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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.[30,65] 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 immuno-suppressive 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 tolerated 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.**

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## Notes

[1] 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.

[2] 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.

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

[4] 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.

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

[6] 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.

[7] 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).

[8] 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 particul r 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.

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# 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 marijuana 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 disease. 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. *Sequencing 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.[157] Methods for such trials have been established and tested in a variety of clinical settings, usually under everyday conditions.[66,105,158] 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 cross-over 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.[102] 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.[86] 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 controls--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.[31]

## 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.[146,147] 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.[45] 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.[116] 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 de nonstrated 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 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.[121,55,101]

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.

## 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 $\Delta^9$-THC and $\Delta^8$-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 th· · given THC. There were many flaws in experimental methods, but tl e 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. $\Delta^8$-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.[2] Two hours before the start of each cancer treatment and every six hours thereafter for 24 hours, the children were given $\Delta^8$-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.

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;[37] 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 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 different 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 suff. from debilitating emesis. It is poss.ble 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. Starvation 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,[3] 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;[190] 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]

## 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.[53,62] 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.[47,114] 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 promoting 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 ß2-adrenergic receptor agonists to increase muscle mass.[14,75] 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 ß2-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.[105] Pharmacological treatments, such as antidepressants, have been used in addition to psychotherapy but tend to lack the desired level of

efficacy. 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.[62,125] 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.[4] 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 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 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.[55] 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.

### *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.[150] 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]

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 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,[5] 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.[1,10,32,76,77,125,193] 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 $\Delta^9$-THC, $\Delta^8$-THC, or 11-OH-THC to healthy adults substantially decreased IOP, whereas cannabinol, CBD, and ß-OH-THC had little effect.[31,140] 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 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 $\Delta^9$-THC was applied topically as eye drops, whether once or four times a day, there was no decrease in IOP.[60,91] 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 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 likel od 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 recommend 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]

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## Notes

[1] 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.

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

[3] 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).

[4] 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.

[5] 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.

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# 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.[2,3] FDA approval of a drug is the culmination of a long, research intensive process of drug development, which often takes well over a decade.[1],[4] 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 development programs--including those for AIDS, cancer, addiction, and epilepsy--have been instrumental in ushering new drugs to market in collaboration with pharmaceutical companies.[5] 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).[21]

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 about $200—$300 million, depending on the method and year of calculation.[23,24]

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.[1] 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. 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.[33]

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 availability 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.[2] 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.[3] 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. 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 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[4] 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.[35] In practice, the DEA usually adheres to the recommendation of the secretary.[5] Beyond the DEA, 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 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.[10]

## 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.[7] 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 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.[45,50] 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.[52]

Marinol's most common adverse events are associated with the central nervous system (CNS): anxiety, confusion, depersonalization, dizziness, euphoria, dysphoria, somnolence, and thinking abnormality.[8,9,35,39] 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.[8,41] 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 Schedule II to Schedule III, which is reserved for medically approved substances that have some potential for abuse (21 U.S.C. § 312 (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.[13] 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;[30] 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.[38] 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,[5] 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 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 vulnerability 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 reimburse-ment 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.[169] 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.

## 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, 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.[25]

## 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.[10] 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[30]; Howlett, 1995[30]; Pertwee 1997[30]). 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,[49,54] 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 $\Delta^8$-THC were demonstrated in a clinical trial in children who were undergoing cancer chemotherapy,[1] but no sponsor was interested in developing $\Delta^8$-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.[12] 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 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.[53] 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).[55]

## 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.