significant difference in either gestational age or frequency of congenital abnormalities.[164] Those results were based on women whose urine tests indicated recent marijuana exposure. However, when the analysis was based only on self-reports of marijuana use (without verification by urine tests), there was no difference in weight between babies born to women who reported themselves as marijuana smokers and those born to women who reported that they did not smoke marijuana. That raises an important concern about the methods used to measure the effects of marijuana smoking in any study, perhaps even more so in studies on the effects of marijuana during pregnancy, when subjects might be 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 pregnancy.)

For most of these studies, much of the harm associated with marijuana use is consistent with that associated with tobacco use, and smoking is an important 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 did or did not ingest marijuana during pregnancy, there was no difference in neurobehavioral assessments made at three days after birth and at one month.[38] A limitation of the 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 United States because less social stigma is associated with marijuana use in Jamaica but still are less reliable than direct measures.

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

Since 1978, the Ottawa Prenatal Prospective Study has measured the cognitive functions of children born to mothers who smoked marijuana during pregnancy.[47] Children of mothers who smoked either moderately (one to six marijuana cigarettes per week) or heavily (more than six marijuana cigarettes per week) have been studied from the age of 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 the deficits were no longer apparent at five years.

Prenatal marijuana exposure was not, however, without lasting effect. At ages 5–6 years and 9–12 years, children in the same study who were prenatally exposed to tobacco smoke scored lower on tests of language skills and cognitive functioning.[48] In another study,[49,50] 9 to 12 year 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 a person's ability to plan, anticipate, and suppress behaviors that are incompatible with a current goal.[50] It was reflected in how the mothers described their children. Mothers of the marijuana-exposed children were more likely to describe their offspring as hyperactive or impulsive than were mothers of control children. The 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 the 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 old), 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 is possible. Despite the uncertainty as to the underlying causes of the effects of prenatal exposure to cannabinoid drugs, it is prudent to advise against smoking marijuana during pregnancy.

SUMMARY AND CONCLUSIONS

This chapter summarizes the harmful effects of marijuana on individual users and, to a lesser extent, on society. The harmful effects on 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 evidence on harmful effects of marijuana is based on *smoked* marijuana, and, except for the psychoactive effects that can be reasonably attributed to THC, it is not possible to distinguish the drug effects from the effects of inhaling smoke from burning plant material.

For most people the primary adverse effect of *acute* marijuana use is diminished psychomotor performance; it is inadvisable for anyone under

the influence of marijuana to operate any equipment that might put the user or others in danger (such as driving or operating complex equipment). Most people can be expected to show impaired performance of complex tasks, and a minority experience dysphoria. People with or at risk of psychiatric disorders (including substance dependence) are particularly vulnerable to developing marijuana dependence, and marijuana use would be generally contraindicated for them. The short-term immunosuppressive effects are not well established; if they exist at all, they are probably not 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 outcome. 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, and people 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 in that they deliver a variable mixture of cannabinoids and a variety of other biologically active substances, not all of which are desirable or even known. Unknown substances include possible contaminants, such as fungi 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. No convincing data support that 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 the use of other medications that have abuse potential, but we acknowledge a lack of data that directly address the 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 related to the safety and efficacy of drugs for individual use; they 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 harm associated with smoking, the adverse effects of marijuana use are within the range toler-

ated for other medications. Thus, the safety issues associated with marijuana do not preclude some medical uses. But the question remains: Is it effective? That question is covered here in two chapters: chapter 2 summarizes what has been learned about the biological activity of cannabinoids in the past 15 years through research in the basic sciences, and chapter 4 reviews clinical data on the effectiveness of marijuana and cannabinoids for the treatment of various medical conditions.

Three factors influence the safety of marijuana or cannabinoid drugs for medical use: the delivery system, the use of plant material, and the side effects of cannabinoid drugs. (1) Smoking marijuana is clearly harmful, especially in people with chronic conditions, and is not an ideal drug delivery system. (2) Plants are of uncertain composition, which renders their effects equally uncertain, so they constitute an undesirable medication. (3) The side effects of cannabinoid drugs are within the acceptable risks associated with approved medications. Indeed, some of the side effects, such as anxiety reduction and sedation, might be desirable for some patients. As with many medications, there are people for whom they would probably 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 it should not be a factor in the evaluation of 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, DC: American Psychiatric Association.
3. American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th ed. Washington, DC: 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, Editors, *Substance Abuse: A Comprehensive Textbook.* 2nd ed. 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-tetrahydrocannabinol 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: CD Klaassen, MO Amdur, and J Doul, Editors, *Casarett and Doul, Toxicology: The Basic Science of Poisons.* 5th ed. 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, Editors, *Marijuana/Cannabinoids: Neurobiology and Neurophysiology.* Boca Raton, FL: CRC Press. Pp. 387–424.
24. Charalambous A, Marciniak G, Shiue CY, 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* 40:503–507.
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* 95(5):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 ed. 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. *Annals of Epidemiology* 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. *American Journal of 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*. Fehr K, Kalant H, Editors, 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 PA. 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 ed. 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, Editor, *Addiction: From Biology to Drug Policy*. New York: W.H. Freeman. Pp. 73–84.
55. Golub A, Johnson BD. 1994. The shifting importance of alcohol and marijuana as gateway substances among serious drug abusers. *Journal of Studies on Alcohol* 55:607–614.

56. 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.
57. Graham JDP. 1986. The cardiovascular action of cannabinoids. In: Mechoulam R, Editor, *Cannabinoids as Therapeutic Agents.* Boca Raton, FL: CRC Press. Pp. 159–166.
58. 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, USA* 93:12040–12045.
59. Hall W, Solowij N. 1998. Adverse effects of cannabis. *The Lancet* 352:1611–1616.
60. 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.
61. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. 1999. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology* 141:385–394.
62. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. 1999. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology* 141:395–404.
62a. Heishman SJ, Huestis MA, Henningfield JE, Cone EJ. 1990. Acute and residual effects of marijuana: Profiles of plasma THC levels, physiological, subjective, and performance measures. *Pharmacology, Biochemistry, and Behavior* 37:561-565.
63. Herha J, Obe G. 1974. Chromosomal damage in chronical users of cannabis: In vivo investigation with two-day lymphocyte cultures. *Pharmakopsychiatric* 7:328–337.
64. 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.
65. 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.
66. Hollister LE. 1986. Health aspects of cannabis. *Pharmacological Reviews* 38:1–20.
67. 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.
68. 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.
69. IOM (Institute of Medicine). 1982. *Marijuana and Health.* Washington, DC: National Academy Press.
70. 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.
71. Johnson V. 1995. The relationship between parent and offspring comorbid disorders. *Journal of Substance Abuse* 7:267–280.
72. Johnston LD, O'Malley PM, Bachman JG. 1989. Marijuana decriminalization: The impact on youth, 1975–1980. *Journal of Public Health Policy* 10:456.
73. Jones RT, Benowitz NL, Herning RI. 1981. Clinical relevance of cannabis tolerance and dependence. *Journal of Clinical Pharmacology* 21:143S–152S.
74. Jones RT, Benowitz N, Bachman J. 1976. Clinical studies of tolerance and dependence. *Annals of the New York Academy of Sciences* 282:221–239.
75. Kaklamani E, Trichopoulos D, Koutselinis A, Drouga M, Karalis D. 1978. Hashis smoking and T-lymphocytes. *Archives of Toxicology* 40:97–101.

76. 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.
77. 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.
78. 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, DC: American Psychological Association. Pp. 211–253.
79. 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.
80. Kandel DB, Raveis VH. 1989. Cessation of illicit drug use in young adulthood. *Archives of General Psychiatry* 46:109–116.
81. Kandel DB, Yamaguchi K. 1993. From beer to crack: developmental patterns of drug involvement. *American Journal of Public Health* 83:851–855.
82. Kandel DB, Yamaguchi K, Chen K. 1992. Stages of progression in drug involvement from adolescence to adulthood: Further evidence for the gateway theory. *Journal of Studies in Alcohol* 53:447–457.
83. Kaplan HB, Martin SS, Johnson RJ, Robbins CA. 1996. Escalation of marijuana use: Application of a general theory of deviant behavior. *Journal of Health and Social Behavior* 27:44–61.
84. 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.
85. Kelly TH, Foltin RW, Fischman MW. 1993. Effects of smoked marijuana on heart rate, drug ratings and task performance by humans. *Behavioural Pharmacology* 4:167–178.
86. Kendler KS, Prescott CA. 1998. Cannabis use, abuse, and dependence in a population-based sample of female twins. *American Journal of Psychiatry* 155:1016.
87. Klein TW, Friedman H, Specter SC. 1998. Marijuana, immunity and infection. *Journal of Neuroimmunology* 83:102–115.
88. Koob GF, Le Moal M. 1997. Drug abuse: Hedonic homeostatic dysregulation. *Science* 278:52–58.
89. 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.
90. Labouvie E, Bates ME, Pandina RJ. 1997. Age of first use: Its reliability and predictive utility. *Journal of Studies on Alcohol* 58:638–643.
91. 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.
92. 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.

93. 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.
94. 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.
95. 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 (Berlin)* 74:208–212.
96. Linzen DH, Dingemans PM, Lenior ME. 1994. Cannabis abuse and the course of recent-onset schizophrenic disorders. *Archives of General Psychiatry* 51:273–279.
97. Lyons MJ., Toomey R, Meyer JM, Green AI, Eisen SA, Goldberg J, True WR, Tsuang MT. 1997. How do genes influence marijuana use? The role of subjective effects. *Addiction* 92:409–417.
98. MacCoun R, Reuter P. 1997. Interpreting Dutch cannabis policy: Reasoning by analogy in the legalization debate. *Science* 278:47–52.
99. 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.
100. 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.
101. 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.
102. Mathre ML. 1998. A survey on disclosure of marijuana use to health care professionals. *Journal of Psychoactive Drugs* 20:117–120.
103. 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.
104. 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.
105. 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.
106. 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.
107. 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.
108. Nahas GG, Osserman EF. 1991. Altered serum immunoglobulin concentration in chronic marijuana smokers. *Advances in Experimental Medicine and Biology* 288:25–32.
109. Nesse RM, Berridge KC. 1997. Psychoactive drug use in evolutionary perspective. *Science* 278:63–66.
110. Nestler EJ, Aghajanian GK. 1997. Molecular and cellular basis of addiction. *Science* 278:58–63.
111. 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.

112. 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 of Experts. Bethesda, MD, February 19–20, 1997. Bethesda, MD: National Institutes of Health.
113. O'Brien CP. 1996. Drug addiction and drug abuse. In: Harmon JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, Editor, *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 9th ed. New York: McGraw-Hill. Pp. 557–577.
114. O'Brien CP. 1996. Recent developments in the pharmacotherapy of substance abuse. *Journal of Consulting and Clinical Psychology* 64:677–686.
115. O'Brien CP. 1997. A range of research-based pharmacotherapies for addiction. *Science* 278:66–70.
116. 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.
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, November 7-12, 1998. Washington, DC: Society for Neuroscience.
118. Ohlsson A, Lindgren J-E, Wahlen A, Agurell S, Hollister LE, 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. Peterson RC. 1979. Importance of inhalation patterns in determining effects of marijuana use. *Lancet* 1:727–728.
120. 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.
121. 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.
122. 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.
123. 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.
124. Rickles Jr WH, Cohen MJ, Whitaker CA, McIntyre KE. 1973. Marijuana-induced state-dependent verbal learning. *Psychopharmacologia* 30:349–354.
125. Robins LN. 1980. The natural history of drug abuse. *Acta Psychiatrica Scandinavica Supplement* 284:7–20.
126. Robins LN. 1998. The intimate connection between antisocial personality and substance abuse. *Social Psychiatry and Psychiatric Epidemiology* 33:393–399.
127. Robins LN, McEvoy LT. 1990. Conduct problems as predictors of substance abuse. In: Robins L, Rutter M, Editors, *Straight and Devious Pathways from Childhood to Adulthood.* New York: Cambridge University Press. Pp. 182–204.
128. 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.
129. Rosenzweig MR, Leiman AL, Breedlove SM. 1996. *Biological Psychology*. Sunderland, MA: Sinauer Associates.

130. 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.
131. 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.
132. 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.
133. Scheier LM, Bovtin GJ. 1996. Cognitive effects of marijuana. *Journal of the American Medical Association* 275:JAMA Letters.
134. Schneier FR, 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.
135. 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.
136. 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.
137. 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.
138. Sidney S, Beck JE, Tekawa IS, Quesenberry CP Jr, Friedman GD. 1997a. Marijuana use and mortality. *American Journal of Public Health* 87:585–590.
139. 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.
140. Solowij N. 1995. Do cognitive impairments recover following cessation of cannabis use? *Life Sciences* 56:2119–2126.
141. 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.
142. Stenchever MA, Kunysz TJ, Allen MA. 1974. Chromosome breakage in users of marijuana. *American Journal of Gynecology* 118:106–113.
143. Stephens RS, Roffman RA, Simpson EE. 1993. Adult marijuana users seeking treatment. *Journal of Consulting and Clinical Psychology* 61:1100–1104.
144. 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.
145. Tart CT. 1971. *On Being Stoned: A Psychological Study of Marijuana Intoxication*. Palo Alto, CA: Science and Behavior Books.
146. Tashkin DP, Coulson AH, Clark VA, Simmons M, Bourque LB, Duann S, Spivey GH, 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.
147. 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.

148. Tashkin E. 1999. Effects of marijuana on the lung and its defenses against infection and cancer. *School Psychology International* 20:23–37.
149. Taylor FM. 1988. Marijuana as a potential respiratory tract carcinogen: A retrospective analysis. *Southern Medical Journal* 81:1213–1216.
150. Tennant FS. 1980. Histopathologic and clinical abnormalities of the respiratory system in chronic hashish smokers. *Substance and Alcohol Actions/Misuse* 1:93–100.
151. Thornicroft G. 1990. Cannabis and psychosis: Is there epidemiological evidence for an association? *British Journal of Psychiatry* 157:25–33.
152. 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.
153. 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.
154. Van Hoozen BE, Cross CE. 1997. Respiratory tract effects of marijuana. *Clinical Reviews in Allergy and Immunology* 15:243–269.
155. 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.
156. Wagner JA, Varga K, Kunos G. 1998. Cardiovascular actions of cannabinoids and their generation during shock. *Journal of Molecular Medicine* 76:824–836.
157. 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.
158. 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.
159. Wenger T, Croix D, Tramu G, Leonardelli J. 1992. Effects of delta-9-tetrahydrocannabinol on pregnancy, puberty, and the neuroendocrine system. In: Murphy L, Bartke A, Editors, *Marijuana/Cannabinoids: Neurobiology and Neurophysiology*. Boca Raton, FL: CRC Press.
160. White SC, Brin SC, Janicki BW. 1975. Mitogen-induced blastogenic responses of lymphocytes from marijuana smokers. *Science* 188:71–72.
161. Whitfield RM, Bechtel LM, Starich GH. 1997. The impact of ethanol and marinol/marijuana usage on HIV+/AIDS patients undergoing azidothymidine, azidothymidine/dideoxycytidine, ordideoxyinosine therapy. *Alcoholism Clinical and Experimental Research* 21:122–127.
162. 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.
163. 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.
164. 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.

4

The Medical Value of Marijuana and Related Substances

During the course of drug development, a typical compound is found to have some medical benefit and then extensive tests are undertaken to determine its safety and proper dosage for medical use. In contrast, marijuana has been widely used in the United States for decades.[162] In 1996, 68.6 million people—32% of the U.S. population over 12 years old—had tried marijuana or hashish at least once; 5% were current users.[162]

The data on the adverse effects of marijuana are more extensive than the data on its effectiveness. Clinical studies of marijuana are difficult to conduct: researchers interested in clinical studies of marijuana face a series of barriers, research funds are limited, and there is a daunting thicket of regulations to be negotiated at the federal level (those of the Food and Drug Administration, FDA, and the Drug Enforcement Agency, DEA) and state levels (see chapter 5). Consequently, the rapid growth in basic research on cannabinoids contrasts with the paucity of substantial clinical studies on medical uses.

This chapter is devoted to an analysis of the therapeutic value of marijuana and cannabinoids for specific symptoms associated with various conditions. The risks associated with the medical use of marijuana are discussed in chapter 3. It should be noted that THC, the primary active ingredient in marijuana, is an FDA-approved drug referred to as dronabinol and marketed as Marinol. Marijuana is advocated primarily for relief from the symptoms of disease rather than as a cure.

For the most part, the logical categories for the medical use of mari-

juana are not based on particular diseases but on symptoms—such as nausea, appetite loss, or chronic pain—each of which can be caused by various diseases or even by treatments for diseases. This chapter is therefore organized by symptoms rather than by diseases. There are eight sections. The first section explains clinical trials, the following five deal with specific symptoms and conditions, and the last two summarize the medical benefits of marijuana and cannabinoids. The five sections on symptoms and conditions are as follows: pain, nausea and vomiting, wasting syndrome and appetite stimulation, neurological symptoms (including muscle spasticity), and glaucoma.

The Institute of Medicine (IOM) study team received reports of more than 30 different medical uses of marijuana, more than could be carefully reviewed in a report of this length; even more uses are reported elsewhere.[62,63] For most of the infrequently mentioned medical uses of marijuana there are only a few anecdotal reports. This report reviews only the most prominent symptoms that are reportedly relieved by marijuana. However, many of those diseases not reviewed here share common symptoms, such as pain, nausea and vomiting, and muscle spasms, which might be relieved by cannabinoid drugs.

STANDARDS FOR EVALUATING CLINICAL TRIALS

Before evaluating individual clinical trials concerning the efficacy and safety of medical uses of marijuana and cannabinoids, it is useful to review the general qualities of clinical trials. Clinical trials involve groups of individuals in which different treatments are compared among different groups. Such trials measure the efficacy of a medication and are required by the FDA for approval of any new drug or new use of a drug (discussed further in chapter 5).

The degree of assurance that the outcome of a clinical trial is due to the treatment being tested depends on how well the trial is designed. Three important factors to consider in evaluating the design of a clinical trial are sample selection, subjective effects, and effects that are independent of the treatment. For *sample selection* it is important to ensure that patients are allocated to different treatment groups in such a way that the groups are not biased toward a particular treatment outcome. For example, the health status, gender, and ages of different treatment groups should be equivalent. *Subjective effects* must be controlled because they influence experimental results in two important ways. First, a patient's expectation that a treatment will be effective can influence the degree of its effect (for example, in the control of nausea). Second, the investigator's expectation can influence his or her interpretation of the treatment effect (for example, when assessing the level of pain experienced by a patient).

For these reasons, double blinding, in which neither the subject nor the person who assesses the drug's effect is aware of the subject's treatment group, is particularly important in cannabinoid drug studies. Another important control for subjective effects includes the use of placebo drugs, which are inert substances, or the use of comparison drugs that have effects similar to the experimental drug. Finally, the quality of the experimental design depends on controlling for factors that are unrelated to the test drug but that might nonetheless influence the treatment outcome. S*equencing effects* are one example of such factors. For example, patients might react differently to the same medication depending on whether the medication was administered after an effective or an ineffective treatment. Likewise, a patient whose symptoms are initially mild might react differently to a drug than would a patient whose symptoms are initially severe. Because psychological effects are associated with cannabinoid drugs, it is important to consider how such side effects might influence the therapeutic value of the treatment. Conditions such as pain and nausea are especially susceptible to subjective influences. For example, depending on the person, THC can reduce or increase anxiety; it is important to determine to what extent this "side effect" contributes to the therapeutic effect.

While double-blind, randomized, controlled clinical trials offer the highest degree of assurance of drug efficacy, such trials are not always feasible. Vulnerable populations, such as children, older patients, and women of child-bearing age, are often excluded from experimental drug trials for safety reasons. Nonetheless, such patients are part of everyday clinical practice. The challenge of integrating the ideal of standardized and rigorous processes for treatment evaluation with everyday clinical practice has encouraged interest in single-patient trials.[67] Methods for such trials have been established and tested in a variety of clinical settings, usually under everyday conditions.[66,105,159] They are particularly valuable when physicians or patients are uncertain about the efficacy of treatment for symptomatic diseases. Controls can be incorporated even in this kind of trial. Such trials can be double blinded and can involve crossover designs in which the patient is treated with alternating treatments, such as placebo-drug-placebo or one drug followed by another drug. As with any other clinical trial, a single-patient trial should be designed to permit objective comparison between treatments.

ANALGESIA

Pain is the most common symptom for which patients seek medical assistance.[5] Pain associated with structural or psychophysiological disorders can arise from somatic, visceral, or neural structures. *Somatic pain* results from activation of receptors outside the brain and is transmitted to

the brain via peripheral nerves. *Visceral pain* results from activation of specific pain receptors in the intestine (visceral nociceptive receptors); it is characterized as a deep aching or cramping sensation, but its source is often experienced at sites remote from the site of receptor activation, a phenomenon known as referred pain. *Neuropathic pain* results from injury to peripheral receptors, nerves, or the central nervous system; it is typically burning, the skin feels abnormally unpleasant when gently touched (dysesthesia), and it often occurs in an area of sensory loss, as in the case of postherpetic neuralgia (shingles).

All of the currently available analgesic (pain-relieving) drugs have limited efficacy for some types of pain. Some are limited by dose-related side effects and some by the development of tolerance or dependence. A cannabinoid, or other analgesic, could potentially be useful under any of the following circumstances:

- There is a medical condition for which it is more effective than any currently available medication.
- It has a broad clinical spectrum of efficacy and a unique side effect profile.
- It has synergistic interactions with other analgesics.
- It exhibits "side effects" that are considered useful in some clinical situations.
- Its efficacy is enhanced in patients who have developed tolerance to opioids.

There have not been extensive clinical studies of the analgesic potency of cannabinoids, but the available data from animal studies indicate that cannabinoids could be useful analgesics. In general, cannabinoids seem to be mild to moderate analgesics. Opiates, such as morphine and codeine, are the most widely used drugs for the treatment of acute pain, but they are not consistently effective in chronic pain; they often induce nausea and sedation, and tolerance occurs in some patients. Recent research has made it clear that CB_1 receptor agonists act on pathways that partially overlap with those activated by opioids but through pharmacologically distinct mechanisms (see chapter 2). Therefore, they would probably have a different side effect profile and perhaps additive or synergistic analgesic efficacy.

In light of the evidence that cannabinoids can reduce pain in animals, it is important to re-evaluate the evidence of analgesic efficacy in humans and to ask what clinical evidence is needed to decide whether cannabinoids have any use in the treatment of pain.

Clinical Studies of Cannabinoids

There have been three kinds of studies of the effects of cannabinoids on pain in human volunteers: studies of experimentally induced acute pain, studies of postsurgical acute pain, and studies of chronic pain. Overall, there have been very few studies—only one since 1981—and they have been inconclusive.

Experimentally Induced Acute Pain

Early studies of cannabinoids on volunteers did not demonstrate consistent analgesia when experimental pain models were used. In fact, three early volunteer studies of THC and experimental pain caused by a variety of pain modalities—electrical stimulation, tourniquet pain, and thermal pain—resulted in an *increase* in pain sensitivity (hyperalgesia).[22,84,108]

Other studies also failed to show an analgesic effect of THC, but they were not well designed. Raft and co-workers found no evidence of THC effect on pain thresholds and pain tolerance following electrical stimulation and noxious pressure.[150] But their study suffers from two major methodological problems. First, they measured only the extremes of pain sensation—*threshold* (the lowest intensity at which a particular stimulus is perceived as painful) and *tolerance* (the maximum intensity of pain that a subject can withstand). However, most pain is experienced in an intermediate range, where effects on pain suppression are most detectable. Modern methods of pain assessment in humans typically use ratings of the intensity of the sensation of pain; those methods are superior to assessing the effects of a drug on the extremes of pain.[192] Second, Raft and co-workers did not include a positive control; that is, they did not demonstrate the adequacy of their method by showing that an established analgesic, such as an opiate or narcotic, was effective under their study conditions.

Clark and co-workers[22] tested the effect of smoked marijuana on thermal pain in volunteers and failed to observe an analgesic effect. However, because of the study design, the results are inconclusive. First, there was no positive control to demonstrate the adequacy of their methods; second, the study subjects were habitual marijuana users. During the study, they were hospitalized and allowed free access to marijuana cigarettes for a period of four weeks, consuming an average of four to 17 marijuana cigarettes per day. Pain was tested "approximately every one to two weeks." Thus, it is quite likely that the subjects were tolerant to THC at the time of testing.

Surgical Acute Pain

Raft and co-workers[150] found no analgesic effect of THC on surgical pain induced by tooth extraction. However, that study suffered from several serious limitations: the tooth extraction included treatment with the local anesthetic lidocaine, the pain during the procedure was assessed 24 hours later, and there was no positive control. Levonantradol (a synthetic THC analogue) was tested in 56 patients who had moderate to severe postoperative or trauma pain.[89] They were given intramuscular injections of levonantrodol or placebo 24 hours after surgery. To control for previous drug exposure, patients with a history of drug abuse or addiction and those who received an analgesic, antiinflammatory, tranquilizer, sedative, or anesthetic agent within 24 hours of the test drug were excluded from the study. On average, pain relief was significantly greater in the levonantradol-treated patients than in the placebo-treated patients. Because the authors did not report the number or percentage of people who responded, it is not clear whether the average represents consistent pain relief in all levonantradol-treated patients or whether some people experienced great relief and a few experienced none.

Chronic Pain

The most encouraging clinical data on the effects of cannabinoids on chronic pain are from three studies of cancer pain. Cancer pain can be due to inflammation, mechanical invasion of bone or other pain-sensitive structure, or nerve injury. It is severe, persistent, and often resistant to treatment with opioids. In one study, Noyes and co-workers found that oral doses of THC in the range of 5–20 mg produced analgesia in patients with cancer pain.[139,140] The first experiment was a double-blind, placebo-controlled study of 10 subjects and measured both pain intensity and pain relief.[140] Each subject received all drug treatments: placebo and 5, 10, 15, and 20 mg of THC in pill form; each pill was identical in appearance and given on successive days. The 15- and 20-mg doses of THC produced significant analgesia. There were no reports of nausea or vomiting. In fact, at least half the patients reported increased appetite. With a 20-mg dose of THC, patients were heavily sedated and exhibited "depersonalization," characterized by a state of dreamy immobility, a sense of unreality, and disconnected thoughts. Five of 36 patients exhibited adverse reactions (extreme anxiety) and were eliminated from the study. Only one patient experienced this effect at the 10-mg dose of THC. The mean age of the patients was 51 years, and they were probably not experienced marijuana smokers. A limitation of this study is that there were no positive con-

trols—that is, other analgesics that could provide a better measure of the degree of analgesia produced by THC.

In a later larger single-dose study, the same investigators reported that the analgesic effect of 10 mg of THC was equivalent to that of 60 mg of codeine; the effect of 20 mg of THC was equivalent to that of 120 mg of codeine.[139] (Note that codeine is a relatively weak analgesic.) The side effect profiles were similar, though THC was more sedating than codeine. In a separate publication the same authors published data indicating that patients had improved mood, a sense of well-being, and less anxiety.[139]

The results of the studies mentioned above on cancer pain are consistent with the results of using a nitrogen analogue of THC. Two trials were reported: one compared this analogue with codeine in 30 patients, and a second compared it with placebo or secobarbital, a short-acting barbiturate.[175] For mild, moderate, and severe pain, the THC analogue was equivalent to 50 mg of codeine and superior to placebo and to 50 mg of secobarbital.

Case Reports and Surveys

The few case reports of clinical analgesia trials of cannabinoids are not convincing.[85,120] There are, however, anecdotal surveys that raise the possibility of a role for cannabinoids in some patients who have chronic pain with prominent spasticity. A recent survey of over 100 patients with multiple sclerosis reported that a large number obtained relief from spasticity and limb pain (discussed further under the section on multiple sclerosis).[28] Several said that it relieved their phantom pain and headache.[41]

Migraine Headaches

There is clearly a need for improved migraine medications. Sumatriptan (Imitrex) is the best available medication for migraine headaches, but it fails to abolish migraine symptoms in about 30% of migraine patients.[118,147] Marijuana has been proposed numerous times as a treatment for migraine headaches, but there are almost no clinical data on the use of marijuana or cannabinoids for migraine. Our search of the literature since 1975 yielded only one scientific publication on the subject. It presents three cases of cessation of daily marijuana smoking followed by migraine attacks—not convincing evidence that marijuana relieves migraine headaches.[43] The same result could have been found if migraine headaches were a consequence of marijuana withdrawal. While there is no evidence that marijuana withdrawal is followed by migraines, when analyzing the strength of reports such as these it is important to consider

all logical possibilities. Various people have claimed that marijuana relieves their migraine headaches, but at this stage there are no conclusive clinical data or published surveys about the effect of cannabinoids on migraine.

However, a possible link between cannabinoids and migraine is suggested by the abundance of cannabinoid receptors in the periaqueductal gray (PAG) region of the brain. The PAG region is part of the neural system that suppresses pain and is thought to be involved in the generation of migraine headaches.[52] The link or lack thereof between cannabinoids and migraine might be elucidated by examining the effects of cannabinoids on the PAG region.[110] Recent results indicating that both cannabinoid receptor subtypes are involved in controlling peripheral pain[15] suggest that the link is possible. Further research is warranted.

Conclusions: Analgesia

A key question to address is whether there is any receptor selectivity for the analgesic efficacy of cannabinoids. Are the unwanted side effects (amnesia and sedation) caused by the same receptors in the same brain regions as those producing the analgesia? If the answer is *yes*, enhancing efficacy will not solve the problem of sedation. Similarly, are the pleasant side effects due to an action at the same receptor? Can the feelings of well-being and appetite stimulation be separated by molecular design? Recent results indicating that both cannabinoid receptor subtypes are independently involved in controlling peripheral pain[15] (discussed in chapter 2) strongly suggest that this is possible and that further research is warranted.

Further research into the basic circuitry underlying cannabinoid analgesia should be valuable. The variety of neural pathways that underlie the control of pain suggests that a synergistic analgesia "cocktail" would be effective. For example, Lichtman and Martin have shown the involvement of an $\alpha 2$ adrenoreceptor in cannabinoid analgesia.[111] Perhaps a combination of a CB_1 agonist and an $\alpha 2$ agonist (such as clonidine) would provide enhanced analgesia with less severe side effects.

Clinical studies should be directed at pain patients for whom there is a demonstrated need for improved management and where the particular side effect profile of cannabinoids promises a clear benefit over current approaches. The following patient groups should be targeted for clinical studies of cannabinoids in the treatment of pain:

- Chemotherapy patients, especially those being treated for the mucositis, nausea, and anorexia.

- Postoperative pain patients (using cannabinoids as an opioid adjunct to determine whether nausea and vomiting from opioids are reduced).
- Patients with spinal cord injury, peripheral neuropathic pain, or central poststroke pain.
- Patients with chronic pain and insomnia.
- AIDS patients with cachexia, AIDS neuropathy, or any significant pain problem.

In any patient group an essential question to be addressed is whether the analgesic efficacy of opioids can be augmented. The strategy would be to find the ceiling analgesic effect with an opioid (as determined by pain intensity and tolerability of side effects) and then add a cannabinoid to determine whether additional pain relief can be obtained. That would begin the investigation of potential drug combinations. As with any clinical study on analgesic drugs, it will be important to investigate the development of tolerance and physical dependence; these are not themselves reasons to exclude the use of cannabinoids as analgesics, but such information is essential to the management of many drugs that are associated with tolerance or physical dependence.

A secondary question would be whether THC is the only or the best component of marijuana for analgesia. How does the analgesic effect of the plant extract compare with that of THC alone? If there is a difference, it will be important to identify the combinations of cannabinoids that are the most effective analgesics.

In conclusion, the available evidence from animal and human studies indicates that cannabinoids can have a substantial analgesic effect. One exception is the lack of analgesic effect in studies on experimentally induced acute pain, but because of limitations in the design of those studies they were inconclusive. Further clinical work is warranted to establish the magnitude of the effect in different clinical conditions and to determine whether the effect is sustained. Although the usefulness of cannabinoids appears to be limited by side effects, notably sedation, other effects such as anxiolysis, appetite stimulation, and perhaps antinausea and antispasticity effects should be studied in randomized, controlled clinical trials. These very "special" effects might warrant development of cannabinoid drugs for particular clinical populations.

NAUSEA AND VOMITING

Nausea and vomiting (emesis) occur under a variety of conditions, such as acute viral illness, cancer, radiation exposure, cancer chemotherapy, postoperative recovery, pregnancy, motion, and poisoning. Both

are produced by excitation of one or a combination of triggers in the gastrointestinal tract, brain stem, and higher brain centers (Figure 4.1, Emesis-stimulating pathways).[127] There are numerous cannabinoid receptors in the nucleus of the solitary tract, a brain center that is important in the control of emesis.[79,80] Although the same mechanisms appear to be involved in triggering both nausea and vomiting, either can occur without the other. Much more is known about the neural mechanisms that produce vomiting than about those that produce nausea, in large part because vomiting is a complex behavior involving coordinated changes in the gastrointestinal tract, respiratory muscles, and posture, whereas nausea is a sensation involving primarily higher brain centers and lacks a discrete observable action.[104,128] Most reports on the antiemetic effects of marijuana or cannabinoids are based on chemotherapy-induced emesis; they are the subject of the following section.

Chemotherapy-Induced Nausea and Vomiting

The use of effective chemotherapeutic drugs has produced cures in some malignancies and retarded the growth of others, but nausea and

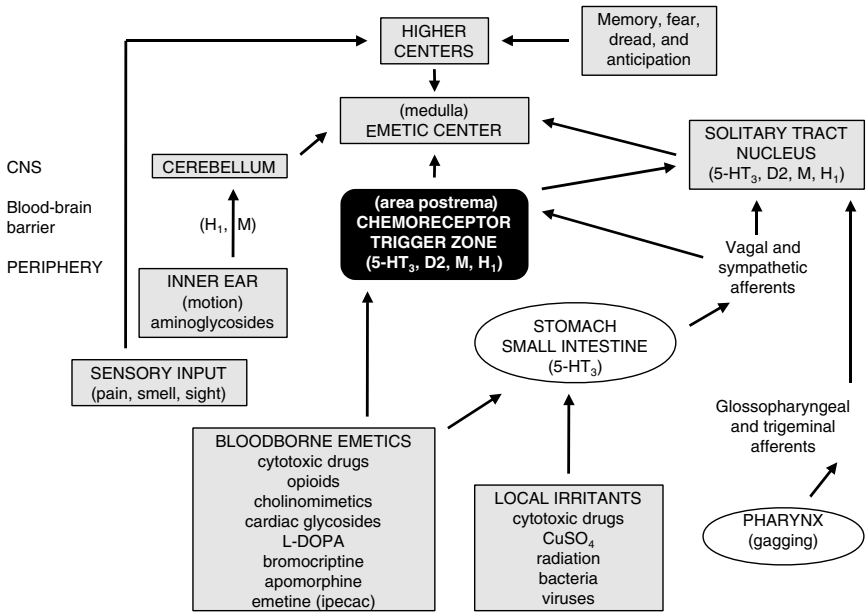


FIGURE 4.1 Emesis-stimulating pathways. SOURCE: Bruton, L.L. 1996. P. 929 in Hardman et al., eds., *The Pharmacological Basis of Therapeutics*, 9th edition. New York: McGraw-Hill. Reprinted with permission.

vomiting are frequent side effects of these drugs. Nausea ranks behind only hair loss as a concern of patients on chemotherapy, and many patients experience it as the worst side effect of chemotherapy. The side effects can be so devastating that patients abandon therapy or suffer diminished quality of life. As a result, the development of effective strategies to control the emesis induced by many chemotherapeutic agents is a major goal in the supportive care of patients with malignancies.

The mechanism by which chemotherapy induces vomiting is not completely understood. Studies suggest that emesis is caused by stimulation of receptors in the central nervous system or the gastrointestinal tract. This stimulation appears to be caused by the drug itself, a metabolite of the drug, or a neurotransmitter.[6,12,35] In contrast with an emetic like apomorphine, there is a delay between the administration of chemotherapy and the onset of emesis. This delay depends on the chemotherapeutic agent; emesis can begin anywhere from a few minutes after the administration of an agent like mustine to an hour for cisplatin.[12]

The most desirable effect of an antiemetic is to control emesis completely, which is currently the primary standard in testing new antiemetic agents (R. Gralla, IOM workshop). Patients recall the number of emetic episodes accurately, even if their antiemetics are sedating or affect memory;[101] thus, the desired end point of complete control is also a highly reliable method of evaluation. The degree of nausea can be estimated through the use of established visual analogue scales.*[21,55,101]

Another consideration in using antiemetic drugs is that the frequency of emesis varies from one chemotherapeutic agent to another. For example, cisplatin causes vomiting in more than 99% of patients who are not taking an antiemetic (with about 10 vomiting episodes per dose), whereas methotrexate causes emesis in less than 10% of patients.[55,82,83] Among chemotherapeutic agents, cisplatin is the most consistent emetic known and has become the benchmark for judging antiemetic efficacy. Antiemetics that are effective with cisplatin are at least as effective with other chemotherapeutic agents. Controlling for the influence of prior chemotherapy and balancing predisposing factors such as, sex, age, and prior heavy alcohol use among study groups are vital for reliability. Reliable randomization of patients and blinding techniques (easier when there are no psychoactive effects) are also necessary to evaluate the control of vomiting and nausea.

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*The *visual analogue scale* is a continuous line representing all possible levels of a particular sensation. It is an estimation of a patient's subjective evaluation and not a true measurement. Patients select a point anywhere on the line to demonstrate the level of sensation they are experiencing, with one end representing one extreme, such as no sensations, and the other end representing the opposite extreme, such as a maximum level of that sensation.

THC and Marijuana Therapy for Chemotherapy-Induced Nausea and Vomiting

Cannabinoids are mildly effective in preventing emesis in some patients who are receiving cancer chemotherapy. Several cannabinoids have been tested as antiemetics, including THC (both Δ^9-THC and Δ^8-THC) and the synthetic cannabinoids nabilone and levonantradol. Smoked marijuana has also been examined.

Antiemetic Properties of THC

The quality and usefulness of antiemetic studies depend on adherence to the methodological considerations outlined above. Many of the reported clinical experiences with cannabinoids are not based on definitive experimental methods. In studies that compared THC with a placebo, THC was usually found to possess antiemetic properties. However, the chemotherapeutic drug varied in most trials, and some studies included small numbers of patients. In one study THC was found to be superior to a placebo in patients receiving methotrexate, an agent that is not a strong emetic.[18] When the same investigators studied THC in a small number of patients who were receiving a chemotherapeutic drug that is more likely to cause emesis than anthracycline, the antiemetic effect was poor.[19]

Other trials were designed to compare THC with that of Compazine (prochlorperazine).[143,160] In the 1980s, prochlorperazine was one of the more effective antiemetics available, but it was not completely satisfactory, and the search for better agents continued. THC and prochlorperazine given orally showed similar degrees of efficacy, but the studies often used various chemotherapeutic agents. Even when administered in combination, THC and prochlorperazine failed to stop vomiting in two-thirds of patients.[50]

In a carefully controlled double-blind study comparing THC with the antiemetic drug metoclopramide, in which no patient had previously received chemotherapy and in which anticipatory emesis was therefore not a factor, all patients received the same dose of cisplatin and were randomly assigned to the THC group or the metoclopramide group. Complete control of emesis occurred in 47% of those treated with metoclopramide and 13% of those treated with THC.[58] Major control (two or fewer episodes) occurred in 73% of the patients given metoclopramide compared to 27% of those given THC. There were many flaws in experimental methods, but those results suggest that THC has some, but not great, efficacy in reducing chemotherapy-induced emesis.[18,19,50,161] The studies also indicate that the degree of efficacy is not high. In 1985, the

FDA approved THC in the form of dronabinol for this treatment (discussed in chapter 5).

The THC metabolite, 11-OH-THC, is more psychoactive than THC but is a weaker antiemetic.[121] Thus, it might be possible to design antiemetic cannabinoids without the psychological effects associated with marijuana or THC. Δ^8-THC is less psychoactive than THC[151] but was found to completely block both acute and delayed chemotherapy-induced emesis in a study of eight children, ages 3–13 years.* Two hours before the start of each cancer treatment and every six hours thereafter for 24 hours, the children were given Δ^8-THC as oil drops on the tongue or in a bite of bread (18 mg/m^2 body surface area). The children received a total of 480 treatments. The only side effects reported were slight irritability in two of the youngest children (3.5 and 4 years old). Based on the prediction that the THC-induced anxiety effects would be less in children than in adults, the authors used doses that were higher than those recommended for adults (5–10 mg/m^2 body surface area).

Antiemetic Properties of Synthetic THC Analogues

Nabilone (Cesamet) and levonantradol were tested in various settings; the results were similar to those with THC. Efficacy was observed in several trials, but no advantage emerged for these agents.[176,185] As in the THC trials, nabilone and levonantradol reduced emesis but not as well as other available agents in moderately to highly emetogenic settings. Neither is commercially available in the United States.

Antiemetic Properties of Marijuana

Among the efforts to study marijuana was a preliminary study conducted in New York state on 56 cancer patients who were unresponsive to conventional antiemetic agents.[188] The patients were asked to rate the effectiveness of marijuana compared with results during prior chemotherapy cycles. In this survey, 34% of patients rated marijuana as moderately or highly effective. The authors concluded that marijuana had antiemetic efficacy, but its relative value was difficult to determine because no control group was used and the patients varied with respect to previous experiences, such as marijuana use and THC therapy.

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*Note that the authors of this study chose to use Δ^8-THC because it is more stable and easier to produce than Δ^9-THC; it does not follow from this particular study that marijuana, with its mixture of cannabinoids, should be a more powerful antiemetic than Δ^9-THC.

A Canadian oncology group conducted a double-blind, cross-over, placebo-controlled study comparing smoked marijuana with THC in pill form in 20 patients who were receiving various chemotherapeutic drugs.[107] The degree of emetic control was similar: only 25% of patients achieved complete control of emesis; 35% of the patients indicated a slight preference for the THC pills over marijuana, 20% preferred marijuana, and 45% expressed no preference. [107]

Neither study showed a clear advantage for smoked marijuana over oral THC, but neither reported data on the time course of antiemetic control, possible advantages of self-titration with the smoked marijuana, or the degree to which patients were able to swallow the pills. Patients with severe vomiting would have been unlikely to be able to swallow or keep the pills down long enough for them to take effect. The onset of drug effect is much faster with inhaled or injected THC than it is for oral delivery.[87,112,141] Although many marijuana users have claimed that smoked marijuana is a more effective antiemetic than oral THC, no controlled studies have yet been published that analyze this in sufficient detail to estimate the extent to which this is the case.

Side Effects Associated with THC and Marijuana in Antiemetic Therapy

Frequent side effects associated with THC or marijuana are dizziness, dry mouth, hypotension, moderate sedation, and euphoria or dysphoria.[18,19,50,107,143,160,176,185] To patients, dry mouth and sedation are the least troubling side effects. Perhaps the most troubling side effects are orthostatic hypotension and dizziness, which could increase the patient's distress.

There is disagreement as to whether the psychoactive effects of THC correlate with its antiemetic activity. In the prospective double-blind trial comparing THC with metoclopramide, the authors reported no relationship between the occurrence of complete antiemetic control and euphoria or dysphoria.[58] Other investigators believe that the occurrence of euphoria or dysphoria is often associated with improved antiemetic control.[160] Nevertheless, there is a consensus among investigators that dysphoric effects are more common among patients who have had no prior experience with cannabinoids. An important and unexpected problem encountered in the New York state open trial with marijuana was the inability of nearly one-fourth of the patients to tolerate the administration of marijuana by smoking.[188] The intolerance could have been due to inexperience with smoking marijuana and is an important consideration.

Therapy for Chemotherapy-Induced Nausea and Vomiting

Present Therapy

New classes of antiemetics that have emerged over the past 10 years have dramatically reduced the nausea and vomiting associated with cancer chemotherapy and transformed the acceptance of cisplatin by cancer patients. The new antiemetics—including selective serotonin type 3 receptor antagonists, substituted benzamides, corticosteroids, butyrophenones, and phenothiazines—have few side effects when given over a short term and are convenient in various clinical settings.

The most effective commonly used antiemetics are serotonin receptor antagonists (ondansetron and granisetron) with or without corticosteroids.[37,56,88,145,155] In a combination trial of dexamethasone (a corticosteroid) and a serotonin antagonist, complete control of acute cisplatin-induced emesis was observed in about 75% of patients. If the chemotherapy was only moderately emetogenic, up to 90% of the patients who received the combination achieved complete control of emesis. Side effects of those antiemetic agents include headache, constipation, and alterations in liver function, but they are generally well tolerated by most patients.[13]

Other commonly used antiemetics are phenothiazines—prochlorperazine (Compazine) and haloperidol—and metoclopramide. Metoclopramide is somewhat less effective than the serotonin antagonists and has more side effects, including acute dystonic reactions, drowsiness, diarrhea, and depression.[13,37] Side effects associated with phenothiazines are severe or acute dystonic reactions, hypotension, blurred vision, drowsiness, dry mouth, urinary retention, allergic reactions, and occasional jaundice.[13]

The cost of effective antiemetic regimens can vary markedly, depending on the agent, dose, schedule, and route of administration. Overall, oral regimens cost less than intravenous regimens because of lower pharmacy and administration costs, as well as lower acquisition costs in many countries. Regimens with a cost to the pharmacy as low as about $30 to $35 per treatment session have been shown to be effective;[57] these costs are for treatment of acute emesis and delayed emesis with generic agents where available.

Although it is generally not well known by the public, major progress in controlling chemotherapy-induced acute nausea and vomiting has been made since the 1970s. Patients receiving the most difficult to control emetic agents now have no more than about a 20–30% likelihood of experiencing acute emesis,[155] whereas in the 1970s the likelihood was nearly 100% despite antiemetics.[55,86] As has been seen, most antiemetic studies with

BOX 4.1
Attitudes of Oncologists Toward Prescribing Marijuana

In the 1990s, two groups of investigators conducted three surveys on the attitudes of clinical oncologists toward prescribing marijuana as an antiemetic. These studies are arguably out of date in that the antiemetics available now are much more effective than those available when the studies were conducted. Nonetheless, the studies merit attention because they are still often cited as evidence for or against the use of marijuana as an antiemetic.

The two groups' results were contradictory. In 1994, by which time serotonin receptor antagonists (5-HT receptors) had become available, Schwartz and Beveridge[171] concluded that oncologists had little interest in prescribing marijuana to control emesis, whereas Doblin and Kleiman[39] had concluded in 1991 that interest was great. Since 1994, the two groups have debated in the literature as to which study represents the true sentiment among oncologists.[38,172,177] In fact, numerous methodological differences between the two studies might explain the different results.[38,172] Ultimately, these studies are irrelevant. Both deal with perceptions rather than pharmacological realities based on well-designed outcome studies.[177]

cannabinoids had methodological difficulties and are inconclusive. The evidence from the well-conducted trials indicate that cannabinoids reduce emesis in about one-fourth of patients receiving cancer chemotherapy. Cannabinoids are not as effective as several other classes of agents, such as substituted benzamides, serotonin receptor antagonists, and corticosteroids. The side effects associated with cannabinoid use are generally tolerable. Like cannabinoids, smoked marijuana, was apparently effective, but the efficacy was no greater than that of available antiemetic agents now considered to be marginally satisfactory. At present, the most effective antiemetic regimens are combinations of oral serotonin receptor antagonists with dexamethasone in single-dose regimens given before chemotherapy. Neither multiple-dose regimens nor intravenous antiemetics provide better control, and both add unnecessary costs.[59,81]

Future Therapy

Advances in therapy for chemotherapy-induced nausea and vomiting will require discovery of agents that work through mechanisms dif-

ferent from those of existing antiemetics, including the serotonin antagonists. Among the proposed new pathways, neurokinin-1 (NK-1) receptor antagonists appear to be the most promising. Neurokinin receptors are found in brain and intestine and are thought to be involved in motor activity, mood, pain and reinforcement. They might well be involved in mediating intestinal sensations, including nausea. In animal models, agents that block the NK-1 receptor prevent cisplatin-induced emesis. At the time of this writing, clinical trials with NK-1 receptor antagonists were under way (phase II or small phase III comparison studies). Preliminary results indicated that these agents have useful activity in both acute and delayed chemotherapy-induced emesis (that is, beginning or persisting 24 or more hours after chemotherapy) and are safe to administer orally.[102,135]

It is theoretically possible, considering that the mechanism of cannabinoid action appears to differ from that of the serotonin receptor antagonists and of corticosteroids, that THC added to more effective regimens might enhance control of emesis. Such combinations should aim to be as convenient as possible and have few additional side effects. The critical issue is not whether marijuana or cannabinoid drugs might be superior to the new drugs, but whether some group of patients might obtain added or better relief from marijuana or cannabinoid drugs.

Even with the best antiemetic drugs, the control of nausea and vomiting that begins or persists 24 hours after chemotherapy remains imperfect. The pathophysiology of delayed emesis appears different from that of acute emesis, and it is more likely to occur with a strong emetic agent, but it varies from patient to patient. Treatment to prevent this emesis requires dosing both before and after chemotherapy.[103]

Conclusions: Chemotherapy-Induced Nausea

Most chemotherapy patients are unlikely to want to use marijuana or THC as an antiemetic. In 1999, there are more effective antiemetic agents available than were available earlier. By comparison, cannabinoids are only modest antiemetics. However, because modern antiemetics probably act through different mechanisms, cannabinoids might be effective in people who respond poorly to currently used antiemetic drugs, or cannabinoids might be more effective in combination with a new drug than is either alone. For both reasons, studies of the effects of adjunctive cannabinoids on chemotherapy-induced emesis are worth pursuing for patients whose emesis is not optimally controlled with other agents.

While some people who spoke to the IOM study team described the mood-enhancing and anxiety-reducing effects of marijuana as a positive contribution to the antiemetic effects of marijuana, one-fourth of the

patients in the New York state study described earlier were unable to tolerate smoked marijuana. Overall, the effects of oral THC and smoked marijuana are similar, but there are differences. For example, in the residential studies of experienced marijuana users by Haney and co-workers, subjects reported that marijuana made them feel "mellow,"[71] whereas comparable doses of oral THC did not.[70] Such differences might be due to the different routes of delivery of THC, as well as the different mixture of cannabinoids found in the marijuana plant. As of this writing, no studies had been published that weighed the relative contributions of those different factors.

The goal of antiemetic medications is to prevent nausea and vomiting. Hence, antiemetics are typically given before chemotherapy, in which case a pill is an effective from of drug delivery. However, in patients already experiencing severe nausea or vomiting, pills are generally ineffective because of the difficulty in swallowing or keeping a pill down and slow onset of the drug effect. Thus, an inhalation (but preferably not smoking) cannabinoid drug delivery system would be advantageous for treating chemotherapy-induced nausea.

Until the development of rapid-onset antiemetic drug delivery systems, there will likely remain a subpopulation of patients for whom standard antiemetic therapy is ineffective and who suffer from debilitating emesis. It is possible that the harmful effects of smoking marijuana for a limited period of time might be outweighed by the antiemetic benefits of marijuana, at least for patients for whom standard antiemetic therapy is ineffective and who suffer from debilitating emesis. Such patients should be evaluated on a case-by-case basis and treated under close medical supervision.

WASTING SYNDROME AND APPETITE STIMULATION

Wasting syndrome in acquired immune deficiency syndrome (AIDS) patients is defined by the Centers for Disease Control and Prevention as the involuntary loss of more than 10% of baseline average body weight in the presence of diarrhea or fever of more than 30 days that is not attributable to other disease processes.[17] Anorexia (loss of appetite) can accelerate wasting by limiting the intake of nutrients. Wasting (cachexia) and anorexia are common end-stage features of some fatal diseases, such as AIDS, and of some types of metastatic cancers. In AIDS, weight loss of as little as 5% is associated with decreased survival, and a body weight about one-third below ideal body weight results in death.[99,158]

There are two forms of malnutrition: starvation and cachexia. Starvation, the deprivation of essential nutrients, results from famine or poverty, malabsorption, eating disorders such as anorexia nervosa, and so on. Star-

vation leads to metabolic adaptations that deplete body fat before losses of lean tissue. Cachexia results from tissue injury, infection, or tumor and is characterized by a disproportionate loss of lean body mass, such as skeletal muscle. The effects of starvation regardless of the cause can usually be reversed by providing food, whereas the effects of cachexia can be reversed only through control of the underlying disease and—at least for some patients—drugs that stimulate metabolism, such as growth hormone or androgenic-anabolic hormones.

Malnutrition in HIV-Infected Patients

By 1997 more than 30 million people worldwide were infected with human immunodeficiency virus (HIV), and the number is predicted to increase to almost 40 million by the year 2000.[126,186] Malnutrition is common among AIDS patients and plays an independent and important role in their prognosis.[95,100,158] Because treatment for malnutrition depends on whether it is caused by starvation or cachexia, one needs to know the effects of HIV infection on metabolic processes. The answer depends on the clinical situation and can be either or both.[94]

The development of malnutrition in HIV infection has many facets. Malnutrition in HIV-infected patients results in a disproportionate depletion of body cell mass,* total body nitrogen, and skeletal muscle mass; all are consistent with cachexia.[97,194] Body composition studies show that the depletion of body cell mass precedes the progression to AIDS (falling CD4 lymphocyte counts); this suggests that malnutrition is a consequence of the inflammatory response to the underlying viral infection, rather than a general complication of AIDS.[144] In contrast, weight loss is often episodic and related to acute complications, such as febrile opportunistic infections.[113] Mechanisms underlying wasting in HIV-infected patients depend on the stage of HIV infection and on specific associated complications.

The many reasons for decreased food intake among AIDS patients include mouth, throat, or esophageal infections or ulcers (oropharyngeal and esophageal pathology); adverse effects of medications;[196] diarrhea; enteric infection; malabsorption; serious systemic infection; focal or diffuse neurological disease; HIV enteropathy; depression; fatigue; and poverty. Nutrient malabsorption is often the result of microorganism overgrowth or infection in the intestine, especially in the later stages of AIDS.[95,157]

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*Body cell mass is the fat-free cellular mass. It is composed of the cells of the muscle and organs, plus circulating hematopoietic cells and the aqueous compartment of adipocytes. It is not fat, extracellular water, or extracellular solids (such as tendons).

Marijuana and THC for Malnutrition in HIV-Infected Patients

Despite their frequency of use, little has been published about the effectiveness of marijuana or cannabinoids for the treatment of malnutrition and wasting syndrome in HIV-infected patients. The only cannabinoid evaluated in controlled clinical studies is THC, or dronabinol. Short-term (six-week) and long-term (one-year) therapy with dronabinol was associated with an increase in appetite and stable weight, and in a previous short-term (five-week) clinical trial in five patients, dronabinol was shown to increase body fat by 1%.[8,9,179] In 1992, the FDA approved THC, under the trade name Marinol (dronabinol), as an appetite stimulant for the treatment of AIDS-related weight loss. Megestrol acetate (Megace) is a synthetic derivative of progesterone that can stimulate appetite and cause substantial weight gain when given in high doses (320–640 mg/day) to AIDS patients. Megestrol acetate is more effective than dronabinol in stimulating weight gain, and dronabinol has no additive effect when used in combination with megestrol acetate.[183] HIV/AIDS patients are the largest group of patients who use dronabinol. However, some reject it because of the intensity of neuropsychological effects, an inability to titrate the oral dose easily, and the delayed onset and prolonged duration of its action.[3] There is evidence that cannabinoids modulate the immune system (see chapter 2, "Cannabinoids and the Immune System"), and this could be a problem in immunologically compromised patients. No published studies have formally evaluated use of any of the other cannabinoids for appetite stimulation in wasting.

Anecdotes abound that smoked marijuana is useful for the treatment of HIV-associated anorexia and weight loss.[23,62] Some people report a preference for smoked marijuana over oral THC because it gives them the ability to titrate the effects, which depend on how much they inhale. In controlled laboratory studies of healthy adults, smoked marijuana was shown to increase body weight, appetite, and food intake.[47,119] Unfortunately, there have been no controlled studies of the effect of smoked marijuana on appetite, weight gain, and body composition in AIDS patients. At the time of this writing, Donald Abrams, of the University of California, San Francisco, was conducting the first clinical trial to test the safety of smoked marijuana in AIDS patients, and the results were not yet available.

A major concern with marijuana smoking in HIV-infected patients is that they might be more vulnerable than other marijuana users to immunosuppressive effects of marijuana or to the exposure of infectious organisms associated marijuana plant material (see chapter 3, "Marijuana Smoke").

Therapy for Wasting Syndrome in HIV-Infected Patients

Present Therapy

Generally, therapy for wasting in HIV-infected people focuses on appetite stimulation. Few therapies have proved successful in treatment of the AIDS wasting syndrome. The stimulant studied most is megestrol acetate, which has been shown to increase food intake by about 30% over baseline for reasons that remain unknown. Its effect in producing substantial weight gain is dose dependent, but most of the weight gained is in fat tissue, not lean body mass. Although the findings are still preliminary, anabolic compounds, such as testosterone or growth hormone, might be useful in preventing the loss of or in restoring lean body mass in AIDS patients.[10,44,64,170] Enteral and parenteral nutrition have also been evaluated and shown to increase weight, but again the increase is due more to body fat than to lean body mass.[96,98]

Encouraging advances in the antiviral treatment of HIV infection and developments in the prophylaxis of and therapy for opportunistic infections have recently changed the outlook for the long-term health of HIV-infected people. Death rates have been halved, and the frequency of serious complications, including malnutrition, has fallen markedly.[94,133]

Future Therapy

The primary focus of future therapies for wasting in HIV-infected patients is to increase lean body mass as well as appetite. Active systemic infections are associated with profound anorexia, which is believed to be mediated by cytokines that stimulate inflammation through their actions in and outside the brain.[132] Cytokine inhibitors, such as thalidomide, have been under investigation as potential treatments to increase lean body mass and reduce malnutrition. Even though cannabinoids do not appear to restore lean body mass, they might be useful as adjunctive therapy. For example, cannabinoids could be used as appetite stimulants, in patients with diminished appetite who are undergoing resistance exercises or anabolic therapy to increase lean body mass. They could also be beneficial for a variety of effects, such as increased appetite, while reducing the nausea and vomiting caused by protease inhibitors and the pain and anxiety associated with AIDS.

Considering current knowledge about malnutrition in HIV infection, cannabinoids, by themselves, will probably not constitute primary therapy for this condition but might be useful in combination with other therapies, such as anabolic agents. Specifically, the proposed mechanism of action of increasing food intake would most likely be ineffective in pro-

moting an increase in skeletal muscle mass and functional capacity—the goal in the treatment of cachexia in AIDS patients.

Malnutrition in Cancer Patients

Malnutrition compromises the quality of life of many cancer patients and contributes to the progression of their disease. About 30% of Americans will develop cancer in their lifetimes, and two-thirds of those who get cancer will die as a result of it.[5] Depending on the type of cancer, 50–80% of patients will develop cachexia and up to 50% of them will die, in part, as a result of cachexia.[11,40] The cachexia appears to result from the tumor itself, and cytokines (proteins secreted by the host during an immune response to tumor) are probably important factors in this development. Cachexia does not occur in all cancer patients, but generally occurs in the late stages of advanced cancer of the pancreas, lung, and prostate.

The only cannabinoid evaluated for treating cachexia in cancer patients is dronabinol, which has been shown to improve appetite and promote weight gain.[54] Present treatments for cancer cachexia are similar to that for cachexia in AIDS patients. These treatments are usually indicated in late stages of advanced disease and include megestrol acetate and enteral and parenteral nutrition. Megestrol acetate stimulates appetite and promotes weight gain in cancer patients, although the gain is mostly in fat mass (reviewed by Bruera 1998[14]). Both megestrol acetate and dronabinol have dose-related side effects that can be troublesome for patients: megestrol acetate can cause hyperglycemia and hypertension, and dronabinol can cause dizziness and lethargy. Cannabinoids have also been shown to modulate the immune system (see chapter 2, "Cannabinoids and the Immune System"), and this could be contraindicated in some cancer patients (both the chemotherapy and the cancer can be immunosuppressive).

Future treatments will probably depend on the development of methods that block cytokine actions and the use of selective β2-adrenergic receptor agonists to increase muscle mass.[14,73] Treatments for cancer cachexia will also most likely need to identify individual patients' needs. Some patients might need only a cytokine inhibitor, whereas others could benefit from combined approaches, such as an appetite stimulant and β2-adrenergic receptor agonists. In this respect, such cannabinoids as THC might prove useful as part of a combination therapy as an appetite stimulant, antiemetic, analgesic, and anxiolytic, especially for patients in late stages of the disease.

Anorexia Nervosa

Anorexia nervosa, a psychiatric disorder characterized by distorted body image and self-starvation, affects an estimated 0.6% of the U.S. population, with a greater prevalence in females than males.[5] Its mortality is high, and response to standard treatments is poor.

THC appears to be ineffective in treating this disease. In one study it caused severe dysphoric reactions in three of 11 patients.[65] One possible explanation of the dysphoria is that THC increases appetite and thus intensifies the mental conflict between hunger and food refusal.[13] Furthermore, such patients might have underlying psychiatric disorders, such as schizophrenia and depression, in which cannabinoids might be hazardous (see chapter 3, "Psychological Harms").

Current treatments include psychological techniques to overcome emotional or behavioral problems and dietary intervention to reverse the malnutrition.[195] Pharmacological treatments, such as antidepressants, have been used in addition to psychotherapy but tend to lack the desired level of efficacy.[33] Recently, alterations in a gene for one of the serotonin receptors have been identified in some patients with anorexia nervosa.[45] The possibility of a genetic component suggests a pathway for the development of new drugs to treat this disease.

Conclusions: Wasting Syndrome and Appetite Stimulation

The profile of cannabinoid drug effects suggests that they are promising for treating wasting syndrome in AIDS patients. Nausea, appetite loss, pain, and anxiety are all afflictions of wasting, and all can be mitigated by marijuana. Although some medications are more effective than marijuana for these problems, they are not equally effective in all patients. A rapid-onset (that is, acting within minutes) delivery system should be developed and tested in such patients. Smoking marijuana is not recommended. The long-term harm caused by smoking marijuana makes it a poor drug delivery system, particularly for patients with chronic illnesses.

Terminal cancer patients pose different issues. For those patients the medical harm associated with smoking is of little consequence. For terminal patients suffering debilitating pain or nausea and for whom all indicated medications have failed to provide relief, the medical benefits of smoked marijuana might outweigh the harm.

NEUROLOGICAL DISORDERS

Neurological disorders affect the brain, spinal cord, or peripheral nerves and muscles in the body. Marijuana has been proposed most often

as a source of relief for three general types of neurological disorders: muscle spasticity, particularly in multiple sclerosis patients and spinal cord injury victims; movement disorders, such as Parkinson's disease, Huntington's disease, and Tourette's syndrome; and epilepsy. Marijuana is not proposed as a cure for such disorders, but it might relieve some associated symptoms.

Muscle Spasticity

Spasticity is the increased resistance to passive stretch of muscles and increased deep tendon reflexes. Muscles may also contract involuntarily (flexor and extensor spasms). In some cases these contractions are debilitating and painful and require therapy to relieve the spasms and associated pain.

There are numerous anecdotal reports that marijuana can relieve the spasticity associated with multiple sclerosis or spinal cord injury, and animal studies have shown that cannabinoids affect motor areas in the brain—areas that might influence spasticity.[51,78,130,168]

Multiple Sclerosis

Multiple sclerosis (MS) is a condition in which multiple areas of the central nervous system (CNS) are affected. Many nerve fibers become demyelinated, some are destroyed, and scars (sclerosis) form, resulting in plaques scattered throughout the white matter of the CNS. (Myelin is the lipid covering that surrounds nerve cell fibers and facilitates the conduction of signals along nerve cells and ultimately between the brain, the spinal cord, and the rest of the body.) MS exacerbations appear to be caused by abnormal immune activity that causes inflammation and myelin destruction in the brain (primarily in the periventricular area), brain stem, or spinal cord. Demyelination slows or blocks transmission of nerve impulses and results in an array of symptoms such as fatigue, depression, spasticity, ataxia (inability to control voluntary muscular movements), vertigo, blindness, and incontinence. About 90% of MS patients eventually develop spasticity. There are an estimated 2.5 million MS patients worldwide, and spasticity is a major concern of many patients and physicians.[134] Spasticity is variably experienced as muscle stiffness, muscle spasms, flexor spasms or cramps, muscle pain or ache. The tendency for the legs to spasm at night (flexor spasms) can interfere with sleep.

Marijuana is often reported to reduce the muscle spasticity associated with MS.[62,123] In a mail survey of 112 MS patients who regularly use marijuana, patients reported that spasticity was improved and the associated pain and clonus decreased.[287] However, a double-blind placebo-controlled

study of postural responses in 10 MS patients and 10 healthy volunteers indicated that marijuana smoking impaired posture and balance in both MS patients and the volunteers.[61] Nevertheless, the 10 MS patients felt that they were clinically improved. The subjective improvement, while intriguing, does not constitute unequivocal evidence that marijuana relieves spasticity. Survey data do not measure the degree of placebo effect, estimated to be as great as 30 percent in pain treatments.[122,131] Furthermore, surveys do not separate the effects of marijuana or cannabinoids on mood and anxiety from the effects on spasticity.

The effects of THC on spasticity were evaluated in a series of three clinical trials testing a total of 30 patients.[24,148,187] They were "open trials," meaning that the patients were informed before treatment that they would be receiving THC. Based on patient report or clinical exam by the investigator, spasticity was less severe after the THC treatment. However, THC was not effective in all patients and frequently caused unpleasant side effects. Spasticity was also reported to be less severe in a single case study after nabilone treatment (Figure 4.2).[117]

In general, the abundant anecdotal reports are not well supported by the clinical data summarized in Table 4.1. But this is due more to the limitation of the studies than to negative results. There are no supporting animal data to encourage clinical research in this area, but there also are no good animal models of the spasticity of MS. Without an appropriate model, studies to determine the physiological basis for how marijuana or THC might relieve spasticity cannot be conducted. Nonetheless, the survey results suggest that it would be useful to investigate the potential therapeutic value of cannabinoids in relieving symptoms associated with MS. Such research would require the use of objective measures of spasticity, such as the pendulum test.* Since THC is mildly sedating, it is also important to distinguish this effect from antispasticity effects in any such investigations. Mild sedatives, such as Benadryl or benzodiazepines, would be useful controls for studies on the ability of cannabinoids to relieve muscle spasticity. The regular use of smoked marijuana, however, would be contraindicated in a chronic condition like MS.

Spinal Cord Injury

In 1990, there were about 15 million patients worldwide with spinal cord injury, and an estimated 10,000 new cases are reported each year in

*The *pendulum test* is an objective and accurate measure of MS-induced spasticity. It is done by videotaping a patient who lies supine on a table with his or her leg extending off the edge. The leg is dropped and the resulting motion is mathematically analyzed by computer to provide a quantitative measure of spasticity.

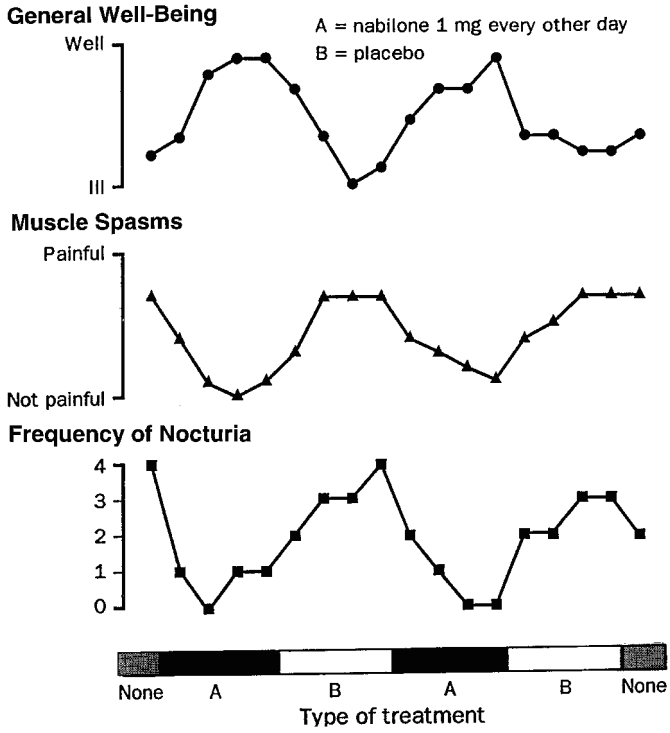

FIGURE 4.2 Effect of nabilone on multiple sclerosis symptoms. This figure shows the results of a trial in which a 45-year-old man with MS was given four-week treatments alternately with placebo and nabilone. The patient served as both experimental subject and control; his treatment sequence was nabilone-placebo-nabilone-placebo. That pattern of alternating treatments reduces the possibility that the observed changes are unrelated to the drug and are not simply due to other factors that changed with time. The results of the trial are consistent with the possibility that THC might relieve spasticity, but although more rigorous than many self-report studies of psychoactive substances, it has problems. First, the patient could not distinguish the treatments at the time of taking them, but after the nabilone treatment he felt sedated. Thus, it is not possible to know how much the expectation of relief contributed to his perception of relief. Second, the study measured his perception of pain, in which spasticity is an important factor but not the only factor. It is not possible to know the extent to which the perception of pain was affected by nabilone and how much by the stimulus that generated the pain—in this case, involuntary muscle contractions. Because it is unaffected by conscious control, the frequency of nocturia is clearer evidence of the effect of THC, although it might also represent how well the patient slept. This trial with a single person is intriguing but not definitive proof that THC can reliably relieve spasticity. SOURCE: Martyn et al. (1995).[117] Reprinted with permission.

TABLE 4.1 Studies on the Effects of Marijuana and Cannabinoids in Multiple Sclerosis

Drug and Dose	Study Design	Results	Reference
Marijuana	Mail survey 112/233 MS patients	Survey was mailed to 233 MS patients, of whom 112 (48%) responded; 97% of respondents reported improved spasticity and reduced pain.	Consroe and co-workers (1997)[28]
Marijuana	Clinical trial 1 MS patient	Reduction in spasticity and improved ataxia.	Meinck and co-workers (1989)[123]
Marijuana	Double-blind, placebo-controlled 10 MS patients; 10 normal individuals	MS patients felt they were improved, but posture and balance were impaired.	Greenberg and co-workers (1994)[61]
Oral THC 5–15 mg every 6 hrs, up to 18 hrs	Open trial 8 MS patients	5 patients experienced subjective but not objective improvement in motor coordination; objective improvement in tremor demonstrated in 2 of the 8 patients.	Clifford (1983)[24]
Oral THC 5 and 10 mg, single doses	Double-blind, placebo controlled 9 MS patients	Spasticity was improved based on examiner ratings.	Petro and Ellenberger (1981)[148]
Oral THC 2.5–15 mg, once or twice daily for 5 days	Double-blind, placebo controlled, crossover 13 MS patients	Patients reported subjective decreases in spasticity at doses of 7.5 mg or greater, but no changes in objective measures of spasticity or weakness were observed.	Ungerleider and co-workers (1987)[187]
Nabilone (THC analogue)	Placebo-controlled 1 MS patient	The patient reported increased well-being, less frequent nocturia, and reduced severity of muscle spasticity during nabilone treatment (Figure 4.2).	Martyn and co-workers (1995)[117]

the United States alone.[134,138] About 60% of spinal cord injuries occur in people younger than 35 years old. Most will need long-term care and some lifelong care.[116]

Many spinal cord injury patients report that marijuana reduces their muscle spasms.[114] Twenty-two of 43 respondents to a 1982 survey of

people with spinal cord injuries reported that marijuana reduced their spasticity.[114] One double-blind study of a paraplegic patient with painful spasms in both legs suggested that oral THC was superior to codeine in reducing muscle spasms.[72,120] Victims of spinal cord injury reporting at IOM workshops noted that smoking marijuana reduces their muscle spasms, their nausea, and the frequency of their sleepless nights. The caveats described for surveys of spasticity relief in MS patients also apply here.

Therapy for Muscle Spasticity

Present Therapy. Present therapy for spasticity includes the various medications listed in Table 4.2. Baclofen and tizanidine, the most commonly prescribed antispasticity drugs, relieve spasticity and spasms with various degrees of success. The benefit of these agents is generally only partial. Their use is complicated by the side effects of drowsiness, dry mouth, and increased weakness.

Future Therapy. The discovery of agents that work through mechanisms different from those of existing antispasticity drugs will be an important advance in the treatment of spasticity. The aim of new treatments will be to relieve muscle spasticity and pain without substantially increasing muscle weakness in conditions that result in spasticity. The treatment for MS itself will likely be directed at immunomodulation. Various immunomodulating agents, such as beta-interferon and glatiramer acetate, have been shown to reduce the frequency of symptomatic attacks, the progression of disability, and the rate of appearance of demyelinated lesions as detected by magnetic resonance imaging.[5]

Conclusion: Muscle Spasticity

Basic animal studies described in chapter 2 have shown that cannabinoid receptors are particularly abundant in areas of the brain that control

TABLE 4.2 Classes of Antispasticity Drugs

Drug Class	Drug
$GABA_B$-receptor agonists	Baclofen
α-Receptor agonists	Tizanidine
Noncompetitive $GABA_A$-receptor agonists	Benzodiazepines, including diazepam
Calcium blockers in skeletal muscle	Dantrolene

movement and that cannabinoids affect movement and posture in animals as well as humans. The observations are consistent with the possibility that cannabinoids have antispastic effects, but they do not offer any direct evidence that cannabinoids affect spasticity, even in animals. The available clinical data are too meager to either accept or dismiss the suggestion that marijuana or cannabinoids relieve muscle spasticity. But the few positive reports of the ability of THC and related compounds to reduce spasticity, together with the prevalence of anecdotal reports of the relief provided by marijuana, suggest that carefully designed clinical trials testing the effects of cannabinoids on muscle spasticity should be considered (see chapter 1).[25,62] Such trials should be designed to assess the degree to which the anxiolytic effects of cannabinoids contribute to any observed antispastic effects.

Spasticity occurring at night can be very disruptive to sleep. Thus, a long-lasting medication would be especially useful for MS patients at bedtime—when drowsiness would be a beneficial rather than an unwanted side effect and mood-altering effects would be less of a problem. One caution is related to the effects of THC on the stages of sleep, which should be evaluated in MS patients who have sleep disturbances. If THC is proven to relieve spasticity, a pill might be the preferred route of delivery for nighttime use because of its long duration of action. Compared to the currently available therapies, the long half-life of THC might allow for a smoother drug effect throughout the day. The intensity of the symptoms resulting from spasticity, particularly in MS, can rapidly increase in an unpredictable fashion such that the patient develops an "attack" of intense muscle spasms lasting minutes to hours. An inhaled form of THC (if it were shown to be efficacious) might be appropriate for those patients.

Movement Disorders

Movement disorders are a group of neurological conditions caused by abnormalities in the basal ganglia and their subcortical connections through the thalamus with cortical motor areas. The brain dysfunctions ultimately result in abnormal skeletal muscle movements in the face, limbs, and trunk. The movement disorders most often considered for marijuana or cannabinoid therapy are dystonia, Huntington's disease, Parkinson's disease, and Tourette's syndrome. Movement disorders are often transiently exacerbated by stress and activity and improved by factors that reduce stress. This is of particular interest because for many people marijuana reduces anxiety.

Dystonia

Dystonia can be a sign of other basal ganglion disorders, such as Huntington's disease and tardive dyskinesia (irreversible development of involuntary dyskinetic movements) and can be a primary basal ganglion disorder. Primary dystonias are a heterogeneous group of chronic slowly progressive neurological disorders characterized by dystonic movements—slow sustained involuntary muscle contractions that often result in abnormal postures of limbs, trunk, and neck. Dystonias can be confined to one part of the body, such as spasmodic torticollis (neck) or Meige's syndrome (facial muscles), or can affect many parts of the body, such as dystonia musculorum deformans.[5] Dystonia can cause mild to severe disability and sometimes pain secondary to muscle aching or arthritis. Some dystonias are genetic; others are caused by drugs. The specific neuropathological changes in these diseases have not been determined.

No controlled study of marijuana in dystonic patients has been published, and the only study of cannabinoids was a preliminary open trial of cannabidiol (CBD) that suggested modest dose-related improvements in the five dystonic patients studied.[30] In mutant dystonic hamsters, however, the cannabinoid receptor agonist, WIN 55,212-2, can produce antidystonic effects.[153]

Huntington's Disease

Huntington's disease is an inherited degenerative disease that usually appears in middle age and results in atrophy or loss of neurons in the caudate nucleus, putamen, and cerebral cortex. It is characterized by arrhythmic, rapid muscular contractions (chorea), emotional disturbance, and dementia (impairment in intellectual and social ability). Animal studies suggest that cannabinoids have antichoreic activity, presumably because of stimulation of CB_1 receptors in the basal ganglia.[129,168]

On the basis of positive results in one of four Huntington's disease patients, CBD and a placebo were tested in a double-blind crossover study of 15 Huntington's disease patients who were not taking any antipsychotic drugs. Their symptoms neither improved nor worsened with CBD treatment.[27,164]

The effects of other cannabinoids on patients with Huntington's disease are largely unknown. THC and other CB_1 agonists are more likely candidates than CBD, which does not bind to the CB_1 receptor. Those receptors are densely distributed on the very neurons that perish in Huntington's disease.[152] Thus far there is little evidence to encourage clinical studies of cannabinoids in Huntington's disease.

Parkinson's Disease

Parkinson's disease, a degenerative disease, affects about 1 million Americans over the age of 50.[53] It is characterized by bradykinesia (slowness in movement), akinesia (abrupt stoppage of movement), resting tremor, muscular rigidity, and postural instability.

Theoretically, cannabinoids could be useful for treating Parkinson's disease patients because cannabinoid agonists specifically inhibit the pathways between the subthalamic nucleus and substantia nigra and probably also the pathways between the subthalamic nucleus and globus pallidus (these structures shown in Figure 2.6).[165,169] The latter effect was not directly tested but is consistent with what is known about these neural pathways. Hyperactivity of the subthalamic neurons, observed in both Parkinson's patients and animal models of Parkinson's disease, is hypothesized to be a major factor in the debilitating bradykinesia associated with the disease.[36] Furthermore, although cannabinoids oppose the actions of dopamine in intact rats, they augment dopamine activation of movement in an animal model of Parkinson's disease. This suggests the potential for adjunctive therapy with cannabinoid agonists.[165–167,169]

At the time of this writing, we could find only one published clinical trial of marijuana involving five cases of idiopathic Parkinson's disease.[48] That trial was prompted by a patient's report that smoking marijuana reduced tremor, but the investigators found no improvement in tremor after the five patients smoked marijuana—whereas all subjects benefited from the administration of standard medications for Parkinson's disease (levodopa and apomorphine).[48] Although new animal data might someday indicate a use for cannabinoids in treating Parkinson's disease, current data do not recommend clinical trials of cannabinoids in patients with Parkinson's disease.

Tourette's Syndrome

Tourette's syndrome usually begins in childhood and is characterized by motor and vocal tics (involuntary rapid repetitive movements or vocalizations). It has been suggested that the symptoms might be mediated by a reduction in the activity of limbic-basal ganglia-thalamocortical circuits (shown in Figure 2.4).[42] These circuits, while not well understood, appear to be responsible for translating a person's intentions to move into actual movements. Damage to these structures leads to either involuntary increases in movement (as in Huntington's disease) or the inability to make voluntary movements (as in Parkinson's disease). The nature of the deficit in Tourette's syndrome is unknown.

No clear link has been established between symptoms of Tourette's

syndrome and cannabinoid sites or mechanism of action. Pimozide and haloperidol, two widely used treatments for Tourette's syndrome, inhibit effects mediated by the neurotransmitter dopamine, whereas cannabinoids can increase dopamine release.[154,181] The physiological relevance, if any, of these two observations has not been established.

Clinical reports consist of four case histories indicating that marijuana use can reduce tics in Tourette's patients.[75,163] In three of the four cases the investigators suggest that beneficial effects of marijuana might have been due to anxiety-reducing properties of marijuana rather than to a specific antitic effect.[163]

Therapy for Movement Disorders

Various drugs are available (Table 4.3) to treat the different movement disorders. Common side effects of many of these drugs are sedation, lethargy, school and work avoidance, social phobia, and increased risk of parkinsonism and tardive dyskinesia. With some of the medications, like those used for dystonia, efficacy is lacking in up to 50% of the patients. In addition to medications, surgical interventions, such as pallidotomy and neurosurgical transplantation of embryonic substantia nigra tissue into the patient's striatum, have been tried in Parkinson's disease patients. Surgery is generally palliative and is still considered to be in the developmental phase.

TABLE 4.3 Drugs Used to Treat Movement Disorders

Dystonia	Parkinson's disease
Benzodiazepines	Levodopa
Tetrabenazine	Carbidopa+levodopa combination
Intramuscular botulinum toxin	Amantadine
Anticholinergics	Bromocriptine
Baclofen	Pergolide
	Pramipexole
Huntington's disease	Ropinirole
Reserpine	Selegiline
Tetrabenazine	Trihexyphenidyl
Haloperidol	Benztropine
Tourette's syndrome tics	
Pimozide	
Clonidine	
Haloperidol	

Conclusion: Movement Disorders

The abundance of CB_1 receptors in basal ganglia and reports of animal studies showing the involvement of cannabinoids in the control of movement suggest that cannabinoids would be useful in treating movement disorders in humans. Marijuana or CB_1 receptor agonists might provide symptomatic relief of chorea, dystonia, some aspects of parkinsonism, and tics. However, clinical evidence is largely anecdotal; there have been no well-controlled studies of adequate numbers of patients. Furthermore, nonspecific effects might confound interpretation of results of studies. For example, the anxiolytic effects of cannabinoids might make patients feel that their condition is improved, despite the absence of measurable change in their condition.

Compared to the abundance of anecdotal reports concerning the beneficial effects of marijuana on muscle spasticity, there are relatively few claims that marijuana is useful for treating movement disorders. This might reflect a lack of effect or a lack of individuals with movement disorders who have tried marijuana. In any case, while there are a few isolated reports of individuals with movement disorders who report a benefit from marijuana, there are no published surveys indicating that a substantial percentage of patients with movement disorders find relief from marijuana. Existing studies involve too few patients from which to draw conclusions. The most promising reports involve symptomatic treatment of spasticity. If the reported neuroprotective effects of cannabinoids discussed in chapter 2 prove to be therapeutically useful, this could benefit patients with movement disorders, but without further data such a benefit is highly speculative. Since stress often transiently exacerbates movement disorders, it is reasonable to hypothesize that the anxiolytic effects of marijuana or cannabinoids might be beneficial to some patients with movement disorders. However, chronic marijuana smoking is a health risk that could increase the burden of chronic conditions, such as movement disorders.

Cannabinoids inhibit both major excitatory and inhibitory inputs to the basal ganglia. This suggests that a cannabinoid agonist could produce opposite effects on movement, depending on the type of transmission (excitatory or inhibitory) that is most active at the time of drug administration. This property could be used to design treatments in basal ganglia movement disorders, such as Parkinson's disease where either the excitatory subthalamic input becomes hyperactive or the inhibitory striatal input becomes hypoactive. The dose employed would be a major factor in the therapeutic uses of cannabinoids in movement disorders; low doses should be desirable, while higher doses could be expected to aggravate pathological conditions. Thus, there is a clear reason to recommend pre-

clinical studies; that is, animal studies to test the hypothesis that cannabinoids play an important role in movement disorders.

With the possible exception of multiple sclerosis, the evidence to recommend clinical trials of cannabinoids in movement disorders is relatively weak. Ideally, clinical studies would follow animal research that provided stronger evidence than is currently available on the potential therapeutic value of cannabinoids in the treatment of movement disorders. Unfortunately, there are no good animal models for these disorders. Thus, double-blind, placebo-controlled clinical trials of isolated cannabinoids that include controls for relevant side effects should be conducted. Such effects include anxiolytic and sedative effects, which might either mask or contribute to the potential therapeutic effects of cannabinoids.

Epilepsy

Epilepsy is a chronic seizure disorder that affects about 2 million Americans and 30 million people worldwide.[156] It is characterized by recurrent sudden attacks of altered consciousness, convulsions, or other motor activity. A seizure is the synchronized excitation of large groups of brain cells. These abnormal electrical events have a wide array of possible causes, including injury to the brain and chemical changes derived from metabolic faults of exposure to toxins.[156]

Seizures are classified as partial (focal) or generalized. Partial seizures are associated with specific sensory, motor, or psychic aberrations that reflect the function of the part of the cerebral cortex from which the seizures arise. Generalized seizures are usually the result of pathological conditions of brain sites that project to widespread regions of the brain. Such pathology can produce petit mal seizures or major grand mal convulsions.

Cannabinoids in Epilepsy

There are anecdotal and individual case reports that marijuana controls seizures in epileptics (reviewed in a 1997 British Medical Association report[13]), but there is no solid evidence. While there are no studies indicating that either marijuana or THC worsen seizures, there is no scientific basis to justify such studies.

In the only known case-controlled study that was designed to evaluate illicit drug use and the risk of first seizure, Ng and co-workers[137] concluded that marijuana is a protective factor for first-time seizures in men but not women. Men who used marijuana reportedly had fewer first-time seizures than men who did not use marijuana. That report was based on a comparison of 308 patients who had been admitted to a hospital after

their first seizure with a control group of 294 patients. The control group was made up of patients who had not had seizures and were admitted for emergency surgery, such as surgery for appendicitis, intestinal obstruction, or acute cholecystitis. Compared to men who did not use marijuana, the odds ratio of first seizure for men who had used marijuana within 90 days of hospital admission was 0.36 (95% confidence interval = 0.18–0.74). An odds ratio of less than one is consistent with the suggestion that marijuana users are less likely to have seizures. The results for women were not statistically significant. However, this was a weak study. It did not include measures of health status prior to hospital admissions for the patients' serious conditions, and differences in their health status might have influenced their drug use rather than—as suggested by the authors—that differences in their drug use influenced their health.

The potential antiepileptic activity of CBD has been investigated but is not promising. Three controlled trials were conducted in which CBD was given orally to patients who had had generalized grand mal seizures or focal seizures (Table 4.4). Two of these studies were never published, but information about one was published in a letter to the *South African Medical Journal*, and the other was presented at the 1990 Marijuana International Conference on Cannabis and Cannabinoids.[184]

TABLE 4.4 Clinical Trials of Cannabidiol (CBD) in Epileptics

Study Design	Results	Reference
Double-blind placebo-controlled trial 8 epileptic patients were given CBD at 200–300 mg/day in conjunction with standard antiepileptic therapies.	4 of 8 remained almost free of convulsions. Three of the 4 were partially improved for up to 4.5 months.	Cunha and co-workers[34]
Double-blind placebo-controlled study 12 epileptic patients were given CBD at 200–300 mg/day along with standard antiepileptic drugs.	CBD had no effect on seizure frequency.	Ames[4]
Double-blind placebo-controlled, add-on crossover trial 10 epileptic patients were given CBD at 300 mg/day for 6 months.	CBD had no effect on seizures.	Trembly and Sherman, 1990[184] (reviewed in Consroe and Sandyk, 1992[29])
Open trial One patient was given CBD at 900–1,200 mg/day for 10 months.	Seizure frequency was reduced in the patient.	Trembly and Sherman, 1990[184] (reviewed in Consroe and Sandyk, 1992[29])

Even if CBD had antiepileptic properties, these studies were likely too small to demonstrate efficacy. Proving efficacy of anticonvulsants generally requires large numbers of patients followed for months because the frequency of seizures is highly variable and the response to therapy varies depending on seizure type.[4,49]

Therapy for Epilepsy

Present Therapy. Standard pharmacotherapy for partial and generalized seizures, listed in Table 4.5, involves a variety of anticonvulsant drugs. These drugs suppress seizures completely in approximately 60% of patients who have chronic epilepsy and improve seizures in another 15% of patients. All of the anticonvulsants listed in Table 4.5 have side effects, some of the more common of which are drowsiness, mental slowing, ataxia, tremor, hair loss, increased appetite, headache, insomnia, and rash. Nevertheless, recurrent seizures are physically dangerous and emotionally devastating, and preventing them outweighs many undesirable side effects of anticonvulsant drugs.

Future Therapy. The goal of epilepsy treatment is to halt the seizures with minimal or no side effects and then to eradicate the cause. Most of the anticonvulsant research on cannabinoids was conducted before 1986. Since then, many new anticonvulsants have been introduced and cannabinoid receptors have been discovered. At present, the only biological evidence of antiepileptic properties of cannabinoids is that CB_1 receptors are abundant in the hippocampus and amygdala. Both regions are involved in partial seizures but are better known for their role in functions unrelated to seizures.[26] Basic research might reveal stronger links between cannabinoids and seizure activity, but this is not likely to be as fruitful a

TABLE 4.5 Anticonvulsant Drugs for Various Types of Seizures

Generalized grand mal seizures	Partial (focal) seizures
Carbamazepine	Carbamazepine
Valproate	Phenytoin
Phenytoin	Valproate
Phenobarbital	Phenobarbital
	Clonazepam
Generalized petit mal seizures	Gabapentin
Ethosuximide	Lamotrigine
Clonazepam	Tiagabine (as adjunct therapy)
Valproate	

SOURCE: Adapted from Andreoli et al. (1997).[5]

subject of cannabinoid research as others. Given the present state of knowledge, clinical studies of cannabinoids in epileptics are not indicated.

Alzheimer's Disease

Food refusal is a common problem in patients who suffer from Alzheimer's type dementia. The causes of anorexia in demented people are not known but may be a symptom of depression. Antidepressants improve eating in some but not all patients with severe dementia. Eleven Alzheimer's patients were treated for 12 weeks on an alternating schedule of dronabinol and placebo (six weeks of each treatment). The dronabinol treatment resulted in substantial weight gains and declines in disturbed behavior.[190] No serious side effects were observed. One patient had a seizure and was removed from the study, but the seizure was not necessarily caused by dronabinol. Recurrent seizures without any precipitating events occur in 20% of patients who have advanced dementia of Alzheimer's type.[189] Nevertheless, these results are encouraging enough to recommend further clinical research with cannabinoids.

The patients in the study discussed above were in long-term institutional care, and most were severely demented with impaired memory. Although short-term memory loss is a common side effect of THC in healthy patients, it was not a concern in this study. However, the effect of dronabinol on memory in Alzheimer's patients who are not as severely disturbed as those in the above study would be an important consideration.

GLAUCOMA

After cataracts, glaucoma is the second-leading cause of blindness in the world; almost 67 million people are expected to be affected worldwide by the year 2000[149] (for an excellent review, see Alward, 1998[2]). The most common form of glaucoma, primary open-angle glaucoma (POAG), is a slowly progressive disorder that results in loss of retinal ganglion cells and degeneration of the optic nerve, causing deterioration of the visual fields and ultimately blindness. The mechanisms behind the disease are not understood, but three major risk factors are known: age, race, and high intraocular pressure (IOP). POAG is most prevalent among the elderly, with 1% affected in those over 60 years old and more than 9% in those over 80. In African Americans over 80, there is more than a 10% chance of having the disease, and older African Caribbeans (who are less racially mixed than African Americans) have a 20–25% chance of having the disease.[106]

The eye's rigid shape is normally maintained in part by IOP, which is

regulated by the circulation of a clear fluid, the aqueous humor,* between the front of the lens and the back of the cornea. Because of impaired outflow of aqueous humor from the anterior chamber of the eye, a high IOP is a risk factor for glaucoma, but the mechanism by which it damages the optic nerve and retinal ganglion cells remains unclear.[174] The two leading possibilities are that high IOP interferes with nutrient blood flow to the region of the optic nerve or that it interferes with transport of nutrients, growth factors, and other compounds within the optic nerve axon (P. Kaufman, IOM workshop). If the interference continues, the retinal ganglion cells and optic nerve will permanently atrophy; the result is blindness.[68] Because high IOP is the only known major risk factor that can be controlled, most treatments have been designed to reduce it. However, reducing it does not always arrest or slow the progression of visual loss.[20,109]

Marijuana and Cannabinoids in Glaucoma

Marijuana and THC have been shown to reduce IOP by an average of 24% in people with normal IOP who have visual-field changes. In a number of studies of healthy adults and glaucoma patients, IOP was reduced by an average of 25% after smoking a marijuana cigarette that contained approximately 2% THC—a reduction as good as that observed with most other medications available today.[1,16,32,76,77,125,193] Similar responses have been observed when marijuana was eaten or THC was given in pill form (10–40 mg) to healthy adults or glaucoma patients.[76,91] But the effect lasts only about three to four hours. Elevated IOP is a chronic condition and must be controlled continuously.

Intravenous administration of Δ^9-THC, Δ^8-THC, or 11-OH-THC to healthy adults substantially decreased IOP, whereas cannabinol, CBD, and β-OH-THC had little effect.[31,146] The cause for the reduction in IOP remains unknown, but the effect appears to be independent of the frequently observed drop in arterial systolic blood pressure (Keith Green, Medical College of Georgia, personal communication).

Three synthetic cannabinoids were investigated; BW29Y, BW146Y, and nabilone. They were given orally to patients who had high IOP. BW146Y and nabilone were as effective as ingesting THC or smoking

*The cornea and lens must be optically clear, which means that there cannot be blood circulation in these tissues. The aqueous humor is a clear fluid that functions as alternative circulation across the rear of the cornea and to the lens, providing nutrients and removing waste from these tissues.

marijuana but again with a very short duration of action; BW29Y was ineffective.[136,182]

Topical treatments with cannabinoids have been ineffective in reducing IOP. When Δ^9-THC was applied topically as eye drops, whether once or four times a day, there was no decrease in IOP.[60,90] Suspensions of lipophilic THC tended to be irritating to the eye.

In summary, cannabinoids and marijuana can reduce IOP when administered orally, intravenously, or by inhalation but not when administered topically. Even though a reduction in IOP by standard medications or surgery clearly slows the rate of glaucoma symptom progression, there is no direct evidence of benefits of cannabinoids or marijuana in the natural progression of glaucoma, visual acuity, or optic nerve atrophy.[92,115]

In addition to lowering IOP, marijuana reduces blood pressure and has many psychological effects. Merritt and co-workers reported hypotension, palpitations, and psychotropic effects in glaucoma patients after inhalation of marijuana.[125] Cooler and Gregg[31] also reported increased anxiety and tachycardia after intravenous infusion of THC (1.5–3 mg). All those side effects are problematic, particularly for elderly glaucoma patients who have cardiovascular or cerebrovascular disease**.** The reduction in blood pressure can be substantial and might adversely affect blood flow to the optic nerve.[124] Many people with systemic hypertension have their blood pressure reduced to manageable and acceptable levels through medication, but this does not seem to affect their IOP. In contrast, there is evidence that reduction in blood pressure to considerably below-normal levels influences IOP and ocular blood flow.[46,74,142] Hence, in the case of an eye with high IOP or an optic nerve in poor condition and susceptibility to high IOP, reduced blood flow to the optic nerve could compromise a functional retina and be a factor in the progression of glaucoma.

Because it is not known how these compounds work, it is also not known how they might interact with other drugs used to treat glaucoma. If the mechanism involves a final common pathway, the effects of cannabinoids might not be additive and might even interfere with effective drugs.

Therapy for Glaucoma

Present Therapy

Six classes of drugs are used to treat glaucoma; all reduce IOP (Table 4.6).[93] In the late 1970s, when early reports of the effects of marijuana on IOP surfaced, only cholinomimetics, epinephrine, and oral carbonic anhydrase inhibitors were available. They are not popular today because of their side effects, such as pupil constriction or dilation, brow ache, tachycardia, and diuresis; all of them have been superseded by the other classes

TABLE 4.6 Classes of Drugs Used to Treat Glaucoma

Cholinergic agonists	**α_2-Adrenergic agonists**
Pilocarpine	Aproclonidine
	Brimonidine
β_2-Adrenergic agonists	**Carbonic anhydrase inhibitors**
Epinephrine	Acetazolamide
Dipivefrin	Dorzolamide (Trusopt)
β_2-Adrenergic antagonists	**Prostaglandin-F_{2a} analogues**
Timolol	Latanoprost
Betaxolol (Betoptic)	Unoprostone

of drugs.[93] Surgical options are also available today to lower IOP, including laser trabeculoplasty, trabeculectomy/sclerostomy, drainage implantation, and cyclodestruction of fluid-forming tissues.[173] Thus, there are now many effective options to slow the progression of glaucoma by reducing IOP.

One important factor in slowing the progression of glaucoma via medications that reduce IOP is patient compliance with dosing regimens. With respect to compliance, the ideal glaucoma drug is one that is applied at most twice a day (P. Kaufman, IOM workshop). If the dose must be repeated every three to four hours, patient compliance becomes a problem; for this reason, marijuana and the cannabinoids studied thus far would not be highly satisfactory treatments for glaucoma. Present therapies, especially combinations of approved topical drugs, can control IOP when administered once or twice a day, at a cost of about $60 per month.

Future Therapy

In all likelihood the next generation of glaucoma therapies will deal with neural protection, neural rescue, neural regeneration, or blood flow, and the optic nerve and neural retina will be treated directly rather than just by lowering IOP (P. Kaufman, IOM workshop). There is some evidence that a synthetic cannabinoid, HU-211, might have neuroprotective effects *in vitro;* this presents a potential approach that has nothing to do with IOP.[197] HU-211 is commonly referred to as a cannabinoid because its chemical structure is similar to THC; however, it does not bind to cannabinoid receptor.

It is known that cannabinoids lower IOP fairly substantially but not how. No one has tested whether the effect is receptor mediated (B. Martin, IOM workshop). To do so, one could test whether a receptor antagonist

blocked the effects of THC or other cannabinoids. If the decrease were shown to be receptor mediated, it would be important to know whether it was through CB_1, which mediates central nervous system effects, or CB_2, which is not involved in CNS effects. If it were CB_2, it might be possible to reduce IOP without the CNS side effects. Finally, it is not known whether the endogenous cannabinoid system is a natural regulator of IOP.

Conclusion: Glaucoma

Although glaucoma is one of the most frequently cited medical indications for marijuana, the data do not support this indication. High intraocular pressure (IOP) is a known risk factor for glaucoma and can, indeed, be reduced by cannabinoids and marijuana. However, the effect is too and short lived and requires too high doses, and there are too many side effects to recommend lifelong use in the treatment of glaucoma. The potential harmful effects of chronic marijuana smoking outweigh its modest benefits in the treatment of glaucoma. Clinical studies on the effects of smoked marijuana are unlikely to result in improved treatment for glaucoma.

Future research might reveal a therapeutic effect of isolated cannabinoids. For example, it might be possible to design a cannabinoid drug with longer-lasting effects on IOP and with less psychoactivity than THC.

SUMMARY

Advances in cannabinoid science of the past 16 years have given rise to a wealth of new opportunities for the development of medically useful cannabinoid-based drugs. The accumulated data suggest a variety of indications, particularly for pain relief, antiemesis, and appetite stimulation. For patients such as those with AIDS or who are undergoing chemotherapy, and who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might offer broad-spectrum relief not found in any other single medication. The data are weaker for muscle spasticity but moderately promising. The least promising categories are movement disorders, epilepsy, and glaucoma. Animal data are moderately supportive of a potential for cannabinoids in the treatment of movement disorders and might eventually yield stronger encouragement. The therapeutic effects of cannabinoids are most well established for THC, which is the primary psychoactive ingredient of marijuana. But it does not follow from this that smoking marijuana is good medicine.

Although marijuana smoke delivers THC and other cannabinoids to the body, it also delivers harmful substances, including most of those found in tobacco smoke. In addition, plants contain a variable mixture of

biologically active compounds and cannot be expected to provide a precisely defined drug effect. For those reasons there is little future in smoked marijuana as a medically approved medication. If there is any future in cannabinoid drugs, it lies with agents of more certain, not less certain, composition. While clinical trials are the route to developing approved medications, they are also valuable for other reasons. For example, the personal medical use of smoked marijuana—regardless of whether or not it is approved—to treat certain symptoms is reason enough to advocate clinical trials to assess the degree to which the symptoms or course of diseases are affected. Trials testing the safety and efficacy of marijuana use are an important component to understanding the course of a disease, particularly diseases such as AIDS for which marijuana use is prevalent. The argument against the future of smoked marijuana for treating any condition is not that there is no reason to predict efficacy but that there is risk. That risk could be overcome by the development of a nonsmoked rapid-onset delivery system for cannabinoid drugs.

There are two caveats to following the traditional path of drug development for cannabinoids. The first is timing. Patients who are currently suffering from debilitating conditions unrelieved by legally available drugs, and who might find relief with smoked marijuana, will find little comfort in a promise of a better drug 10 years from now. In terms of good medicine, marijuana should rarely be recommended unless all reasonable options have been eliminated. But then what? It is conceivable that the medical and scientific opinion might find itself in conflict with drug regulations. This presents a policy issue that must weigh—at least temporarily—the needs of individual patients against broader social issues. Our assessment of the scientific data on the medical value of marijuana and its constituent cannabinoids is but one component of attaining that balance.

The second caveat is a practical one. Although most scientists who study cannabinoids would agree that the scientific pathways to cannabinoid drug development are clearly marked, there is no guarantee that the fruits of scientific research will be made available to the public. Cannabinoid-based drugs will become available only if there is either enough incentive for private enterprise to develop and market such drugs or sustained public investment in cannabinoid drug research and development. The perils along this pathway are discussed in chapter 5. Although marijuana is an abused drug, the logical focus of research on the therapeutic value of cannabinoid-based drugs is the treatment of specific symptoms or diseases, not substance abuse. Thus, the most logical research sponsors would be the several institutes within the National Institutes of Health or organizations whose primary expertise lies in the relevant symptoms or diseases.

CONCLUSION: Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances.

RECOMMENDATION: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.

RECOMMENDATION: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.

RECOMMENDATION: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

- **failure of all approved medications to provide relief has been documented,**
- **the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,**
- **such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness, and**
- **involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.**

Until a nonsmoked rapid-onset cannabinoid drug delivery system becomes available, we acknowledge that there is no clear alternative for people suffering from *chronic* conditions that might be relieved by smoking marijuana, such as pain or AIDS wasting. One possible approach is to treat patients as *n*-of-1 clinical trials, in which patients are fully informed of their status as experimental subjects using a harmful drug delivery system and in which their condition is closely monitored and documented under medical supervision, thereby increasing the knowledge base of the risks and benefits of marijuana use under such conditions. We recom-

mend these *n*-of-1 clinical trials using the same oversight mechanism as that proposed in the above recommendations.

OTHER REPORTS ON MARIJUANA AS MEDICINE

Since 1996, five important reports pertaining to the medical uses of marijuana have been published, each prepared by deliberative groups of medical and scientific experts (Appendix E). They were written to address different facets of the medical marijuana debate, and each offers a somewhat different perspective. With the exception of the report by the Health Council of the Netherlands, each concluded that marijuana can be moderately effective in treating a variety of symptoms. They also agree that current scientific understanding is rudimentary; indeed, the sentiment most often stated is that more research is needed. And these reports record the same problem with herbal medications as noted here: the uncertain composition of plant material makes for an uncertain, and hence often undesirable, medicine.

The 1996 report by the Health Council of the Netherlands concluded that there is insufficient evidence to justify the medical use of marijuana *or* THC, despite the fact that the latter is an approved medication in the United States and Britain. However, that committee addressed only whether there was sufficient evidence to warrant the prescription of marijuana or cannabinoids, not whether the data are sufficient to justify clinical trials. Conclusions of the Health Council of the Netherlands contrast with that country's tolerance of marijuana use. The health council's report noted that marijuana use by patients in the terminal stages of illness is tolerated in hospitals. It also said that the council did "not wish to judge patients who consume marihuana (in whatever form) because it makes them feel better. . . ."

In contrast, the American Medical Association House of Delegates, National Institutes of Health (NIH), and the British Medical Association recommend clinical trials of smoked marijuana for a variety of symptoms. The NIH report, however, was alone in recommending clinical studies of marijuana for the treatment of glaucoma—and even then there was disagreement among the panel members (William T. Beaver, chair, NIH Ad Hoc Expert Panel on the Medical Use of Marijuana, personal communication, 1998).

Recent reviews that have received extensive attention from those who follow the medical marijuana debate have been written by strong advocates *for* (Grinspoon and Bakalar, 1993[62]; Zimmer and Morgan, 1997[198]) or *against* (Voth and Schwartz, 1997[191]) the medical use of marijuana. Those reports represent the individual views of their authors, and they are not reviewed here but have been reviewed in major scientific journals.[7,69,178,180]

REFERENCES

1. Alm A, Camras CB, Watson PG. 1997. Phase III latanoprost studies in Scandanavia, the United Kingdom and the United States. *Survey of Ophthalmology* 41:S105–S110.
2. Alward WL. 1998. Medical management of glaucoma. *The New England Journal of Medicine* 339:1298–1307.
3. AMA (American Medical Association Council on Scientific Affairs). 1997. *Report to the AMA House of Delegates.* Chicago: AMA.
4. Ames FR. 1986. Anticonvulsant effect of cannabidiol. *South African Medical Journal* 69:14.
5. Andreoli TE, Carpenter CC, Bennet CJ, Plum F, eds. 1997. *Cecil Essentials of Medicine*. Fourth Edition. Philadelphia: W.B. Saunders Co.
6. Andrews PL, Davis CJ. 1995. The physiology of emesis induced by anti-cancer therapy. In: Reynolds DJ, Andrews PL, Davis CJ, Editors, *Serotonin and the Scientific Basis of Anti-Emetic Therapy.* Oxford: Oxford Clinical Communications. Pp. 25–49.
7. Bayer R, O'Connell TJ, Lapey JD. 1997. Medicinal uses of marijuana (Letter to the Editor). *Annals of Internal Medicine* 127:1134–1135.
8. Beal JE, Olson RLL, Morales JO, Bellman P, Yangco B, Lefkowitz L, Plasse TF, Shepard KV. 1995. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *Journal of Pain and Symptom Management* 10:89–97.
9. Beal JE, Olson R, Lefkowitz L, Laubenstein L, Bellman P, Yangco B, Morales JO, Murphy R, Powderly W, Plasse TF, Mosdell KW, Shepard KV. 1997. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *Journal of Pain and Symptom Management* 14:7–14.
10. Bhasin S, Storer TW, Asbel-Sethi N, Kilbourne A, Hays R, Sinha-Hikim I, Shen R, Arver S, Beall G. 1998. Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. *Journal Clinical of Endocrinology and Metabolism* 83:3155–3162.
11. Billingsley KG, Alexander HR. 1996. The pathophysiology of cachexia in advanced cancer and AIDS. In: Bruera E, Higginson I, Editors, *Cachexia-Anorexia in Cancer Patients.* New York: Oxford Universtiy Press. Pp. 1–22.
12. Borison HL, McCarthy LE. 1983. Neuropharmacology of chemotherapy-induced emesis. *Drugs* 25:8–17.
13. British Medical Association. 1997. *Therapeutic Uses of Cannabis.* Amsterdam, The Netherlands: Harwood Academic Publishers.
14. Bruera E. 1998. Pharmacological treatment of cachexia: Any progress? *Supportive Care of Cancer* 6:109–113.
15. Calignano A, La Rana G, Giuffrida A, Piomelli D. 1998. Control of pain initiation by endogenous cannabinoids. *Nature* 394:277–281.
16. Camras CB, Alm A, Watson P, Stjernschantz J. 1996. Latanoprost, a prostaglandin analog, for glaucoma therapy: Efficacy and safety after 1 year of treatment in 198 patients. Latanoprost Study Groups. *Ophthalmology* 103:1916–1924.
17. (CDC) Centers for Disease Control. 1992. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR (Morbidity Mortality Weekly Report)* 41(RR-17):1–19.
18. Chang AE, Shiling DJ, Stillman RC, et al. 1979. Delta-9-tetrahydrocannabinol as an antiemetic in patients receiving high-dose methotrexate: A prospective, randomized evaluation. *Annals of Internal Medicine* 91:819–824.
19. Chang AE, Shiling DJ, Stillman RC, Goldberg NH, Seipp CA, Barofsky I, Rosenberg SA. 1981. A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and cytoxan chemotherapy. *Cancer* 47:1746–1751.

20. Chauhan BC, Drance SM. 1992. The relationship between intraocular pressure and visual field progression in glaucoma. *Graefe's Archives for Clinical and Experimental Ophthalmology* 230:521–526.
21. Clark RA, Tyson LB, Frisone M. 1985. A correlation of objective and subjective parameters in assessing antiemetic regimens. *Proceedings of the Tenth Anniversary Congress of the Oncology Nursing Society* 2:96.
22. Clark WC, Janal MN, Zeidenberg P, Nahas GG. 1981. Effects of moderate and high doses of marihuana on thermal pain: A sensory decision theory analysis. *Journal of Clinical Pharmacology* 21:299S–310S.
23. Clarke RC. 1995. *Marijuana Botany—An Advanced Study: The Propagation and Breeding of Distinctive Cannabis*. Berkeley, CA: Ronin Publishing.
24. Clifford DB. 1983. Tetrahydrocannabinol for tremor in multiple sclerosis. *Annals of Neurology* 13:669–671.
25. Consroe P. 1998a. Clinical and experimental reports of marijuana and cannabinoids in spastic disorders. In: Nahas GG, Sutin KM, Harvey DJ, Agurell S, Editors, *Marijuana and Medicine.* Totowa, NJ: Humana Press.
26. Consroe P. 1998b. Brain cannabinoid systems as target for the treatment of neurological disorders. *Neurobiology of Disease* 5:534–551.
27. Consroe P, Laguna J, Allender J, Snider S, Stern L, Sandyk R, Kennedy K, Schram K. 1991. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacology, Biochemistry and Behavior (New York)* 40:701–708.
28. Consroe P, Musty R, Rein J, Tillery W, Pertwee RG. 1997. The perceived effects of smoked cannabis on patients with multiple sclerosis. *European Neurology* 38:44–48.
29. Consroe P, Sandyk R. 1992. Potential role of cannabinoids for therapy of neurological disorders. In: Bartke A, Murphy LL, Editors, *Marijuana/Cannabinoids: Neurobiology and Neurophysiology.* Boca Raton, FL: CRC Press. Pp. 459–524.
30. Consroe P, Sandyk R, Snider SR. 1986. Open label evaluation of cannabidiol in dystonic movement disorders. *International Journal of Neuroscience* 30:277–282.
31. Cooler P, Gregg JM. 1977. Effect of delta–9–tetrahydrocannabinol on intraocular pressure in humans. *Southern Medical Journal* 70:951–954.
32. Crawford WJ, Merritt JC. 1979. Effects of tetrahydrocannabinol on arterial and-intraocular hypertension. *International Journal of Clinical Pharmacology and Biopharmacy* 17:191–196.
33. Crow S. 1997. Investigational drugs for eating disorders. *Expert Opinion on Investigational Drugs* 6:427–436.
34. Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, Sanvito WL, Lander N, Mechoulam R. 1980. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology* 21:175–185.
35. Davis CJ. 1995. Emesis research: A concise history of the critical concepts and experiments. In: Reynolds DJ, Andrews PL, Davis CJ, Editors, *Serotonin and the Scientific Basis of Anti-Emetic Therapy.* Oxford : Oxford Clinical Communications. Pp. 9–24.
36. DeLong MR, Georgopoulos AP, Crutcher MD, Mitchell S J, Richardson RT, Alexander GE. 1984. Functional organization of the basal ganglia: Contributions of single-cell recording studies. *CIBA Foundation Symposium* 107:64–82.
37. DeMulder PH, Seynaeve C, Vermorker JB, et al. 1990. Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting: A multicenter, randomized, double-blind, crossover study. *Annals of Internal Medicine* 113:834–840.
38. Doblin R, Kleiman MA. 1995. The medical use of marijuana: The case for clinical trials [editorial; comment]. *Journal of Addictive Diseases* 14:5–14; Comment in *Journal of Addictive Diseases* 1994, 13(1):53–65.

39. Doblin R, Kleiman M. 1991. Marijuana as antiemetic medicine: A survey of oncologists' experiences and attitudes. *Journal of Clinical Oncology* 9:1314–1319.
40. Dunlop R. 1996. Clinical epidemiology of cancer cachexia. In: Bruera E, Higginson I, Editors, *Cachexia-Anorexia in Cancer Patients.* Vol. 5. Oxford: Oxford University Press. Pp. 76–82.
41. Dunn M, Davis R. 1974. The perceived effects of marijuana on spinal cord injured males. *Paraplegia* 12:175.
42. Eidelberg D, Moeller JR, Antonini A, Kazumata K, Dhawan V, Budman C, Feigin A. 1997. The metabolic anatomy of Tourette's syndrome. *Neurology* 48:927–934.
43. El-Mallakh RS. 1987. Marijuana and migraine. *Headache* 27:442–443.
44. Engelson ES, Rabkin JG, Rabkin R, Kotler DP. 1996. Effects of testosterone upon body composition. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* 11:510–511.
45. Enoch M, Kaye WH, Rotondo A, Greenberg BD, Murphy DL, Goldman D. 1998. 5-HT2A promoter polymorphism-1438G/A, anorexia nervosa, and obsessive-compulsive disorder. *The Lancet* 351:1785–1786.
46. Follmann P, Paltotas C, Suveges I, Petrovits A. 1996–1997. Nocturnal blood pressure and intraocular pressure measurement in glaucoma patients and healthy controls. *International Ophthalmology* 20:83–87.
47. Foltin RW, Fischman MW, Byrne MF. 1988. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite* 11:1–14.
48. Frankel JP, Hughes A, Lees AJ, Stern GM. 1990. Marijuana for Parkinsonian tremor. *Journal of Neurology, Neurosurgery and Psychiatry* 53:436.
49. French J. 1998. The art of antiepileptic trial design. *Advances in Neurology* 76:113–123.
50. Frytak S, Moertel CG, O'Fallon J, et al. 1979. Delta-9-tetrahydrocannabinol as an antiemetic in patients treated with cancer chemotherapy: A double comparison with prochloperazine and a placebo. *Annals of Internal Medicine* 91:825–830.
51. 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.
52. Goadsby PJ, Gundlach AL. 1991. Localization of [3H]-dihydroergotamine binding sites in the cat central nervous system: Relevance to migraine. *Annals of Neurology* 29:91–94.
53. Gonzalez EC, Brownlee HJ. 1998. Movement disorders. In: Taylor RB, Editor, *Family Medicine: Principles and Practice.* 5th Edition. New York: Springer-Verlag. Pp. 565–573.
54. Gorter R. 1991. Management of anorexia-cachexia associated with cancer and HIV infection. *Oncology (Supplement)* 5:13–17.
55. Gralla RJ, Itri LM, Pisko SE, et al. 1981. Antiemetic efficacy of high dose metoclopramide: Randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. *New England Journal of Medicine* 305:905–909.
56. Gralla RJ, Navari RM, Hesketh PJ, et al. 1998. Single-dose oral granisetron has equivalent antiemetic efficacy to intravenous ondansetron for highly emetogenic cisplatin-based chemotherapy. *Journal of Clinical Oncology* 16:1–7.
57. Gralla RJ, Rittenberg CN, Lettow LA, et al. 1995. A unique all-oral, single-dose, combination antiemetic regimen with high efficacy and marked cost saving potential. *Proceedings of the American Society for Clinical Oncology* 14:526.
58. Gralla RJ, Tyson LB, Borden LB, et al. 1984. Antiemetic therapy: A review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. *Cancer Treatment Reports* 68:163–172.

59. Grandara DR, Roila F, Warr D, Edelman MJ, Perez EA, Gralla RJ. 1998. Consensus proposal for 5HT3 antagonists in the prevention of acute emesis related to highly emetogenic chemotherapy: Dose, schedule, and route of administration. *Supportive Care in Cancer* 6:237–243.
60. Green K, Roth M. 1982. Ocular effects of topical administration of delta-9-tetrahydrocannabinol in man. *Archives of Ophthalmology* 100:265–267.
61. Greenberg HS, Werness SA, Pugh JE, Andrus RO, Anderson DJ, Domino EF. 1994. Short-term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers. *Clinical Pharmacology and Therapeutics* 55:324–328.
62. Grinspoon L, Bakalar JB. 1993. *Marijuana: The Forbidden Medicine*. New Haven: Yale University Press.
63. Grinspoon L, Bakalar JB, Zimmer L, Morgan JP. 1997. Marijuana addiction [Letter]. *Science* 277:749; discussion, 750–752.
64. Grinspoon S, Corcoran C, Askari H, Schoenfeld D, Wolf L, Burrows B, Walsh M, Hayden D, Parlman K, Anderson E, Basgoz N, Klibanski A. 1998. Effects of androgen administration in men with the AIDS wasting syndrome. *Annals of Internal Medicine* 129:18–26.
65. Gross H, Egbert MH, Faden VB, Godberg SC, Kaye WH, Caine ED, Hawks R, Zinberg NE. 1983. A double-blind trial of delta-9-THC in primary anorexia nervosa. *Journal of Clinical Psychopharmacology* 3:165–171.
66. Guyatt GH, Keller JL, Jaeschke R, Rosenbloom D, Adachi JD, Newhouse MT. 1990. The N-of-1 randomized controlled trial—clinical usefulness: Our three-year experience. *Annals of Internal Medicine* 112:293–299.
67. Guyatt GH, Sackett D, Taylor DW, Chong J, Roberts R, Pugsley S. 1986. Determining optimal therapy: Randomized trials in individual patients. *New England Journal of Medicine* 314:889–892.
68. Guyton AC. 1986. *Textbook of Medical Physiology*. 7th ed. Philadelphia: WB Saunders Company.
69. Hall W. 1997. An ongoing debate. *Science* 278:75.
70. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. 1999. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology* 141:385–394.
71. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. 1999. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology* 141:395–404.
72. Hanigan WC, Destree R, Truong XT. 1986. The effect of delta-9-THC on human spasticity. *Clinical Pharmacology and Therapeutics* 39:198.
73. Hardin TC. 1993. Cytokine mediators of malnutrition: Clinical implications. *Nutrition in Clinical Practice* 8:55–59.
74. Hayreh SS, Zimmerman MB, Podhajsky P, Alward W. 1994. Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. *American Journal of Ophthalmology* 117:603–624.
75. Hemming M, Yellowlees PM. 1993. Effective treatment of Tourette's syndrome with marijuana. *Journal of Psychopharmacology* 7:389–391.
76. Hepler RS, Frank IM, Petrus R. 1976. Ocular effects of marijuana smoking. In: Braude MC, Szara S, Editors, *The Pharmacology of Marijuana*. New York: Raven Press. Pp. 815–824.
77. Hepler RS, Frank IR. 1971. Marihuana smoking and intraocular pressure. *Journal of the American Medical Association* 217(10):1392.
78. 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.

79. Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC. 1991b. Characterization and localization of cannabinoid receptors in rat brain: A quantitative *in vitro* autoradiographic study. *Journal of Neuroscience* 11:563–583.
80. 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.
81. Herrstedt J, Aapro MS, Smyth JF, Del Favero A. 1998. Corticosteroids, dopamine antagonists and other drugs. *Supportive Care in Cancer* 6:204–214.
82. Hesketh PJ, Gralla RJ, duBois A, Tonato M. 1998. Methodology of antiemetic trials: Response assessment, evaluation of new agents and definition of chemotherapy emetogenicity. *Supportive Care in Cancer* 6:221–227.
83. Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, Aapro MS, Gandara D, Lindley CM. 1997. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *Journal of Clinical Oncology* 15:103–109.
84. Hill SY, Schwin R, Goodwin DW, Powell BJ. 1974. Marihuana and pain. *Journal of Pharmacology and Experimental Therapeutics* 188:415–418.
85. Holdcroft A, Smith M, Jacklin A, Hodgson H, Smith B, Newton M, Evans F. 1997. Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia* 5:483–486.
86. Homesley HD, Gainey JM, Jobson VN, et al. 1982. Double-blind placebo-controlled study of metoclopramide in cisplatin-induced emesis. *New England Journal of Medicine* 307:250–251.
87. Huestis MA, Henningfield JE, Cone EJ. 1992. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. *Journal of Analytical Toxicology* 16:276–282.
88. Italian Group for Antiemetic Trials. 1995. Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. *New England Journal of Medicine* 332:332–337.
89. Jain AK, Ryan JR, McMahon FG, Smith G. 1981. Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *Journal of Clinical Pharmacology* 21:320S–326S.
90. Jay WM, Green K. 1983. Multiple-drop study of topically applied 1% Δ^9-tetrahydrocannabinol in human eyes. *Archives of Ophthalmology* 101:591–593.
91. Jones RT, Benowitz NL, Herning RI. 1981. Clinical relevance of cannabis tolerance and dependence. *Journal of Clinical Pharmacology* 21:143S–152S.
92. Kass MA, Gordon MO, Hoff MR, Pardinson JM, Kolker AE, Hart WM, Becker B. 1989. Topical timolol administration reduces the incidence of glaucomatous damage in ocular hypertensive individuals: A randomized, double-masked, long-term clinical trial. *Archives of Ophthalmology* 107:1590–1598.
93. Kaufman P, Mittag TW. 1994. Medical therapy of glaucoma. In: Kaufman P, Mittag TW, Editors, *Textbook of Ophthalmology*. Volume 7. London: Mosby-Yearbook.
94. Kotler DP. 1997. Wasting Syndrome Pathogenesis and Clinical Markers. *Institute of Medicine Workshop*. Irvine, CA, December 15, 1997. Pp. 56–66. Washington, DC: Institute of Medicine.
95. Kotler DP, Gaetz HP, Klein EB, Lange M, Holt PR. 1984. Enteropathy associated with the acquired immunodeficiency syndrome. *Annals of Internal Medicine* 101:421–428.
96. Kotler DP, Tierney AR, Culpepper-Morgan JA, Wang J, Peirson RN. 1990. Effect of home total parental nutrition on body composition in patients with acquired immunodeficiency syndrome. *Journal of Parenteral Nutrition* 14:454–458.

97. Kotler DP, Tierney AR, Dilmanian FA, Kamen Y, Wang J, Pierson Jr RN, Weber D. 1991. Correlation between total body potassium and total body nitrogen in patients with acquired immunodeficiency syndrome. *Clinical Research* 39:649A.
98. Kotler DP, Tierney AR, Ferraro R, et al. 1991. Enteral alimentation and repletion of body cell mass in malnourished patients with acquired immunodeficiency syndrome. *American Journal of Clinical Nutrition* 53:149–154.
99. Kotler DP, Tierney AR, Wang J, Pierson RN. 1989. Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. *American Journal of Clinical Nutrition* 50:444–447.
100. Kotler DP, Wang J, Pierson RN. 1985. Studies of body composition in patients with the acquired immunodeficiency syndrome. *American Journal of Clinical Nutrition* 42:1255–1265.
101. Kris MG, Gralla RJ, Clark RA, et al. 1987. Antiemetic control and prevention of side effects of anticancer therapy with lorazepam or diphenhydramine when used in combination with metoclopramide plus dexamethasone: A double-blind randomized trial. *Cancer* 60:2816–2822.
102. Kris MG, Radford JE, Pizzo BA, et al. 1997. Use of an NK-1 receptor antagonist to prevent delayed emesis following cisplatin. *Journal of the National Cancer Institute* 89:817–818.
103. Kris MG, Roila F, De Mulder PH, Marty M. 1998. Delayed emesis following anticancer chemotherapy. *Supportive Care in Cancer* 6:228–232.
104. Lang IM, Sarna SK. 1989. Motor and myoelectric activity associated with vomiting, regurgitation, and nausea. In: Wood JD, Editor, *Handbook of Physiology: The Gastrointestinal System.* 1, Motility and Circulation. Bethesda, MD: American Physiological Society. Pp. 1179–1198.
105. Larson EB, Ellsworth AJ, Oas J. 1993. Randomized clinical trials in single patients during a 2-year period. *Journal of the American Medical Association* 270:2708–2712.
106. Leske MC, Connell AM, Schachat AP, Hyman L. 1994. The Barbados Eye Study: Prevalence of open angle glaucoma. *Archives of Ophthalmology* 112:821–829.
107. Levitt M, Faiman C, Hawks R, et al. 1984. Randomized double-blind comparison of delta-9-THC and marijuana as chemotherapy antiemetics. *Proceedings of the American Society for Clinical Oncology* 3:91.
108. Libman E, Stern MH. 1985. The effects of delta-9-tetrahydrocannabinol on cutaneous sensitivity and its relation to personality. *Personality, Individuality and Difference* 6:169–174.
109. Lichter PR. 1988. A wolf in sheep's clothing. *Ophthalmology* 95:149–150.
110. Lichtman AH, Cook SA, Martin BR. 1996. Investigation of brain sites mediating cannabinoid-induced antinociception in rats: Evidence supporting periaqueductal gray involvement. *Journal of Pharmacology and Experimental Therapeutics* 276:585–593.
111. Lichtman AH, Martin BR. 1991. Cannabinoid-induced antinociception is mediated by a spinal alpha-noradrenergic mechanism. *Brain Research* 559:309–314.
112. 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 (Berlin)* 74:208–212.
113. Macallan DC, Noble C, Baldwin C, Foskett M, McManus T, Griffin GE. 1993. Prospective analysis of patterns of weight change in stage IV human immunodeficiency virus infection. *American Journal of Clinical Nutrition* 58:417–424.
114. Malec J, Harvey RF, Cayner JJ. 1982. Cannabis effect on spasticity in spinal cord injury. *Archives of Physical Medicine and Rehabilitation* 63:116–118.

115. Mao LK, Stewart WC, Shields M. 1991. Correlation between intraocular pressure control and progressive glaucomatous damage in primary open-angle glaucoma. *American Journal of Ophthalmology* 111:51–55.
116. Marotta JT. 1995. Spinal injury. In: Rowland LP, Editor, *Merrit's Textbook of Neurology.* 9th Edition. Philadelphia: Lea and Febiger. Pp. 440–447.
117. Martyn CN, Illis LS, Thom J. 1995. Nabilone in the treatment of multiple sclerosis [Letter]. *Lancet* 345:579.
118. Mathew NT. 1997. Serotonin 1D (5-HT 1D) agonists and other agents in acute migraine. *Neurologic Clinics* 15:61–83.
119. Mattes RD, Engelman K, Shaw LM, Elsohly MA. 1994. Cannabinoids and appetite stimulation. *Pharmacology, Biochemistry and Behavior* 49:187–195.
120. Maurer M, Henn V, Dittrich A, Hoffman A. 1990. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. *European Archives of Psychiatry and Clinical Neuroscience* 240:1–4.
121. McCarthy LE, Flora KP, Vishnuvajjala BR. 1984. Antiemetic properties and plasma concentrations of delta-9-tetrahydrocannabinol against cisplatin vomiting in cats. In: Agurell S, Dewey WL, Willette RE, Editors, *The Cannabinoids: Chemical, Pharmacologic and Therapeutic Aspects.* Orlando, FL: Academic Press. Pp. 859–870.
122. McQuay H, Carroll D, Moore A. 1996. Variation in the placebo effect in randomised controlled trials of analgesics: All is as blind as it seems. *Pain* 64:331–335.
123. Meinck HM, Schonle PW, Conrad B. 1989. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. *Journal of Neurology* 236:120–122.
124. Merritt JC, Cook CE, Davis KH. 1982. Orthostatic hypotension after delta 9-tetrahydrocannabinol marihuana inhalation. *Ophthalmic Research* 14:124–128.
125. Merritt JC, Crawford WJ, Alexander PC, Anduze AL, Gelbart SS. 1980. Effect of marihuana on intraocular and blood pressure in glaucoma. *Ophthalmology* 87:222–228.
126. Mertens TE, Low-Beer D. 1996. HIV and AIDS: Where is the epidemic going? *Bulletin of the World Health Organization* 74:121–129.
127. Miller AD. 1998. Nausea and vomiting: Underlying mechanisms and upcoming treatments. *Journal of the Japanese Broncho-Esophagological Society* 49:57–64.
128. Miller AD, Nonaka S, Siniaia MS, Jakus J. 1995. Multifunctional ventral respiratory group: Bulospinal expiratory neurons play a role in pudendal discharge during vomiting. *Journal of the Autonomic Nervous System* 54:253–260.
129. Miller AS, Walker JM. 1995. Effects of a cannabinoid on spontaneous and evoked neuronal activity in the substantia nigra pars reticulata. *European Journal of Pharmacology* 279:179–185.
130. Miller AS, Walker JM. 1996. Electrophysiological effects of a cannabinoid on neural activity in the globus pallidus. *European Journal of Pharmacology* 304:29–35.
131. Moertel CG, Taylor WF, Roth A, Tyce FA. 1976. Who responds to sugar pills? *Mayo Clinic Proceedings* 51:96–100.
132. Moldawer LL, Andersson C, Gelin J, Lundholm KG. 1988. Regulation of food intake and hepatic protein synthesis by recombinant-derived cytokines. *American Journal of Physiology* 254:G450–G456.
133. Mulligan K, Tai VW, Schambelan M. 1997. Cross-sectional and longitudinal evaluation of body composition in men with HIV infection. *Journal of Acquired Immunodeficiency Syndrome* 15:43–48.
134. Murray CJL, Lopez AD. 1996. *Global Health Statistics: A Compendium of Incidence, Prevalence, and Mortality Estimates for Over 200 Conditions.* Global Burden of Disease and Injury Series, Volume II. Boston, MA: The Harvard School of Public Health.

135. Navari RM, Reinhardt RR, Gralla RJ, Kris MG, Hesketh PJ, et al. 1999. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. *The New England Journal of Medicine* 340:190–195.
136. Newell FW, Stark P, Jay WM, Schanzlin DJ. 1979. Nabilone: A pressure-reducing synthetic benzopyran in open-angle glaucoma. *Ophthalmology* 86:156–160.
137. Ng SKC, Brust JCM, Hauser WA, Susser M. 1990. Illicit drug use and the risk of new-onset seizures. *American Journal of Epidemiology* 132:47–57.
138. NIH. 1997. Spinal cord injury: Emerging concepts: An NIH workshop. *Proceedings of an NIH Workshop on Spinal Cord Injury*. Bethesda, MD, September 30–October 1, 1996. Bethesda, MD: National Institute of Neurological Disorders and Stroke.
139. Noyes R, Jr, Brunk SF, Avery DH, Canter A. 1975b. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clinical Pharmacology and Therapeutics* 18:84–89.
140. Noyes Jr R, Brunk SF, Baram DA, Canter A. 1975a. Analgesic effect of delta-9-tetrahydrocannabinol. *Journal of Clinical Pharmacology* 15:139–143.
141. Ohlsson A, Lindgren J-E, Wahlen A, Agurell S, Hollister LE, 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.
142. Orgul S, Kaiser HJ, Flammer J, Gasser P. 1995. Systemic blood pressure and capillary blood-cell velocity in glaucoma patients: A preliminary study. *European Journal of Ophthalmology* 5:88–91.
143. Orr LE, McKernan JF, Bloome B. 1980. Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. *Archives of Internal Medicine* 140:1431–1433.
144. Ott M, Lambke B, Fischer H, Jagre R, Polat H, Geier H, Rech M, Staszeswki S, Helm EB, Caspary WF. 1993. Early changes of body composition in human immunodeficiency virus-infected patients: Tetrapolar body impedance analysis indicates significant malnutrition. *American Journal of Clinical Nutrition* 57:15–19.
145. Perez EA, Chawla SP, Kaywin PK, et al. 1997. Efficacy and safety of oral granisetron versus IV ondansetron in prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. *Proceedings of the American Society for Clinical Oncology* 16:43.
146. Perez-Reyes M, Wagner D, Wall ME, Davis KH. 1976. Intravenous administration of cannabinoids and intraocular pressure. In: *The Pharmacology of Marihuana*, New York: Raven Press. Pp. 829–832.
147. Peroutka SJ. 1996. Drugs effective in the therapy of migraine. In: Hardman JG, Limbird LE, Editors, *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 9th Edition. New York: McGraw-Hill. Pp. 487–502.
148. Petro D, Ellenberger Jr C. 1981. Treatment of human spasticity with delta 9-tetrahydrocannabinol. *Journal of Clinical Pharmacology* 21:413S–416S.
149. Quigley HA. 1996. Number of people with glaucoma worldwide. *British Journal of Ophthalmology* 80:389–393.
150. Raft D, Gregg J, Ghia J, Harris L. 1977. Effects of intravenous tetrahydrocannabinol on experimental and surgical pain: Psychological correlates of the analgesic response. *Clinical Pharmacology and Therapeutics* 21:26–33.
151. Razdan RK. 1986. Structure-activity relationships in cannabinoids. *Pharmacology Review* 38:75–149.
152. Richfield EK, Herkenham M. 1994. Selective vulnerability in Huntington's disease: Preferential loss of cannabinoid receptors in lateral globus pallidus. *Annals of Neurology* 36:577–584.

153. Richter A, Loscher W. 1994. (+)-WIN55,212-2 A novel cannabinoid receptor agonist, exerts antidystonic effects in mutant dystonic hamsters. *European Journal of Pharmacology* 264:371–377.
154. 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.
155. Roila F, Tonato M, Cognetti F, et al. 1991. Prevention of cisplatin-induced emesis: A double-blind multicenter randomized crossover study comparing ondansetron and ondansetron plus dexamethasone. *Journal of Clinical Oncology* 9:674–678.
156. Rosenzweig MR, Leiman AL, Breedlove SM. 1996. *Biological Psychology*. Sunderland, MA: Sinauer Associates, Inc.
157. Roth RI, Owen RL, Keren DF, Volberding PA. 1985. Intestinal infection with Mycobacterium avium in acquired immune deficiency syndrome (AIDS): Histological and clinical comparison with Whipple's disease. *Digestive Disease Science* 30:497–504.
158. Süttmann U, Ockenga J, Selberg O, Hoogestraat L, Deicher H, Müller MJ. 1995. Incidence and prognostic value of malnutrition and wasting in human immunodeficiency virus—infected outpatients. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* 8:239–246.
159. Sackett D, Rosenberg W, Haynes B, Richardson S. 1997. *Evidence-Based Medicine: How to Practice and Teach EBM*. New York: Churchhill Livingston.
160. Sallan SE, Cronin CM, Zelen M, et al. 1980. Antiemetics in patients receiving chemotherapy for cancer: A randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *New England Journal of Medicine* 302:135–138.
161. Sallan SE, Zinberg NE, Frei E. 1975. Antiemetic effect of delta-9-THC in patients receiving cancer chemotherapy. *New England Journal of Medicine* 293:795–797.
162. 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.
163. Sandyk R, Awerbuch G. 1988. Marijuana and Tourette's syndrome. *Journal of Clinical Psychopharmacology* 8:444–445.
164. Sandyk R, Consroe P, Stern P, Biklen D. 1988. Preliminary trial of cannabidiol in Huntington's disease. Chesher G, Consroe P, Musty R., Editors, *Marijuana: An International Research Report*. Canberra: Australian Government Publishing Service.
165. Sanudo-Pena MC, Patrick SL, Patrick RL, Walker JM. 1996. Effects of intranigral cannabinoids on rotational behavior in rats: Interactions with the dopaminergic system. *Neuroscience Letters* 206:21–24.
166. Sanudo-Pena MC, Tsou K, and Walker JM. Cannabinoid dopamine interactions in the basal ganglia in an animal model of Parkinson disease. (in preparation).
167. Sanudo-Pena MC, Tsou K, and Walker JM. Superior colliculus and turning: Dopamine and cannabinoids. (in preparation).
168. 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.
169. Sanudo-Pena MC, Walker JM. 1998. Effects of intrastriatal cannabinoids on rotational behavior in rats: Interactions with the dopaminergic system. *Synapse* 30:221–226.
170. Schambelan M, Mulligan K, Grunfeld C, Daar ES, LaMarca A, Kotler DP. 1996. Recombinant human growth hormone in patients with HIV-associated wasting: A randomized, placebo-controlled trial: Serostim Study Group. *Annals of Internal Medicine* 125:873–882.
171. Schwartz RH, Beveridge RA. 1994. Marijuana as an antiemetic drug: How useful is it today? Opinions from clinical oncologists [see Comments]. *Journal of Addictive Diseases* 13:53–65.

172. Schwartz RH, Voth EA. 1995. Marijuana as medicine: Making a silk purse out of a sow's ear. *Journal of Addictive Diseases* 14:15–21.
173. Shields MB. 1998. *Textbook of Glaucoma*. 4th Edition. Baltimore, MD: Williams & Wilkins.
174. Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt J, Singh K. 1991. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans: The Baltimore Eye Survey. *Archives of Ophthalmology* 109:1090–1095.
175. Staquet M, Gantt C, Machin D. 1978. Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. *Clinical Pharmacology and Therapeutics* 23:397–401.
176. Steele N, Gralla RJ, Braun Jr DW. 1980. Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. *Cancer Treatments Report* 64:219–224.
177. Stimmel B. 1995. Medical marijuana: To prescribe or not to prescribe, that is the question [Editorial]. *Journal of Addictive Diseases* 14:1–3.
178. Strassman RJ. 1998. *Marijuana: The Forbidden Medicine* (book review). *Journal of the American Medical Association* 279:963–964.
179. Struwe M, Kaempfer SH, Geiger CJ, Pavia AT, Plasse TF, Shepard KV, Ries K, Evans TG. 1993. Effect of dronabinol on nutritional status in HIV infection. *Annals of Pharmacotherapy* 27:827–831.
180. Swift RM. 1994. *Marijuana: The Forbidden Medicine* (book review). *The New England Journal of Medicine* 331:749–750.
181. 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.
182. Tiedeman JS, Shields MB, Weber PA, Crow JW, Cocchetto DM, Harris WA, Howes JF. 1981. Effect of synthetic cannabinoids on elevated intraocular pressure. *Ophthalmology* 88:270–277.
183. Timpone JG, Wright DJ, Li N, Egorin MJ, Enama ME, Mayers J, Galetto G, DATRI 004 Study Group. 1997. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome: The DATRI 004 study group. *AIDS Research and Human Retroviruses* 13:305–315.
184. Trembly B, Sherman M. 1990. Double-blind clinical study of cannabidiol as a secondary anticonvulsant. Unpublished manuscript presented at the Marijuana '90 International Conference on Cannabis and Cannabinoids. Kolympari, Crete, July 8–11.
185. Tyson LB, Gralla RJ, Clark RA, et al. 1985. Phase I trial of levonantradol in chemotherapy-induced emesis. *American Journal of Clinical Oncology* 8:528–532.
186. UNAIDS, WHO. 1998. *Report on the Global HIV/AIDS Epidemic, June 1998.*
187. Ungerleider JT, Andrysiak TA, Fairbanks L, Ellison GW, Myers LW. 1987. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. *Advances in Alcohol and Substance Abuse* 7:39–50.
188. Vinciguerra V, Moore T, Brennan E. 1988. Inhalation marijuana as an antiemetic for cancer chemotherapy. *New York State Journal of Medicine* 88:525–527.
189. Volicer L, Smith S, Volicer BJ. 1995. Effect of seizures on progression of dementia of the Alzheimer type. *Dementia* 6:258–263.
190. Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. 1997. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry* 12:913–919.
191. Voth EA, Schwartz RH. 1997. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. *Annals of Internal Medicine* 126:791–798.

192. Wall PD, Melzack R. 1994. *Textbook of Pain*. Edinburgh: Churchill Livingstone.
193. Walters TR. 1996. Development and use of brimonidine in treating acute and chronic elevations of intraocular pressure: A review of safety, efficacy, dose response, and dosing studies. *Survey of Ophthalmology* 41(Suppl. 1):S19–S26.
194. Wang ZM, Visser M, Ma R, Baumgartner RN, Kotler DP, Gallagher D, Heymsfield SB. 1996. Skeletal muscle mass: Validation of neutron activation and dual energy X-ray absorptiometry methods by computerized tomography. *Journal of Applied Physiology* 80:824–831.
195. Whitney EN, Cataldo CB, Rolfes SR. 1994. *Understanding Normal and Clinical Nutrition*. 4th Edition. Minneapolis, MN: West Publishing Co.
196. Wood. 1998. HIV-protease inhibitors. *Drug Therapy* 338:1281–1292.
197. Yoles E, Belkin M, Schwartz M. 1996. HU-211, a nonpsychotropic cannabinoid, produces short- and long-term neuroprotection after optic nerve axotomy. *Journal of Neurotrauma* 13:49–57.
198. Zimmer L, Morgan JP. 1997. *Marijuana Myths, Marijuana Facts*. New York: The Lindesmith Center.

5

Development of Cannabinoid Drugs

Medicines today are expected to be of known composition and quality. Even in cases where marijuana can provide relief of symptoms, the crude plant mixture does not meet this modern expectation. The future of medical marijuana lies in classical pharmacological drug development, and indeed there has been a resurgence of scientific, as well as public, interest in the therapeutic applications of cannabinoids. After an initial burst of scientific activity in the 1970s, today's renewed interest has been fueled by major scientific discoveries discussed in previous chapters: the identification and cloning of endogenous cannabinoid receptors, the discovery of endogenous substances that bind to these receptors, and the emergence of synthetic cannabinoids that also bind to cannabinoid receptors. These scientific accomplishments have propelled interest in developing new drugs that can treat more effectively or more safely the constellation of symptoms for which cannabinoids might have therapeutic benefit (see chapter 4). Through the process of what is referred to as "rational drug design," scientists manipulate the chemical structures of known cannabinoids to design better therapeutic agents. Several new cannabinoids are being developed for human use, but none has reached the stage of human testing in the United States.

The purpose of this chapter is to describe the process of and analyze the prospects for development of cannabinoid drugs. It first discusses the regulatory hurdles that every new drug encounters en route to market. It then proceeds to describe the regulatory and market experiences of

dronabinol (tetrahydrocannabinol, or THC, in sesame oil), the only approved cannabinoid in the United States. These sections serve as a road map to determine whether the therapeutic potential of cannabinoids is likely to be exploited commercially to meet patient needs. Finally, the chapter describes what would be needed to bring marijuana to market as a medicinal plant.

The term *cannabinoids* is used in this chapter to refer to a group of substances that are structurally related to THC—by virtue of a tricyclic chemical structure—or that bind to cannabinoid receptors, such as the natural ligand anandamide. From a chemist's point of view, this definition encompasses a variety of distinct chemical classes. But because the purpose of this chapter is to explore prospects for drug development, both chemical structure and pharmacological activity are important; therefore, the broader definition of cannabinoids is used.

FEDERAL DRUG DEVELOPMENT POLICY

Like controlled substances, cannabinoids developed for medical use encounter a gauntlet of public health regulatory controls administered by two federal agencies: the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (DHHS) and the Drug Enforcement Administration (DEA) of the U.S. Department of Justice. The FDA regulates human testing and the introduction of new drugs into the marketplace, whereas the DEA determines the schedule of and establishes production quotas for drugs with potential for abuse to prevent their diversion to illicit channels. The DEA also authorizes registered physicians to prescribe controlled substances. Some drugs, such as marijuana, are labeled Schedule I in the Controlled Substance Act, and this adds considerable complexity and expense to their clinical evaluation. It is important to point out that Schedule I status does not necessarily apply to all cannabinoids.

Food and Drug Administration

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, the FDA approves new drugs for entry into the marketplace after their safety and efficacy are established through controlled clinical trials conducted by the drugs' sponsors.[23] FDA approval of a drug is the culmination of a long, research intensive process of drug development, which often takes well over a decade.[19,44] Drug development is performed largely by pharmaceutical companies, but some targeted drug development programs are sponsored by the National Institutes of Health (NIH) to stimulate further development and marketing by the private sector. The NIH's drug devel-

opment programs—including those for AIDS, cancer, addiction, and epilepsy—have been instrumental in ushering new drugs to market in collaboration with pharmaceutical companies.[33] In fact, as noted later, most of the preclinical and clinical research on dronabinol was supported by NIH.

Drug development begins with discovery, that is, the synthesis and purification of a new compound with expected biological activity and therapeutic value. The next major step is the testing of the compound in animals to learn more about its safety and efficacy and to predict its utility for humans. Those early activities are collectively referred to as the preclinical phase. When evidence from the preclinical phase suggests a promising role in humans, the manufacturer submits an Investigational New Drug (IND) application to the FDA. The IND submission contains a plan for human clinical trials and includes the results of preclinical testing and other information.[20] Absent FDA objection, the IND becomes effective after 30 days, allowing the manufacturer to conduct clinical testing (testing in humans), which generally involves three phases (see Figure 5.1). The three stages of clinical testing are usually the most time-consuming phases of drug development, lasting five years on average.[22] The actual time depends on the complexity of the drug, availability of patients, duration of use, difficulty of measuring clinical end points, therapeutic class, and indication (the disease or condition for which the drug has purported benefits).[31]

Drug development is a long and financially risky process. For every drug that ultimately reaches clinical testing through an IND, thousands of drugs are synthesized and tested in the laboratory. And only about one in five drugs initially tested in humans successfully secures FDA approval for marketing through a new drug application (NDA).[19]

The manufacturer submits an NDA to the FDA to gain approval for marketing when clinical testing is complete. An NDA is a massive document, the largest portion of which contains the clinical data from Phase I–III testing. The other technical sections of an NDA include chemistry, manufacturing, and controls; nonclinical pharmacology and toxicology; and human pharmacokinetics and bioavailability.[23] In the case of a new cannabinoid, an abuse liability assessment would also probably be part of an NDA submission. In 1996 the median time for FDA review of an NDA, from submission to approval, was 15.1 months, a review period considerably shorter than that in 1990, when the figure was 24.3 months.[22] The shortening of approval time is an outgrowth of the Prescription Drug User Fee Act of 1992, which authorized the FDA to hire additional review staff with so-called user fees paid by industry and imposed clear deadlines for FDA action on an NDA. With respect to the cost of a single drug's development, a number of recent studies have provided a range of estimates of

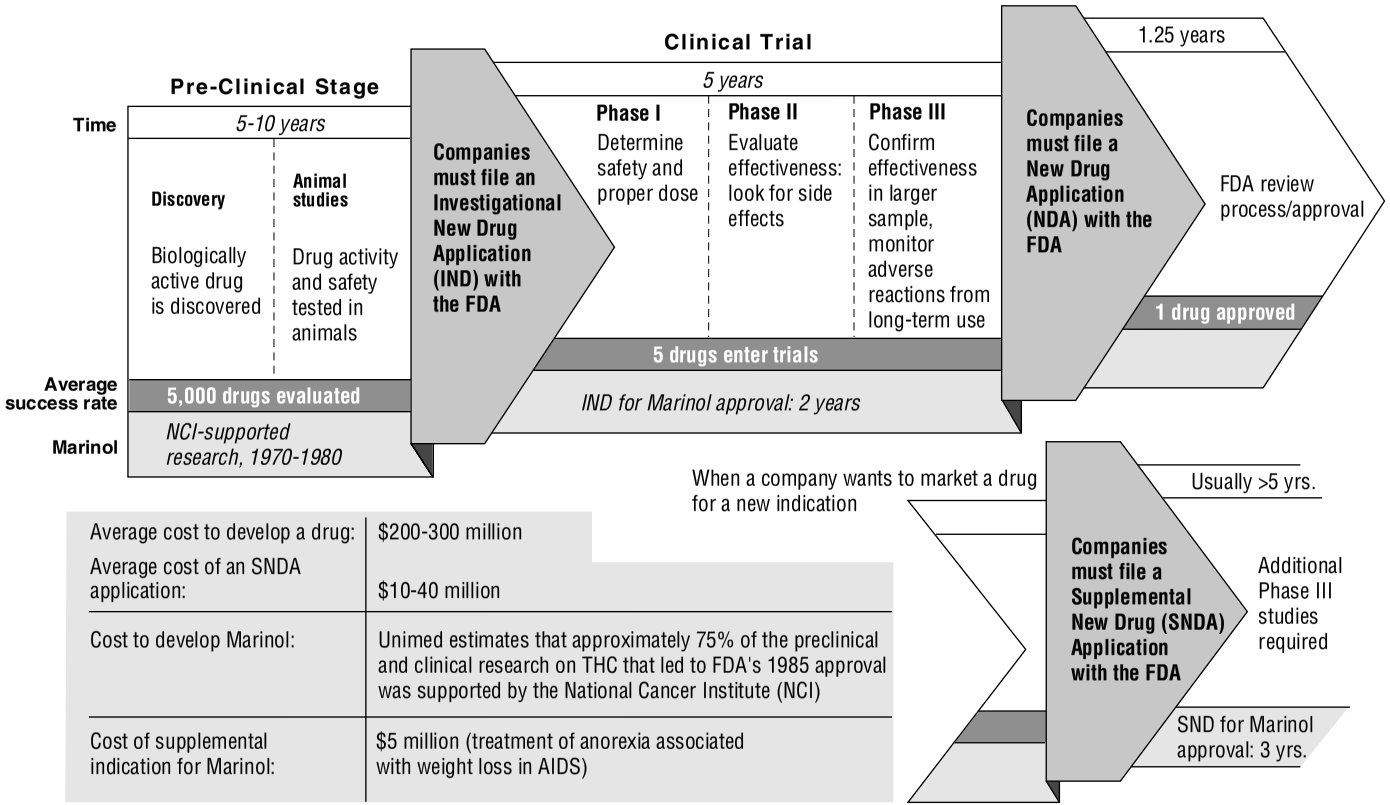

FIGURE 5.1 Stages of clinical testing.

about $200–$300 million, depending on the method and year of calculation.[33,44]

With FDA approval of an NDA, the manufacturer is permitted to market the drug for the *approved indication*. At that point, although any physician is at liberty to prescribe the approved drug for another indication (an "off-label use"), the manufacturer cannot promote it for that indication unless the new indication is granted separate marketing approval by the FDA.* To obtain such approval, the manufacturer is required to compile another application to the FDA for what is known variously as an "efficacy supplement," a "supplemental application," or a "supplemental new drug application." Those terms connote that the application is supplemental to the NDA. In general, collecting new data for FDA approval of an efficacy supplement is not as intensive a process as that for an NDA; it generally requires the firm to conduct two additional Phase III studies, although under some circumstances only one additional study of the drug's efficacy is needed.[24] The preclinical studies, for example, ordinarily need not be replicated. The average cost to the manufacturer for obtaining approval for the new indication is typically about $10–$40 million.[33] The review time to obtain FDA approval for the new indication can be considerable; a recent study of supplemental indications approved by the FDA in 1989–1994 found the approval time to exceed that for the original NDA,[18] a reflection, in part, of the lower priority that the FDA accords to the review of efficacy supplements as opposed to new drugs.[23]

The manufacturer also must apply to the FDA to receive marketing approval for a new formulation of a previously approved drug. A new formulation is a new dosage form, including a new route of administration. An example of such a new formulation is an inhaled version of Marinol, which is currently approved only in capsule form. The manufacturer is required to establish bioequivalence, safety, and efficacy of the new formulation. The amount of evidence required for approval is highly variable, depending on the similarities between the new formulation and the approved formulation. New formulations are evaluated case by case by the FDA. In the case of Marinol, for example, an inhaled version is likely to require not only new studies of efficacy but also new studies of abuse liability. There appear to be no published peer-reviewed studies of the average cost and time for approval of a new formulation.

Two other FDA programs might be relevant to the potential availabil-

*FDA policies for off-label use are being transformed as a result of the Food and Drug Administration Modernization Act of 1997. The FDA recently promulgated new rules to give manufacturers greater flexibility to disseminate information about off-label uses (FDA, 1998b[24a]). As of this writing, however, court decisions have left the status of the new rules somewhat unclear.

ity of new cannabinoids. One program is authorized under the Orphan Drug Act of 1983, which provides incentives to manufacturers to develop drugs to treat "orphan diseases." An orphan disease, as defined in an amendment to the act, is one that affects 200,000 or fewer people in the United States.* The act's most important incentive is a period of exclusive marketing protection of seven years, during which time the FDA is prohibited from approving the same drug for the same indication.[5,6] Some of the medical conditions for which cannabinoids have been advocated—Huntington's disease, multiple sclerosis, and spinal cord injury (see chapter 4)—might meet the definition of an orphan disease and thus enable manufacturers to take advantage of the act's financial incentives to bring products to market. If a disease affects more than 200,000 people, the manufacturer sometimes subdivides the patient population into smaller units to qualify. For example, a drug for the treatment of Parkinson's disease is not likely to receive an orphan designation because its prevalence exceeds 200,000, but orphan designation has been accorded to drugs for subsets of Parkinson's patients, such as those suffering from early-morning motor dysfunction in the late stages of the disease.[25]

The other program is the Treatment-IND program, which was established by regulation in 1987 (and codified into law in 1997) to allow patients with serious and life-threatening diseases to obtain experimental medications, such as marijuana, before their general marketing.† Treatment INDs may be issued during Phase III studies to patients who are not enrolled in clinical trials, provided among other requirements that no comparable alternative drug is available.[22,32,33] Thus, the treatment IND program can provide a mechanism for some patients to obtain a promising new cannabinoid before its widespread commercial availability if it reached the late stages of clinical testing for a serious or life-threatening disease.

Drug Enforcement Administration

The DEA is responsible for scheduling controlled substances, that is, drugs and other agents that possess a potential for abuse. *Abuse* is generally defined as nonmedical use that leads to health and safety hazards, diversion from legitimate channels, self-administration, and other untoward results.[15,21] The legislation that gives DEA the authority to regulate

*The FDA can grant orphan designation to a drug intended for a condition that affects a larger population if the manufacturer's estimated expenses are unlikely to be recovered by sales in the United States (Public Law 98-551).

†Marijuana cigarettes were available under a special FDA-sponsored Compassionate Investigational New Drug Program for desperately ill patients until March 1992, when the program was closed to new participants.[48]

drugs of abuse is the Controlled Substances Act, which was passed in 1970 and amended several times. The overall purpose of the CSA is to restrict or control the availability of drugs to prevent their abuse.

Under the CSA, the DEA places each drug that has abuse potential into one of five categories. The five categories, referred to as Schedules I–V, carry different degrees of restriction. Schedule I is the most restrictive, covering drugs that have "no accepted medical use" in the United States and that have high abuse potential. The definitions of the categories and examples of drugs in each are listed in Appendix C. Each schedule is associated with a distinct set of controls that affect manufacturers, investigators, pharmacists, practitioners, patients, and recreational users. The controls include registration with the DEA, labeling and packaging, production quotas, security, recordkeeping, and dispensing.[15] For instance, patients with a legitimate medical need for drugs in Schedule II, the most restrictive schedule for drugs "currently with accepted medical use," can neither refill their prescriptions nor have them telephoned to a pharmacy (except in an emergency).

The scheduling of substances under the CSA is handled case by case. It may be initiated by DEA, by DHHS, or by petition from an interested party, including the drug's manufacturer or a public-interest group.[15] The final decision for scheduling rests with the DEA, but for this purpose the secretary of DHHS is mandated to provide a recommendation. The secretary's recommendation* to DEA is based in part on results from abuse liability testing that the FDA requires of the manufacturer seeking approval of a new drug. Abuse liability testing is not a single test; it is a compilation of several *in vitro* human and animal studies, of which some of the best known are drug self-administration and drug discrimination studies.[21,34] The secretary's recommendation for scheduling is formally guided by eight legal criteria, including the drug's actual or relative potential for abuse, scientific evidence of its pharmacological effect, risk to public health, and its psychic or physiological dependence liability (21 U.S.C. § 811 (b), (c)). Once the DEA receives a scheduling recommendation, its scheduling decision, including the requirement for obtaining public comment, usually takes weeks to months.[33] In practice, the DEA usually adheres to the recommendation of the secretary.† Beyond the DEA,

*The FDA and the National Institute of Drug Abuse, two agencies of DHHS, work jointly to develop the medical and scientific analysis that is forwarded to the secretary, who makes a recommendation to the administrator of the DEA (DEA, 1998[15]).

†Under the CSA, "the recommendations of the Secretary to the Attorney General shall be binding on the Attorney General as to such scientific and medical matters, and if the Secretary recommends that a drug or other substance not be controlled, the Attorney General shall not control the drug or other substance" (21 U.S.C.§ 811 (b)).

various state scheduling laws also affect the manufacture and distribution of controlled substances.[33,50]

Under the CSA, marijuana and THC* are in Schedule I, the most restrictive schedule. The scheduling of any other cannabinoid under this act first hinges on whether it is found *in the plant*. All cannabinoids in the plant are automatically in Schedule I because they fall under the act's definition of marijuana (21 U.S.C. § 802 (16)). In addition, under DEA's regulations, synthetic equivalents of the substances contained in the plant and "synthetic substances, derivatives, and their isomers" whose "chemical structure and pharmacological activity" are "similar" to THC also are automatically in Schedule I (21 CFR § 1308.11(d)(27). Based on the examples listed in the regulations, the word *similar* probably limits the applicability of the regulation to isomers of THC, but DEA's interpretation of its own regulations would carry significant weight in any specific situation.

Prompted by a 1995 petition from Jon Gettman, a former president of the National Organization for the Reform of Marijuana Laws (NORML), to remove marijuana and THC from Schedule I, DEA gathered information which was then submitted to DHHS for a medical and scientific recommendation and scheduling recommendation, as required by the CSA. For the reasons noted above, any changes in scheduling of marijuana and THC would also affect other plant cannabinoids. For the present, however, any cannabinoid found in the plant is automatically controlled in Schedule I.

Investigators are affected by Schedule I requirements even if their research is being conducted *in vitro* or on animals. For example, researchers studying cannabinoids found in the plant are required under the CSA to submit their research protocol to DEA, which issues a registration that is contingent on FDA's evaluation and approval of the protocol (21 CFR § 1301.18). DEA also inspects the researcher's security arrangements. However, the regulatory implications are quite different for cannabinoids *not found in the plant*. Such cannabinoids appear to be unscheduled unless the FDA or DEA decides that they are sufficiently similar to THC to be placed automatically into Schedule I under the regulatory definition outlined above or the FDA or the manufacturer deems them to have potential for abuse, thereby triggering *de novo* the scheduling process noted above. Thus far, the cannabinoids most commonly used in preclinical research (Table 5.1) appear to be sufficiently distinct from THC that they are not currently considered controlled substances by definition (F. Sapienza, DEA, personal communication, 1998). No new cannabinoids other than

*Technically, the CSA and the regulations use the term "tetrahydrocannabinols."

TABLE 5.1 Cannabinoids and Related Compounds Commonly Used in Research

Agonists
THC
WIN 55,212-2
CP-55940
HU-210
Anandamide (natural ligand)
2-Arachidonylglycerol (natural ligand)
Antagonists
SR 141716A
SR 144528

SOURCES: Felder and Glass (1998)[26] and Mechoulam et al. (1998).[36]

THC have yet been clinically tested in the United States, so scheduling experience is limited. The unscheduled status of some cannabinoids might change as research progresses. Results of early clinical research could lead a manufacturer to proceed with or lead the FDA to require abuse liability testing. Depending on the results of such studies, DHHS might or might not recommend scheduling *de novo* to DEA, which makes the final decision case by case.

Will newly discovered cannabinoids be subject to scheduling? That is a complex question that has no simple answer. The answer depends entirely on each new cannabinoid—whether it is found in the plant, its chemical and pharmacological relationship to THC, and its potential for abuse. Novel cannabinoids with strong similarity to THC are likely to be scheduled at some point before marketing, whereas those with weak similarity might not be. The manufacturer's submission to FDA, which contains its own studies and its request for a particular schedule, can also shape the outcome. Cannabinoids found in the plant are automatically in Schedule I until the manufacturer requests and provides justification for rescheduling. The CSA does permit DEA to reschedule a substance (move it to a different schedule) and to deschedule a substance (remove it from control under the CSA) according to the scheduling criteria (see Appendix F) and the process outlined above.

The possibility of scheduling is a major determinant of whether a manufacturer proceeds with drug development.[33] In general, pharmaceutical firms perceive scheduling to be a deterrent because it limits their ability to achieve market share for the following reasons: restricted access,

physician disinclination to prescribe scheduled substances, stigma, the additional expense for abuse liability studies, and expensive delays in reaching the market due to federal and state scheduling processes.[33] Empirical evidence to support that widely held perception is difficult to find, but at least one large survey of physicians found them to have moderate concerns about prescribing opioids because of actual or perceived pressure from regulatory agencies, such as DEA.[57] On the basis of a legal analysis and widespread complaints from researchers and pharmaceutical executives, the Institute of Medicine (IOM, 1995)[33] recommended changes in the CSA to eliminate the act's barriers to undertaking clinical research and development of controlled substances; this position was supported in a later report on marijuana.[40]

DEVELOPMENT AND MARKETING OF MARINOL

The following material is based on the published literature (where cited), workshops sponsored by the IOM, and an interview with Robert Dudley, senior vice president of Unimed Pharmaceuticals, Inc., the manufacturer of Marinol and the holder of the NDA. Unimed markets Marinol jointly with Roxane Laboratories, Inc.

Marinol (dronabinol) is the only cannabinoid with approval for marketing in the United States.* The following description covers its development, regulatory history, pharmacokinetics, adverse effects, abuse liability, and market growth. The experience with Marinol can serve as a possible bellwether for the regulatory and commercial fate of new cannabinoids being considered for development.

Development and Regulatory History

Marinol is manufactured as a capsule containing THC in sesame oil; it is taken orally. It was approved by the FDA in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy. In 1992, the FDA approved marketing of dronabinol for the treatment of anorexia associated with weight loss in patients with AIDS.[45] The preclinical and clinical research on THC that culminated in the FDA's 1985 approval was supported primarily by the National Cancer Institute (NCI), whose research support goes back to the 1970s. NCI's contribution appears pivotal, considering that Unimed, the pharmaceutical company that holds

*The only cannabinoid licensed outside the United States is nabilone (Cesamet), which is an analogue of THC available in the United Kingdom for the management of nausea and vomiting associated with cancer chemotherapy (Pertwee, 1997).[46]

the NDA, estimates its contribution to have been only about 25% of the total research effort. The FDA's review and approval of Marinol took about two years after submission of the NDA, according to Unimed. To obtain approval for Marinol's second indication (through an efficacy supplement), the FDA required two more relatively small Phase III studies. The studies lasted three years and cost $5 million to complete.

Physical Properties, Pharmacokinetics, and Adverse Events

Marinol is synthesized in the laboratory rather than extracted from the plant. Its manufacture is complex and expensive because of the numerous steps needed for purification. The poor solubility of Marinol in aqueous solutions and its high first-pass metabolism in the liver account for its poor bioavailability; only 10–20% of an oral dose reaches the systemic circulation.[45,60] The onset of action is slow; peak plasma concentrations are not attained until two to four hours after dosing.[45,56] In contrast, inhaled marijuana is rapidly absorbed. In a study comparing THC administered orally, by inhalation, and intravenously, plasma concentration peaked almost instantaneously after both inhalation and intravenous administration; most participants' peak plasma concentrations after oral administration occurred at 60 or 90 minutes. Variation in individual responses is highest for oral THC and bioavailability is lowest.[42]

Marinol's most common adverse events are associated with the central nervous system (CNS): anxiety, confusion, depersonalization, dizziness, euphoria, dysphoria, somnolence, and thinking abnormality.[8,9,45,59] In two recent clinical trials, CNS adverse events occurred in about one-third of patients, but only a small percentage discontinued the drug because of adverse effects.[8,9] Lowering the dose of dronabinol can minimize side effects, especially dysphoria (disquiet or malaise).[47]

Abuse Potential and Scheduling

On commercial introduction in 1985, Marinol was placed in Schedule II. This schedule, the second most restrictive, is reserved for medically approved substances that have "high potential for abuse" (21 U.S.C. § 812 (b) (2)). Unimed did not encounter any delays in marketing as a result of the scheduling process because the scheduling decision was made by the DEA before FDA's approval for marketing. Nor did Unimed encounter any marketing delays as a result of state scheduling laws. Unimed was not specifically asked by the FDA to perform abuse liability studies for the first approval, presumably because such studies had been conducted earlier.

Unimed later petitioned the DEA to reschedule Marinol from Sched-

ule II to Schedule III, which is reserved for medically approved substances that have some potential for abuse (21 U.S.C. § 812 (b) (3)). To buttress its request for rescheduling, Unimed supported an analysis of Marinol's abuse liability by researchers at the Haight Ashbury Free Clinic of San Francisco, which treats many cannabis-dependent patients and people who have HIV/AIDS. The analysis found no evidence of abuse or diversion of Marinol after a literature review and surveys and interviews of medical specialists in addiction, oncology, cancer research, and treatment of HIV, and people in law enforcement. The authors attribute Marinol's low abuse potential to its slow onset of action, its dysphoric effects, and other factors.[12] On November 5, 1998, the DEA announced a proposal to reschedule Marinol to Schedule III.[17] As of this writing, no formal action on that proposal had been taken.

The rescheduling of a drug from Schedule II to Schedule III is considered important because it lifts some of the restrictions on availability. For example, Unimed expects a sales increase of about 15–20% as a result of rescheduling. In its judgment and that of many other pharmaceutical companies,[33] scheduling limits market penetration; the more restrictive the schedules, the greater the limitation. The reasons are that physicians and other providers are reluctant to prescribe Schedule II drugs; patients are deterred from seeking prescriptions because of Schedule II prohibition of refills, as opposed to other commercially available scheduled substances; additional restrictions are imposed by several states, such as quantity restrictions (for example, 30-day supply limits) and triplicate prescriptions;[50] and some Schedule II drugs are excluded from hospital formularies because of onerous security and paperwork requirements under federal and state controlled substances laws.

Market Growth and Transformation

Annual sales of Marinol are estimated at $20 million, according to Unimed. Of Marinol's patient population 80% use it for HIV, 10% for cancer chemotherapy, and about 5–10% for other reasons. The latter group is thought to consist of Alzheimer's patients drawn to the drug by a recently published clinical study indicating Marinol's promise for the treatment of their anorexia and disturbed behavior.[58] As noted earlier, Unimed cannot promote Marinol for this unlabeled indication, but physicians are free to prescribe it for such an indication. Unimed is conducting additional research in pursuit of FDA approval of a new indication for Marinol in the treatment of Alzheimer disease.

The 1992 approval of Marinol for the treatment of anorexia in AIDS patients marked a major transformation in the composition of the patient population. Marinol's use had been restricted to oncology patients. The

oncology market for Marinol gradually receded as a result of the introduction of newer medications, including such serotonin antagonists as ondansetron, which are more effective (see chapter 4, "Nausea and Vomiting) and are not scheduled. Much of the recent growth of the market for Marinol (which is about 10% per year) is attributed to its increasing use by HIV patients being treated with combination antiretroviral therapy. Marinol appears to have a dual effect, not only stimulating appetite but also combating the nausea and vomiting associated with combination therapy. Unimed is supporting a Phase II study to examine this combined effect and, with promising results, plans to seek FDA approval for this new indication.

Unimed has two forms of market protection for Marinol. In December 1992, the FDA granted Marinol seven years of exclusive marketing under the Orphan Drug Act. The market exclusivity is related to Marinol's use in anorexia associated with AIDS. Because of the designated orphan indication, the active ingredient, THC, cannot be marketed by another manufacturer for the same indication until December 1999. Other pharmaceutical manufacturers are not constrained from manufacturing and marketing THC for its *other* indication, antiemesis for cancer chemotherapy, but none appears to be interested in what is, by pharmaceutical company standards, a small market. In addition to market exclusivity, Unimed secured in June 1998 a "use patent" for dronabinol for the treatment of disturbed patients with dementia; this confers patent protection to Unimed for this use for 20 years from the date of filing of the application,* assuming that this indication eventually gains FDA approval.

The rate-limiting factors in the growth of the market for Marinol, according to Unimed are the lack of physician awareness of the drug's efficacy, its adverse effects, and its restricted availability as a result of placement in Schedule II. Unimed perceives only a small percentage of its market to be lost to "competition" from marijuana itself, but there are, admittedly, no reliable statistics on the number of people who have chosen to treat their symptoms with illegally obtained marijuana, despite their ability to obtain Marinol.

New Routes of Administration

It is well recognized that Marinol's oral route of administration hampers its effectiveness because of slow absorption and patients' desire for

*A use patent—also known as a process patent—accords protection for a method of using a composition or compound. A use patent is not considered as strong as a product patent, which prohibits others from manufacturing, using, or selling the product for all uses, rather than for the specific use defined in a use patent.

more control over dosing. A drug delivered orally is first absorbed from the stomach or small intestine and then passed through the liver, where it undergoes some metabolism before being introduced into the circulation. To overcome the deficiencies of oral administration, Unimed activated an IND in 1998 as a step toward developing new formulations for Marinol. Four new formulations—deep lung aerosol, nasal spray, nasal gel, and sublingual preparation—are under study in Phase I clinical studies being conducted in conjunction with Roxane Laboratories. These formulations seek to deliver Marinol to the circulation more rapidly and directly. The first two fall under inhalation as a route of administration. Inhalation is considered the most promising method, owing to the rapidity of onset of its effects and potential for better titration of the dose by the patient, but it might also carry an increased potential for abuse. The abuse of a drug correlates with its rapidity of onset (G. Koob, IOM workshop). Sublingual route (under the tongue) administration also affords rapid absorption into the circulation, in this case from the oral mucosa. Other researchers are pursuing the delivery of THC through rectal suppositories, but this slower route might not be acceptable to many patients. Transdermal (skin patches) administration, which is best suited to hydrophilic drugs, is precluded by the lipophilicity of THC. Thus, the choice of routes of administration depends heavily on the physicochemical characteristics of the drug and on its safety, abuse liability, and tolerability.

Unimed expects the FDA to require it to conduct studies of the bioavailability, efficacy, and possibly abuse liability of any new formulation it seeks to market. Any formulation that expedites Marinol's onset of action, as suggested above, is thought to carry greater possibility of abuse. The cost of developing each new formulation is estimated by Unimed at $7–$10 million.

Unimed and Roxane are developing, or considering development of, five new indications for Marinol: disturbed behavior in Alzheimer's disease, nausea and vomiting in HIV patients who are receiving combination therapy, spasticity in multiple sclerosis, intractable pain, and anorexia in cancer and renal disease.

Costs of Marinol and Marijuana

During the IOM public workshops held during the course of this study, many people commented that an important advantage of using marijuana for medical purposes is that it is much less expensive than Marinol. But this comparison is deceptive. While the direct costs of marijuana are relatively low, the indirect costs can be prohibitive. Individuals who violate federal or state marijuana laws risk a variety of costs associated with engaging in criminal activity, ranging from increased vulner-

ability to theft and personal injury legal fees to long prison terms. In addition, when purchasing illicit drugs there is no guarantee that the product purchased is what the seller claims it is or that it is not contaminated.

The price of Marinol for its most commonly used indication, anorexia in AIDS, is estimated at $200 per month. The less common indication—nausea and vomiting with cancer chemotherapy—is not as expensive because it is not chronic. Regardless of indication, patients' out-of-pocket expenses tend to be much less—often minimal—because of reimbursement through public or private health insurance. For indigent patients who are uninsured, Roxane sponsors a patient assistance program to defray the cost.

The street value of marijuana, according to the DEA's most recent figures, is about $5–$10 per bag of loose plant.[16]* At the California buyers' clubs, the price is $2–$16 per gram, depending on the grade of marijuana. The cost to a patient using marijuana depends on the number of cigarettes smoked each day, their THC content, and the duration of use. Insurance does not cover the cost of marijuana. In addition, it is possible for a person to cultivate marijuana privately with little financial investment.

Thus, Marinol appears to be less expensive than marijuana for patients with health insurance or with financial assistance from Roxane. But if the full cost of Marinol is borne out of pocket by the patient, the cost comparison is not so unambiguous. In this case the daily cost in relation to marijuana varies according to the number of cigarettes smoked: If the patient smokes two or more marijuana cigarettes per day, Marinol might be less expensive than marijuana; if the patient smokes only one marijuana cigarette per day, Marinol might be more expensive than marijuana, according to an analysis submitted to the DEA by Unimed. The cost comparisons will depend on fluctuations in the retail price and street value of Marinol and marijuana, respectively, and will vary if marijuana becomes commercially available.

In summary, Marinol has been on the U.S. market since 1985. Its commercial development depended heavily on research supported by the NIH. Marinol's market has grown to $20 million in annual sales. Further market growth is expected but is still constrained by lack of awareness, adverse effects, the oral route of administration, and restrictions imposed by drug scheduling. The manufacturer is proceeding with research on new forms of delivery to overcome the problems associated with oral administration. The manufacturer also is proceeding with research on an array of new indications for Marinol.

*The DEA did not provide an estimate of the weight of marijuana per bag.

MARKET OUTLOOK FOR CANNABINOIDS

The potential therapeutic value of cannabinoids is extremely broad. It extends well beyond antiemesis for chemotherapy and appetite stimulation for AIDS, the two indications for which the FDA has approved dronabinol (Marinol). Chapter 4 of this report assesses the possible wider therapeutic potential of marijuana and THC in neurological disorders, glaucoma, and analgesia—all conditions for which clinical research has been under way to fulfill unmet patient needs. New therapeutic uses are being explored in preclinical research. For any of these therapeutic indications, will novel cannabinoids reach the market to satisfy the medical needs of patients?

Economic Factors in Development

The outcomes of preclinical and clinical research determine whether a drug is sufficiently safe and effective to warrant FDA approval for marketing. But the decisions to launch preclinical research and to proceed to clinical trials if early results are promising are dictated largely by economic factors. A pharmaceutical company must decide whether to invest in what is universally regarded as a long and risky research path. For any given drug the question is, Will there be an adequate return on investment? The investment in this case is the high cost of developing a drug. The expectation of high financial returns on investment is what drives drug development.[44,53]

Market analyses are undertaken to forecast whether a drug will reap a substantial return on investment. The market analysis for a cannabinoid is likely to be shaped by various factors. The average cost of developing a cannabinoid is likely to be higher than that of developing other drugs if its clinical indication is in the therapeutic categories of neuropharmaceutical or nonsteroidal antiinflammatory drug, the two therapeutic categories associated with the highest research and development costs.[19] One reason for higher costs is the need to satisfy the DEA's regulatory requirements related to drug scheduling.

On the "market return" side are multiple factors. A market analysis examines the expected returns from the possible markets for which a cannabinoid could be clinically pursued. The financial size of each market is calculated mostly on the basis of the current and projected patient prevalence (for a given clinical indication), sales data (if available), and competition from other products. The duration of use is also factored in—a drug needed for long-term use in a condition with an early age of onset is desirable from a marketing perspective. Factors that can augment or diminish market return include patentability and other forms of market protection,

TABLE 5.2 Cannabinoids Under Development for Human Use

Name of Drug	Investigator	Stage of Development	Pharmacology	U.S. FDA Status	Possible Indication(s)
HU-211	Pharmos Corp.	Clinical Phase II in Israel	NMDA receptor antagonist	None	Neuroprotection (neurotrauma, stroke, Parkinson's, Alzheimer's)
CT-3	Atlantic Pharmaceuticals	Preclinical	Nonpsycho-active	None	Antiinflammatory analgesia
THC	Unimed Roxane Labs	Clinical Phase I	Cannabinoid receptor agonist	IND	(See text)
Marijuana plant	HortaPharm GW Pharma-ceuticals	Clinical in England[a]	Cannabinoid mixture	None	Multiple sclerosis
	Donald Abrams, M.D.	Clinical Phase I	Cannabinoid mixture	IND	HIV-related appetite stimulation
	Ethan Russo, M.D.		Cannabinoid mixture	IND pending	Migraine

[a]Clinical trials are to proceed in the next few years under a license from the British Home Office.[10]

SOURCES: Glain, 1998[27]; Atlantic Pharmaceuticals, 1997[7]; Striem et al., 1997[55]; Nainggolan, 1997[37]; Zurier et al., 1998[61]; D. Abrams and E. Russo, personal communications, 1998; R. Dudley, personal communication, 1998; Pharmaprojects Database, 1998.

reimbursement climate, restrictions in access due to drug scheduling, social attitudes, adverse effect profile, and drug interactions.[33,53] New cannabinoids generally can receive product patents, giving the patent holder 20 years of protection from others seeking to manufacture or sell the same product. According to U.S. patent law, the product must be novel and "nonobvious" in relation to prior patents.[28]

Cannabinoids under Development

From publicly available sources, the IOM was able to learn of several cannabinoids being developed for human use (Table 5.2). With the exception of Marinol and marijuana, all are in the preclinical phase of testing in the United States. This list might not be comprehensive, inasmuch as other compounds could be under development, but that information is

proprietary.* The table does not list the full complement of cannabinoids, both agonists and antagonists, being used in research as tools to understand the pharmacology of cannabinoids (for more comprehensive lists of cannabinoids, see Felder and Glass, 1998[26]; Mechoulam et al., 1998[36]; Howlett, 1995[30]; Pertwee 1997[46]). Nor does it list cannabinoids once considered for development but later discontinued. An 18-year survey of analgesics in development in 1980–1998 found that six of the nine cannabinoids under development for analgesia were discontinued or undeveloped,[49,†] but work on most of these was halted before 1988, when the first endogenous cannabinoid receptor was discovered (chapter 3).

Three points can be made on the basis of Table 5.2. First, virtually all of the listed cannabinoids are being developed by small pharmaceutical companies or by individuals. In general, that implies that their development is considered especially risky from a commercial standpoint in that small companies are often willing to assume greater development risks than larger more established firms (W. Schmidt, personal communication, 1998). Without the benefit of sales revenues, small companies are able to fund their research through financing from venture capital, stock offerings, and relationships with established pharmaceutical companies.[43]

Second, with the exception of THC, no constituents of the marijuana plant appear to be undergoing development by pharmaceutical companies. A number of plant compounds have been tested in experimental models and humans. For example, the antiemetic properties and negligible side effects of Δ^8-THC were demonstrated in a clinical trial in children who were undergoing cancer chemotherapy,[1] but no sponsor was interested in developing Δ^8-THC for commercial purposes (R. Mechoulam, Hebrew University, personal communication, 1998). The absence of plant cannabinoids under development implies that the specter of automatic placement in Schedule I under the CSA is an important deterrent, even though rescheduling would occur before marketing.[††] The point from the earlier discussion is that automatic, as opposed to *de novo*, scheduling appears to cast a pall over development of a cannabinoid found in the plant. Another impediment is that a cannabinoid extracted

*Information about the existence of an IND is proprietary; it can be confirmed only by the manufacturer, not the FDA.

[†]Discontinued: levonantradol, nabitan, nantradol, and pravadoline. Undeveloped: CP-47497 and CP-55244.

[††]As a result of the FDA's approval of an NDA, the drug would be, at a minimum, rescheduled in Schedule II. Depending on abuse liability data supplied by the manufacturer and the FDA's recommendation, the drug could be moved to a less restrictive schedule or be descheduled.

from the plant is not likely to fulfill the criteria for a product patent, although other forms of market protection are possible. Marinol, for example, was accorded orphan drug status and its manufacturer obtained a use patent.

Third, cannabinoids are being developed for therapeutic applications beyond those discussed earlier in this chapter and in chapter 4. One of the most prominent new applications of cannabinoids is for "neuroprotection," the rescue of neurons from cell death associated with trauma, ischemia, and neurological diseases.[29,36] Cannabinoids are thought to be neuroprotective—through receptor-dependent[51] as well as receptor-independent pathways; both THC, which binds to CB_1 receptors, and CBD, which does not, are potent antioxidants, effective neuroprotectants because of their ability to reduce the toxic forms of oxygen (free radicals) that are formed during cellular stress.[29] The synthetic cannabinoid HU-211 (dexanabinol) is an antioxidant and an antagonist of the NMDA receptor, rather than an agonist at the cannabinoid receptor.[52] Earlier research demonstrated that HU-211 protects neurons from neurotoxicity induced by excess concentrations of the excitatory neurotransmitter glutamate. Excess release of glutamate, which acts by binding to the NMDA receptor, is associated with trauma and disease.[54] As an NMDA antagonist, HU-211 blocks the damaging action of glutamate and other endogenous neurotoxic agents.[52,55] After having been studied in the United Kingdom in Phase I clinical trials, HU-211 progressed to Phase II clinical trials in Israel for treatment of severe closed-head trauma (Knoller et al., 1998).[35]

Market Prospects

It is difficult to gauge the market prospects for new cannabinoids. There certainly appears to be scientific interest, particularly for the discovery of new cannabinoids, but whether this interest can be sustained commercially through the arduous course of drug development is an open question. Research and development experience is limited; only one cannabinoid, dronabinol, is commercially available, and most of its research and development costs were shouldered by the federal government. Furthermore, the size of dronabinol's market (at about $20 million) is modest by pharmaceutical company standards. None of the other cannabinoids in development has reached clinical testing in the United States. Their scientific, regulatory, and commercial fates are likely to be very important in shaping future investment patterns. Experience with the drug scheduling process also is likely to be watched very carefully. If the early products are heavily regulated in the absence of strong abuse liability, future development might be deterred. For the present, what seems to be clear

from the dearth of products in development and the small size of the companies sponsoring them is that cannabinoid development is seen as especially risky.

One scenario is that cannabinoids will be pursued for lucrative markets that reflect large unmet medical needs. Of the therapeutic needs for which cannabinoid receptor agonists have been tested, analgesia is by far the largest. The annual U.S. prescription and over-the-counter analgesic market in 1997 was $4.4 billion.[49] Given the long-standing need for less addictive, safer, easier to use, and more effective drugs for acute and chronic pain, it would not be surprising to see cannabinoids developed to treat some segments of the current analgesic market, if their safety and effectiveness were clearly established in clinical trials.

In addition to cannabinoid receptor agonists, two classes of cannabinoid-related drugs might prove therapeutically useful: cannabinoid antagonists and inverse agonists, compounds that bind to receptors but produce effects opposite those of agonists. Neither would be subject to the same scheduling concerns as cannabinoid agonists because they are not found in marijuana and would be highly unlikely to have any abuse potential. Another set of cannabinoid-related drugs, such as those that affect the synthesis, uptake, or inactivation of endogenous cannabinoids might, however, have abuse potential because they would influence the signal strength of endogenous cannabinoids.

The development of specific cannabinoid antagonists, like SR141716A for CB_1 receptors and SR144528 for CB_2 receptors, has provided a substantial impetus to understand cannabinoid actions. Those compounds block many of the effects of THC in animals, and their testing in humans has just begun. Cannabinoid antagonists have physiological effects on their own, in the absence of THC. They might have important therapeutic potential in a variety of clinical situations. For example, THC reduces short-term memory, so it is possible that a CB_1 antagonist like SR141716A could act as a memory-enhancing agent. Similarly, for conditions in which cannabinoids decrease immune function (presumably by binding to CB_2 receptors in immune cells), a CB_2 antagonist might be useful as an immune stimulant.

Cannabinoid inverse agonists would exert effects opposite those of THC and might thus cause appetite loss, short-term memory enhancement, nausea, or anxiety. Those effects could possibly be separated by molecular design, in which case inverse agonists might have some therapeutic value. One report has been published suggesting that the CB_1 receptor antagonist, SR141617A,[11] is an inverse agonist, and there will likely be others.

REGULATION OF AND MARKET OUTLOOK FOR MARIJUANA

Marijuana is not legally marketed in the United States.* No sponsor has ever sought marketing approval from the FDA for medical use of marijuana. One sponsor has an IND for a clinical safety study on HIV anorexia (D. Abrams, University of California at San Francisco, personal communication, 1998). Another has an IND pending for the treatment of migraine headaches (E. Russo, Western Montana Clinic, personal communication, 1998). Since 1970, marijuana's manufacture and distribution have been tightly restricted under the CSA, which places marijuana in Schedule I, which is reserved for drugs or other substances with "a high potential for abuse," "no currently accepted medical use," and "lack of accepted safety for use . . . under medical supervision" (21 U.S.C. § 812 (b)(1)).

Marijuana has remained in Schedule I despite persistent efforts at rescheduling since the 1970s by advocacy groups, such as NORML. Through petitions to the DEA, advocacy groups contend that marijuana does not fit the legal criteria for a Schedule I substance, owing to its purported medical uses and lack of high abuse liability.[3,4,48] Another rescheduling petition, which was filed in 1995, is being evaluated by the FDA and DEA.

Availability for Research

To use marijuana for research purposes, researchers must register with the DEA, as well as adhere to other relevant requirements of the CSA and other federal statutes, such as the FD&C act. The National Institute on Drug Abuse (NIDA), one of the institutes of NIH, is the only organization in the United States licensed by the DEA to manufacture and distribute marijuana for research purposes. NIDA performs this function under its Drug Supply Program.† Through this program, NIDA arranges for marijuana, to be grown and processed through contracts with two organizations: the University of Mississippi and the Research Triangle Institute. The University of Mississippi grows, harvests, and dries marijuana; and the institute processes it into cigarettes. A researcher can obtain marijuana free of charge from NIDA through an NIH-approved research grant to investigate marijuana, or through a separate protocol review.[39] Research grant approvals are handled through the conventional NIH peer review

*Under the CSA, its only legal use is in research under strictly defined conditions.

†This is also the program through which several patients receive marijuana under a compassionate use program monitored by the FDA. For history and information on this effort, see Randall (1993).[48]

process for extramural research, a highly competitive process with a success rate in 1997 of 32% of approved NIDA grants.[41] Through the separate protocol review, in which a researcher funds research independently of an NIH grant, NIDA submits the researcher's protocol to several external reviewers who evaluate the protocol on the basis of scientific merit and relevance to the mission of NIDA and NIH.

Through those two avenues marijuana has been supplied to several research groups—most of those that apply. While there has been much discussion of NIDA's alleged failure to supply marijuana for research purposes, we are unaware of recent cases in which they failed to supply marijuana to an investigator with an NIH-approved grant for research on marijuana. Donald Abrams's difficulty in obtaining research funding and marijuana from NIDA has been much discussed,[2] but the case of a single individual should not be presumed to be representative of the community of marijuana researchers. Failure of investigators who apply to NIH for marijuana research grants to receive funding is hardly exceptional: in 1998 less than 25% of *all* first-time investigator-initiated grant applications (known as RO1s) to the NIH were funded.[38]

To import marijuana under the CSA for research purposes, the procedures are more complex. Under DEA regulations, marijuana can be imported, provided that the researcher is registered with the DEA, has approval for marijuana research (21 CFR § 1301.11, .13, and .18), and has a DEA-approved permit for importation (21 CFR § 1312.11, .12, and .13), and that the exporter in the foreign country has appropriate authorization by the country of exportation. Importation would enable U.S. researchers to conduct research on marijuana grown by HortaPharm, a company that has developed unique strains of marijuana. However, no U.S. researcher has imported HortaPharm's marijuana because Dutch authorities have refused to issue an export permit, despite the issuance of an import permit by the DEA (D. Pate, HortaPharm, personal communication, 1998).*

HortaPharm, which is in the Netherlands, grows marijuana as a raw material for the manufacture of pharmaceuticals. Through selective breeding and controlled production, HortaPharm has developed marijuana strains that feature single cannabinoids, such as THC or cannabidiol. The plants contain a consistently "clean" phytochemical profile and a higher

*It might eventually be possible to import HortaPharm's marijuana from England, where HortaPharm is growing its marijuana strains for research use in clinical trials for multiple sclerosis (Boseley, 1998).[10] England, as the country of origin, would have to provide appropriate authorization for export of the strains to the United States. Permission to export for research purposes is part of the basis for HortaPharm's participation in this project with GW Pharmaceuticals through a special set of licenses with the British Home Office (David Pate, HortaPharm, personal communication, 1998).

concentration of THC (16%) or other desired cannabinoids than seized marijuana. Marijuana seized in the United States in 1996 had a THC content averaging about 5%.[16] Consistency of THC content is desirable because it overcomes the natural variability due to latitude, weather, and soil conditions. Product consistency is a basic tenet of pharmacology because it enables standardized dosing for regulatory and treatment purposes.

The difficulties of conducting research on marijuana were noted in the 1997 NIH report[40] that recommended that NIH facilitate clinical research by developing a centralized mechanism to promote design, approval, and conduct of clinical trials.

Regulatory Hurdles to Market

For marijuana to be marketed legally in the United States, a sponsor with sufficient resources would be obliged to satisfy the regulatory requirements of both the FD&C act and the CSA.

Under the FD&C act, a botanical product like marijuana *theoretically* might be marketed in oral form as a dietary supplement;* however, as a practical matter, only a new drug approval is likely to satisfy the provisions of the CSA, which require prescribing and distribution controls on drugs of abuse that also have an "accepted medical use." (The final paragraphs of this section clarify the criteria for "accepted medical use.")

Bringing marijuana to market as a new drug is uncharted terrain. The route is fraught with uncertainty for at least three pharmacological reasons: marijuana is a botanical product, it is smoked, and it is a drug with abuse potential. In general, botanical products are inherently more difficult to bring to market than are single chemical entities because they are complex mixtures of active and inactive ingredients. Concerns arise about product consistency, potency of the active ingredients, contamination, and stability of both active and inactive ingredients over time. These are among the concerns that a sponsor would have to overcome to meet the requirements for an NDA, especially those related to safety and to chemistry, manufacturing, and control.

A handful of botanical preparations are on the market, but none received formal approval as a new drug by today's standards of safety and efficacy (FDA, Center for Drug Evaluation and Research, personal communication, 1998). The three marketed botanical preparations are older drugs that came to market years before safety and efficacy studies were required by legislative amendments in 1938 and 1962, respectively.

*Inhaled products may not lawfully be marketed as dietary supplements.

One of the botanical preparations is the prescription product digitalis. Because it came to market before 1938, it is available today, having been "grandfathered" under the law; but it does not necessarily meet contemporary standards for safety and effectiveness.[20] Two other botanical preparations, psyllium and senna, came to market between 1938 and 1962. Drugs entering the market during that period were later required to be evaluated by the FDA in what is known as the over-the-counter drug review process,[20] through which psyllium and senna were found to be generally recognized as safe and effective and so were allowed to remain on the market as over-the-counter drugs.* Although no botanical preparations have been approved as new drugs, it is important to point out that a number of individual plant constituents, either extracted or synthesized *de novo*, have been approved (for example, taxol and morphine). But these drug approvals were for single constituents rather than botanical preparations themselves. The FDA is developing guidance for industry to explain how botanicals are reviewed as new drugs, but the final document might not be available before 1999.

That marijuana is smoked might pose an even greater regulatory challenge. The risks associated with smoking marijuana are described in chapter 2. The FDA would have to weigh those risks with marijuana's therapeutic benefits to arrive at a judgment about whether a sponsor's NDA for marijuana met the requirements for safety and efficacy under the FD&C act. Marijuana delivered in a novel way that avoids smoking would overcome some, but not all, of the regulatory concerns. Vaporization devices that permit inhalation of plant cannabinoids without the carcinogenic combustion products found in smoke are under development by several groups; such devices would also require regulatory review by the FDA.

The regulatory hurdles to market posed by the CSA are formidable but not insurmountable. If marijuana received market approval as a drug by the FDA, it would most likely be rescheduled under the CSA, as was the case for dronabinol. That is because a new drug approval satisfies the "accepted medical use" requirement under the CSA for manufacture and distribution in commerce.[13] But a new drug approval is not the *only* means to reschedule marijuana under the CSA.[14] For years advocates for rescheduling have argued that marijuana does enjoy "accepted medical use," even in the absence of a new drug approval. Although advocates have been unsuccessful in rescheduling efforts, their actions prompted

*Over-the-counter monographs for these products have been issued as tentative final monographs (proposed rules) but have not yet been issued in final form as final rules (FDA, Center for Drug Evaluation and Research, personal communication, 1998).

the DEA to specify the criteria by which it would determine whether a substance had "accepted medical use." In the DEA's 1992 denial of a rescheduling petition, it listed these elements as constituting "accepted medical use": the drug's chemistry must be known and reproducible, there must be adequate safety studies, there must be adequate and well-controlled studies proving efficacy, the drug must be accepted by qualified experts, and the scientific evidence must be widely available.[14]

Assuming that all of those criteria were satisfied, marijuana could be rescheduled—but into which schedule? The level of scheduling would be dictated primarily by a medical and scientific recommendation to the DEA made by the secretary of DHHS.* As noted earlier, this recommendation is determined by the five scheduling criteria listed in the CSA. However, scheduling in a category less restrictive than Schedule II might be prohibited by international treaty obligations. The Single Convention on Narcotic Drugs, a treaty ratified by the United States in 1967, restricts scheduling of the plant and its resin to at least Schedule II (the more restrictive Schedule I is another option).[13]

Market Outlook

The market outlook for the development of marijuana as a new drug, on the basis of the foregoing analysis, is not favorable, for a host of scientific, regulatory, and commercial reasons. From a scientific point of view, research is difficult because of the rigors of obtaining an adequate supply of legal, standardized marijuana for study. Further scientific hurdles are related to satisfying the exacting requirements for FDA approval of a new drug. The hurdles are even more exacting for a botanical product because of the inherent problems with, for example, purity and consistency. Finally, the health risks associated with smoking pose another barrier to FDA approval unless a new smoke-free route of administration is demonstrated to be safe. Depending on the route of administration, an additional overlay of regulatory requirements might have to be satisfied.

From a commercial point of view, uncertainties abound. The oft-encited cost of new drug development, about $200–$300 million, might not apply, but there are probably additional costs needed to satisfy the FDA's requirements for a botanical product. As noted above, no botanical products have ever been approved as new drugs by the FDA under today's stringent standards for safety and efficacy. Satisfying the legal require-

*At present, there is no practical mechanism for generating such a recommendation outside the new drug approval process, although such a mechanism could, theoretically, be developed.[33]

ments of the CSA also will add substantially to the cost of development. On the positive side, so much research already has been done that some development costs will be lower. The cost of bringing dronabinol to market, for example, was reduced dramatically as a result of clinical trials supported with government funding. Nevertheless, it is impossible to estimate the cost of developing marijuana as a new drug. Estimating return on investment is similarly difficult. A full-fledged market analysis would be required for the indication being sought. Such an analysis would take into account the market limitations resulting from drug scheduling restrictions, stigma, and patentability.

The plant does not constitute patentable subject matter under U.S. patent law because it is unaltered from what is found in nature. So-called products of nature are not generally patentable.[28] New marijuana strains, however, could be patentable in the United States under a product patent or a plant patent because they *are* altered from what is found in nature. (A product patent prohibits others from manufacturing, using, or selling each strain for 20 years; a plant patent carries somewhat less protection.) HortaPharm has not yet sought any type of patent for its marijuana strains in the United States, but it has received approval for a plant registration in Europe (David Watson, HortaPharm, personal communication, 1998).

In short, development of the marijuana plant is beset by substantial scientific, regulatory, and commercial obstacles and uncertainties. The prospects for its development as a new drug are unfavorable unless return on investment is not a driving force. It is noteworthy that no pharmaceutical firm has sought to bring it to market in the United States. The only interest in its development appears to be in England in a small pharmaceutical firm (see Boseley, 1998[10]) and in the United States among physicians without formal ties to pharmaceutical firms (D. Abrams, University of California at San Francisco, and E. Russo, Western Montana Clinic, personal communications, 1998).

CONCLUSIONS

Cannabinoids are an interesting group of compounds with potentially far-reaching therapeutic applications. There is a surge of scientific interest in their development as new drugs, but the road to market for any new drug is expensive, long, risky, and studded with scientific, regulatory, and commercial obstacles. Experience with the only approved cannabinoid, dronabinol, might not illuminate the pathway because of the government's heavy contribution to research and development, dronabinol's scheduling history, and its small market.

There appear to be only two novel cannabinoids actively being developed for human use, but they have yet to be tested in humans in the

United States. Their experience is likely to be more predictive of the marketing prospects for other cannabinoids. It is too early to forecast the prospects for cannabinoids, other than to note that their development at this point is considered to be especially risky, to judge by the paucity of products in development and the small size of the pharmaceutical firms sponsoring them.

The market outlook in the United States is distinctly unfavorable for the marijuana plant and for cannabinoids found in the plant. Commercial interest in bringing them to market appears nonexistent. Cannabinoids in the plant are automatically placed in the most restrictive schedule of the Controlled Substances Act, and this is a substantial deterrent to development. Not only is the plant itself subject to the same scheduling strictures as are individual plant cannabinoids, but development of marijuana also is encumbered by a constellation of scientific, regulatory, and commercial impediments to availability.

REFERENCES

1. Abrahamov A, Abrahamov A, Mechoulam R. 1995. An efficient new cannabinoid antiemetic in pediatric oncology. *Life Sciences* 56:2097–2102.
2. Abrams DI. 1998. Medical marijuana: Tribulations and trials. *Journal of Psychoactive Drugs* 30:163–169.
3. AMA (American Medical Association Council on Scientific Affairs). 1997. *Report to the AMA House of Delegates.* Chicago: AMA.
4. Annas GJ. 1997. Reefer madness—the federal response to California's medical-marijuana law. *The New England Journal of Medicine* 337:435–439.
5. Arno PS, Bonuck K, Davis M. 1995. Rare diseases, drug development, and AIDS: The impact of the Orphan Drug Act. *Milbank Quarterly* 73:231–252.
6. Asbury C. 1991. The Orphan Drug Act: The first seven years. *Journal of the American Medical Association* 265:893–897.
7. Atlantic Pharmaceuticals. 1997. Atlantic Pharmaceuticals' proprietary compound shows promising anti-inflammatory effects in pre-clinical trials [WWW document]. URL http://www.atlan.com/p-11-10-97ct3zurier.htm (accessed September 1998).
8. Beal JE, Olson RLL, Morales JO, Bellman P, Yangco B, Lefkowitz L, Plasse TF, Shepard KV. 1995. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *Journal of Pain and Symptom Management* 10:89–97.
9. Beal JE, Olson R, Lefkowitz L, Laubenstein L, Bellman P, Yangco B, Morales JO, Murphy R, Powderly W, Plasse TF, Mosdell KW, Shepard KV. 1997. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *Journal of Pain and Symptom Management* 14:7–14.
10. Boseley S. 1998. Multiple sclerosis victims to test medicinal effects of marijuana [WWW document].URL http://www.anomalous-images/news/news/227.HTML (accessed September 8, 1998).

11. Bouaboula M, Perrachon S, Milligan L, Canat X, Rinaldi-Carmona M, Portier MB, Calandra B, Pecceu F, Lupker J, Maffrand JP, Le Fur G, Casellas P. 1997. A selective inverse agonist for central cannabinoid receptor inhibits mitogen-activated protein kinase activation stimulated by insulin or insulin-like growth factor 1. Evidence for a new model of receptor/ligand interactions. *Journal of Biological Chemistry* 272:22330–22339.
12. Calhoun, SR, Galloway GP , Smith DE . 1998. Abuse potential of dronabinol (Marinol). *Journal of Psychoactive Drugs* 30:187–196.
13. Cooper RM. 1980. Therapeutic use of marijuana and heroin: The legal framework. *Food Drug Cosmetic Law Journal* 35:68–82.
14. DEA (Drug Enforcement Administration). 1992. Marijuana scheduling petition; denial of petition; remand. *Federal Register* 57:10499–10508.
15. DEA. 1998. Drugs of abuse [WWW document].URL http://www.usdoj.gov/dea/pubs/abuse/contents.htm (accessed September 1998).
16. DEA. 1996. The National Narcotics Intelligence Consumers Committee (NNICC) report [WWW document].URL www.usdoj.gov/dea/pubs/intel/nnicc97.htm (accessed September 1998).
17. DEA. 1998b. Rescheduling of synthetic dronabinol from Schedule II to Schedule III. *Federal Register* 63:59751–59753.
18. DiMasi JA, Brown JS, Lasagna L. 1996. An analysis of regulatory review times of supplemental indications for already-approved drugs: 1989–1994. *Drug Information Journal* 30:315–337.
19. DiMasi JA, Hanson RW, Grabowski HG, Lasagna L. 1995. Research and development costs for new drugs by therapeutic category: A study of the U.S. pharmaceutical industry. *PharmacoEconomics* 7:152–169.
20. FDA (Food and Drug Administration). 1990. *From Test Tube to Patient: New Drug Development in the United States*. Rockville, MD: U.S. Department of Health and Human Services.
21. FDA. 1997b. *Draft Guidelines for Research Involving the Abuse Liability Assessment of New Drugs.* Rockville, MD: U.S. Department of Health and Human Services. Division of Anesthetic, Critical Care and Addiction Drug Products.
22. FDA. 1997a. Center for Drug Evaluation and Research Fact Book [WWW document]. URL http://www.fda.gov/cder/homepage (accessed September 1998).
23. FDA. 1998a. Center for Drug Evaluation and Research Handbook [WWW document]. URL http://www.fda/cder/handbook.htm (accessed September 1998).

24a. FDA. 1998b. FDA proposes rules for dissemination information on off label uses (press release, June 5). Washington, DC: U.S. Department of Health and Human Services.

24. FDA. 1998c. Guidance for industry: Providing clinical evidence of effectiveness for human drugs and biological products. Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. May 1998 [WWW document].URL http://www.fda.gov/cder/guidance/1397fnl.pdf (accessed September 1998).
25. FDA. 1998d. Office of Orphan Products Development Program Overview [WWW document].URL http://www.fda.gov/orphan/DESIGNAT/recent.htm (accessed October 14, 1998).
26. Felder CC, Glass M. 1998. Cannabinoid receptors and their endogenous agonists. *Annual Reviews of Pharmacology and Toxicology* 38:179–200.
27. Glain SJ. 1998. I. *Wall Street Journal*.
28. Gollin MA. 1994. Patenting recipes from nature's kitchen: How can a naturally occurring chemical like taxol be patented? *Biotechnology (NY)* 12:406–407.

29. Hampson AJ, Grimaldi M, Axelrod J, Wink D. 1998. Cannabidiol and (–)delta-9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences USA* 95:8268–8273.
30. Howlett AC. 1995. Pharmacology of cannabinoid receptors. *Annual Review of Pharmacology and Toxicology* 35:607–634.
31. IOM (Institute of Medicine). 1990. *Modern Methods of Clinical Investigation.* Washington, DC: National Academy Press.
32. IOM. 1991. *Expanding Access to Investigational Therapies for HIV Infection and AIDS.* Washington, DC: National Academy Press.
33. IOM. 1995. *The Development of Medications for the Treatment of Opiate and Cocaine Addictions: Issues for the Government and Private Sector.* Washington, DC: National Academy Press.
34. IOM. 1996. *Pathways of Addiction: Opportunities in Drug Abuse Research.* Washington, DC: National Academy Press.
35. Knoller N, Levi L, Israel Z, Razon N, Reichental E, Rappaport Z, Ehrenfreund N, Biegon A. Safety and outcome in a Phase II clinical trail of dexanabinol in severe head trauma. Congress of Neurological Surgeons Annual Meeting. Seattle, WA, Oct. 7, 1998.
36. Mechoulam R, Hanus L, Fride E. 1998. Towards cannabinoid drugs—revisited. In: Ellis GP, Luscombe DK, Oxford AW, Editors, *Progress in Medicinal Chemistry.* vol. 35. Amsterdam: Elsevier Science. Pp. 199–243.
37. Nainggolan L. 1997. Marijuana—a missed market opportunity? *Scrip Magazine*.
38. National Institutes of Health (NIH). 1999. http://www.nih.gov/grants/award/award.htm.
39. NIDA (National Institute on Drug Abuse). 1996. *Research Resources: Drug Supply System, 10th Edition*. Rockville, MD.
40. 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 of Experts. Bethesda, MD, February 19–20, 1997. Bethesda, MD: National Institutes of Health.
41. NIH. 1998. FY (1970–1997 NIH (Preliminary) competing research project applications [WWW document].URL http:/silk.nih.gov/public/cbz2rfm.@www.comic.dsncc (accessed October 1998).
42. Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, 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.
43. OTA (Office of Technology Assessment). 1991. *Biotechnology in a Global Economy*. OTA-BA-494. Washington, DC: U.S. Government Printing Office.
44. OTA. 1993. *Pharmaceutical R&D: Costs, Risks and Rewards.* OTA-H-522. Washington, DC: U.S. Government Printing Office.
45. PDR (Physicians' Desk Reference). 1996. *Physicians' Desk Reference*. 50th ed. Montvale, NJ: Medical Economics Co.
46. Pertwee RG. 1997. Cannabis and cannabinoids: Pharmacology and rationale for clinical use. *Pharmaceutical Science* 3:539–545.
47. Plasse TF, Gorter RW, Krasnow SH, Lane M, Shepard KV, Wadleigh RG. 1991. Recent clinical experience with dronabinol. *Pharmacology Biochemistry and Behavior* 40:695–700.
48. Randall IV B. 1993. *Medical Use of Marijuana: Policy and Regulatory Issues.* 93-308 SPR. Washington, DC: Congressional Research Service.

49. Schmidt WK. 1998. Overview of current investigational drugs for the treatment of chronic pain. National Managed Health Care Congress, Second Annual Conference on Therapeutic Developments in Chronic Pain. Annapolis, MD, May 18, 1998.
50. Shapiro RS. 1994. Legal bases for the control of analgesic drugs. *Journal of Pain and Symptom Management* 9:153–159.
51. 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.
52. Shohami E, Weidenfeld J, Ovadia H, Vogel Z, Hanus L, Fride E, Breuer A, Ben-Shabat S, Sheskin T, Mechoulam R. 1996. Endogenous and synthetic cannabinoids: Recent advances. *CNS Drug Reviews* 2:429–451.
53. Spilker B. 1989. *Multinational Drug Companies: Issues in Drug Discovery and Development*. New York: Raven Press.
54. Standaert DG, Young AB. 1996. Treatment of central nervous system degenerative disorders. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RR, Gilman AG, Editors, *Goodman & Gilman's: The Pharmacological Basis of Therapeutics.* 9th ed. New York: McGraw-Hill. Pp. 503–519.
55. Striem S, Bar-Joseph A, Berkovitch Y, Biegon A. 1997. Interaction of dexanabinol (HU-211), a novel NMDA receptor antagonist, with the dopaminergic system. *European Journal of Pharmacology* 388:205–213.
56. Timpone JG, Wright DJ, Li N, Egorin MJ, Enama ME, Mayers J, Galetto G, DATRI 004 Study Group. 1997. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. The DATRI 004 study group. *AIDS Research and Human Retroviruses* 13:305–315.
57. Turk DC, Brody MC, Akiko OE. 1994. Physicians' attitudes and practices regarding the long-term prescribing of opioids for non-cancer pain. *Pain* 59:201–208.
58. Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. 1997. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry* 12:913–919.
59. Voth EA, Schwartz RH. 1997. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. *Annals of Internal Medicine* 126:791–798.
60. Wall ME, Sadler BM, Brine D, Taylor H, Perez-Reyes M. 1983. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. *Clinical Pharmacology and Therapeutics* 34:352–363.
61. Zurier RB, 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.

Appendixes

APPENDIX A
Individuals and Organizations That Spoke or Wrote to the Institute of Medicine About Marijuana and Medicine

Donald I. Abrams
University of California at San Francisco

Jill Aguilera
Colorado Federation of Parents

William F. Alden
D.A.R.E. America

Roger D. Anderson
Anderson Clinical Research

M. Douglas Anglin
UCLA Drug Abuse Research Center

Dave Baleria
Jackson County Sheriff's Office

Joe Barker

Frank Bartosic
Minister of Universal Life Church

Dana Beal
Cures Not Wars

J. Bellam
Center for Drug Information

Sandra S. Bennett
Northwest Center for Health and Safety

Anna T. Boyce
California Senior Legislature (Prop 215)

William Britt

Richard Brookhiser
National Review

Ronald Brooks
California Narcotic Officers Association

Bonnie Broussard
L.A. Takes a Stand, Inc.

Al Byrne
Patients Out of Time

Marvin Edward Chavez, Sr.
O.C. Patient-Doctor-Nurse Support Group Cannabis Co-Op

Steven Childers
Bowman Gray School of Medicine
Wake Forest University

Barb Christensen
Prevention Partners

Gale Cincotta
National People's Action

Carol Coburn
Prevention Partners

Chris Conrad
Author of *Hemp for Health*

Paul Consroe
University of Arizona

J. Richard Crout
Private Consultant

Judy Cushing
Oregon Partnership, National Family Partnership

John De Miranda
Peninsula Health Concepts

Mahendra Dedhiya
Roxane Laboratories, Inc.

Robert Deitch
Cannabis Freedom Fund

Philip Diaz
Physicians for Prevention

Stephen L. Dilts
American Academy of Addiction Psychiatry

Rick Doblin
MAPS and Kennedy School of Government

Del Dolton

Barbara Douglass

Drug-Free Youth—USA

Robert Dudley
UNIMED

Victoria Duran
National Parents and Teachers Association

David Edwards

Edward Ehman
Certified Prevention Specialist

Mahmoud ElSohly
University of Mississippi

Mouncey Ferguson

Howard L. Fields
University of California at San Francisco

Jody Fitt

Richard W. Foltin
Columbia University

Etienne Fontan
Cannabis Alliance of Veterans, 1st CAV

Meg Foster

Phyllis Gardner
ALZA Corporation

Charles V. Giannasio
American Academy of Addiction Psychiatry

Dale Gieringer
California NORML, Friends of 215

Mark Gold
University of Florida Brain Institute

Richard Gralla
OCHSNER Cancer Institute

Linda Hall
Pride, Omaha, Inc.

Margaret Haney
Columbia University

Ann Hansen
Michigan Communities in Action for Drug-Free Youth

Jim Hardin

Terry Hensley
Drug-Free America Foundation

Kimberly Hessel
American Cancer Society and Muscatine General Hospital

Michele Hodak
National Education Association

Leo Hollister
Harris County Psychiatric Center

Jennifer Hudson
Oregonians Against Dangerous Drugs

Paul Isford

Becki Jelinek
Family Service/South Omaha Counseling

Jeffery Jones
Oakland Cannabis Buyers' Cooperative

Linda R. Wolf Jones
Therapeutic Communities of America

Norbert E. Kaminski
Michigan State University

Robert Kampia
Marijuana Policy Project

Paul L. Kaufman
University of Wisconsin Medical School

Andrew Kinnon

Thomas Klein
University of South Florida College of Medicine

Audra Koerber
Orange County Patient, Doctor, Nurse Support Group

Ellen Komp
San Luis Obispo Citizens for Medical Marijuana

George Koob
Scripps Research Institute

Thomas R. Kosten
American Academy of Addiction Psychiatry

Donald Kotler
St. Luke's-Roosevelt Hospital

Michael Krawitz
Disabled American Veterans, American Legion

Kiyoshi Kuromiya
Critical Path AIDS Project

Karin Kyles
Connecticut Communities for Drug-Free Youth, Inc.

Eric Larson
University of Washington Medical Center

Linda B. Ledger
O. J. Federation for Drug-Free Communities

Carla Lowe

Ray Lozano
C.A.D.F.Y.

Patrick Magee
Orange County Hemp Council

Robert L. Maginnis
Family Research Council

Billy R. Martin
Virginia Commonwealth University

Mary Lynn Mathre
Patients Out of Time

Jeane McCarty
West Coast Neonatology

Todd McCormick

JoAnna McKee
Green Cross Patient Co-Op

Manon McKinnon
Empower America

George McMahon

Peter McWilliams

John Edward Mendelson
University of California at San Francisco

Bonnie Metcalf
Yuba County Compassionate Use Co-Op

R. Mikin
American Academy of Addiction Psychiatry

Alan D. Miller
The Rockefeller University

Jim Montgomery

John P. Morgan
City University of New York Medical School

Arlene Munoz
Office of Substance Abuse, San Joaquin County

Elvy Musikka

Richard E. Musty
University of Vermont

Edgar P. Nace
American Academy of Addiction Psychiatry

Joyce Nalepka
America Cares

Tammera Nauts
Great Falls Public Schools

Dan Noelle
Multnomah County Sheriff

Stephen O'Brien
East Bay Aids Center

Jerry Olli
Michigan Elks and Michigan Communities in Action for Drug-Free Youth

Lynn Osburn
Access Unlimited

Robert Pandina
Rutgers, The State University of New Jersey

David Pate
HortaPharm B.V.

Maggie Petito
Drug Watch International

Stephen Popolizio
The International Association of Lions Clubs

Jo Prang
NFP Networker (Oregon Partnership)
Adolescent Substance Abuse Prevention, Inc./MEDICAP Pharmacy

Beny Primm
Addiction Research and Treatment Corporation

Carol Reeves
Greenville Family Partnership

Irvin Rosenfeld
Stockbroker

Michael Rowbotham
University of California at San Francisco

A. Kenison Roy
American Society of Addiction

Reid Rubsamen
Aradigm

Sue Rusche
National Families in Action

Clara Sanudo-Pena
Brown University

Peggy Sapp
Informed Families

C. Robert Schuster
Wayne State University School of Medicine

Greg Scott

Richard Scribner
Louisiana State University
Medical School

Betty S. Sembler
S.O.S.

Richard W. Sharke
McDowell Drug Task Force/
CADCA

Lynette Shaw
Marin Alliance for Medical
Marijuana

John Sheridan
New York City Marijuana
Buyers' Club

Cathy Shipp
PRIDE-Omaha, Inc.

Stephen Sidney
Kaiser Permanente

Brian Slater

Kenneth Smuland
Women's Alliance for Medical
Marijuana

Mark Stone
Washington, D.C., Police
Department

Barb Sweeney
Flower Therapy

Donald Tashkin
University of California at Los
Angeles School of Medicine

Dana Taub

Chuck Thomas
Marijuana Policy Project
Foundation

Bill Tiuen
Gainesville Family Partnership

Joyce Tobias
Parents' Association to
Neutralize Drug and Alcohol
Abuse, Inc.

Jeanne Trumble
American Academy of Addiction
Psychiatry

Barbara Urist-Fenton
OCHC

Eric A. Voth
International Drug Strategy
Institute

Michelle Voth
Kansas Family Partnership

C. Gary Wainwright
American Civil Liberties Union

J. Michael Walker
Brown University

Gene Weeks
Southern California Medical
Cannabis Consumers' Co-Op

Sandra Welch
Medical College of Virginia

Tracy Wells
Family Service–Healthy Alternatives for Little Ones

Sgt. Larry L. Welty
Oregon State Police

Sis Wenger
National Association of Children of Alcoholics

Lennice Werth
Virginians Against Drug Violence

Casey Wilbanks
Green Cross

Carol Wortman
Drug Watch Pennsylvania

Kevin Zeese
Common Sense for Drug Policy

APPENDIX B

Workshop Agendas

Workshop on Perspectives on the Medical Use of Marijuana: Basic and Clinical Science

December 14–16, 1997
Beckman Center, Irvine, California

AGENDA

Sunday, December 14, 1997

2:00 p.m. Introduction
Constance Pechura, *IOM Division Director*, Neuroscience and Behavioral Health

2:30 p.m. Public Input Session, *5 minutes per person*
Moderator: Stanley Watson, Jr., *IOM Study Investigator,* University of Michigan

5:30 p.m. ADJOURN

Monday, December 15, 1997

CANNABINOID NEUROSCIENCE

8:30 a.m. **Moderator:** Stanley Watson, *IOM Study Investigator,* University of Michigan

8:45 a.m. **Neuropharmacology of Cannabinoids and Their Receptors**
Steven R. Childers, Wake Forest University School of Medicine

9:15 a.m. **Precipitated Cannabinoid Withdrawal and Sensory Processing of Painful Stimuli**
J. Michael Walker, Brown University

9:45 a.m. **Role of Cannabinoids in Movement**
Clara Sanudo, Brown University

10:15 a.m. **Tolerance and Cannabinoid-Opioid Interactions**
Sandra P. Welch, Medical College of Virginia

10:45 a.m. BREAK

MEDICAL USES OF MARIJUANA:
CLINICAL DATA AND BASIC BIOLOGY

11:10 a.m. **Moderator:** John A. Benson, Jr., *IOM Study Investigator,* Oregon Health Sciences University

11:15 a.m. **Profile of Medical Marijuana Users**
John Mendelson, University of California at San Francisco

11:45 a.m. **Immune Modulation by Cannabinoids**
Norbert Kaminski, Michigan State University

12:15 p.m. **Psychological Effects of Marijuana Use**
Charles R. Schuster, Wayne State University

12:45 p.m. LUNCH

1:45 p.m. **Marijuana and Glaucoma**
Paul Kaufman, University of Wisconsin

2:15 p.m. **Effects of Marijuana and Cannabinoids in Neurological Disorders**
Paul Consroe, University of Arizona Health Sciences Center

2:45 p.m. **Neural Mechanisms of Cannabinoid Analgesia**
Howard Fields, University of California at San Francisco

3:15 p.m. **Pain Management**
Michael Rowbotham, University of California at San Francisco

3:45 p.m. **Wasting Syndrome Pathogenesis and Clinical Markers**
Donald Kotler, St. Luke's-Roosevelt Hospital

4:15 p.m. **Clinical Experience with Marijuana**
Stephen O'Brien, East Bay AIDS Center

4:45 p.m. ADJOURN

Tuesday, December 16, 1997

MEDICAL USES OF MARIJUANA:
CLINICAL DATA AND BASIC BIOLOGY

8:30 a.m. **Moderator:** John A. Benson, Jr., *IOM Study Investigator,*
Oregon Health Sciences University

8:45 a.m. **Marijuana in AIDS Wasting: Tribulations and Trials**
Donald I. Abrams, University of California at San Francisco

9:15 a.m. N**ausea and Vomiting: Underlying Mechanisms and Upcoming Treatments**
Alan D. Miller, The Rockefeller University

9:45 a.m. **Postchemotherapy Nausea and Antiemetics**
Richard J. Gralla, Ochsner Cancer Center

10:15 a.m. BREAK

SUMMARY VIEWS

10:30 a.m. **Marijuana Is Different from THC: A Review of Basic Research and State Studies of Antiemesis**
Richard E. Musty, University of Vermont

11:00 a.m. **Medical Uses of Crude Marijuana: Medical and Social Issues**
Eric A. Voth, The International Drug Strategy Institute

11:30 a.m. **General Questions**
Moderator: John A. Benson, Jr., *IOM Study Investigator*

12:00 noon ADJOURN

Workshop on
Acute and Chronic Effects of Marijuana Use

January 22–23, 1998
New Orleans Marriott Hotel
New Orleans, Louisiana

AGENDA

Thursday, January 22, 1998

2:00 p.m. Introduction
Constance Pechura, *IOM Division Director,*
Neuroscience and Behavioral Health

2:30 p.m. Public Input Session, *5 minutes per person*
Moderator: Stanley Watson, Jr., *IOM Study Investigator,*
University of Michigan

4:30 p.m. ADJOURN

Friday, January 23, 1998

8:30 a.m. **Moderator:** John A. Benson, Jr., *IOM Study Investigator,*
Oregon Health Sciences University

HEALTH CONSEQUENCES OF MARIJUANA USE

9:00 a.m. **Health Consequences of Marijuana Use: Epidemiological Studies**
Stephen Sidney, Kaiser Permanente, Oakland, CA

9:30 a.m. **Immunity, Infections, and Cannabinoids**
Thomas Klein, University of South Florida

10:00 a.m. **Pulmonary Effects of Smoked Marijuana**
Donald Tashkin, Unversity of California at Los Angeles

10:30 a.m. BREAK

10:45 a.m. **Is Marijuana Carcinogenic?: Epidemiological and Biological Evidence**

Panel Discussion
Stephen Sidney
Donald Tashkin

12:00 noon LUNCH

EFFECTS OF MARIJUANA ON BEHAVIOR

1:30 p.m. **Marijuana: Addictive and Amotivational States, the Scientific Evidence**
John Morgan, City University of New York Medical School

2:00 p.m. **Marijuana's Acute Behavioral Effects in Humans**
Richard Foltin, Columbia University

2:30 p.m. **Tolerance and Dependence Following Chronic Administration of Oral THC or Smoked Marijuana to Humans**
Margaret Haney, Columbia University

3:00 p.m. **Patterns of Continuity and Discontinuity of Marijuana Use in Relationship to Other Drugs**
Robert Pandina, Rutgers University

3:30 p.m. ADJOURN

Workshop on Prospects for Cannabinoid Drug Development

February 23–24, 1998
National Academy of Sciences Building
Washington, D.C.

AGENDA

Monday, February 23, 1998

1:30 p.m. Introduction
Constance Pechura, *IOM Division Director,*
Neuroscience and Behavioral Health

2:00 p.m. Public Input Session, *5 minutes per person*
Moderator: John A. Benson, Jr., *IOM Study Investigator,*
Oregon Health Sciences University

5:30 p.m. ADJOURN

Tuesday, February 24, 1998

8:30 a.m. Introduction
Constance Pechura, *IOM Division Director*
Neuroscience and Behavioral Health

Moderator: Stanley J. Watson, Jr., *IOM Study Investigator,*
University of Michigan

OVERVIEWS OF PRECEDING WORKSHOPS

8:45 a.m. **Acute and Chronic Effects of Marijuana**
Billy R. Martin, Medical College of Virginia

9:25 a.m. **Perspectives on the Medical Use of Marijuana**
Eric B. Larson, University of Washington Medical School

9:55 a.m. **The Neurobiology of Cannabinoid Dependence**
George F. Koob, Scripps Research Institute

10:25 a.m. BREAK

DRUG DEVELOPMENT

10:45 a.m. **Regulatory Requirements Affecting Marijuana**
J. Richard Crout, Crout Consulting

11:15 a.m. **Marinol and the Market**
Robert E. Dudley, Unimed Pharmaceuticals, Inc.

11:45 a.m. **Development of Cannabis-based Therapeutics**
Dave Pate, HortaPharm, B.V.

12:15 p.m. LUNCH

DRUG DELIVERY

1:30 p.m. **Alternative Drug Delivery Technologies for the Therapeutic Use of Marijuana**
Phyllis I. Gardner, ALZA Corporation, Stanford University

2:00 p.m. **Delivery of Analgesics via the Respiratory Track**
Reid M. Rubsamen, Aradigm Corporation

2:30 p.m. **Current Concepts for Delivery of THC**
Mahendra G. Dedhiya, Roxanne Laboratories, Inc.

3:00 p.m. **Δ^9-THC-Hemisuccinate in Suppository Formulation: An Alternative to Oral and Smoked THC**
Mahmoud A. ElSohly, University of Mississippi, ElSohly Laboratories, Inc.

3:30 p.m. **Concluding Remarks**
John A. Benson, Jr., *IOM Study Investigator,* Oregon Health Sciences University

3:45 p.m. ADJOURN

APPENDIX C

Scheduling Definitions

SCHEDULING DEFINITIONS ESTABLISHED BY THE CONTROLLED SUBSTANCES ACT OF 1970

Schedule I (includes heroin, LSD, and marijuana)

(A) The drug or other substance has a high potential for abuse.

(B) The drug or other substance has no currently accepted medical use in treatment in the United States.

(C) There is a lack of accepted safety for the use of the drug or other substance under medical supervision.

Schedule II (includes Marinol, methadone, morphine, methamphetamine, and cocaine)

(A) The drug or other substance has a high potential for abuse.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.

(C) Abuse of the drug or other substances may lead to severe psychological or physical dependence.

Schedule III (includes anabolic steroids)

(A) The drug or other substance has a potential of abuse less than the drugs or other substances in Schedules I and II.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

(C) Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.

Schedule IV (includes Valium and other tranquilizers)

(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

(C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.

Schedule V (includes codeine-containing analgesics)

(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule IV.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

(C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.

SOURCES: LeCraw (1996) and 21 U.S.C. 812.

APPENDIX D

Statement of Task

The study will assess what is currently known and not known about the medical use of marijuana. It will include a review of the science base regarding the mechanism of action of marijuana, an examination of the peer-reviewed scientific literature on the efficacy of therapeutic uses of marijuana, and the costs of using various forms of marijuana versus approved drugs for specific medical conditions (e.g., glaucoma, multiple sclerosis, wasting diseases, nausea, and pain).

The study will also include an evaluation of the acute and chronic effects of marijuana on health and behavior; a consideration of the adverse effects of marijuana use compared with approved drugs; an evaluation of the efficacy of different delivery systems for marijuana (e.g., inhalation vs. oral); an analysis of the data concerning marijuana as a gateway drug; and an examination of the possible differences in the effects of marijuana due to age and type of medical condition.

SPECIFIC ISSUES

Specific issues to be addressed fall under three broad categories: the science base, therapeutic use, and economics.

Science Base

- Review of neuroscience related to marijuana, particularly the relevance of new studies on addiction and craving.
- Review of behavioral and social science base of marijuana use, par-

ticularly assessment of the relative risk of progression to other drugs following marijuana use.

- Review of the literature determining which chemical components of crude marijuana are responsible for possible therapeutic effects and for side effects.

Therapeutic Use

- Evaluation of any conclusions on the medical use of marijuana drawn by other groups.
- Efficacy and side effects of various delivery systems for marijuana compared to existing medications for glaucoma, wasting syndrome, pain, nausea, or other symptoms.
- Differential effects of various forms of marijuana that relate to age or type of disease.

Economics

- Costs of various forms of marijuana compared with costs of existing medications for glaucoma, wasting syndrome, pain, nausea, or other symptoms.
- Assessment of the differences between marijuana and existing medications in terms of access and availability.

These specific areas along with the assessments described above will be integrated into a broad description and assessment of the available literature relevant to the medical use of marijuana.

APPENDIX E
Recommendations Made in Recent Reports on the Medical Use of Marijuana

Recommendations from five recent key reports pertaining to the medical use of marijuana are listed below by subject. Recommendations made on issues outside the scope of this report, such as drug law and scheduling decisions, are not included here. The following reports were reviewed:

- Health Council of the Netherlands, Standing Committee on Medicine. 1996. *Marihuana as Medicine.* Rijswikj, the Netherlands: Health Council of the Netherlands.
- *Report of the Council on Scientific Affairs*. 1997. Report to the American Medical Association House of Delegates. Subject: Medical Marijuana. Chicago: AMA.
- British Medical Association. 1997. *Therapeutic Uses of Cannabis.* United Kingdom: Harwood Academic Publishers.
- National Institutes of Health. 1997. *Workshop on the Medical Utility of Marijuana*. Bethesda, MD: National Institutes of Health.
- World Health Organization. 1997. *Cannabis: A Health Perspective and Research Agenda.* Geneva: WHO.

In November 1998, the British House of Lords Science and Technology Committee published *Medical Use of Cannabis*, in which the committee reported its conviction that "cannabis almost certainly does have genuine medical applications." The House of Lords report was released too late in the preparation of the present Institute of Medicine report to per-

mit careful analysis and is not summarized here. It is available on the Internet at: *www.parliament.uk*.

GENERAL RECOMMENDATIONS

Health Council of the Netherlands

In order to assess the efficacy of marijuana and cannabinoids, the committee studied literature published during the past 25 years. Based on those findings, the committee concluded that there was insufficient evidence to justify the medical use of marijuana.

AMA House of Delegates

Adequate and well-controlled studies of smoked marijuana should be conducted in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy, including AIDS wasting syndrome, severe acute or delayed emesis induced by chemotherapy, multiple sclerosis, spinal cord injury, dystonia, and neuropathic pain.

British Medical Association

Research on the clinical indications for medical prescription of cannabinoids should be undertaken. For all indications listed below (antiemetics, pain, epilepsy, glaucoma, asthma, immunological effects, multiple sclerosis, spinal cord injury, and other spastic disorders) further research is required to establish suitable methods of administration, optimal dosage regimens, and routes of administration. A central registry should be kept of patients prescribed cannabinoids so that the effects can be followed up over the long term.

National Institutes of Health

For at least some potential indications, marijuana looks promising enough to recommend that new controlled studies be done. The indications in which varying levels of interest were expressed are the following: appetite stimulation and wasting, chemotherapy-induced nausea and vomiting, neurological and movement disorders, analgesia, [and] glaucoma. Until studies are done using scientifically acceptable clinical trial design and subjected to appropriate statistical analysis, the question concerning the therapeutic utility of marijuana will likely remain largely un-

answered. To the extent that the NIH can facilitate the development of a scientifically rigorous and relevant database, the NIH should do so.

World Health Organization

Therapeutic uses of cannabinoids warrant further basic pharmacological and experimental investigation and clinical research into their effectiveness. More research is needed on the basic neuropharmacology of THC and other cannabinoids so that better therapeutic agents can be found.

ANALGESIA

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

Controlled evidence does not support the view that THC or smoked marijuana offers clinically effective analgesia without causing significant adverse events when used alone. Preclinical evidence suggests that cannabinoids can potentiate opioid analgesia and that cannabinoids may be effective in animal models of neuropathic pain. Further research into the use of cannabinoids in neuropathic pain is warranted.

British Medical Association

The prescription of nabilone, THC, and other cannabinoids should be permitted for patients with intractable pain. Further research is needed into the potential of cannabidiol as an analgesic in chronic, terminal, and postoperative pain.

National Institutes of Health

Evaluation of cannabinoids in the management of neuropathic pain, including HIV-associated neuropathy, should be undertaken.

World Health Organization

No recommendations made, although the report notes that some newly synthesized cannabinoids are extremely potent analgesics; how-

ever, separation of the analgesia and side effects remains to be demonstrated.

NAUSEA AND VOMITING

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

THC and smoked marijuana are considerably less effective than currently available therapies to treat acute nausea and vomiting caused by chemotherapy, although certain patients still do not respond adequately to conventional therapy. Research involving THC and smoked marijuana should focus on their possible use in treating delayed nausea and vomiting and their adjunctive use in patients who respond inadequately to 5-HT_3 antagonists. The use of an inhaled substance has the potential to benefit ambulatory patients who are experiencing the onset of nausea and are thus unable to take oral medications.

British Medical Association

Further research is needed on the use of Δ^8-THC as an antiemetic, the use of cannabidiol in combination with THC, and the relative effectiveness of cannabinoids compared with 5-HT_3 antagonists. Further research is needed in other cases, such as postoperative nausea and vomiting.

National Institutes of Health

Inhaled marijuana merits testing in controlled, double-blind, randomized trials for nausea and vomiting.

World Health Organization

More basic research on the central and peripheral mechanisms of the effects of cannabinoids on gastrointestinal function may improve the ability to alleviate nausea and emesis.

WASTING SYNDROME AND APPETITE STIMULATION

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

THC is moderately effective in the treatment of AIDS wasting, but its long duration of action and intensity of side effects preclude routine use. The ability of patients who smoke marijuana to titrate their dosage according to need and the lack of highly effective, inexpensive options to treat this debilitating disease create the conditions warranting formal clinical trials of smoked marijuana as an appetite stimulant in patients with AIDS wasting syndrome.

British Medical Association

Allowing the prescription of nabilone and THC for cancer chemotherapy and HIV/AIDS seems justified for preventing weight loss and treating anorexia in HIV/AIDS irrespective of whether the patient is experiencing nausea and/or vomiting.

National Institutes of Health

Areas of study for the potential appetite-stimulating properties of marijuana include the cachexia of cancer, HIV/AIDS symptomatology, and other wasting syndromes. Investigations should be designed to assess long-term effects on immunology status, the rate of viral replication, and clinical outcomes in participants as well as weight gain. In therapeutic trials of cachexia, research should attempt to separate out the effect of marijuana on mood versus appetite. Some questions need to be answered in the studies: (1) Does smoking marijuana increase total energy intake in patients with catabolic illness? (2) Does marijuana use alter energy expenditure? (3) Does marijuana use alter body weight and to what extent? (4) Does marijuana use alter body composition and to what extent?

World Health Organization

No specific recommendations are made, although the report notes that dronabinol is an effective appetite stimulant for patients with AIDS wasting syndrome.

MUSCLE SPASTICITY

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

Considerably more research is required to identify patients who may benefit from THC or smoked marijuana and to establish whether responses are primarily subjective in nature. A therapeutic trial of smoked marijuana or THC may be warranted in patients with spasticity who do not derive adequate benefit from available oral medications, prior to their considering intrathecal baclofen therapy or neuroablative procedures.

British Medical Association

A high priority should be given to carefully controlled trials of cannabinoids in patients with chronic spastic disorders that have not responded to other drugs are indicated. In the meantime, there is a case for the extension of the indications for nabilone and THC for use in chronic spastic disorders unresponsive to standard drugs.

National Institutes of Health

No recommendations are made, although the report notes that marijuana or the use of other cannabinoids as human therapies might be considered for treating spasticity and nocturnal spasms complicating multiple sclerosis and spinal cord injury.

World Health Organization

The report notes that cannabinoids have not yet been proven useful in treating multiple sclerosis, but therapeutic uses of cannabinoids are being demonstrated by controlled studies as an antispasmodic. Research in this area should continue.

MOVEMENT DISORDERS

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

Considerably more research is required to identify dystonic patients who may benefit from THC or smoked marijuana and to establish whether responses are primarily subjective in nature.

British Medical Association

The potential of (+)-HU-210 for neruodegenerative disorders should be explored through further research.

National Institutes of Health

No recommendations made, although the report notes that marijuana or the use of other cannabinoids as human therapies might be considered for treating for some forms of dystonia.

World Health Organization

No recommendations made, although the report notes that cannabinoids have not yet been proven useful in the treatment of movement disorders.

EPILEPSY

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

No recommendations made.

British Medical Association

Trials with cannabidiol (which is nonpsychoactive), used to enhance the activity of other drugs in cases not well controlled by other anticonvulants, are needed.

National Institutes of Health

No recommendations made, although the report notes that marijuana

or the use of other cannabinoids as human therapies might be considered for treating various active epilepsy states.

World Health Organization

No recommendations made, although the report notes that cannabinoids have not yet been proven useful in the treatment of convulsant disorders, but therapeutic uses of cannabinoids are being demonstrated by controlled studies as an anticonvulsant.

GLAUCOMA

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

Neither smoked marijuana nor THC is a viable approach in the treatment of glaucoma, but research on their mechanism of action may be important in developing new agents that act in an additive or synergistic manner with currently available therapies.

British Medical Association

Cannabinoids do not at present look promising for this indication, but much further basic and clinical research is needed to develop and investigate cannabinoids that lower intraocular pressure, preferably by topical application (e.g., eye drops, inhalant aerosols), without producing unacceptable systemic and central nervous system effects.

National Institutes of Health

Further studies to define the mechanism of action and to determine the efficacy of Δ^9-tetrahydrocannabinol and marijuana in the treatment of glaucoma are justified. There does not appear to be any obvious reason to use smoked marijuana as a primary "stand-alone" investigational therapy, as there are many available agents for treatment, and these topical preparations seem to be potentially ideal. An approach that may be useful is to study smoked marijuana in incomplete responders to standard therapies. The suggested design for clinical studies is to add marijuana, oral THC, or placebo to standard therapy under double-blind conditions: (1) Establish dose-response and dose-duration relationships for intraocular pressure

(IOP) and central nervous system effects. (2) Relate IOP and blood pressure measurements longitudinally to evaluate potential tolerance development to cardiovascular effects. (3) Evaluate central nervous system effects longitudinally for tolerance development.

World Health Organization

No recommendations made, although the report notes that, while THC has long been known to reduce the increased intraocular pressure of glaucoma, it has not been fully studied therapeutically. The report also notes that therapeutic uses of cannabinoids are being demonstrated by controlled studies in the treatment of glaucoma.

PHYSIOLOGICAL HARMS

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

No recommendations made.

British Medical Association

Further research is needed to establish the suitability of cannabinoids for immunocompromised patients, such as those undergoing cancer chemotherapy or those with HIV/AIDS.

National Institutes of Health

Risks associated with smoked marijuana must be considered not only in terms of immediate adverse effects but also long-term effects in patients with chronic diseases. The possibility that frequent and prolonged marijuana use might lead to clinically significant impairments of immune system function is great enough that relevant studies should be part of any marijuana medication development research.

Additional studies of long-term marijuana use are needed to determine if there are or are not important adverse pulmonary, central nervous system, or immune system problems.

World Health Organization

Further studies are needed on the fertility effects in cannabis users in view of the high rate of use during the early reproductive years. Further clinical and experimental research is required on the effects of cannabis on respiratory function and respiratory diseases. More studies are needed to show whether cannabis affects the risk of lung malignancies and at what level of use that may occur. In addition, more studies are needed to clarify the rather different results of pulmonary histopathological studies in animals and man.

More clinical and experimental research is needed on the effects of cannabis on immunological function. More clarity should be sought concerning the molecular mechanisms responsible for immune effects, including both cannabinoid receptor and nonreceptor events.

The possibility that chronic cannabis use has adverse effects on the cardiovascular system should have a priority in epidemiological research.

Research on chronic and residual cannabis effects is also needed. The pharmacokinetics of chronic cannabis use in humans are poorly described, and this lack of knowledge restricts the ability of researchers to relate drug concentrations in blood or other fluids and observed effects.

PSYCHOLOGICAL HARMS

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

No recommendations made.

British Medical Association

No recommendations made.

National Institutes of Health

No recommendations made.

World Health Organization

There is a need for controlled studies investigating the relationships between cannabis use, schizophrenia, and other serious mental disorders.

There is also a need for case-controlled studies comparing those experiencing cannabis problems with people who have, and do not have, alcohol and other psychoactive substance use problems.

There is a need for better delineation of the clinical features of cannabis dependence and for studies of its responsiveness to interventions aimed at assisting users to stop.

Insufficient research has been undertaken on the "amotivational" syndrome which may or may not result from heavy cannabis use. It is not clear that the syndrome exists, even though heavy cannabis use is sometimes associated with reduced motivation to succeed in school and work. New research is needed to show whether the reduced motivation seen in some cannabis users is due to other psychoactive substance use and whether it precedes cannabis use.

Further development of cognitive and psychomotor tests for controlled studies that are sensitive to the performance effects of cannabis use and that reflect the complexity of specific daily functions (e.g., driving, learning, reasoning) also need additional research.

More research is needed to examine the relationship between THC concentrations in blood and other fluids and the degree of behavioral impairment produced.

SMOKED MARIJUANA AND USE OF PLANTS AS MEDICINE

Health Council of the Netherlands

The committee believes that physicians cannot accept responsibility for a product of unknown composition that has not been subjected to quality control.

AMA House of Delegates

No specific recommendations made, but related issues are discussed in the general recommendation and drug development sections.

British Medical Association

Prescription formulations of cannabinoids or substances acting on the cannabinoid receptors should not include either cigarettes or herbal preparations with unknown concentrations of cannabinoids or other chemicals.

National Institutes of Health

Smoked marijuana should be held to standards equivalent to other

medications for efficacy and safety considerations. There might be some patient populations for whom the inhalation route might offer advantages over the currently available capsule formulation. Smoking plant material poses difficulties in standardizing testing paradigms, and components of the smoke are hazardous, especially in the immunocompromised patient. Therefore, the experts generally favored the development of alternative dosage forms, including an inhaler dosage form into which a controlled unit dose of THC could be placed and volatilized.

World Health Organization

Not discussed in the context of medical use, although many health hazards associated with chronic marijuana smoking are noted.

DRUG DEVELOPMENT

Health Council of the Netherlands

Not discussed.

AMA House of Delegates

The National Institutes of Health should use its resources to support the development of a smoke-free inhaled delivery system for marijuana or THC to reduce the health hazards associated with the combustion and inhalation of marijuana.

British Medical Association

Pharmaceutical companies should undertake basic laboratory investigations and develop novel cannabinoid analogs that may lead to new clinical uses.

National Institutes of Health

NIH should use its resources and influence to rapidly develop a smoke-free inhaled delivery system for marijuana or THC. A recommendation was made for the development of insufflation/inhalation devices or dosage forms capable of delivering purer THC or cannabinoids to the lungs free of dangerous combustion byproducts.

World Health Organization

Not discussed.

APPENDIX F

Rescheduling Criteria

DRUG ENFORCEMENT AGENCY'S FIVE-FACTOR TEST FOR RESCHEDULING*

1. The drug's chemistry must be known and reproducible.

The substance's chemistry must be scientifically established to permit it to be reproduced in dosages which can be standardized. The listing of the substance in a current edition of one of the official compendia, as defined by section 201(j) of the Food, Drug, and Cosmetic Act, 21 USC 321(f), is sufficient generally to meet this requirement.

2. There must be adequate safety studies.

There must be adequate pharmacological and toxicological studies done by all methods reasonably applicable on the basis of which it could be fairly and responsibly concluded, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that the substance is safe for treating a specific, recognized disorder.

3. There must be adequate and well-controlled studies proving efficacy.

There must be adequate, well-controlled, well-designed, well-conducted, and well-documented studies, including clinical investigations, by experts qualified by scientific training and experience to evaluate

*Formulated in 1992 in response to a court challenge to scheduling.

the safety and effectiveness of drugs on the basis of which it could fairly and responsibly be concluded by such experts that the substance will have its intended effect in treating a specific, recognized disorder.

4. The drug must be accepted by qualified experts.

The drug must have a New Drug Application (NDA) approved by the Food and Drug Administration . . . or, a consensus of the national community of experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, accepts the safety and effectiveness of the substance for use in treating a specific, recognized disorder. A material conflict of opinion among experts precludes a finding of consensus.

5. The scientific evidence must be widely available.

In the absence of NDA approval, information concerning the chemistry, pharmacology, toxicology, and effectiveness of the substance must be reported, published, or otherwise widely available in sufficient detail to permit experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, to fairly and responsibly conclude the substance is safe and effective for use in treating a specific, recognized disorder.

SOURCES: LeCraw (1996) and 57 *Federal Register* 10499 (1992).

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