SB 74

DOCUMENTS AGAINST (FILE 3)

National Commission on Marihuana and Drug Abuse

History of Alcohol Prohibition*

***This section is based in large part on a paper prepared for the Commission by Jane Lang McGrew, an attorney from Washington, D.C.**

In 1920, the national policy of Prohibition began. The 18th Amendment to the Constitution had been officially ratified:

It sought, by law, to make the whole Nation into enforced teetotalers and to put an end to all evils associated with drinking. It sought to eradicate a taste deeply rooted in the habits and customs of a large part of the population through outlawing the business that ministered to its satisfaction (Hu, 1950: 48).

1650-1750: THE FIRST HUNDRED YEARS

In fact, it started earlier. "Ministers shall not give themselves to excess in drinkinge, or riott, or spending their tyme idellye day or night," ruled the Virginia Colonial Assembly in 1629 (Cherrington, 1920:16).

Massachusetts ordered that no person shall remain in any tavern "longer than necessary occasions" in 1637, while Plymouth Colony in 1633 prohibited the sale of spirits "more than 2 pence worth to anyone but strangers just arrived" (Cherrington, 1920: 18).

This sampling of the earliest colonial laws is representative of the attempt, continued since those times, to control excessive consumption. Excessive drinking, it was considered, produced behavior unseemly in some, such as ministers, and dangerous in others, such as Indians.

But drinking per se was not frowned upon. Indeed, when the Puritans set sail to Massachusetts, they had taken care to carry with them 42 tons of beer (in contrast with 14 tons of water) and 10,000 gallons of wine (Lee, 1963: 15).

The regulation of liquor consumption was a matter of considerable concern in certain colonies. Thus, for a time, Massachusetts went so far as to prohibit the drinking of healths in 1638 (Lee, 1963: 19). The law was soon abandoned for reasons obvious, albeit unrecorded. It rapidly became clear, however, that liquor laws could do more and perhaps better, than control consumption: they could provide a source of revenue. By the turn of the 18th century, the regulatory impulse was concentrated on fines, excise taxes and license

fees.

Fines were imposed for drunken behavior, unlawful sales to a drunken tippler or to Indians, and for selling without a license. Court records indicate that these laws were enforced with reasonable regularity (Krout 1967: 29-30). Licenses often carried their own fees, and excise taxes were levied upon distilled spirits as well as beer and fermented drink in many cases.

Until the 18th century, however, there was no attempt to prohibit the manufacture, importation, sale, or consumption of alcoholic beverages. Quite the contrary, at least one individual-in some cases a reluctant individual-was required in many towns to run the local inn or public house for visitors and travelers.

Although colonial statutes made it clear that tipplers and idlers were unwelcome, the diary of a colonial traveler, Sarah Kemble Knight, suggests that such laws were unsuccessful in containing the ribaldry which took place in many such houses. Madam Knight complained:

I could get no sleep, because of the Clamor of some of the Town Tope-ers in the next room.... I heartily fretted & wish't 'am tongue tyed.... They kept calling for Tother Gill, Wch while they were swallowing, was some Intermission, But presently, like Oyle to fire, encreased the flame (Miller, Johnson, eds., 1963: 430-431).

Persons other than Madam Knight were to become more outspoken about their concern for the use of spirits. The most significant premonition was the Colony of Georgia's action in 1735 when the first prohibitory statute against the importation of "ardent spirits" was enacted. At the same time, however, the consumption of beer was encouraged (Grant, 1932: 1). The time for temperance had not yet arrived.

1750-1825: TEMPERANCE STIRRINGS

As the evils of intemperance began to attract the attention of the ministry, John Wesley denounced the sin of distilling -and declared for its Prohibition in 1773 (Cherrington, 1920: 37-38).

On his heels came the publication of a pamphlet entitled "The Mighty Destroyer Displayed and Some Account of the Dreadful Havoc Made by the Mistaken Use, As Well As the Abuse, of Distilled Spirituous Liquors," by Anthony Benezet, a member of the Society of Friends, advising against the use of any drink "which is liable to steal away a man's senses and render him foolish, irrascible, uncontrollable, and dangerous" (Cherrington, 1920: 38).

Nevertheless, typical of the century's ambivalence, the first master at Harvard was fired when it was found that Harvard students had been left "wanting beer betwixt brewings a week and a week and a half together" (Lee, 1963: 16).

Concern for the effect of liquor upon the public weal was expressed by John Adams who noted in his diary on February 29, 1760, that the taverns were "becoming the eternal haunt of loose, disorderly people . . ." (Cherrington, 1920: 37). Worst of all he continued:

... These houses are become the nurseries of our legislators. An artful man, who has neither sense nor sentiments, may, by gaining a little sway among the rabble of the town, multiply taverns and dram shops and thereby secure the votes of taverner and retailer and

of all; and the multiplication of taverns will make many, who may be induced to flip and rum, to vote for any man whatever (Dobyns, 1940: 215).

The health argument in behalf of temperance was first made by Nathaniel Ames, in the 1752 edition of his Almanack, who wrote that

Strong Waters were formerly used only by the Direction of Physicians; but now Mechanicks and low-li'd Labourers drink Rum like Fountain-Water, and they can infinitely better endure it than the idle, unactive and sedentary Part of Mankind, but DEATH is in the bottom of the cup of every one (Lee, 1963: 22).

Dr. Benjamin Rush shared his concern, publishing in 1785 his now famous "Inquiry into the Effects of Ardent Spirits Upon the Human Body and Mind." Enumerating the diseases of the body and mind which plague the drinker of distilled liquors, Dr. Rush outlined the symptoms, including "unusual garrulity, unusual silence, captiousness ... an insipid simpering ... profane swearing ... certain immodest actions" and "certain extravagant acts which indicate a temporary fit of madness" (Rush, 1943: 323, 325-326).

Although the rumblings of the temperance movement were thus perceptible in the late 18th century, there is no evidence that its effects were felt. In 1766, it is recorded that the repeal of the Stamp Act was greeted in Providence, Rhode Island with "32 of the most loyal, patriotic and constitutional toasts" (Lee, 1963: 18). Notwithstanding this evidence of devotion to His Majesty, it was often thereafter the tavern which provided the meeting places for the most defiant revolutionaries.

Subsequently, when the colonial period disappeared into the post-Revolutionary era, Alexander Hamilton adopted the idea earlier effected by the individual colonies, to tax distilled liquors for revenue purposes. In 1791 , the tax was enacted as part of the Revenue Act. The following year, the Second Congress of the United States added license fees for distilleries and taxes on liquors distilled from imported materials.

Incensed by this federal action, farmers in Western Pennsylvania mobbed revenue collectors and armed to resist this intrusion by the new Federal Government. It required 15,000 militia to bring the so-called Whiskey Rebellion to an end (Peterson, 1969: 119-120). Such was the first indication that the liquor industry in the United States would be a force with which the government would have to reckon.

Toward the end of the 18th century, a temperance movement, as such, became discernible. The Methodist Church took a staunch position against the sale or imbibing of ardent spirits "unless in cases of extreme necessity." Five years later, in 1789, even the exception was excised (Cherrington, 1920: 50). A similar platform was adopted by the Presbyterian Synod of Pennsylvania and by the Yearly Meeting of Friends of New England (Cherrington, 1920: 51, 58).

On a non-clerical level, the movement began to organize. Although there is some dispute as to the identity of the original temperance society, it appears that as early as 1778, there was an organization calling itself the Free African Society which excluded men of drinking habits, followed soon thereafter by the Organization of Brethren, and the Litchfield, Connecticut Association of "the most respectable farmers" in Connecticut determined to discourage the use of spirits (Cherrington, 1920: 49, 58).

The turn of the century saw the vitalization of the temperance spirit. Religious leaders, including Cotton Mather, Dr. Lyman Beecher, John Wesley and Reverend Andrew Elliott

inveighed against the consumption of liquors. Temperance activity figured prominently in the concerns of the Presbyterian, Methodist, Universalist, Baptist, and Friends churches.

"*Had. the temperance reform in America awaited for a non-church or a non-Christian leadership,*" theorizes one historian.

... the temperance revolution of the past century would yet remain to be accomplished.... Every successful temperance movement of the last century has been merely the instrument- the machinery and equipment through which the fundamental principles of the Christian religion have expressed themselves in terms of life and action (Cherrington, 1920:92).

Whatever the Christian input, however, it is also apparent that a desire to reform was aroused in the country, very much like that which was to be experienced a century later during the Progressive Movement. Thus, Massachusetts Society for the Suppression of Intemperance of 1813, damned not only rum, but all of the "kindred vices, profaneness and gambling" and beseeched members to "discourage... by ... example and influence, every kind of..... immorality" (Lee, 1963: 23). Mingling with the potential temperance leaders during this period were the future spokesmen of abolitionism, feminism, and utopianism.

In the meantime, the industry was able to report triumphantly that the federal taxes on distilling and importing spirits were repealed in 1802. From 1813 until 1817, the retailers' and distillers' licenses bore a federal tax, but beginning in 1818 the industry enjoyed a tax-free era which was to last until 1862. Thomas Jefferson rejoiced-"as a moralist"-explaining that:

It is an error to view a tax on that liquor as merely a tax on the rich. It is a prohibition of its use in the middling class of our citizens, and a condemnation of them to the poison of whisky, which is desolating their houses. No nation is drunken where wine is cheap; and none sober, where the only antidote is the bane of whisky (Peterson, 1969: 122-123).

Future prohibitionists would likewise castigate the government for drawing its revenues from the liquor industry and participating in the profits of evil thereby.

1825-1870: THE PLEDGE

Temperance was not always equated with teetotalism. Beer and usually wine were initially exempt from denunciation in both sermons and treatises. There developed in the mid-19th century, however, the conviction that all brews, be they "ardent spirits," beer, ale, or wine, were anathema.

The, new temper of the movement was epitomized by the travels of Father Theobald Matthew of Ireland who toured the United States from 1849 to 1851, administering the pledge of total abstinence to some 600,000 persons in 25 states. A White House dinner and a Senate reception stamped official approval upon his sojourns (Furnas, 1968: 80). Thus did temperance drift into a new phase, with its ardent spokesman, Congressman Gerrit Smith, crying that:

I would that no person were able to drink intoxicating liquors without immediately

becoming a drunkard. For, who, then would . . . drink the poison that always kills, or jump into the fire that always burns? (Furnas, 1968: 15).

It was in this atmosphere that the first prohibition experiments were undertaken on a statewide basis. "Until the liquor traffic is abolished . . . all efforts at moral reform must languish," judged one of the earliest prohibitionists.

In 'Grappling with the Monster," T. S. Arthur stated, "The CURSE is upon us, and there is but one CURE: Total Abstinence, by the help of God, for the Individual, and Prohibition for the State" (Furnas, 1968: 15).

In 1847, the first such cure was enacted for the state of Maine (Cherrington, 1920: 134). (Actually, the first Prohibition law went into effect in 1843 in the territory of Oregon. This was repealed five years later.)

A wave of prohibition statutes followed. Delaware, on the heels of Maine, passed its first prohibition law only to have it declared unconstitutional the following year. Similar laws were enacted in Ohio, Illinois, Rhode Island, Minnesota, Massachusetts, Connecticut, Pennsylvania and New York during the next few years. They met with varying fates, including veto by the governors, repeal by the legislatures and invalidation by the state supreme courts.

The evaluations by several historians of these early trials were to be heard again in the 20th century: the enactments lacked support from a large portion of the population, making enforcement exceedingly difficult. Ultimately, all but one of the states repealed the prohibition statutes of the 19th century (Grant, 1932: 5; Peterson, 1969: 123).

Notwithstanding this record, prohibitionists took heart. "This thing is of God," cried Lyman Beecher from the pulpit. "That glorious Maine law was a square and grand blow right between the horns of the Devil" (Furnas, 1968: 167). Temperance societies, established in all but three states by 1832 and destined to proliferate, began to consolidate as well.

The American Temperance Society, later to become the American Temperance Union, was organized in 1826. It quickly begat auxiliaries, so that by 1835, 8,000 locals existed (Cherrington, 1920: 92-93).

As the years passed, they witnessed the founding of more temperance, organizations of a general and national character than during any other period in the United States' history. The Washingtonian movement, organized in the City of Baltimore in 1840, was followed by the Martha Washington movement in 1841.

The Sons of Temperance came into existence in 1842, at the same time the Order of Rechabites was organized, and the Congressional Temperance Society of 1833 was revived on the basis of total abstinence. They took heart at their early state, successes and fought against the defeats of repeal.

In the meantime, however, the United States government, which had heaped honors upon Father Matthew, concluded a treaty with King Kamehameha III of Hawaii in 1850 permitting the introduction and sale of liquor on his island.

As further evidence of the national dichotomy, Chicagoans in the 1850's fought virulently against the enforcement of Sunday closing laws. To protest, an armed mob burst into the business district of the city, to be met by police. Fortunately, the mob was dispersed before

the mayor found it necessary to use the cannon he had hurriedly planted around City Hall (Peterson, 1969: 120).

It was the time when patent medicines, 40 proof and more, began to develop their clientele. And although the Demon Rum might threaten their health and life, Lydia Pinkham's Compound offered a cure for any and all ails and aches.

By the time of the Civil War, both the assimilative and coercive traditions of the temperance movement had crystallized: that is, temperance proponents were determined to save the weak and to destroy the recalcitrant (Gusfield, 1963: 69-70). The hardening of positions was accompanied by the development of political consciousness in the movement and recognition of political objectives. These processes were only temporarily blunted by the Civil War in the 1860's and the diversion of interest to the abolitionist cause.

Part of the heritage of the Civil War was the tax on liquor and beer imposed in 1862. Rates were increased several times between 1863 and 1868, so that the tax imposed at the rate of 20 cents per gallon rose to $2 per gallon.

An interesting phenomenon was noted by the Federal Government: as the rates increased, the revenue did not. In fact, the number of gallons reported actually declined. As the decade went on, attempts were made to enforce the tax laws and in 1868, $25,000 was actually appropriated to detect violators. Fraud continued almost unabated. Stockpiling of liquor was popular to hedge against future, increases, for they were not applicable to liquor on hand.

The infamous Whiskey Ring was active in these days and was not finally broken up until 1875, when, in a peak of nerve, members established a corruption fund in the District of Columbia to halt the prosecution of 321 persons charged with violations of the revenue laws. Before then, however, Congress apparently had second thoughts about the implications of the revenue collections and reduced the tax from the high of $2 per gallon to 50 cents in 1869. The happy result was to see a rise in collections from $13.5 million in 1868, to $45 million in 1869, and $55 million the following year. Taking further precautions, the government stipulated that new stamps be developed to preclude counterfeiting and tampering (History of the Alcohol 14-20; Cherrington, 1920: 156162).

Congress did not escape unscathed by criticism and reaction. It came from both sides of the temperance issue. Temperance advocates such as Senator Wilson of Massachusetts and Senator Pomeroy of Kansas decried the fact that federal revenues would be drawn from the liquor industry.

At the same, time, however, the industry revolted, leading to mass tax evasion schemes and devices and the organization of their first industry lobby, the United States Brewers Association. The Association rapidly launched a, legislative campaign and succeeded in 1863 in reducing the tax rate of beer from $1 to 60 cents (Cherrington, 1920:157).

By 1870, the Civil War dust had cleared and the temperance battle lines were drawn, already tested by the skirmishes of the 1840's and 1850's. The most interesting feature of their war strategy was soon to become apparent: women and children were welcomed at the battlements.

1870-1913: TOWARD A NATIONAL CONSCIENCE

A series of "isms" was aroused in this era: feminism, unionism, socialism, and

progressivism. Prohibition absorbed elements of them all, and vice versa.

The feminist movement originated early in the 1800's. Until the 1870's, however, feminine involvement in the temperance effort was largely peripheral. The Women's Crusade of 1873 and the organization of the Women's Christian Temperance Union in 1874 marked the formal entrance of women into the temperance movement.

The WCTU was devotedly headed by Frances E. Willard, a lady equally committed to the principle of equality of the sexes. Temperance was to bridge the gap, she believed:

Drink and tobacco are the great separatists [sic] between men and women. Once they used these things together, but woman's evolution has carried her beyond them; man will climb to the same level . . . but meanwhile ... the fact that he permits himself fleshly indulgence that he would deprecate in her, makes their planes different, giving her an instinct of revulsion (Furnas, 1968: 281).

Although the WCTU was organized initially around the temperance issue, it was not long before Miss Willard's leadership expanded its conscience.

A statement of principles was adopted in its early years:

We believe in a living wage; in an 8-hour day; in courts of conciliation and arbitration, in justice as opposed to greed in gain; in "Peace on Earth and Good Will to Men" (Gusfield, 1963: 76).

Within three years of its inception, the WCTU reported that its concerns included "a better Indian policy" and "wiser civil service reform" (Gusfield, 1963: 77). There were those in the Union who felt that their interests should be limited to temperance. But, forecasting the mood of Progressivism, Miss Willard steered the organization along the broader lines to social reform.

The WCTU was responsible for part of the early campaign to educate the public about temperance. Children were recruited to sing praises of "the true and the brave" who signed the abstinence pledge. They were assisted in this effort by McGuffey's Readers which denounced the licensing of liquor stores and saloons:

Licensed-to do thy neighbor harm,

Licensed-to kindle hire and strife,

Licensed-to nerve the robber's arm,

Licensed-to whet the murderer's knife,

Licensed-like spider for a fly,

To spread thy nets for man, thy prey,

To mock his struggles, crush his soul,

Then cast his worthless form away (Lee, 1963: 34-35).

Whiskey makes "the happy miserable" and impoverishes the rich, the, McGuffey books concluded. And the word spread. By 1902, the temperance campaign had permeated the public school systems: every state but Arizona had introduced compulsory temperance education. Their texts teemed with both facts and misinformation such as "Alcohol sometimes causes the coats of the blood vessels to grow thin. They are then liable at any time to cause death by bursting." (Sinclair, 1962: 43).

The WCTU was not carrying the burden of reform alone, however. In 1869, the National Prohibition Party was born. Three years later, the first party ticket was put forth in the presidential campaign of 1872, headed by John Black, who received 5,607 votes for President. Success at the polls ultimately peaked in 1892 when John Dedwell, the Prohibition presidential candidate, received a total of 270,710 votes. Thereafter, its partisans declined in number, having failed to break voters away from their traditional affiliations (Cherrington, 1920: 165-169).

As a rule, the WCTU eschewed partisanship. Their objectives were far broader and more practical than those contemplated by the Prohibition Party. Only once it supported the Prohibition Party in the notorious election of 1884.

The election of 1884 carried a variety of implications for future candidates on the temperance issue. In New York City alone, 1,007 primaries and conventions reportedly were held by the various parties. Of these, over 60% took place in saloons (Peterson, 1969: 123), recalling to mind the complaint of John Adams a century before (Cherrington, 1920: 37; Dobyns, 1940: 215). The meeting places were indicative of the fact that at this time neither party could afford to adopt a dry plank in its platform, for New York would be a pivotal state in the race between Republican James G. Blaine and Democrat Grover Cleveland.

Blaine campaigned hard, trying to overcome the defection of several thousand dry Republicans to the Prohibition Party. Speaking in behalf of Blaine at a New York City rally, Presbyterian minister Samuel Burchard denounced the Democrats as the party of "Rum, Romanism, and Rebellion." Needless to say, the Catholic vote, as well as the wet vote, quickly swelled the Democratic totals. Blaine, having thus alienated both wets and drys, lost the state--and the election-by a tiny margin (Furnas, 1968: 273; Lee, 1963: 29-30).

In case the lesson that temperance was an issue to be reckoned with in national politics was lost on the parties after 1884, the events of the decade culminating in the birth of the Anti-Saloon League in 1895, dramatized the point. A second wave of state prohibition laws was experienced between 1880 and 1890. The results of much of the legislation during those years were less than satisfying to temperance advocates, however; only six states emerged with state-wide prohibition by statute or constitutional amendment. Numerous other states had enacted local option, which permitted towns to go dry if they so chose by referendum. Without state or federal insulation from wet communities, however, the so-called dry towns were scarcely temperance models.

In the wake of these state legislative actions, South Carolina introduced a state dispensary system in order to eliminate the motive of private gain from the liquor business. Political

scandals which quickly developed tended to discredit it, however, if indeed it had enjoyed much support from any corner (Cherrington, 1920: 250-251).

With this discomfiting history behind it, the Anti-Saloon League arose to the challenge, while Carrie Nation independently thrust her way into the public eye. The League was to develop the art of lobbying or "pressure political" to its most dramatic heights. Scarcely more than 10 years after organization, it was described as "the most dangerous political movement that this country has ever known" by the National Model License League, a wet (and harassed) association. A more rational viewpoint was expressed by the president of the New York State Brewers Association in 1913:

We are not dealing with a theory which is the delusion of the fanatic alone, but with a real condition which is in the hands of a well organized force, led by aggressive, experienced, and untiring leaders (Odegard, 1928: 23).

The focus of the League's indictments included not simply alcohol, but the saloon itself, as the purveyor of spirits. The myriad League publications denounced the saloon for "*annually sending thousands of our youths to destruction, for corrupting politics, dissipating workmen's wages, leading astray 60,000 girls each year into lives of immorality and banishing children from school*" (Odegard, 1928: 40-59).

"*Liquor is responsible for 19% of the divorces, 25% of the poverty, 25% of the insanity, 37% of the pauperism, 45% of child desertion, and 50% of the crime in this country*," the League determined. "*And this*," it concluded , "*is a very conservative estimate*" (Odegard, 1928: 60).

League posters appeared everywhere depicting the saloon-keeper as a profiteer who feasted on death and enslavement. Others screamed out the dire consequences of alcohol. "Alcohol inflames the passions, thus making the temptation to sex-sin unusually strong," advertised one (Sinclair, 1962: 51).

It was the League which geared up the campaign, but it was not alone. As the Progressive spirit caught the national interest in the early 19th century, the movement for reform embraced the cause of temperance. The temperance movement assumed an aura of evangelism, combining the concept of America's mission with the vision of Messianism. Through the combination of temperance and progressivism, it was believed that the Kingdom of God could actually come to the United States.

In an article in Appleton's Magazine in 1908, the Reverend Charles F. Aked articulated the aspirations of the reformers:

We are spending our lives, many of us, in the effort to make the world a little better and brighter for those that shall come after us.... we want to open out life and liberty to all the sons of men. We want to make possible for all of life in the whole, the good and the beautiful ... and the common sale of intoxicating liquor renders our work a thousand times more difficult ... (Timberlake, 1063: 34-38).

Others were more mundane. Scientists began accumulating evidence of the effect of quantities of alcohol on the nervous system and general physical condition. The myth that alcohol consumption improved muscular power was exploded. The relationship between mental psychoses and alcohol was documented, and thus did the condemnation of alcohol

as a poison assume scientific support. Finally, in 1915, whiskey and brandy were discreetly removed from the list of authoritative medicinal drugs contained in the United States Pharmacopoeia (Timberlake, 1963: 47).

Who were the people fueling the movement? Largely middle class, rural, Anglo-Saxon and Protestant comprised the temperance movement and they confronted the urban and industrial communities head-on. "The Anglo-Saxon stock is the best improved, hardiest and fittest.... [I]f we are to preserve this nation and the Anglo-Saxon type we must abolish [saloons]," proclaimed one temperance publication (Gusfield, 1963: 100). Calling itself "The Protestant church in action" (Sinclair, 1962: 108), the Anti-Saloon League concentrated single-mindedly and evangelically on the cause of temperance and refrained from dabbling in other reforms (Gusfield, 1963: 108).

Nevertheless, the Episcopal and Lutheran churches never aligned themselves with the AntiSaloon League, while Jewish and Catholic groups generally opposed their objective. The conviction shared by Anti-Saloon Leaguers expressed by Reverend Francis Ascott McBride was: "The League was born of God" (Lee, 1963: 35). Thus one had to be for or against the movement; there was no half-way commitment.

When the sides were lined up initially, industrialists and union leaders alike preferred to keep God on their side. From the company's point of view, the saloon was often responsible for industrial injuries and absenteeism. Some believed that the drinking man demanded higher wages than his sober counterparts. Furthermore, union locals tended to congregate in saloon meeting halls maintained for that purpose and, it was sometimes suspected, for the plottings of anarchistic conspirators (Furnas, 1968: 310).

Accordingly, it was not long before industry moved from an acquiescent position to an active role in the temperance movement. Various methods were adopted to encourage sobriety, including lectures, literature and job preferences for teetotalers. Businessmen opined that sobriety expanded productivity, increased bank deposits, improved collections and stimulated the retail trade (Timberlake, 1963: 67-79).

At the same time, the prospect of diverting patronage of the liquor industry to other products tantalized some industries. Thus the Welch Grape Juice Company advertised:

Get the Welch Habit-It's one that won't get you! (Timberlake, 1963: 77).

Opinion was not unanimous, of course. Businessmen, including bankers, whose interests were tied to the liquor industry could ill afford to be beneficent toward temperance. Others, including the DuPonts, Rockefellers, Kresges, and Wanamakers spent freely to cover the League's annual campaign costs of $2.5 million (Odegard, 1928: 126).

As surely as liquor was the enemy of the home, it was also proclaimed the enemy of the working man. "The great sinkhole for the workers' wages is the saloon," wrote the editors of one League publication, The California Liberator. "When that abomination is destroyed, labor is freed from its greatest curse" (Odegard, 1928: 53). The logic appealed to the union leadership. According to one official of the American Federation of Labor:

No force in our country has been as effective in the promotion of temperance among working people as the organized labor movement. The labor movement has achieved more for the cause of temperance than all the temperance societies combined ... (Timberlake, 1963: 83).

Since similar credit has been claimed for the League, the Protestant church, and business interests, it is difficult to apportion the plaudits. Subsequent events suggest that the labor interests failed to live up to this claim however.

Notwithstanding Terrence V. Powerderly's early speech against "the strong right hand of labor itself . . . that carries with it the rum which drowns reason," his own Knights of Labor repealed their constitutional provision which denied membership to anyone connected with the liquor trade (Timberlake, 1963: 85-86).

As the reports of the National Commission on Enforcement of the Prohibition Laws (known as the "Wickersham Commission") were later to record, it was particularly the workers who resented the paternal legislation which they believed was directed at them and their habits (National Commission on Law Observance, 1931: 345).

In addition, there were those whose livelihoods would be directly affected-indeed, effaced-by the success of the campaign: brewery workers, bartenders, glass workers, waiters, and musicians among others.

Thus, even though the Socialist Party resolved in 1908 that *"any excessive indulgence in intoxicating liquors by members of the working class is a serious obstacle to the triumph of our cause since it impairs the vigor of the fighters in political and economic struggle"* (Timberlake, 1963: 98), the industrial urban centers of the country continued to harbor and stimulate antagonism towards the temperance movement.

The identification of the saloon and its offerings with the urban, immigrant working class further enraged Prohibitionists. As one sociologist observed, "The saloon appeared as the symbol of a culture which was alien to the ascetic character of American values . . ." (Gusfield, 1963: 100). Thus, Americanism became a central issue in the temperance movement.

One temperance spokesman, cited in Barker's "The Saloon Problem," vented these sentiments:

The influx of foreigners into our urban centers, many of whom have liquor habits [sic], is a menace to good government. . . . [T] he foreign born population is largely under the social and political control of the saloon. If the cities keep up their rapid growth they will soon have the balance of political power in the nation and become storm centers of political life (Timberlake, 1963: 118).

1913-1933: NATIONAL PROHIBITION -- PROLOGUE AND FINISH

The distrust of the immigrant population became more pronounced as the economic, political, and social power of the cities developed. It was given a strong impetus by the anti-German tremors which shook the country in a mood of anticipation before World War I.

The United States Brewers Association misread the prevailing temper and associated itself with the German-American Alliance to oppose the temperance advocates and defend German kultur in the United States.

As the United States came closer to war, the antipathy which developed against the Central

Powers was directed with equal force against brewers and tipplers (Furnas, 1968: 334-35) :

Pro-Germanism is the only froth from the German's beer saloon. Our German Socialist Party and the German American Alliance are the spawn of the saloon. . . . Prohibition is the infallible submarine chaser (Sinclair, 1962:122).

The war gave the prohibition cause new ammunition. Literature depicted brewers and licensed retailers as treacherously stabbing American soldiers in the back. Raw materials and labor were being diverted from the war effort to an industry which debilitated the nation's capacity to defend itself. It was urged that wartime prohibition would stop the waste of grain and molasses and would remove a handicap on workers' efficiency.

"Liquor is a menace to patriotism because it puts beer before country," preached Prohibitionist Wayne Wheeler (Odegard, 1928: 72). The fact that names Pabst, Schlitz, and Blatz broadcast their national origin only did further injury to their interests.

In this atmosphere the Wartime Prohibition Act was passed in 1918. It followed a series of federal laws such as the Wilson Original Packages Act and the Webb-Kenyon Act, attempts to protect dry states from their wet neighbors.

The Wilson Original Packages Act was passed on August 8, 1890, and provided that all intoxicating beverages shipped interstate would be subject to the laws of the destination state upon arrival. No mechanism for federal enforcement was provided.

The Webb-Kenyon Act, enacted March 1, 1913, was intended to reinforce the 1890 Act by providing that it was a violation of federal law to ship an intoxicating beverage interstate with the intent that it be used or sold in any manner in violation of the laws of the destination state. The lack of federal enforcement rendered the statute virtually meaningless.

The Reed Amendment, enacted four years later, provided a fine of $1,000 for transporting liquor into a dry state with no greater effect.

None of the earlier acts met with substantial success in curbing the flow of liquor into purportedly dry regions, but they did mark a change in federal policy. Formerly liquor laws were designed solely to produce federal revenue; Congress now took cognizance of the role it could play in the regulation of consumption.

The role was actually forced upon a reluctant Congress at first. Indeed, the government had passed up numerous prior opportunities to involve itself in the temperance movement as such. The particular part it was to play was forecast by the Sons of Temperance who, in 1856, declared themselves for national constitutional prohibition.

Twenty years later, Congressman Henry Blair of New Hampshire introduced a prohibition amendment to the Constitution for the first time in Congress. As a senator, he introduced another such resolution in 1885, along with Senator Preston Plum of Kansas. After consideration by the Senate Committee on Education, the bill was reported out favorably and placed on the Senate Calendar in 1886. Nevertheless, no action resulted (Cherrington, 1920: 317).

In the meantime, states continued the struggle between the wets and the drys, with great success for the temperance advocates. By 1913, nine states were under stateside prohibition. In 31 other states, local option laws were in effect. By reason of these and other variants of regulatory schemes, more than 50% of the United States population was then under

prohibition.

The national constitutional campaign was resumed as such in 1913 when the Anti-Saloon League went on record at its 15th National Convention in favor of immediate prosecution of the objective of constitutional amendment.

The National Temperance Council, founded at the same time, coordinated the activities of numerous temperance organizations with the same object. In 1913, the demands of the League were formally presented to Congress by the Committee of 1,000.

The measure was then introduced in the House by Congressman Thompson and in the Senate by Senator Sheppard. The following year, the first joint resolution failed to secure the necessary two thirds majority for submitting a constitutional amendment to the states. A second resolution was submitted in 1915 and favorably considered by the Judiciary Committees of both houses, but neither ever came to a vote.

Ultimately, in 1917, the resolution to prohibit the manufacture, sale, transportation or importation of alcoholic beverages in the United States was approved by Congress and sent to the states for ratification (Cherrington, 1920: 317-330).

It took only one year and eight days for the 18th Amendment to secure the necessary ratification. On January 8, 1918, Mississippi proudly became the first state to ratify, and on January 16, 1919, Nebraska completed the job as the 36th state (Lee, 1963: 42). By the end of February 1919, there remained only three hold-outs: New Jersey, Connecticut, and Rhode Island (Cherrington, 1920: 330).

October 28, 1919, was the day that Congress enacted the National Prohibition Act-more often known as the Volstead Act-with the intent to give effect to the new constitutional amendment. Officially, the liquor drought was to begin on January 17, 1920. The celebrants of the occasion were concentrated in the membership of the Anti-Saloon League, which could rightly claim that its consummate skill in pressure politics had maneuvered the country into its dry state.

The early experience of the Prohibition era gave the government a taste of what was to come. In the three months before the 18th Amendment became effective, liquor worth half a million dollars was stolen from Government warehouses. By midsummer of 1920, federal courts in Chicago were overwhelmed with some 600 pending liquor violation trials (Sinclair, 1962: 176-177). Within three years, 30 prohibition agents were killed in service.

Other statistics demonstrated the increasing volume of the bootleg trade. In 1921, 95,933 illicit distilleries, stills, still works and fermentors were seized. in 1925, the total jumped to 172,537 and up to 282,122 in 1930. In connection with these seizures, 34,175 persons were arrested in 1921; by 1925, the number had risen to 62,747 and to a high in 1928 of 75,307 (Internal Revenue, Service, 1921, 1966, 1970: 95, 6, 73). Concurrently, convictions for liquor offenses in federal courts rose from 35,000 in 1923 to 61,383 in 1932.

The law could not quell the continuing demand for alcoholic products. Thus, where legal enterprises could no longer supply the demand, an illicit traffic developed, from the point of manufacture to consumption. The institution of the speakeasy replaced the institution of the saloon. Estimates of the number of speakeasies throughout the United States ranged from 200,000 to 500,000 (Lee, 1963: 68).

Writers of this period point out that the law was circumvented by various means. Although there may have been legitimate, medicinal purposes for whiskey, the practice of obtaining a

1912
17,570
1,567
8.9
...

1913
17,525
1,633
9.3
9.3

1914
19,134
1,573
8.2
7.4

1915
18,875
1,331
7.1
5.7

1916
17,929
1,370
7.6
6.1

1917
20,041
1,576
7.9
8.2

1918
19,741
1,021
5.2
5.2

1919
19,737
841
4.3
4.1

1920
19,579
485
2.5
2.0

1921
20,368
567
2.8
2.8

1922
20,741
798
3.8
3.2

1923
20,316
861
4.2
4.0

1924
19,818
896
4.9
5.4

1925
20,857
1,017
4. 9
5.8

1926
20,911
997
4.8
5.9

1927
21,982
1,268
5.8
7.0

1928
23,293
1,257
5.4
6.0

1929
23,242
1,380
5.9
6.2

1930
24,100
1,251
5.2
6.0

Deaths from Alcoholism. In New York City, from 1900 through 1909, there was an average of 526 deaths annually attributable to alcoholism. From 1910 through 1917, the average number was 619. It plummeted to 183 for the years 1918 through 1922. Thereafter, the figure rose, averaging a new high of 639 for the years 1923 through 1927 (Rice, ed., 1930: 122).

Total deaths from alcoholism in the United States show a comparable trend, with the gradual increase resuming somewhat earlier, about 1922 (Brown, 1932: 61, 77; Feldman, 1927: 397; U.S. Department of Commerce, 1924: 55).

Year
Deaths from all causes rate per 100,000
Deaths from alcoholism rate per 100,000

1910
1,496.1
5.4

1911
1,418.1
4.9

1912
1,388.8
5.3

1913
1,409.6
5.9

1914
1,364.6
4.9

1915
1,355.0
4.4

1916
1,404.3
5.8

1917
1,425.5
5.2

1918

1,809.1
2 7

1919
1,287.4
1.6

1920
1,306.0
1.0

1921
1,163.9
1.8

1922
1,181.7
2.6

1923
1,230.1
3.2

1924
1,183.5
3.2

1925
1,182.3
3.6

1926
1,222.7
3.9

1927
1,141.9
4.0

1928
1,204.1
4.0

1929
1,192.3
3.7

The highest death rates from alcoholism occurred during the decade prior to Prohibition as did the highest death rates from cirrhosis of the liver. These statistics should be qualified by the observations of Dr. Charles Morris, Chief Medical Examiner for New York City: "*In making out death certificates (which are basic to Census Reports) private or family physicians commonly avoid entry of alcoholism as a cause of death whenever possible. This practice was more prevalent under the National Dry Law than it was in preprohibition time*" (Tillitt, 1932: 114-115).

Even if reliable, per se, such statistics may be unrelated to the consumption of alcoholic beverages in any given year. Another writer of this period noted: "The relation of fatal alcoholic diseases to consumption of alcohol must be one extending over a long period of years and the actual duration of the critical period can hardly be estimated" (Jellinek, 1942: 48-1). According to one sociologist, rates of alcoholism and related mental and physical diseases reflect past drinking habits, developed ten to 15 years earlier (Gusfield, 1963: 119).

A shorter "lead time" is suggested by a mental hygiene statistician who attributes the temporary reduction in alcoholic psychoses "to the legal restriction of the sale and use of alcoholic beverages, made effective by the support of public opinion which during the war period had discountenanced self-indulgence, of all sorts" (Brown, 1932: 88). He adds, however, that the notable increase in alcoholic psychoses and deaths from alcoholism towards the end of the prohibition era (1927-1932) indicated that:

... since 1920, prohibition has become increasingly impotent as a means of preventing excessive use of alcohol to an extent productive of serious mental disorders and untimely deaths (Brown, 1932: 88).

The highly limited statistical label of death from alcoholism has been noted elsewhere:

The trend of death from alcoholism reflects hardly anything else than progress in the treatment of the so-called diseases of chronic alcoholism. Nevertheless, statistics of death from alcoholism have been used by both Drys and Wets to prove that Prohibition or repeal has greatly improved the rate of death from alcoholism. . . . Death from alcoholism is simply not an index of the prevalence of inebriety. Death from alcoholism could fall to zero in response to medical progress, while at the same time the rate of inebriety might rise many fold (Jellinek, 1947: 39).

Arrests Arrests for drunkenness also provide a source of information about the extent of drinking in the United States. It must be noted, however, that statistics of this sort vary with local police policies. For example, during a six-year period in the 1930's, the arrests for drunkenness were from 14 to 31 times higher in Philadelphia than in New York (Kolb, 1941: 608).

Nevertheless, gross statistics drawn from 383 cities indicate that arrests for drunkenness per 10,000 population reached a high of 192 in 1916 and fell to 71 in 1920. From this level, they rose steadily again to reach 157 in 1928 (Warburton, 1932: 102). Of course, arrests prior to Prohibition may not bear the same relation to the use of alcohol as they did subsequently, Warburton theorizes:

. . . [U]nder Prohibition, especially during the early years, police were more strict in making arrests, and . . . a larger proportion than formerly of persons appearing on the streets under the influence of liquor are arrested. Also, since the sale of liquor is illegal and cannot be obtained in public saloons, and when the police are more strict in arresting intoxicated persons, it is reasonable to suppose that drinking is less public and that fewer drunken persons appear on the streets relative to the quantity of liquor consumed (Warburton, 1932: 103).

Nevertheless, the cyclical trend suggested by these figures coincides with statistics on

alcoholism (Brown, 1932: 61, 71, 77). Whatever their independent validity, however, they correlate earth the theory of one author that:

[T] he 18th Amendment could not have been passed without the support of the psychologically tolerant, made temporarily intolerant by the stress of war. But when the moderates deserted the drys in the time of peace, the hard core of the movement was revealed (Sinclair, 1962: 23--24).

Without the support of the moderates, the author theorizes, Prohibition was to become itself a symbol of excess, unsupported by the vast majority of the population.

Outcome. What, then, did Prohibition accomplish? To a great extent it eliminated the saloon from American life. While bars and taverns reopened joyfully following repeal, they ceased to be the centers of systematic political corruption and debauchery which they had once been. Part of this may be attributable to the greater sophistication of the electorate and politics generally. Part, no doubt, is owing to the fact that women were welcome as customers in the new cocktail lounges, having shown themselves to be eager patrons of the speakeasies.

And finally, the change in the character of the saloon was effected by public determination that it should be changed. This attitude was expressed in the post-repeal statutes concerned with the physical appearance of the saloon and the character of persons authorized to operate them.

Prohibition did make the nation conscious that corruption of the law and of the populace may be the consequence of a law which is not reflective of the morals and mores of the time. It played out some of the deepest social class resentments, culminating in the realization that the behavioral standards of some could not be impressed upon others. It demonstrated that the fervor of war and the cult of patriotism may be abused-and abuse the country in return.

Repeal reimposed the burden of regulation upon the states. They were required to develop a system of control directed at the particular objectives they wished to achieve. The post-repeal era was to prove an exercise not only in states' rights but in states' responsibilities.

1933-1971: AFTER THE DELUGE

On December 4, 1933, the day before final ratification of the repeal amendment, the President established the Federal Alcohol Control Administration, pursuant to Executive Order No. 6474. FACA was to have the power to grant or revoke permits to engage in the alcoholic beverage industry-not the brewing industry-as well as the power to control plant capacity and production; it was also to engage in consumer protection through regulations designed to prevent misbranding and false advertising of alcoholic beverages. In addition, FACA prohibited the ownership of retail outlets by manufacturers and wholesalers (Harrison & Laine, 1936: 24-29).

This scheme fell under the Schecter Poultry decision by the Supreme Court. The Treasury, Federal Trade, Commission and Food and Drug Administration then moved in. A new alcohol control agency was proposed, leading to a dispute as to whether it should be independent or part of the Treasury.

Joseph H. Choate, Jr., first head of the FACA, testified that:

The Treasury has not been an organization whose duty it was to study and understand the liquor business, the interest of the public in that business, or the method by which that business ought to be carried on in order to subserve the interests of both the public and state governments. It has been a creature of one idea, that one idea being, quite properly, to get revenue and get it as fast and as copiously as it could (Harrison & Laine, 1936: 33).

The Department of the Treasury agreed with Choate's analysis.

Nevertheless, this testimony was disregarded and the Federal Alcohol Administration was created as a division of Treasury in 1935. This arrangement was superseded in 1936 when the Liquor Tax Administration Act established FACA as an independent agency of the government. Soon thereafter it was reorganized, once again as an arm of the Department of Treasury, and even its separate identity was abolished as of June 30, 1940. Today, the Treasury retains full authority to administer all federal liquor laws.

The current federal laws regulating trade in intoxicating beverages may be classified in the following categories:

(1) Revenue: Taxes are imposed on rectifiers, brewers, manufacturers of stills, dealers; wholesale and retail stamps are required on distilled spirits (26 USC, 1971a).

(2) Criminal Penalties: Criminal penalties are provided for unauthorized production, sale or possession, transportation into states prohibiting sale, C.O.D. shipments and unlabeled shipments (26 USC, 1971b; 18 USC, 1971).

(3) Interstate Transportation: Interstate shipments of alcoholic beverages are subject to the laws of the receiving state (27 USC, 1971a).

(4) Permits: Importers, manufacturers and sellers of intoxicating beverages must have permits (27 USC, 1971b).

(5) Unfair Practices: Exclusive sales arrangements, tying, bribery and false advertising or labeling are prohibited (27 USC, 1971b).

The intent of the Federal Government to reserve all decisions regarding regulation of consumption is quite clear from federal statutes presently in force. The states have reacted with a variety of regulatory schemes controlling to varying degrees the seller, the buyer, the place, time and opportunity for sale and, through revenue measures, the cost.

In 18 states, the state store or state monopoly system has entirely displaced the private wholesale or retail sale of intoxicating beverages. Other states permit the sale of liquor, wine and beer through private, licensed outlets.

The license system may be implemented by different, means. Administration may be solely by the state, or control may be shared by the counties or municipalities.

Local control may be exercised to a greater or lesser degree. For example, in the 1930's, immediately after repeal, Massachusetts and New Mexico permitted local boards to grant retail licenses only after investigation and approval of applicants by the state board. During the same period, other states, predominantly in the South, gave local authorities supplemental powers to issue licenses while requiring concurrent state licenses as well.

In some jurisdictions, the local license had to be obtained first, and the state license could be granted thereafter. In Illinois, however, the state commission's power was curtailed by requiring that a state license be granted once the local license was secured. And although the state was given the power to revoke its license, it was given no power to inspect places of sale to determine grounds for revocation (Harrison & Laine, 1936: 50-53).

The license system has been suspect by many wets as well as drys because of the opportunities it may afford for political abuse. On the other hand, there is substantial opinion which holds direct participation in the sale of liquor in contempt. As to the relative efficacy of each, there are no reliable means of making a judgment. Each apparently depends on the integrity and capacity of the individuals charged with the job of enforcement and oversight.

Superimposed on the basic system of regulating the sale of liquor are other sumptuary laws which are directed at the purchaser. Sales are not permitted to minors or intoxicated persons. Credit is often prohibited on liquor sales as well. Criminal penalties may be imposed for driving under the influence of alcohol as well as for drunken behavior.

The sale of liquor by the drink is permitted in most states, but some still require that it be sold in packaged form only, reflecting the continuing fear of the resurrection of the saloon. In many states Sunday closing laws are enforced, and mandatory closing times are imposed upon bars and package stores alike. Sales are prohibited almost uniformly on Election Day, at least during polling hours, and, in many places, on Thanksgiving, Memorial Day, Christmas and other holidays.

Local option is still granted in most states, in voting units ranging from the plantation to the city or county. Of the monopoly or control states, only Utah and Wyoming fail to make provision for local option at all. Wyoming maintains a state monopoly at the wholesale level only. Private retailer sellers are licensed.

In the remaining monopoly states, it is often possible for towns within a wet county to go dry, and sometimes vice versa. Of the 33 license states, only 10 (including the District of Columbia) do not permit local option at any level.

Notwithstanding the various patterns of regulation, Senator Arthur Capper's words of the 1930's still seem to be correct:

We can repeal prohibition, but we cannot repeal the liquor problem (Peterson, 1969: 126).

Neither the states nor the population have yet come to grips with the problems of alcoholism and alcohol abuse. Both the monopoly system and the license system are directed at other concerns. They, no more than Prohibition, have been able to control or even alleviate the very real and dire consequences of alcohol use by society.

References

Brown, F. W.: "Prohibition and mental Hygiene" Annals, 163: 61, 71, 76-77, 88, 1176 (September, 1932).

Cherrington, E. H.: The Evolution of Prohibition In The United States of America, Westerville, Ohio: American Issue Press (1920), pp. 16, 18, 37-38, 49-51, 58, 92-93, 134, 156-162, 165-169, 250-251, 317-330.

Dobyns, F.: The Amazing Story of Repeal, Chicago: Willett, Clark & Co. (1940), pp. 5, 5-130 pas im, 9, 22, 107, 132, 160, 215, 292, 297.

Feldman, H.: "Prohibition: Its Economic and Industrial Aspects," New York City: Appleton and Co. (1927), p. 397.

Furnas, J. C.: The Life and Times of the Late Demon Rum, New York City: Putnam (1965), pp. 15, 80, 167, 183, 273, 281, 310, 334-335.

Grant: "The Liquor Traffic Before the 18th Amendment,"

Annals, 163: 1, 5 (September, 1932).

Gustield, J. R.: The Symbolic Crusade, Urbana: University of Illinois Press (1963), pp. 69-70, 76-77, 100, 108, 119, 127-128, 135.

Harrison, L. V. and Laine, E.: After Repeal, New York

City: Harper & Bros. (1936), pp. 1-2, 24-29, 33, 50-53, 63.

Health, Education and Welfare: "Alcohol and Alcoh ism," p. 41 (1968). Prepared for National Clearinghouse for Mental Health Information.

History of the Alcohol and Tobacco Tax Division, pp. 1420, 28 (undated, unsigned monograph in the library of the Distilled Spirits Institute).

Hu, T.: The Liquor Tax in the U.S.: 1791-1947, New York City: Columbia University Press (1950), pp. 48, 51-52. Internal Revenue Service: "Alcohol and Tobacco Summary Statistics," pp. 6, 73, 95 (1966, 1970, 1921).

Jellinek, E. M.: "Death From Alcoholism in the U.S. in 1940," Quarterly Journal of Studies on Alcohol, 3 (3): 484 (December, 1942).

: "Recent Trends in Alcoholism," Quartely Journal of Studies on Alcohol, 8 (1) : 39 (September, 1947).

Kolb., L.: "Alcoholism and Public Health," Quarterly Journal of Studies on Alcohol. 1: 608, 610, 613 (March, 1941).

Krout, J. A.: The Origins of Prohibition, New York City: Russell & Russell (1967), pp. 29-30.

Lee, H.: How Dry We Were: Prohibition Revisited, EngleWood Cliffs: Prentice Hall Inc. (1963), pi). 15-16, 1819, 22-23, 29-30, 34-35, 42, 68, 212, 231.

Malzburg, B.: "A Study of First Admissions with Alcohol Psychoses in New York State 1943-44," Quarterly Journal of Studies on Alcohol, 10: 294 (December, 1949). Miller, P. and Johnson, T. H. (eds.) : 11 The Puritans, New York City: American Book Co. (1963), pp. 430-431.

National Commission on Law Observance and Enforcement: "Report On The Enforcement of the, Prohibition Laws of the U.S.," H.R. Doe. No. 722, 71st Cong., 3d Sess., 8, 345 (1931).

Odegard, P. H.: Pressure Politics-The Story of The AntiSaloon League, New York City: Columbia University Press (1928), pp. 23, 40-60, 53, 70-72, 126.

Peterson, W.: "Vitalizing Liquor Control," Journal of Criminal Law and Crime, 40: 119-120, 122-123, 126 (July, 1939).

Pollock, H. M.: Mental Disease and Social Welfare, Utica, N.Y.: State Hospital Press (1942), 1). 113.

Rice, S. A. (ed.) : Statistics In Social Studies, Philadelphia: University of Pennsylvania Press (1930), 1). 122.

Rosenbloom, M. V.: The Liquor Industry: A Surrey of Its History, Manufacture, Problems of Control and IMportance, Braddock: Ruffsdale Distilling Co. (1937 ed.), pp. 27, 51-52 (1935)).

Rush, B.: "Inquiry Into the Effects of Ardent Spirits Upon The Human Body and Mind," Quarterly Journal of Studies on Alcohol, 4: 323,325-326 (September, 1943). Rutgers Center of Alcohol Studies: "Selected Statistics on Consumption of Alcohol (1850-1968) And On Alcoholism (1930-1968)," 1). 4 (1970).

Sinclair, A. : The Era of Excess, Boston: Little, Brown (1962), pp. 23-24, 43, 51. 108, 122, 176-177, 190, 193-195, 198, 206, 303, 364-365, 367-368.

Tillitt, M. H. : The Price of Prohibition, -New York City: Harcourt, Brace & Co. (1932), pp. 35-36, 114-115.

Timberlake, J. H.: Prohibition and the Progressive Morement, Cambridge: Harvard University Press (1963), pp. 34-38, 42-55, 67-79, 83, 85-86, 98, 118.

Towne, C. IL: The Rise and Fall of Prohibition, New York City: The MacMillan Co. (1923), pp. 211-212.

U.S. Department of Commerce: "U.S. Census Mortality Statistics," 55 (1924).

Warburton, C.: The Economic Results of Prohibition, New York City: Columbia University Press (1932), pp. 102104, 216.

26 U SC § § 5081-5416 (1971a).

26 USC §§ 5061-5691 (1971b).

18 U SC § § 1261-1265 (1971).

27 USC §§ 121, 122 (1971a).

27 USC § 205 (1971b).

National Commission on Marihuana and Drug Abuse

History of Tobacco Regulation*

***This section is based in part on a paper prepared for the Commission by Jane Lang McGrew, an attorney from Washington, D.C.**

Since 1613, when John Rolfe introduced a successful experiment in tobacco cultivation in Virginia (Morison, 1965 : 52) the leaf has assumed major social, industrial, economic and medical implications. Consequently, persons concerned with tobacco on a commercial or personal basis have been subject to a variety of different regulations over the past 360 years.

Tobacco has been attacked by social observers and medical authorities for the damage it has allegedly done, to the social and physical condition of man. Yet it has also provided a substantial source of revenue to the state and Federal governments of the United States.

As is now the case with alcohol, tobacco has long been subject to regulatory controls over the quantity and quality of production. On the other hand, sumptuary laws affecting tobacco have been far fewer-and weaker-than those aimed at alcohol. In fact, there has never been a time when tobacco was prohibited throughout the United States although consumption under certain circumstances has been forbidden at various times in different jurisdictions.

Tobacco-associated today with smoking of cigarettes, and to a lesser extent, of pipes and cigars-has been popular at times for both snuffing and chewing. Indeed, until about 1870 cigarettes were relatively rare in the United States, and almost all tobacco consumed domestically was chewed during the mid-19th century (Gottsegen, 1940: 9-10).

What ever the preferred mode of consumption, however, the, commodity has always been the subject of debate respecting the appropriate governmental attitude. On the one hand, proponents of the leaf stress its social benefits and its economic and industrial significance. Some enthusiasts even endorse its alleged medical and psychological benefits. Opposed are those who cite the health hazards of smoking and others who are convinced of its immorality.

The motivation for regulation has come from both sides of the controversy. Most sumptuary restrictions were fostered by the latter group in an effort to suppress the habit. Those who seek to institutionalize and foster use of the drug focus on the regulation of the quantity and quality of production.

This section does not attempt to weigh the merits of the various regulatory schemes. Rather, it will trace from John Rolfe's day the three threads of regulation which have circumscribed both the producer and consumer of tobacco in the United States.

REGULATION OF PRODUCTION

In the opinion of King James I of England, tobacco was "loathsome to the eye, hateful to the nose, harmful to the brain" and "dangerous to the lungs" (Middleton, 1953: 93). Whether the King was prescient, or simply sensitive, was irrelevant in the 17th and 18th centuries, however, for tobacco rapidly became the mainstay of the Maryland and Virginia economics. Within seven years of John Rolfe's first imaginative experiment,, Virginia exported nothing but tobacco and a little sassafrass to England (Middleton, 1953: 93-94). Almost as quickly, the leaf became the staple of the colony of Maryland and competition developed in Carolina as well.

In Massachusetts Bay, the product fared less well. The first general letter (April 17,1629) from an official of the New England Company to the Massachusetts Bay settlers prohibited the planting of tobacco except in small quantities for medicinal purposes (Werner, 1922: 100). Next door in Connecticut, however, the colonists attempted to rival the southern planters with a local leaf. Indeed, the infant industry was coddled by the protectionist General Court at New Haven, which promulgated a rule in 1641 that:

No persons within this jurisdiction shall [smoke] any other Tobacco but such as is or shall be planted within these [districts], except they have license from the Courte (Tobacco Institute, Connecticut, undated: 20).

Notwithstanding the royal attitude and the fear of certain patent holders of the London Company that Virginia had become a "colony founded on smoke" (Tobacco Institute,, Virginia, 1971 : 19; Middleton, 1953: 94), England encouraged the growth of the tobacco industry. Monopolies to import tobacco from the colonies were granted by the Crown to court favorites who soon prospered as a result of this trade.

In 1621, a bill was introduced which, according to one contemporary commentator, was "extremely remarkable": No tobacco was to be imported after the 1st of October, 1621, except from Virginia and Bermuda; and, after that day, none was to be planted in England. Although the act was initially defeated by the House of Lords, James I in 1922 himself granted the import monopoly to the Virginia and Bermuda, companies and prohibited the domestic cultivation of tobacco (Brooks, 1952: 88).

The system worked well for the British importers, but the methods of financing they employed became onerous to the colonial planters. The tobacco was marketed by consignment to an English merchant who deposited the proceeds of the sale to the planters' accounts. Often, however, the high commissions charged and the cost, of goods ordered by the Virginians in payment for their crop contributed to the growth of colonial indebtedness. The extension of credit to cover the deficiencies caused the debts to grow constantly, but the only alternative to the consignment system was to sell the product in the colony at a lower price (Middleton, 1953: 104-107).

Industrial competition in this market provided the impulse for certain regulatory relief. Importation of the Carolinian product into Virginia was forbidden by an act of 1679, amended in 1726 to prohibit importation by land as well as by sea. Nor was North Carolina permitted to export its tobacco from Virginia ports. In Great Britain, the Privy Council looked with disfavor upon such colonial legislation which threatened the financial well-being of the merchants and so disallowed the Virginia Act in 1731 (Middleton, 1953: 114-115).

Competition similarly induced both Virginia and Maryland to enact laws prescribing the dimensions of the hogshead in which tobacco was packaged in 1658. Vying for purchasers, the two colonies gradually enlarged the statutory size of the hogshead until, under edict from the Privy Council in Britain, Maryland was ordered to pass a gauge act establishing the size of the hogshead in the same dimensions as those fixed in Virginia.

Notwithstanding such legislation, however, the manufacture of hogsheads was still characterized by carelessness and irregularity until the warehouse inspection system went into effect in the 18th century (Middleton, 1953: 116-117).

It was not long before the colonial planters were faced with a more serious problem-overproduction-which was causing a decline in prices as well as quality of the leaf. In 1619, the first tobacco inspection law was passed by the Virginia House of Burgesses, ordering the lowest grade of tobacco to be destroyed and prohibiting "second growth" tobacco and the marketing of trash leaves.

This act was followed in 1621 by a more direct attempt to restrict production. Each cultivator was required to limit his growth to 1000 plants of nine leaves each. Although this order was soon rescinded as a patent failure, an act of 1629 permitted each planter to tend only 3000 plants with an additional allowance of 1000 for non-laboring 'women and each child (Brooks, 1952: 96).

Notwithstanding the statutory effort, the problem intensified. Virginia attempted to encourage the other tobacco colonies to reach agreements restricting plantings, but in Maryland, Lord Baltimore resisted. If planters were poor, he asserted:

It is not from the low price of Tobacco, but from their owne sloth, ill husbandry and profusely spending their croppe in Brandewine, and other liquors (Robert, 1949: 11).

Carolina, Maryland and Virginia actually reached a decision to prohibit the planting of the staple from. February 1667 to February 1668. This "stint" proved a less effective means of control than the winds of 1667, which almost destroyed the, crop ready for harvest that year (Tobacco Institute, Virginia, 1971: 19).

Acts of God failed to provide an ultimate solution, however, and severe economic dislocation in Maryland and Virginia intensified. By 1681, the Virginia governor, Lord Culpeper, complained:

... [T]hat which is more to us than all other things put together, and will be the speedy and certain ruin of the colony, is the low price of tobacco. The thing is so fatal and desperate that there is no remedy; the market is overstocked and every crop overstocks it more. It is commonly said that there is tobacco enough now in London to last all England for five years.... Our thriving is our undoing, and our purchase of negroes, by increasing the supply of tobacco, has greatly contributed thereto (Brooks, 1952: 112-113).

The failure of the Virginia Assembly to pass another act requiring a "stint"' led the so-called "cutters and pluckers" to take the matter into their own hands in 1682 by burning both their own crops and the plants of their neighbors (Roberts, 1949: 11). The riot stimulated legislative action in 1684 of a less helpful sort: the destruction of tobacco was made a criminal offense,, subject to the death penalty (Brooks, 1952: 12).

Seventeenth century quality control laws proved no more successful in the effort to relieve the depression of the industry. Renewed efforts were made in early years of the next century, however.

In 1713, the Virginia House of Burgesses established a warehouse system to enforce tobacco inspection. Forty public warehouses were created. Strong opposition to the system led the Privy Council to disallow the act In 1717, but the ensuing depression of the 1720's was convincing evidence of the need for relief. Accordingly, the system was reinstated with British approval in 1730, cornplete with public warehouses and official inspectors (Middleton, 1953: 120-121).

The apparent success of the system appealed to Maryland, suffering also from a surfeit of tobacco. "Tobacco, our money, is worth nothing wrote one Marylander in 1724, "'and [there is] not a Shirt to be had for Tobacco this year in all our country" (Tobacco Institute, Maryland, 1971: 21).

Tobacco riots ensued when the Mary] and Assembly initially refused to follow Virginia's example. One individual was moved to inform Lord Baltimore that no improvement in the economic state of the colony was possible until inspection laws were passed that "will prevent the sending to Market Such trash as is unfit for any other use but Manure" (Tobacco Institute,,, Maryland, 1971: 23). Accordingly, Maryland followed Virginia in the creation of an inspection system in 1747,and Carolina did likewise in 1754 (Brooks, 1952: 165).

Tobacco entirely dominated the economic and social structure of Virginia and Maryland. "Tobacco requires us to abhor communities or townships," wrote a 17th century governor of Maryland, "since a planter cannot carry on his affairs without considerable elbow room within his plantation" (Brooks, 1952: 98).

In Virginia, tobacco had gained such ascendancy that it was used as money. For example, when, in 1621, a cargo of twelve young women made its way to the colony, each one was valued at 120 pounds of the best leaf (Brooks, 1952: 93). By law, Virginia's ministers were paid in tobacco at 16,000 pounds annually in 1696. The law provided that:

A competent and sufficient provision for the clergy will be the only means to supply this dominion with able and faithful Ministers whereby the glory of God may be advanced,the church propagated, and the people edified (Werner, 1922: 102).

Not until the Option Act was passed by the Virginia Assembly in 1755 could the clergy's fees be paid in either money or tobacco (Brooks, 1952: 167).

The regulation of tobacco in the colonies was devised in response to the industry with the intent to further the prosperity of the planters who dominated the economy. This theme continued to pervade all related regulatory efforts in the tobacco-producing states thereafter, as new practices developed in the marketing of the leaf.

The initial hogshead inspection system gradually gave way to the sale of loose-leaf tobacco by auction. In 1849 the Virginia Code recognized these methods in lieu of the sale of hogsheads of the leaf as provided in the 1730 Act. By 1865, the tobacco auction had completely replaced the earlier marketing techniques in Virginia (Tobacco Institute, Virginia, 1971: 28-29).

More than a half century later Maryland followed suit. In 1939, the loose-leaf auction warehouse system was introduced to replace the hogshead system, and the conversion occurred almost overnight. The practices engaged in are regulated by the Maryland State Tobacco Authority, established in 1947 by law. The Authority itself is supervised by eight representatives selected by the Governor from the producing counties, the University of Maryland, the buyers and the sellers (Tobacco Institute, Maryland, 1971: 9-10).

The Federal Government came to recognize the significance of the tobacco industry in response to state pressures. Accordingly, since 1930, several bills have been enacted to aid the growers.

Enacted in 1935, the Tobacco Inspection Act directs the Secretary of Agriculture to establish quality standards and to designate auction markets (7 U.S.C. 511 (b) and (d)). The following year, the Tobacco Control Act was passed, bestowing Congressional approval upon state compacts which regulate the production of tobacco, and subsidizing the expenses of the state commissions involved (7 U.S.C. 515). Thus, the two elements of initial colonial regulation were preserved: the encouragement of quality and the discouragement of quantity.

The latter objective was further implemented by the Agricultural Adjustment Act of 1938. Since that time, parity payments have been made to tobacco producers:

In amounts which, together with the proceeds thereof, will provide a return to such producers which is as nearly equal to parity price as the funds so made available will permit (7 U.S.C. 1303).

In addition, the Secretary of Agriculture is authorized to set national marketing quotas respecting each kind of tobacco (7 U.S.C. 1312), to apportion the quotas among the states, and to allot the portions among the farms (7 U.S.C. 1314). Penalties are imposed for overproduction (7 U.S.C. 1314).

There is nothing subtle about these measures, of course. Their intent is obvious: to assure the economic stability of an industry which, as of 1960, provided the United States population with more than 150,000,000 pounds of manufactured tobacco for consumption annually (Heimann, 1960: 93), and which provided more than $4.8 billion in taxes in 1971 (USDA, Tobacco Situation, 1971b: 44).

During the same year, growers' gross receipts reached about $900 million (Tobacco Tax Council, 1970: 2), while cigarette sales alone grossed for the manufacturer and seller approximately $5 billion (Tobacco Tax Council, 1970: 53). The commercial motivation is sound enough if considered abstractly. When combined with the revenue incentive, however, it has largely obscured sumptuary controls.

REGULATION FOR REVENUE

Alexander Hamilton's tax package of 1794 proposed the first federal excise taxes upon tobacco products. To the distress of Philadelphia snuff manufacturers (Brooks, 1952: 146), however, the tax was restricted after serious Congressional debate to their product only.

James Madison led the opposition to a general tobacco tax; his views were summarized in the Annals of Congress on May 2, 1794:

As to the subject before the House, it was proper to choose taxes the least unequal. Tobacco excise was a burden the most unequal. It fell upon the poor, upon the sailors, day-laborers, and other people of these classes, while the rich will often escape it (Robert, 1949: 100).

The legislative decision was probably tempered as well by considerations of the enforceability of the measure: snuff had to be manufactured, while quid and pipe tobacco were often homegrown leaf at the time (Heimann, 1960: 155). In any case, the snuff bill was ultimately enacted, modified, suspended and repealed, with small, if any, effect upon federal revenues.

The opportunity to distill tax money from tobacco was seized upon more vigorously at the time of the Civil War. On July 1, 1862, an ad valorem tax was imposed upon cigars for the first time. This tax was raised two years later when a separate tax upon cigarettes was also imposed (Werner, 1922: 358). (Even the Confederacy sought to levy a tax-in-kind upon tobacco crops, but was precluded from doing so by the inspection system which required the inspector to deliver the full amount of tobacco specified in the warehouse receipt (Robert, 1949: 117).)

Thereafter, the taxes were raised in 1865, 1866 and 1875. A temporary reduction followed, until the Spanish-American War necessitated further increases. Concurrently, taxes were levied upon smoking and manufactured tobacco and snuff, lest the burden fall unequally upon smokers (Werner, 1922: 559).

By 1880, the tobacco taxes bad largely stabilized. At that time, they accounted for 31% of total federal tax receipts, or $38.9 million. Of this, 50% of the collections was derived from smoking and chewing tobacco, 40% from cigars and cheroots, and less than 2% from cigarettes (Heimann, 1960: 156).

Since that time, federal tax collections on tobacco products have risen almost annually. Between 1910 and 1920, they increased more than 500%, the greatest increase in any single decade. By 1970, they accounted for almost $2.1 billion, down slightly from the two preceding years (Tobacco Tax Council, 1970: 5).

Indicative of changing patterns of consumption, the taxes on cigarettes, as a percentage of the total federal tobacco revenue jumped from 13.6% in 1910 to 51.1% in 1920. By 1970, the percentage at 97.2% far outdistanced those revenues derived from other forms of the product (Tobacco Tax Council, 1970: 5).

Excise taxes have proved profitable and easy to collect. The revenue schemes are simple on both the federal (26 U.S.C. 5701 et seq.) and state levels. In the past, no justification for them has been deemed necessary since Madison's protest. No elaborate licensing or state monopoly system, such as those designed to control commerce in alcohol, has ever been imposed.

In 1921, Iowa became the first state to cash in on the crop directly by taxing cigarettes. By 1930, 11 other states had adopted the revenue measure (Robert, 1949: 256).

In 1950, 40 states and the District of Columbia taxed cigarettes. The rates ranged from one cent to five cents for a pack of 20 except in Louisiana which levied an eight cent tax on cigarettes. In 1958, Montana imposed an equivalent rate.

Between 1950 and 1962, 43 of the 47 taxing states raised their rates at least once. The frequent increase in cigarette taxes narrowed the gap between the rates in low tax states and higher tax states. In the 12-year period, the median tax rate rose from three cents to six cents per pack (Federal Trade Commission, 1970: 3) ; the maximum rate remained at eight cents in Texas, Louisiana. Montana and New Mexico, in contrast to the two cent rate in the District of Columbia and Kentucky.

The four leading states in terms of both production and relative dependence on the crop have been North Carolina, South Carolina, Kentucky and Virginia, the latter two being the only states in the history of cigarette taxation to decrease their taxes; the reduction was only .5 cent (from three cents to two and a half cents) in 1960 and 1961, respectively.

By 1966, Oregon became the 49th state to impose a tax on cigarettes; the rate was four cents per pack. Finally, in 1969 North Carolina imposed a cigarette tax-two cents.

The cigarette excise taxes continued to increase during the sixties. By 1970, the taxes ranged from North Carolina's two cents to Pennsylvania's 18 cents for a weighted average of 10.7 cents. Twenty nine states levied taxes of 10 cents or more per pack (USDA, Tobacco Situation, 1971b: 40). Local governments superimposed further excise taxes on the state taxes, ranging from one cent to 10 cents per package (Tobacco Tax Council, 1970: iv).

By mid-1971, the range had widened further Connecticut at 21 cents and North Carolina at two cents, the weighted average state tax being 11.1 cents (USDA, Tobacco Situation , 1971a: 7).

TOBACCO REVENUES

A peculiar relationship exists between production and revenue. In 1970, cash receipts from tobacco brought in $11 million for Pennsylvania; tobacco farmers and cigarette taxes amassed $194.6 million for the state. By comparison growers in North Carolina collected $576 million while the state collected only $13.4 million in cigarette revenues (USDA, Tobacco Situation, 1971b: 43).

The federal excise tax on a package of cigarettes is currently eight cents and has remained so since 1951. The combined state and federal tax was highest in Pennsylvania; 26 cents for 20 cigarettes, which was 58.2% of the retail price. Connecticut's 24 cents and Texas's 23.5 cents were close behind; the average for the United States was 46.8%.

To the Federal and state governments today, tobacco is a financial asset. The total federal and state revenue collected f rom all tobacco products in 1971 amounted to over $4.7 billion. Local governments excised the product further bringing the sum total to $4.8 million (USDA, Tobacco Situation, 1971b: 44).

From the years 1890 to 1930 cigarette tax collections from tobacco soared from approximately $1 million to over $339 million. By 1950, they exceeded $1.2 billion.

Totals for the years 1890 to 1970 are recorded in the following chart (Tobacco Tax Council, 1970: 5)

Cigarette tax

Years	Collections
1890	$1,100,000
1900	4,000,000
1910	7,900,000
1920	151,300,000
1930	359,800,000
1940	533,000,000
1950	1,242,800,000
1960	1,863,600,000
1970	2,036,100,000

REGULATION OF CONSUMPTION

Even as far back as the 16th century, smoking was considered to have medicinal value. Juan de Cardenas, a Spanish physician who lived in Mexico in the late 1500's, wrote that "Soldiers subject to privations, kept off cold, hunger, thirst by smoking and all the inhabitants of the hot countries of the Indies alleviate their discomforts by the smoke of this blessed and medicinal weed" (Wagner, 1971: 63-64).

During, the recurrent epidemics of plague in the 17th century, it was widely believed that smokers were spared; it has been reported that men who attended the sick and accompanied the dead kept their pipes lit (Wagner, 1971: 63-64).

In 1614, one Scottish doctor praised the tobacco plant which:

Preparеth the stomach for meat; it maketh a clear voice: it maketh a sweet breath . . . in a few words it is the princess of physical plants (Gottsegen, 1940: 87).

King James disagreed strenuously, and in 1604 ordered a substantial increase in the import

duty on the leaf. Smoking, he wrote in "A Counterblaste to Tobacco", is:

A custom loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs, and in the black stinking fume thereof, nearest resembling the horrible Stygian smoke of the pit that is bottomless (Brooks, 1952:56, 71).

Another more passionate moralist wrote:

. . . imagine thou beheldest here a firme-sucker's wife most fearfully fuming forth very fountains of blood, howling for anguish of heart, weeping, wailing, and wringing her hands together . . . while she pitifully pleads with her husband thus: Oh husband, my husband . . . ! Why dost thou so vainly prefer a vanishing filthy fume before my permanent virtues? (Brooks, 1952: 72).

Notwithstanding such alliterative literature, the habit of smoking increased in popularity, particularly in the colonies. A French visitor observed in 1686 that:

Large quantities of it [tobacco] are used in this country, besides what they sell. Everyone smokes while working and idling. I sometimes went to hear the sermon; their churches are in the woods, and when everyone has arrived the minister and all the others smoke before going in. The preaching over, they do the same thing before parting. They have seats for that purpose. It was here I saw that everybody smokes, men, women, girls and boys from the age of seven years (Robert, 1949: 99).

It was said that even in New England women of the colony "smoke in bed, smoke as they knead their bread, smoke whilst they're cooking" (Gottsegen, 1940: 147).

In the tobacco colonies, of course, there was no attempt to restrict Consumption of tobacco. It was, after all, their economic mainstay.

Officials in the northern colonies were less enthusiastic about the habit, however. In 1632, the General Court of Massachusetts Bay took the initiative and forbade smoking in public tinder penalty of a fine (Tobacco Institute, Massachusetts, 1971 : 17). In 1638, the proscription was expanded to prohibit anyone from smoking in any inn or public house except in his own room "so as neither the master of the house nor any of the guests there shall take offense thereat which if they do, then such person is forthwith to forebear upon paying of two shillings sixpence fine for every offense" (Werner, 1922: 100).

This law was followed by another in 1646 which prohibited smoking except on a journey of five miles or more from any town. Nor could a citizen of the colony bring a pipe or tobacco into the precincts of the court (Werner, 1922: 100), although he might smoke at "the ordinary tyme of repast comonly called dynner" (Heimann, 1960: 83).

Plymouth colony was similarly strict. In 1638, a law was passed forbidding anyone from smoking on the streets. The following year, it was decreed that jurymen might not smoke, on pain of a five shilling penalty.

In 1641, even the importation of tobacco was forbidden, although the law was repealed a year later. A law passed in 1646 prohibited all from smoking, but exempted "soldiers in time of their training." And, finally, in 1669, it was ordered that anyone found smoking on the Sabbath within two miles of a meeting house, would be fined 12 pence (Werner, 1922:

101).

The colony at New Haven, Connecticut, essayed a like series of statutes to regulate tobacco consumption. In 1646 the General Court decreed that:

No person under the age of twenty years nor any other that hath not already accustomed himself to the use thereof, shall take any tobacko, until he hath brough a certificate under the hands of [a physician] that it is usefull for him, and also, that he hath received a license from the court for the same.... None shall take any tobacko, publickly in the street or any open places unless on a journey of at least ten miles. (Tobacco Institute, Connecticut: 20-21).

Within three years those laws were repealed (Werner, 1922: 102). However, it was further ordered in 1655 that:

No tobacco shall be taken in the streets, yards or aboute the howses in any plantation or farme in this jurisdiction without dores, neere or aboute the towne, or in the meeting howse, or body of the trayne Souldiors, or any other place where they may doe mischief thereby, under the penalty of 84 pence a pipe for a time, wch is to goe to him that informs and prosecuts (Heimann, 1960: 83).

As a result of the regulation, snooping became a profitable undertaking. In the end, however, the laws were of no avail in suppressing tobacco.

By 1680, the governor of Connecticut recognized the significance of the leaf and reported that, "We have no need of Virginia's trade, most people planting so much Tobacco as they spend," (Heimann, 1960: 84). Indeed, by the early 18th century, New England-grown tobacco was being produced in great enough quantity for both domestic consumption and export (Tobacco Institute, Connecticut: 22-23).

Tobacco was not one of the major concerns of the 18th century either before or after the Revolution. Social reform was generally secondary to political issues. By the end of the century, however, Dr. Benjamin Rush had published his "Observations upon the influence of the Habitual use of Tobacco upon Health, Morals, and Property" in his collection of Essays, Literary, Moral and Philosophical. It appeared in 1798, and stressed the Doctor's thesis that smoking and chewing provoked drunkenness:

One of the usual effects of smoking and chewing is thirst. This thirst cannot be allayed by water, for no sedative or even insipid liquor will be relished after the mouth and throat have been exposed to the stimulus of the smoke, or juice of Tobacco. A desire of course is excited for strong drinks, and these when taken between meals soon lead to intemperance and drunkenness. One of the greatest sots I ever knew, acquired a love for ardent spirits by swallowing ends of Tobacco, which he, (lid, to escape detection in the use of it. . . (Robert, 1949: 106).

There was little immediate response to Rush's dire warnings, although in the year his tract was published, Boston enacted a statute to prohibit the carrying of a lighted pipe or cigar in public streets-apparently with the intent to reduce the hazard of fire (Brooks, 1952: 245).

An anti-tobacco crusade was launched in the 19th century, although with considerably less fervor that its sister movement against alcohol. Among the leaders were Rev. George Trask who said tobacco and alcohol were Satan's twins; and the Rev. Orin Fowler, who declared in 1833: "Rum-drinking will not cease,, till tobacco-chewing and tobacco smoking and snuff - taking shall cease" (Robert, 1949: 107). Another, Dr. Joel Shew, attributed delirium tremens, perverted sexuality, impotency, insanity and cancer to the effects of smoking and chewing (Brooks, 1952: 219).

The crusade warned as the pipe continued to attract adherents. From the 18th century on, the cigar too began to grow in favor, particularly after 1840. It is estimated that by 1850, the average number of cigars smoked was approximately 19 per capita. Within 10 years, the number had increased to about 26 (Gottsegen, 1940: 8-10).

Women smoked and chewed as well as the men. Indeed, Mrs. Andrew Jackson and Mrs. Zachary Taylor both smoked their pipes in the White House (Heimann, 1960: 90). And, of course, the other residents of the Capital engaged heavily in the practices of both chewing and spitting, to the extent that Charles Dickens, during his tour of the States, felt called upon to report that:

Washington may be called the headquarters of tobaccotinctured saliva.... In all the public places of America, this filthy custom is recognized. In the courts of law, the judge has his spittoon, the crier his, the witness his, and the prisoner his; while the jurymen and spectators are provided for. . . . The stranger will find [the custom] in its full bloom of glory, luxuriant in all its alarming recklessness, at Washington (Brooks, 1952: 215-216).

Chewing and snuffing remained popular until the time of the Civil War. Thereafter, cigarette smoking was gradually adopted in North America, a habit indirectly acquired through the British from their Turkish and French allies during the Crimean War (Werner, 1922: 105).

By 1870, approximately 13.9 million cigarettes were smoked annually in the United States, or .36 per capita. Over the next 60 years, the number was to reach 976.91 per capita (Gottsegen, 1940: 28).

As more persons took to cigarettes, the zeal of reformers, which had ebbed during the Civil War, was renewed. Pamphlets, like those of the Temperance Movement, were published, urging abstinence from smoking:

"I'll never use tobacco, no;

It is a filthy weed;

I'll never put it in my mouth."

Said Little Robert Reed.

"It hurts the health ; it makes bad breath;

'Til very bad indeed.

I'll never, never use it, no!"

Said Little Robert Reed (Brooks, 1952: 242-243).

During the period following the Civil War and prior to the formation of the American Tobacco Company in 1890, the anti-liquor forces continued to snipe at tobacco in all forms. A reformed drinker and temperance lecturer, John B. Gough, would pull from his pocket a square of tobacco, smell it as if it were a rose, cry out "Ali you black devil, I love-you" and throw it away.

The anti-tobacconists were led by Lucy Gaston, the greatest, warrior in the anti -cigarette campaign who was trained in the office of the Women's Christian Temperance Union and then moved over into the anti-tobacco Movement in the 1890's. Miss Gaston encouraged children to wear anti-tobacco pins or buttons and organized armies of children to sing and preach to and against their smoking elders (Wagner, 1971: 40).

"All hostility to tobacco seems nowadays to be concentrated on cigarettes," noted Harper's Weekly, observing the scene in 1905 (Robert, 1949: 169). It was scarcely a startling revelation. Twenty years earlier, the New York Times editorialized that:

A grown man has no possible excuse for thus imitating the small boy.... The decadence of Spain began when the Spaniards adopted cigarettes and if this pernicious habit obtains among adult Americans the ruin of the Republic is close at hand . . . (Brooks, 1952: 253).

Miss Gaston witnessed some legislation victories. Between 1895 and 1921, 14 states banned the sale of cigarettes (Neuberger, 1963: 52). Even in the city of New York it was declared unlawful for women to smoke in public (Brooks, 1952: 271). Curiously, However, the city of Boston repealed its law which prohibited smoking in public in 1880 (Gottsegen, 1940: 153).

The apparent success of the prohibitionists revived the anti-tobacconists' enthusiasm. "Prohibition is won; now for tobacco!" pledged Billy Sunday. Miss Gaston also renewed her dedication and actually announced her candidacy for the presidency of the United States in 1920 on an antitobacco platform.

For many anti-tobacconists, when it became apparent that the elder generation may be lost, the war against tobacco was focused on the youth of the country. The National Education Association pledged its membership to cooperate in efforts made in the city, state and nation to safeguard the health and morals of youth from cigarette smoking to the end that high ideals for American manhood may be, preserved for the coming generation (Hamilton, 1927: 168).

The National Congress of PTA, in Atlanta, Georgia, in 1926 resolved "to lend its force to the cause of eliminating throughout the United State-, the use of cigarettes by minors and make this a special work for the ensuing year for the good of our youth" (Hamilton, 1927: 168).

It is for these reasons that the WCTU declared an educational war against tobacco, but declined to seek prohibitory legislation (Robert, 1949: 247).

The disenchanting experience of Prohibition, the omnipresence of the tobacco industry, the need for new sources of state revenues and the prevalence and popularity of cigarette smoking combined to frustrate the anti-tobacco campaign. Cigarettes did provide a new source of revenue. Federal income from tobacco taxes soared to new heights because of

increased cigarette consumption and advanced rates.

In any event, by 1927, each of the 14 states which had enacted prohibitory laws against cigarettes had repeated them (Neuberger, 1963: 52). Immediately thereafter these, states imposed taxes upon the once forbidden product (Robert, 1949: 256; Federal Trade Commission, 1970: 3).

STATE REGULATION

Only those laws which forbade the sale of tobacco products to minors remain on the books, a trend set by New Jersey and Washington in 1883 (Gottsegen, 1940: 155).

All but a few statutes restricting tobacco products to minors were enacted between 1916-1920, simultaneous to the development and popularity of the domestic-blend cigarette.

All 50 states bad laws banning sales to minors by 1950. Since then, Georgia,. Louisiana, and Wisconsin have repealed theirs le o 47 states plus the District of Columbia, WIL Vs prohibiting sales to minors.

The most common age of restriction for cigarettes and tobacco products today applies to persons under the age of 18. In an effort to ensure stricter enforcement 11 states have lowered the age of restriction from 21 to 15 (Tobacco Merchants Association, 1971: 1-2). In contrast to this trend, however, the, California Legislature, 1971 defeated a bill to allow school smoking areas and lowering the sale to minor restrictions to 15 years old (NIC Smoking and Health, 1971: 1).

According to a Special Report released by the Tobacco Merchants Association of the United States, the liability for infractions in all states is on the vendor and donor of cigarettes. In a few states, manufacturer and persons advising or compelling the minors to smoke, or owning the premise where such behavior occurs are also liable. However, in some states the infraction does not extend to the parent or guardian. Some states penalize the minor himself and others require that he divulge his source.

Most of the statutes that prohibit the furnishing of cigarettes to minors extend the ban also to one or more other tobacco products. Only 1 1 states restrict the sale "only" to cigarettes. The efficacy of such statutes, in the day of the cigarette machine, is subject to substantial skepticism.

A complete listing of existing state statutes concerning possession by and sales to minors follows (Tobacco Merchants Association, 1971: 3-4) :

State

Alabama

Alaska

Arizona

Arkansas	
California	
Colorado	
Connecticut	
Delaware	
District of Columbia	
Florida	
Georgia	

,see footnotes at end of table.

Sale to minors	
Prohi I bited Age	
Yes Minor	
Yes Under 18	
Yes Minor	
YeS Under 18	
Yes Under 18	
Yes Under 16	
Yes Under 16	
Yes Under 17	
.. Yes Under 16	
Yes Minor	
No provision	

Use or possession	

Prohibited Age

No provision

No provision

Yes I Minor.

No provision

Yes (4).

No provision

No provision

No provision

No provision

No provi..ion

No provision

Sale to minors Use or possession

State

Prohibited Age Prohibited Age

Hawaii Yes Under 15 No provision

Idaho Yes Under 18 Yes Under 18.

Illinois Yes 5 Under 18 Yes Under 18.

Indiana Yes Under 16 Yes Under 21.

Iowa Yes Under 18 (57) Under 18.

Kansas Yes Under 18 Yes Under 18.

Kentucky Yes Under 18 Yes Under 18.

Louisiana No provision No provision

Maine Yes Under 16 No provision

Maryland Yes Under 15 No provision

Massachusetts Yes' Under 18 No provision

Michigan Yes Under 21 Yes Under 21.

Minnesota Yes Under 18 Yes Under 18.

Mississippi Yes5 Under 18 No provision

Missouri Yes Under 18 Yes Under 18.

Montana Yes Under 18 No provision

Nebraska Yes Under 18 Yes Under 18.

Nevada Yes 5 Under 18 No provision

New Hampshire Yes Minor No provision

New Jersey Yes Under 16 No provision

New Mexico Yes5 Under 18 8 No provision

New York Yes Under 18 No provision

North Carolina Yes Under 17 No provision

North Dakota Yes Under 21 Yes Under 18.9

Ohio Yes Under 18 No provision

Oklahoma Yes Minor (6) Minor.

Oregon Yes Under 18 Yes Under 18.

Pennsylvania Yes Minor (6) Minor.

Rhode Island Yes Under 16 Yes Under 16.

South Carolina Yes Under 18 (6) Under 18.

South Dakota Yes Under 18 Yes Under 18.

Tennessee Yes Under 18 No provision

Texas Yes,' Under 16 No provision

Utah Yes Under 19 Yes' Under 19.

Vermont Yes5 Under 17 No provision

Virginia Yes Under 18 No provision

Washington Yes Under 21 Yes Between 18 and 21.1

West Virginia Yes Under2l Yes Under 21.

'Wisconsin No provision No provision

Wyoming Yes Under 18 No provision

1 Includes a prohibition against the purchase of cigarettes by minors (in Illinois without written order of parent or guardian), as well as use or possession by

2 if other than parent or guardian.

3 However, inmates in State correction institutions 16 or over, with consent of parent or guardian, may be furnished tobacco and tobacco products.

Eighteen and over. in junior college if not permitted by governing board.

Without consent of parent or guardian.

Minors smoking or in possession of cigarettes are required to give source of cigarettes; use or possession not otherwise regulated.

in addition, high school students may not smoke.

And any pupil of any school in State.

Or a minor pupil in any school.

Purchase or possession by misrepresentation of age a misdemeanor.

THE IMPETUS FOR FEDERAL SUMPTUARY REGULATION

The effect of smoking on health has been the subject of discussion for hundreds of years. Early participants in the tobacco controversy, beginning in the late 16th century, did not associate the use of tobacco with the production of cancers although they credited it with causing or curing nearly every other known disease.

Dr. John Hill, of London, a physician, botanist and prolific writer, first suggested the relation in 1761. In Cautions Against the Immoderate Use ol Snuff, he reported six cases of "polypusses" related to excessive indulgence in tobacco in the form of snuff. One such "polypus" was described as a swelling in one nostril that was hard, black and adherent on a broad base. Painless at first, it later developed "all the frightful symptoms of an open cancer." Dr. Hill believed that this lesion could be fatal and placed the blame for its origin

on tobacco. Dr. Hill has been noted as the first to report an association of tobacco with cancer (Redmond, 1970: 21).

In 1939, the first scientific study linking lung cancer with smoking was published. Between 1950 and 1954, 14 studies associating cigarettes and serious diseases were completed (Fritschler, 1969: 145).

At the present time, there is no government agency with clear jurisdiction over the health aspects of cigarettes. The Federal Trade Commission can act on matters of advertising and package information. The Food and Drug Administration concerns itself only with foods, drugs, solids, or liquids that are eaten or drunk. Tobacco is neither a food nor a drug under current legal definitions. Nor are cigarettes eaten or drunk; they are inhaled.

The 1890 edition of the U.S. Pharmacopoeia, an official listing of drugs published by the government, included tobacco. In later editions, tobacco was dropped. Former Senator Maurine Neuberger has claimed that the removal of tobacco from the Pharmacopoeia was the price paid to get support of tobacco-state legislators for the Food and Drug Act of 1906. The leaf was thereby removed from the jurisdiction of the FDA (Wagner, 1971: 74).

The first statement from the Public Health Service on the subject was made by its Surgeon General, Leroy F. Burney, M.D., in the Journal of the American Medical Association in November, 1959. The heart of this statement was that "the weight of evidence at present implicates smoking as the principal etiological factor in the increased incidence of lung cancer" (Diehl, 1969: 154).

In June, 1961 the American Cancer Society, the American Heart Association and the National Tuberculosis and Respiratory Disease Association jointly requested that a commission be appointed "to consider the responsibilities of government, of business and of voluntary agencies relative to the health hazards of cigarette smoking and to recommend a solution of this health problem that would protect the public and would interfere least with the freedom of industry and the happiness of individuals" (Diehl, 1969: 155).

On June 7, 1962, the then Surgeon General, Dr. Luther Terry, announced, with the approval of the President, that he was establishing an "expert committee to undertake a comprehensive review of all data on smoking and health."

The members of this committee were respected scientists who had previously expressed no opinion about the relationship of tobacco to health. All members were approved for appointment by the tobacco industry as well as by the American Medical Association and several national health agencies. Half of the committee members were cigarette smokers.

On January 11, 1964, after some 15 months of intensive study, this Advisory Committee to the Surgeon General issued its monumental unanimous report stating that "cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action."

The committee stated unequivocally that "cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs other factors. The data for women, though less extensive, point in the same direction." Air pollution was found to be a very minor factor in the cause of the disease, far outweighed by cigarette smoking.

The death rate from heart disease, the report noted, was 70 percent higher in cigarette smokers than in nonsmokers, and although there was not enough evidence to say positively that smoking causes heart disease, there was enough to assume that it is a cause and to take action against it.

Another conclusion of great importance was that "cigarette smoking is the most important of the causes of chronic bronchitis in the United States and increases the risk of dying from chronic bronchitis and emphysema."

The report analyzed the statistical, pathological, clinical, and experimental evidence in relation to smoking and other diseases. A total of more than 4,000 published reports were studied and more than 150 investigators were personally interviewed. "The result was the most comprehensive and authoritative report on this subject ever made" (Diehl, 1969: 156).

THE HEALTH WARNING REQUIREMENT

At the time the Surgeon General's Report was published, no statute, administrative ruling or court decision required that cigarette packaging or advertising contain any statement about the dangers to health attributable to cigarette smoking.

After Trade Regulation Rule Proceedings in March and June 1964, the Federal Trade Commission concluded that cigarette advertising was deceptive (misleading) and that advertisers had a responsibility to warn the public of the health hazards of cigarette smoking.

To accomplish this, the Commission proposed that cigarette packages state the amount of tar and nicotine in the smoke of the cigarette which the package contains and that cigarette packages and cigarette advertising carry a statement such as: "Caution: Cigarette 'Smoking is Dangerous to Health. It May Cause Death from Cancer and Other Diseases."

This warning was to be required on cigarette packages beginning January 1, 1965, and in cigarette advertising beginning July 1, 1965. The tobacco industry first obtained a postponement of the effective dates of this ruling and then prevailed upon Congress to vitiate the ruling by passing the Cigarette Labeling and Advertising Act, requiring all packages of cigarettes sold in this country to carry the label "Cigarette Smoking May be Hazardous to Your Health," but prohibiting the Federal Trade Commission and state and local governments from requiring any other label on cigarette packages and any warnings in cigarette advertising at least until 1969.

A New York Times editorial called the Cigarette Labeling and Advertising Act of 1965 "a shocking piece of special-interest legislation-a bill to protect the economic health of the tobacco industry by freeing it of proper regulation" (Cigarette Labeling and Advertising, 1965). An article in the Atlantic Monthly described the political maneuvering behind this legislation under the title "The Quiet Victory of the Cigarette Lobby: How It Found the Best Filter Yet-Congress" (Diehl, 1969:162).

Public concern attending publication of the Surgeon General's report, Smoking and Health, and the pending FTC regulations for warnings on cigarette packages and in cigarette advertising apparently convinced the tobacco industry that some action by Congress was inevitable.

Reportedly the industry decided to accept a weak label on cigarette packages provided that the legislation would prevent any regulation of cigarette advertising. This was accomplished by inserting into the proposed law the provision precluding the FTC and all state or local governments from requiring any warning on cigarette packages other than the one approved by Congress and also preventing any warnings in cigarette advertising.

At House and Senate committee hearings, committee members friendly to the industry attempted to discredit both the Surgeon General's Report and the testimony given by the Surgeon General, the Chairman of the Federal Trade Commission, and the representatives of various medical and health organizations. The tobacco industry then presented a number of physicians who testified that they disagreed with the conclusions of the Surgeon General's Advisory Committee and that in their opinion there was no real evidence that cigarette smoking is harmful (Diehl, 1969: 162).

Although this act temporarily prevented any requirement that tar and nicotine content be indicated on cigarette packages, the Federal Trade Commission did establish a laboratory to determine the, tar and nicotine content of the smoke of cigarettes on the American market, making the results of these tests available periodically to the public.

The Cigarette Labeling and Advertising Act also required that about July 1, 1967, and annually thereafter the Federal Trade Commission report to Congress concerning the effectiveness of the warning label, and upon current practices of cigarette advertising and promotion, with "recommendations for legislation that are deemed appropriate."

After an intensive study the Federal Trade Commission made a detailed report to Congress with the following summary and recommendations: "There is virtually no evidence that the warning statement on cigarette packages has had any significant effect."

Sales remained constant and the industry continued to invest hundreds of millions of dollars in advertising; $200 million a year was being spent on radio and television alone in 1967; cigarette advertisers had become the single largest product advertisers on television accounting for about eight per cent of television advertising time (Wagner, 1971: 166).

THE FAIRNESS DOCTRINE

Another government agency had become concerned with cigarette advertising. The Federal Communications Commission is mandated to assure that the airways, which belong to the public, are used in the public interest.

John P. Banzhaf, III, who has been called the "Ralph Nader of the tobacco industry" was responsible for the FCC's involvement in the cigarette advertising controversy. After viewing several cigarette commercials on television, Banzhaf concluded that "what he was seeing might be considered legally 'controversial'" (Wagner, 1971: 168). He then wrote to WCBS-TV in New York on December 1, 1966, requesting that he or some other responsible spokesman be given an opportunity to present contrasting views on the issue of the benefits and advisability of smoking.

Banzhaf's letter cited three commercials that presented the view that smoking is "socially acceptable and desirable, manly, and a necessary part of a rich full life. "He asked-free time roughly approximate to that spent on the promotion of the "virtues and values of smoking." CBS routinely turned down the request. He sent a second letter to CBS and submitted a formal complaint against WCBS-TV to the FCC in Washington.

The FCC, in a letter to the television station dated June 2, 1967, said programs it had broadcast dealing with the effect of smoking on health were insufficient to offset the effects of paid advertisements broadcast for a total of five to 10 minutes each broadcast day. "We hold that the fairness doctrine is applicable to such advertisements" the Commission said. They rejected Banzhaf's claim for equal time, however.

The FCC called on the station to provide free each week "a significant amount of time for the other viewpoint," thereby implementing the smoking education campaigns launched by the government under the cigarette labeling law. "This requirement will not preclude or curtail presentation by stations of cigarette advertising which they choose to carry." The FCC basically decided that it was not in the public interest for the airways to be used by radio and television to advertise cigarettes without some warning of the health hazards involved with smoking (Wagner, 1971: 169).

The FCC was deluged with requests to reconsider its action. The agency stood firm in its unanimous decision. As a result of the ruling many of the voluntary health agencies and the Public Health Service made available to the television and radio industries spot announcements and other program materials on the serious consequences to health caused by cigarette smoking.

The FCCs decision was upheld by the U.S. Court of Appeals on November 21, 1968; the court said the agency could indeed use its fairness doctrine to require free time for anti-smoking commercials. "The danger cigarettes may pose to health is, among others, a danger to life itself," the Court said.

As the Commission emphasized, it is a danger inherent in the normal use of the product, not one merely associated with its abuse or dependent on intervening fortuitous events. It threatens a substantial body of the population, not merely a peculiarly susceptible fringe group. Moreover, the danger, though not established beyond all doubt, is documented by a compelling cumulation of statistical evidence (Wagner, 1971: 166-173).

(The cigarette manufacturers then asked the Supreme Court to review their case, but the high court turned down the request, leaving the appeals court decision standing.)

"*Most observers agree that the dramatic entrance of the FCC into the smoking controversy was probably the most important single event during the three-year moratorium on requiring health warnings in cigarette advertisements imposed by Congress on the FTC*" (Wagner, 1971 : 175).

THE BAN ON ADVERTISING

Both the U.S. Public Health Service and Federal Trade Commission have annually reported findings to Congress since passage of the cigarette labeling law. The FTC recommended that the Act should be amended to: "Warning: Cigarette Smoking Is Dangerous to Health and May Cause Death From Cancer and Other Diseases."

Additionally, the FTC recommended legislation to require the same warning to appear in all cigarette advertisements and to require statements of tar and nicotine content on all cigarette packages and in all advertising.

Legislation to accomplish these objectives as well as the following were recommended by

the FTC:

Cigarette advertising on television and radio should be barred entirely. Alternately, cigarette advertising on television and radio should be limited as to hours in which it may appear; the extent to which it may appear; and the types of programs on which it may appear;

Increased appropriations, s/ ld be made to the Department of Health, Education, and Welfare for education of the public (especially young people) as to the health hazards of smoking;

Appropriations should be made for research under the direction of the National Institutes of Health on the development of less hazardous cigarettes.

"By 1969, the stage had been set for a showdown over cigarette advertising and promotion" (Wagner, 1971: 190). The U.S. Government was increasing its efforts to discourage the sale of cigarettes. Post office trucks carried posters: "100,000 Doctors Have Quit Smoking."

The Surgeon General continued to release reports about the adverse health effects of smoking.

Dr. Daniel Horn, director of the National Clearinghouse for Smoking and Health, was urging doctors to deliver antismoking appeals to patients in their offices.

Movie personalities had become involved in the American Cancer Society's campaign called I.Q. (for "I Quit") that passed out lapel buttons and dispatched public speakers around the country to discourage the habit. Doris Day, Debbie Reynolds and Lawrence Welk refused to allow tobacco companies to sponsor their TV shows.

Two ad agencies--Ogilivy and Mather and Doyle Dane Bernbach-and a few radio and television stations would not accept cigarette business. Several magazines did not accept cigarette advertising as a matter of principle: Reader's Digest, the New Yorker, and the Saturday Review. The Christian Science Monitor had never carried cigarette ads; the Boston Globe announced in May, 1969 that it would no longer accept such advertising "because accumulated medical evidence has indicated that cigarette smoking is hazardous to health" (Wagner, 1971: 220).

In April 1969, a few weeks before the House Interstate and Foreign Commerce Committee was scheduled to open hearings on the FTC proposals, a series of bills were introduced in the House by representatives of tobacco producing states. One such bill, H.R. 7177, co-sponsored by all eleven of North Carolina's House Delegation, proposed "to establish a comprehensive Federal program to deal with cigarette labeling and advertising with respect to any relationship between smoking and health."

Identical measures were introduced under the sponsorship of congressmen from Virginia, Maryland, Kentucky, and Florida. Some accounts of the activity on Capitol Hill during this period attribute these bills to the tobacco interests' intention "to prevent strengthening of the warning label and make permanent the ban on state and Federal regulation of cigarette advertising, which was due to expire on June 30. Passage of this legislation was the best tobacco interests could have hoped for under the circumstances" (Wagner, 1971: 205).

After testimony from both sides, the House Committee approved a stiffer health warning but prohibited regulatory action on cigarette advertising for six years and in other ways generally upheld the status quo.

The Senate, Commerce Committee, on December 5, 1970, voted out a bill banning cigarette commercials from the air as of January 1, 1971. The FTC was prohibited from acting on cigarette ads in newspapers and magazines until the middle of 1972. The labeling provision in the Senate bill was weaker than that established in the House-voted measure, and the bill also precluded cigarette regulatory action by the fifty states and local governments.

In a session on December 12, a floor amendment was introduced which loosened the Committee's proposed restriction on the FTC by allowing the agency to require health warnings in advertising as of July 1, 1971. The bill also authorized the FTC to move sooner if it found that tobacco companies were switching from broadcast to print advertising so massively that it could be considered a " gross abuse." This bill also approved a new required health warning for cigarette packages"Warning: Cigarette Smoking Is Dangerous to Your Health."

After Senate passage, the measure still had to -pass a joint Senate-House Conference Committee where important differences between the two bills had to be reconciled.

The bill that emerged from conference differed only slightly from the Senate measure. The cautionary label to which the conferees agreed provides: "Warning: The Surgeon General Has Determined That Cigarette Smoking is Dangerous to Your Health." "In a final concession to the broadcasters, the conferees agreed to delay for one day the blackout of cigarette commercials from December 31, 1970, to midnight January 1, 1971. That would give them a last shower of cash from the New Year's Day football bowl games" (Wagner, 1971: 216). It was estimated that the loss to television and radio stations would amount to about $220 million a year, or about 7.5% of their total advertising revenues.

President Nixon signed the Act on April 1, 1970.

Some observers marvel that the bill was passed "in spite of massive pressure that had been brought to bear against it and against the regulation of cigarette advertising generally, by the tobacco industry, the broadcasting industry, and the lobbyists and their political allies. This was a combination that for years had proved invincible against a counterforce of scientists and public health and public interest advocates who, armed with formidable statistics on the damage to health and life caused by cigarette smoking, had sought to protect consumers by requiring all cigarette advertising to provide adequate warnings of these dangers" (Whiteside, 1970: 58).

There are those observers , on the other hand, who do not view the ban of cigarette advertising on television and radio as such a success for the consumer. Rather, they cite the statistics on consumption in other countries to point up the fact that bans on advertising do not reduce sales.

In Czechoslovakia, for example, no direct advertising of tobacco is permitted; yet consumption increased 14% between 1953 and 1958. Advertising of foreign cigarettes was banned in 1962 in Italy; the following year sales increased 39.4% and in 1964, 11.7 %. Sales increased in England after television cigarette advertisements were banned in 1965. Consumption figures for the following three years in Britain reveal increases: 112 billion cigarettes in 1965, 118 billion in 1966; and 119.1 billion in 1967 (Cigarette Advertising, 1970: 113-114).

Robert Miller, an agricultural economist in the Department of Agriculture's Economic Research Service, reports that cigarette consumption is up in every part of the world although advertising was banned in several European countries some years ago. He predicts an eventual decrease in sales during the next five years and perhaps a 12-13% decrease in tobacco consumption (Tobacco Advertising Could End, 1970: 7).

Other observers can see a gradual reduction in cigarette consumption as a result of a prohibition on advertising; some feel a ban on advertising merely makes it difficult to launch a new brand. Others predict that the ban will eliminate the social acceptability of the habit although consumption will not go down.

The "live dangerously novelty" has also been identified as a possible cause for gains in consumption; "such a philosophy might well be prevalent among the young, the very ones that antismoking advocates are most anxious to protect" (Cigarette Advertising, 1970: 112-113).

Another consequence of the ban on cigarette commercials was the FCC ruling that the broadcasters' obligation to air antismoking messages had ended. The stations continue to run them as public service spots; however, the volume was decreased considerably from the former 1 to 3 ratio established by the FCC. The antismoking forces are fearful that a decrease in these spots is harmful to their cause and may retard their efforts to reduce cigarette consumption.

On October 20,1971, a U.S. District Court ruled that the Congressional ban on cigarette advertising is constitutional. The ruling stated that such advertising does not qualify under the First Amendment's guarantee of freedom of speech; a sharp distinction was drawn between guarantees of freedom. of speech for individuals and the "limited extent" to which broadcast advertising qualifies for such protection.

The court also ruled that Congress had more than one "rational basis" for excluding cigarette ads from television and not the printed media one being that broadcasts are the "most persuasive" types of advertising (Cigarette Ad Ban, 1971). Ultimately, the constitutional question will have to be decided by the United States Supreme Court.

CONSUMPTION TRENDS

Cigarette smoking is widespread in America today; 45.9% of the male population 17 years of age and over and 30.5% of females 17 and over are smokers. In 1970, about $10.6 billion of individuals' expenditures was for cigarettes.

Data on cigarette sales and advertising has been obtained by the FTC from domestic cigarette manufacturers; the table below provides cigarette sales for the years 1963 to the present (Federal Trade Commission, 1970: 3):

TOTAL CIGARETTES SOLD

Year	Billions
1963	516.5

1964 505.0

1965 521.1

1966 529.9

1967 535.3

1968 540.3

1969 527.9

1970 534.2

The reduction in sales in 1964 coincides with the public attention given the Report of the Surgeon General issued on January 11, 1964. Public awareness of the dangers cited in the Report was high. It was soon forgotten, for in 1965 the total number of cigarettes sold was almost 5 billion higher than the year prior to the Surgeon General's Report.

In 1969 there was another significant decline; it has been suggested that this decline is attributable to several high-visibility events and also by sales tax increases. For example, the FCC ruling was upheld in November 1968 giving impetus to the antismoking TV campaign; the federal government's anti-smoking campaign was in full swing during 1968-69; the public outcry was being felt by economic interests-magazines, newspapers, personalities and advertising agencies which refused sponsorship for business from tobacco companies.

There were significant state tax increases immediately prior to 1969 which probably contributed to the reduction in sales during that year. During fiscal year 1967, 15 states increased their cigarette tax rates; the average increase was 3.5 cents. The rate increase ranged from New York's, Ohio's, and Illinois' two cents to California's and Florida's seven cents. The next year, seven more states increased their cigarette taxes. The rates ranged from Massachusetts' and Vermont's two cents to Minnesota's, Rhode Island's, and Tennessee's five cents the average increase approximately four cents (Council of State Governments, 1968: 196-197).

The ban on cigarette advertising on television and radio began on January 2, 1971, yet several calculations reflect a rise in cigarette sales during the past year. Business Week projections of industry sales and brand rankings show that a record 529 billion cigarettes were consumed in 1971, 1.5% more than 1970's sales (Where Cigarette Makers Spend, 1971: 56). Tobacco industry sources estimate that consumption has risen in 1971 by 1.5% to 535 billion cigarettes (Cigarette Sales Up, 1972: 3).

John C. Maxwell, tobacco analyst for Oppenheimer & Company, a brokerage firm, also reported a rise-2.3% in domestic unit sales in 1971. He relates part of the growth in cigarette consumption to the population mix the increase hit the 20-40 year age group, where smoking is heaviest. The Maxwell report suggests that the rest of this growth must be related to "government overkill, wherein many voices in Washington suggest that everything we eat or drink is harmful" (Maxwell, 1971: 1).

An industry specialist with Manufacturers Hlanover Trust Company, on the other hand, attributes both the lag in sales in 1969 and the new increase to the "very effective antismoking ads on television. Since the ban, these commercials rarely appear" (Cigarette

Sales Up, 1972: 3).

Another industry executive notes, "For years we have believed that the role of cigarette advertising is to attract smokers from competitive brands rather than induce nonsmokers to start smoking. We failed to convince the Federal Communications Commission of this, but it is borne out by our industry's experience since the TV ban. Within a relatively stable market, some companies have continued to gain while others lost. Some brands have increased their share of market while others have declined" (Where Cigarette Makers Spend, 1971: 56). Skeptics continue to argue that tobacco companies ha e also been trying to recruit new young smokers.

TOBACCO: ECONOMICS AND POLITICS

It is generally accepted that tobacco has been an extremely powerful force in American politics. Approximately 50 million smokers smoked 535 billion cigarettes in the past year. More than 100,000 employees receive $500 million in wages annually from tobacco manufacturing companies; over 4,500 wholesalers handle the distribution of tobacco products and hundreds of thousands of merchants depend on tire sale of cigarettes as a source of their income.

Cigarette companies had been spending over $200 million per year on radio and television advertising, and since the ban, almost all of this money has been diverted to other media advertising providing many thousands of jobs in ad agencies and in the various media. Three million people from about 750,000 families receive $1.4 billion annually for the cultivation of tobacco used in cigarettes.

Peripherally affected are those involved in producing the 40 million pounds of moisture-proof cellophane, the 70 million pounds of aluminum foil, the 27 billion printed packs, and the 2.7 billion cartons (Cigarette Advertising, 1970: 110-111; Wagner, 1971: 120; USDA, Tobacco Situation, 1971a: 29-31).

One writer, reporting on the present public policy trend, notes that "attempts to discourage smoking would affect the lives of millions of people and would have profound economic and political consequences" (Wagner, 1971: 121).

Advocates of cigarette smoking today are organized into extremely powerful groups, each having its own specific function and plentiful resources.

The Tobacco Tax Council, established in 1949, compiles data on the taxation of tobacco products by the Federal, state and local governments. The Council's annual booklet, "Cigaret Taxes in the United States" has been superseded by " The Tax Burden on Tobacco" since 1966. This pamphlet "undertakes to trace the history of tobacco taxes from the years of the Civil War down through [the present year]" (Tobacco Tax Council, 1970: iii).

The trade association promoting the welfare of the tobacco industry is the Tobacco Merchants Association of the U.S. It is composed of manufacturers, wholesalers, retailers, importers, exporters, leaf dealers, suppliers, and firms interested in the industry. Its Bulletins cover legislation, trends, special reports; its numerous other publicauons and activities seek to improve industry operations and expand outlets (e.g., international) f or potential sales (Tobacco Merchants Association, 1971: 1-4).

The tobacco industry's point of view is nurtured and protected by the Tobacco Institute, a nonprofit corporation founded in 1958. Its membership includes major U.S. manufacturers of cigarettes, smoking and chewing tobacco, and snuff: The Bloch Brothers Tobacco Company, Brown & Williamson Tobacco Corporation, Conwood Corporation, G. A. Georgopulo & Company, Helme Products, Larus & Brother Company, Liggett & Myers, Lorillard, Philip Morris Incorporated, R. J. Reynolds Industries, Scotten-Dillion Company, and United States Tobacco Company.

The Institute is financed by contributions from the large corporations according to their share of the market. The institute reports on the pro-tobacco side of the medical story, attempting to discredit antismoking publicity, and publishes information on the historical role of tobacco, its place in the national economy, the industry itself, and the public's use of tobacco products.

The Council for Tobacco Pesearch, created in 1953 in response to medical bulletins reporting on the hazards of smoking, processes and administers millions of research grants. "Although research money was to be awarded with no strings attached [The Council] nicely serve[s] the purpose of identifying the industry with the welfare of humanity and spreading good will through the scientific community" (Wagner, 1971: 80).

The scientific data continue to be attacked from both sides. Since 1954 a great quantity of research has been published and, in turn, disputed. For example, "the press played up the Hammond and Auerbach study and the claim that twelve beagles had developed lung cancer" from cigarettes. "The findings have subsequently been downgraded by ' v the author to two microscopic tumors with the further revelation that two dogs in the control group also developed tumors" (Maxwell, 1971: 1).

Another area of contention has developed around the relationship between cigarette smoke itself and lung cancer. A recent paper by Dr. Geoffrey Myddelton given at the Second World Conference on Smoking and Health in London, September 20-24, 1971, compares the incidence of smoking and lung cancer in various countries. He indicates, "Japan smokes 86% as much as Britain but has only . % of its lung cancer. Canada smokes twice as many cigarettes as the Netherlands but has only 69% as much lung cancer." He goes on to correlate the use of diesel file] in England to lung cancer (Maxwell. 1971: 2).

From the other side, the United States Public Health Service 1972 report The Health Consequences of Smoking maintains that "nonsmokers as well as smokers may be harmed by cigarettes, . . . tobacco smoke in closed cars and poorly ventilated rooms can contaminate the atmosphere for everyone. . . . The chief danger is exposure to low levels of the deadly gas, carbon monoxide. Experiments, with animals have shown that various concentrations of the colorless, odorless, and tasteless gas 'adversely affect' the structure and function of the heart and lungs. The implication is that this may also be true in man" (Study Says Cigarette Smoke Also May Harm Nonusers, 1972: 1).

It is estimated that at the present time one and a half to two million adults give up smoking every year. Sensing the hazards of the future, some cigarette, companies sought fiscal security in diversification and substitution; tobacco manufacturers are now marketing, for example, safety razors, fertilizers, dog food, ballpoint pens, peanut butter and other non-nicotine products. By 1967, sales on non-tobacco products accounted for approximately one-third of the, total sales of cigarette manufacturers.

It remains to be seen whether tobacco power will be whittled away any further in the next few years. Some feel that "the tobacco subsystem has succeeded in keeping the health

question a low priority item on the government's agenda by playing one government agency off against another.... This subsystem cuts across institutional lines and includes the paid representatives of tobacco growers, marketing organizations and manufacturers.,. Congressmen representing tobacco growing states [are] leading members of four subcommittees, including two ,appropriations subcommittees and two committees in each house of Congress handling tobacco legislation. . . . Tobacco power [is] thus firmly entrenched and well supported" (Wagner, 1971: 121).

On the other hand, a strongly worded commentary by an industry spokesman cites Justice John Marshall's statement to illustrate industry's precarious position: "The power to tax involves the power to destroy." He continues with a description of the tobacco industry's present situation:

The onslaught of state and local taxes on tobacco products ... represents a most serious threat to all segments of our industry.... We are now facing a calculated attempt to destroy, or at least drastically curtail, the sale of smoking products. The political and economic climate is most favorable for this attack. Smoking and health is a prime political issue in the same context as air pollution, crime in the streets, and consumerism. At the same time, local governments are verging on bankruptcy. Revenue of any sort is therefore a must. It is a tough battle, and cigarette industry is currently bearing the largest part of the attack (Regensburg, 1971: 146).

The revenues gained from tobacco tax collections are significant. Over $2.1 billion in Federal taxes and over $2.5 billion in state cigarette taxes were collected in Fiscal Year 1971 (Tobacco Tax Council, 1970: 4-6, 8; USDA, Tobacco Situation, 1971b: 44). Total tobacco taxes were $4.8 billion in 1971 compared with $1.7 billion in 1950.

In 1970 tobacco taxes accounted for 1.1% of total federal tax receipts and represented 13.8 percent of all excise taxes (USDA, Tobacco Situation, 1971b: 40). This places the tobacco tax as the seventh largest source of collection by the Federal government behind the major giants, e.g., income and profit taxes (both corporate and individual), employment taxes, manufacturers excise taxes, alcohol taxes, and estate and gift taxes. In terms of individual commodities it ranks behind only alcohol. Thus, federal revenue would be importantly affected if tobacco consumption were to decline.

CONCLUSION

The big question is how the Federal government plans to proceed. Six tobacco bills are now pending in Congress. One of these bills would give the Federal Trade Commission authority to set maximum permissible limits on tar and nicotine. Another would establish a graduated cigarette tax based on tar content.

The FTC is presently carrying on negotiations with the industry to come up with a "clear and conspicuous" health warning for its print advertising. It is expected that the industry, " which has been working closely with the FTC 'will' take some 'voluntary' labeling action" (Where Cigarette Makers Spend, 1971: 57).

The industry feels the pressure; one member explains: "We are resigned to it. Over-all.... the industry mood is much more relaxed-now that we have this first big year behind us" (Where Cigarette Makers Spend, 1971: 57).

The public is clamoring for government action; a 1970 College Poll'. surveying-youths 18 and older on more than 100 campuses reveals that 96% believe that smoking is dangerous to one's health (College Poll, 1971).

Further, a 1969 study on teenage (13- to 18-yearolds) smoking attitudes, motivation and habits indicates "deep teenage dissatisfaction with cigarette smoking, considerable knowledge of its ill effects, but a very exaggerated estimate of the acceptance of smoking by the adult world" (Lieberman Research, 1969: 1-20). And, a 1970 nationwide survey of teenagers revealed: "72% of non-smokers identified physicians as the one group that could persuade them not to start smoking and 42% of those who smoked said their physician's advice would influence them to stop" (Doctors, 1970: 24).

Critics of the industry claim: "The controversy about smoking and health continues largely because of the energy, time and money spent by the tobacco industry in keeping this controversy alive" (College Poll, 1971).

In September, 1935, Fortune Magazine published a discussion of the medical implications of smoking. It concluded that:

This much can be said: That the possible benefit to be derived from tobacco is always less than the possible harm (Robert, 1949: 256).

Official policy has never accepted this judgment. In recent years, steps have been taken to discourage smoking, although there is little conclusive evidence that consumption patterns are changing. It can be expected that official policy and alterations in individual behavior will both evolve slowly during the coming years. The socioeconomic impact of a sudden change in official policy would be great, a circumstance reflecting the momentum of several centuries of intense commercial activity.

References

Brooks, J. E. The Mighty Leaf: Tobacco Thru the Centuries, Boston: Little, Brown & Co., 1952, 12, 27, 56, 71-72, 88, 93-98, 102, 112-113, 146-147, 165, 167, 215216. 219, 242-243, 245, 258, 271, 274.

"Cigarette Ad Ban Ruled Constitutional by Panel," Washington Post (Washington, D.C.), October 21, 1971. "Cigarette Advertising and the Public Health," Columbia Journal of Law: Social Problems, 6 (1) : 110-114, 1970. "Cigarette Labeling and Advertising Act of 1965," New York Times (New York, New York), July 9, 1965. "Cigarette Sales Up Despite Ad Curbs," Washington Post (Washington, D.C.), January 1, 1972,3.

"College Poll Shows Students' Smoking Habits," Tobacco Reporter, June, 1971.

Council of State Governments. The Book of the States, 1968,196-197,200-208,212-213.

Diehl, H. Tobacco and Your Health, New York: McGrawHill Book Co., 1969, 154-156, 161-162.

"Doctors Could Disuade Youths From Smoking," Pediatric News, 4(2) :24, 1970.

Federal Trade Commission. "FTC Statistical Supplement," December, 1970, 3.

Fritschler, A. T. Smoking and Politics, New York: Appleton-Century-Cross, Inc., 1969, 145.

Gottsegen, J. J. Tobacco-A Study of its Consumption in the United States, New York-Chicago: Pitman Publishing Corp., 1940, 8-10, 28 87, 147, 153, 155.

Hamilton, A. E. This Smoking World, New York: The Century Co., 1927, 168, 205.

Heimann, R. K. Tobacco and Americans, New York:

McGraw-Hill Book Co., 1960, 22-23, 83-84, 90, 93, 155-156.

Lehman Brothers. About Tobacco, (N.P.), 1955, 39.

Lieberman Research, Inc. "The Teenager Looks at Cigarette Smoking," Report of a Study Conducted for the American Cancer Society, November, 1969, 1-20.

Maxwell, J. C., Jr. "Preliminary Year End Estimate," The Maxwell Report, November, 1971,1-2.

Middleton, A. P. Tobacco Coast, Charlottesville: University of Virginia Press, 1953, 93-94, 104-107, 114-117, 120-121.

Morison, S. E. The Oxford History of the American People, New York: Oxford University Press, 1965, 93-94. National Interagency Council on Smoking and Health. "State Activities," Bulletin, July-September 1971, 1.

Neuberger, M. B. Smoke Screen: Tobacco and the Public Welfare, Englewood Cliffs: Prentice Hall, Inc., 1963, 52, 62.

Redmond, D. E., Jr., "Tobacco and Cancer: The First Clinical Report, 1761," New England Journal of Medicine, 28-9 (1) : 21, 1970.

Regensburg, A. "The Tax That Destroys," NATD Coordinator, XXXI: 146, April, 1971.

Robert, J. C. The Story of Tobacco, Chapel Hill: University of North Carolina Press, 1949, 11, 99-101, 106107, 117, 169, 247, 256.

"Study Says Cigarette Smoke Also May Harm Nonusers," Washington Post (Washington, D.C.), January 10, 1972, 1 (6).

"Tobacco Advertising Could End in 1975," Herald (Lexington, Kentucky), January 18, 1970, 7.

Tobacco Institute. "Connecticut and Tobacco," Washington: Tobacco Institute, Undated], 20-23.

"Kansas and Tobacco," Washington: Tobacco Institute, 1970, 9.

"Kentucky and Tobacco," Washington: Tobacco Institute, 1971, 0.

- "Maryland and Tobacco," Washington: Tobacco Institute, 1971, 9-10, 21, 23.
- "Massachusetts and Tobacco," Washington: Tobacco Institute, 1971, 17.
-"Virginia and Tobacco," Washington: Tobacco Institute, 1971, 19, 22, 28, 29.

Tobacco Merchants Association. "Sales of Tobacco Products to Minors," March 1971, 1-4.

Tobacco Tax Council. "The Tax Burden on Tobacco," 1970, iii-iv, v, 2, 4-6,8,17,53.

U.S. Department of Agriculture. "Tobacco Situation,"

Economic Research Service, TS-136, June, 1971a, 29-31. - "Tobacco Situation," Economic Research Service, TS-137, September, 1971b, 7, 39-44.

Vlassis, T. "Should Pharmacists Sell Cigarettes?" Iowa Pharmacists, 24 (9) : 10, 15, 1969.

Wagner, S. Cigarette Country, -New -York: Praeger Publishers, 1971, 40, 63-64, 74, 80, 120-121, 166-173, 175, 190, 205, 216, 220.

Werner, C. Tobacco Land, New York: Tobacco Leaf Publishing Co., 1922, 100-102, 105, 358-359, 559. "Where Cigarette Makers Spend Ad Dollars Now," Business Week, December 25, 1971, 56-57.

Whiteside, T. "Annals of Advertising: Cutting Down," The New Yorker, December 19, 1970, 58-80.

7 USC § 511 (b) (d), 1935.

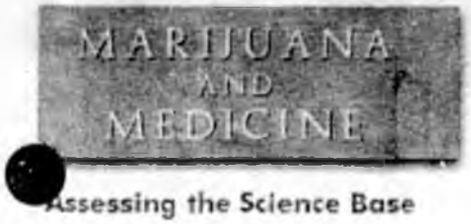
7 USC § 515, 1936.

7 USC § 1303,1938.

7 USC § 1312, 1938.

7 USC § 1314, 1938.

26-USC §-5701, et seq.



Marijuana and Medicine

Assessing the Science Base

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

Division of Neuroscience and Behavioral Health

INSTITUTE OF MEDICINE

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The principal investigators responsible for the report were chosen for their special competences and with regard for appropriate balance.

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

MARIJUANA AND MEDICINE

Assessing the Science Base

INSTITUTE OF MEDICINE

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Reviewers

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

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

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Preface

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

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

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

against the medical use of marijuana were invited to present scientific evidence in support of their positions. Finally, the Institute of Medicine appointed a panel of nine experts to advise the study team on technical issues.

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

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

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

Although marijuana smoke delivers THC and other cannabinoids to the body, it also delivers harmful substances, including most of those found in tobacco smoke. In addition, plants contain a variable mixture of biologically active compounds and cannot be expected to provide a precisely defined drug effect. For those reasons, the report concludes that the future of cannabinoid drugs lies not in smoked marijuana but in chemically defined drugs that act on the cannabinoid systems that are a natural component of human physiology. Until such drugs can be developed and made available for medical use, the report recommends interim solutions.

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

Acknowledgments

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

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

The following people wrote invaluable background papers for the report: Steven R. Childers, Paul Consroe, Howard Fields, Richard J. Gralla, Norbert Kaminski, Paul Kaufman, Thomas Klein, Donald Kotler, Richard Musty, Clara Sanudo-Pellectual frameworkster, Stephen Sidney, Donald P. Tashkin, and J. Michael Walker. Others provided expert technical commentary on draft sections of the report: Richard Bonnie, Keith Green, Frederick Fraunfelder, Andrea Hohmann, John McAnulty, Craig Nichols, John Nutt, and Robert Pandina. Still others responded to many inquiries, provided expert counsel, or shared their unpublished data: Paul Consroe, Geoffrey Levitt, Raphael Mechoulam, Richard Musty, David Pate, Roger Pertwee, Clara Sanudo-Pe Craig Nichols, John Nutt, and RWalker, and Scott Yarnell. Miriam Davis, consultant to the study team, provided excellent written material for the chapter on cannabinoid drug development.

The reviewers for the report (see page iv) provided extensive, constructive suggestions for improving the report. It was greatly enhanced by their thoughtful attention. Many of these people assisted us through

many iterations of the report. All of them made contributions that were essential to the strength of the report. At the same time, it must be emphasized that responsibility for the final content of report rests entirely with the authors and the Institute of Medicine.

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

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

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

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

Executive Summary

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

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

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

This report summarizes and analyzes what is known about the medical

use of marijuana: it emphasizes evidence-based medicine (derived from knowledge and experience informed by rigorous scientific analysis), as opposed to belief-based medicine (derived from judgment, intuition, and beliefs untested by rigorous scienc).

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

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

1. Evaluation of the effects of isolated cannabinoids;

2. Evaluation of the risks associated with the medical use of marijuana: and

3. Evaluation of the use of smoked marijuana.

EFFECTS OF ISOLATED CANNABINOIDS

Cannabinoid Biology

Much has been learned since the 1982 IOM report *Marijuana and Health*. Although it was clear then that most of the effects of marijuana were due to its actions on the brain, there was little information about how THC acted on brain cells (neurons), which cells were affected by THC, or even what general areas of the brain were most affected by THC. In addition, too little was known about cannabinoid physiology to offer any scientific insights into the harmful or therapeutic effects of marijuana. That all changed with the identification and characterization of cannabinoid receptors in the 1980s and 1990s. During the past 16 years, science has advanced greatly and can tell us much more about the potential medical benefits of cannabinoids.

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

Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.

The natural role of cannabinoids in immune systems is likel' multi-faceted and remains unclear.

The brain develops tolerance to cannabinoids.

Animal research demonstrates the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.

Withdrawal symptoms can be observed in animals but appear to be mild compared to opiates or benzodiazepines, such as diazepam (Valium).

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

Recommendation 1: Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.

Efficacy of Cannabinoid Drugs

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

The effects of cannabinoids on the symptoms studied are generally modest, and in most cases there are more effective medications. However, people vary in their responses to medications, and there will likely always be a subpopulation of patients who do not respond well to other medications. The combination of cannabinoid drug effects (anxiety reduction, appetite stimulation, nausea reduction, and pain relief) suggests that cannabinoids would be moderately well suited for particular conditions, such as chemotherapy-induced nausea and vomiting and AIDS wasting.

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

Although most scientists who study cannabinoids agree that the

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

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

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

Influence of Psychological Effects on Therapeutic Effects

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

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

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

RISKS ASSOCIATED WITH MEDICAL USE OF MARIJUANA

Physiological Risks

Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, except for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications. The harmful effects to individuals from the perspective of possible medical use of marijuana are not necessarily the same as the harmful physical effects of drug abuse. When interpreting studies purporting to show the harmful effects of marijuana, it is important to keep in mind that the majority of those studies are based on *smoked* marijuana, and cannabinoid effects cannot be separated from the effects of inhaling smoke from burning plant material and contaminants.

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

The *chronic* effects of marijuana are of greater concern for medical use and fall into two categories: the effects of chronic smoking and the effects of THC. Marijuana smoking is associated with abnormalities of cells lining the human respiratory tract. Marijuana smoke, like tobacco smoke, is associated with increased risk of cancer, lung damage, and poor pregnancy outcomes. Although cellular, genetic, and human studies all suggest that marijuana smoke is an important risk factor for the development of respiratory cancer, proof that habitual marijuana smoking does or does not cause cancer awaits the results of well-designed studies.

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

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

Marijuana Dependence and Withdrawal

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

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

Marijuana as a "Gateway" Drug

Patterns in progression of drug use from adolescence to adulthood are strikingly regular. Because it is the most widely used illicit drug, marijuana is predictably the first illicit drug most people encounter. Not surprisingl most users of other illicit drugs have used marijuana first. In fact, most drug users begin with alcohol and nicotine before marijuana--usually before they are of legal age.

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

Finally, there is a broad social concern that sanctioning the medical use of marijuana might increase its use among the general population. At this point there are no convincing data to support this concern. The existing data are consistent with the idea that this would not be a problem if the medical use of marijuana were as closely regulated as other medications with abuse potential.

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

USE OF SMOKED MARIJUANA

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

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

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

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

failure of all approved medications to provide relief has been documented,

the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,

such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness, and

involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.

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

STATEMENT OF TASK

The study will assess what is currently known and not known about the medical use of marijuana. It will include a review of the science base regarding the mechanism of action of marijuana, an examination of the peer-reviewed scientific literature on the efficacy of therapeutic

uses of marijuana, and the costs of using various forms of marijuana versus approved drugs for specific medical conditions (e.g., glaucoma, multiple sclerosis, wasting diseases, nausea, and pain).

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

Specific Issues

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

Science Base

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

Therapeutic Use

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

marijuana that relate to age or type of disease

Economics

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

RECOMMENDATIONS

Recommendation 1: Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.

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

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

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

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

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

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

Because marijuana is a crude THC delivery system that also delivers harmful substances, smoked marijuana should generally not be recommended for medical use. Nonetheless, marijuana is widely used by certain patient groups, which raises both safety and efficacy issues.

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

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

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

- **failure of all approved medications to provide relief has been documented,**
- **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.

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1

Introduction

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

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

Can marijuana relieve health problems? Is it safe for medical use? Those straightforward questions are embedded in a web of social concerns, which lie outside the scope of this report. Controversies concerning nonmedical use of marijuana spill over onto the medical marijuana debate and tend to obscure the real state of scientific knowledge. In contrast with the many disagreements bearing on the social issues, the study team found substantial consensus, among experts in the relevant disciplines, on the scientific evidence bearing on potential medical use. This report analyzes science, not the law. As in any policy debate, the value of scientific analysis is that it can provide a foundation for further discussion. Distilling scientific evidence does not in itself solve a policy problem. What it can do is illuminate the common ground, bringing to light fundamental differences

out of the shadows of misunderstanding and misinformation that currently prevail. Scientific analysis cannot be the end of the debate, but it should at least provide the basis for an honest and informed discussion.

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

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

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

HOW THIS STUDY WAS CONDUCTED

Information was gathered through scientific workshops, site visits, analysis of the relevant scientific literature, and extensive consultation with biomedical and social scientists. The three 2-day workshops--in Irvine, California; New Orleans, Louisiana; and Washington, D.C.--were open to the public and included scientific presentations and reports, mostly from patients and their families, about their experiences with and perspectives on the medical use of marijuana. Scientific experts in various fields were selected to talk about the latest research on marijuana, cannabinoids, and related topics (listed in Appendix B). Selection of the experts was based on

recommendations by their peers, who ranked them among the most accomplished scientists and the most knowledgeable about marijuana and cannabinoids in their own fields. In addition, advocates for (John Morgan) and against (Eric A. Voth) the medical use of marijuana were invited to present scientific evidence in support of their positions.

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

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

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

The study team visited four cannabis buyers' clubs in California (the Oakland Cannabis Buyers' Cooperative, the San Francisco Cannabis Cultivators Club, the Los Angeles Cannabis Resource Center, and Californians Helping Alleviate Medical Problems, or CHAMPS) and two HIV/AIDS clinics (AIDS Health Care Foundation in Los Angeles and Louisiana State University Medical Center in New Orleans). We listened to many individual stories from the buyers' clubs about using marijuana to treat a variety of symptoms and heard clinical observations on the use of

Marinol to treat AIDS patients. Marinol is the brand name for dronabinol, which is Δ^9-tetrahydrocannabinol (THC) in pill form and is available by prescription for the treatment of nausea associated with chemotherapy and AIDS wasting.

MARIJUANA TODAY

The Changing Legal Landscape

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

In the late 1960s and early 1970s, there was a sharp increase in marijuana use among adolescents and young adults. The current legal status of marijuana was established in 1970 with the passage of the Controlled Substances Act, which divided drugs into five schedules and placed marijuana in Schedule I, the category for drugs with high potential for abuse and no accepted medical use (see Appendix C, Scheduling Definitions). In 1972, the National Organization for the Reform of Marijuana Legislation (NORML), an organization that supports decriminalization of marijuana, unsuccessfully petitioned the Bureau of Narcotics and Dangerous Drugs to move marijuana from Schedule I to Schedule II. NORML argued that marijuana is therapeutic in numerous serious ailments, less toxic, and in many cases more effective than conventional medicines.[13] Thus, for 25 years the medical marijuana movement has been closely linked with the marijuana decriminalization movement, which has colored the debate. Many people criticized that association in their letters to IOM and during the public workshops of this study. The argument against the medical use of marijuana presented most often to the IOM study team was that "the medical marijuana movement is a Trojan horse"; that is, it is a deceptive tactic used by advocates of marijuana decriminalization who would exploit the public's sympathy for seriously ill patients.

Since NORML's petition in 1972, there have been a variety of legal decisions concerning marijuana. From 1973 to 1978, 11 states adopted statutes that decriminalized use of marijuana, although some of them recriminalized marijuana use in the 1980s and 1990s. During the 1970s, reports of the medical value of marijuana began to appear, particularly

claims that marijuana relieved the nausea associated with chemotherapy. Health departments in six states conducted small studies to investigate the reports. When the AIDS epidemic spread in the 1980s, patients found that marijuana sometimes relieved their symptoms, most dramatically those associated with AIDS wasting. Over this period a number of defendants charged with unlawful possession of marijuana claimed that they were using the drug to treat medical conditions and that violation of the law was therefore justified (the so-called medical necessity defense). Although most courts rejected these claims, some accepte em.[5]

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

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

Several months after the passage of the California and Arizona medical marijuana referendums, the Office of National Drug Control Policy (ONDCP) asked whether IOM would conduct a scientific review of the medical value of marijuana and its constituent compounds. In August 1997, IOM formally began the study and appointed John A. Benson Jr. and Stanley J. Watson Jr. to serve as principal investigators for the study. The charge to IOM was to review the medical use of marijuana and the harms and benefits attributed to it (details are given in Appendix D).

Medical Marijuana Legislation Among the States

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

marijuan[illegible]ll provide relief.

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

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

MARIJUANA AND MEDICINE

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

Marijuana's use as an herbal remedy before the 20th century is well documented.[1,10,11] However, modern medicine adheres to different standards from those used in the past. The question is not whether

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

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

Although plants continue to be valuable resources for medical advances, drug development is likely to be less and less reliant on plants and more reliant on the tools of modern science. Molecular biology, bioinformatics software, and DNA array-based analyses of genes and chemistry are all beginning to yield great advances in drug discovery and development. Until recently, drugs could only be *discovered*; now they can be *designed*. Even the discovery process has been accelerated through the use of modern drug-screening techniques. It is increasingly possible to identify or isolate the chemical compounds in a plant, determine which compounds are responsible for the plant's effects, and select the most effective and safe compounds--either for use as purified substances or as tools to develop even more effective, safer, or less expensive compounds.

Yet even as the modern pharmacological toolbox becomes more sophisticated and biotechnology yields an ever greater abundance of therapeutic drugs, people increasingly seek alternative, low-technology therapies.[4,5] In 1997, 46 percent of Americans sought nontraditional medicines and spent over 27 billion unreimbursed dollars; the total number of visits to alternative medicine practitioners appears to have exceeded the number of visits to primary care physicians.[5,6] Recent interest in the medical use of marijuana coincides with this trend toward self-help and a search for "natural" therapies. Indeed, several people who spoke at the IOM public hearings in support of the medical use of marijuana said that

they generally preferred herbal medicines to standard pharmaceuticals. However, few alternative therapies have been carefully and systematically tested for safety and efficacy, as is required for medications approved by the FDA (Food and Drug Administration).[2]

WHO USES MEDICAL MARIJUANA?

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

John Mendelson, an internist and pharmacologist at the University of California, San Francisco (UCSF) Pain Management Center, surveyed 100 members of the SFCCC who were using marijuana at least weekly. Most of the respondents were unemployed men in their forties. Subjects were paid $50 to participate in the survey; this might have encouraged a greater representation of unemployed subjects. All subjects were tested for drug use. About half tested positive for marijuana only; the other half tested positive for drugs in addition to marijuana (23% for cocaine and 13% for amphetamines). The predominant disorder was AIDS, followed by roughly equal numbers of members who reported chronic pain, mood disorders, and musculoskeletal disorders (Table 1.1).

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

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

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

using marijuana for chronic pain also reported that it reduced nausea and vomiting.

Note that the medical conditions referred to are only those reported to the study team or to interviewers; they cannot be assumed to represent complete or accurate diagnoses. Michael Rowbotham, a neurologist at the UCSF Pain Management Center, noted that many pain patients referred to that center arrive with incorrect diagnoses or with pain of unknown origin. At that center the patients who report medical benefit from marijuana say that it does not reduce their pain but enables them to cope with it.

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

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

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

CANNABIS AND THE CANNABINOIDS

Marijuana is the common name for *Cannabis sativa*, a hemp plant that grows throughout temperate and tropical climates. The most recent review of the constituents of marijuana lists 66 cannabinoids (Table 1.5).[16] But that does not mean there are 66 different cannabinoid effects or interactions. Most of the cannabinoids are closely related; they fall into only 10 groups of closely related cannabinoids, many of which differ by only a single chemical moiety and might be midpoints along biochemical pathways--that is, degradation products, precursors, or byproducts.[16,18] Δ^9-tetrahydrocannabinol (Δ^9-THC) is the primary psychoactive ingredient; depending on the particular plant, either THC or cannabidiol is the most abundant cannabinoid in marijuana (Figure 1.1). Throughout this report, THC is used to indicate Δ^9-THC. In the few cases where variants of THC are discussed, the full names are used. All the cannabinoids are lipophilic--they are highly soluble in fatty fluids and tissues but not in water. Indeed, THC is so lipophilic that it is aptly described as "greasy."

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

Cannabinoids are produced in epidermal glands on the leaves (especially the upper ones), stems, and the bracts that support the flowers of the marijuana plant. Although the flower itself has no epidermal glands, it has the highest cannabinoid content anywhere on the plant, probably because of the accumulation of resin secreted by the supporting bracteole (the small leaf-like part below the flower). The amounts of cannabinoids and their relative abundance in a marijuana plant vary with growing conditions, including humidity, temperature, and soil nutrients (reviewed in Pate, 1994[14]). The chemical stability of cannabinoids in harvested plant material is also affected by moisture, temperature, sunlight, and storage. They degrade under any storage condition.

ORGANIZATION OF THE REPORT

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

Chapter 2 reviews basic cannabinoid biology and provides a foundati to understand the medical value of marijuana or its constituent cannabinoids. In consideration of the physician's first rule, "first, do no harm," the potential harms attributed to the medical use of marijuana are

reviewed before the potential medical benefits. Chapter 3 reviews the risks posed by marijuana use, with emphasis on medical use.

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

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

REFERENCES

[1] Abel EL. 1980. *Marijuana: The First Twelve Thousand Years*. New York: Plenum Press.

[2] Angell M, Kassirer JP. 1998. Alternative medicine--The risks of untested and unregulated remedies. *New England Journal of Medicine* 339:839—841.

[3] Bonnie RJ, Whitebread II CH. 1974. *The Marihuana Conviction: A History of Marihuana Prohibition in the United States*. Charlottesville, VA: University Press of Virginia.

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

[5] Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kessler RC. 1998. Trends in alternative medicine use in the United States, 1990—1997: Results of a follow-up national survey. *Journal of the American Medical Association* 280:1569—1575.

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

[7] Grifo F, Newman D, Fairfield A, Bhattacharya B, Grupenhoff JT. 1997. The origins of prescription drugs. In: Grifo F, Rosenthal J, Editors. *Biodiversity and Human Health*. Washington, DC: Island Press. Pp. 131—163.

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

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

Mathre ML, Editor. 1997. *Cannabis in Medical Practice*. Jefferson, NC: MacFarland and Co.

[11] Mechoulam R. 1986. The pharmacohistory of *Cannabis Sativa*. In: Mechoulam R , Editor. *Cannabinoids as Therapeutic Agents*. Boca Raton, FL: CRC Press. Pp. 1—19.

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

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

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

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

[16] Ross SA, Elsohly MA. 1995. Constituents of *Cannabis sativa L.* XXVIII. A review of the natural constituents: 1980—1994. *Zagazig Journal for Pharmaceutical Sciences* 4:1—10.

[17] Taura F, Morimoto S, Shoyama Y. 1995. First direct evidence for the mechanism of delta 1-tetrahydrocannabinolic acid biosysnthesis. *Journal of the American Chemical Society* 117:9766—9767.

[18] Turner CE, Elsohly MA, Boeren EG. 1980. Constituents of *Cannabis sativa L.* XVII. A review of the natural constituents. *Journal of Natural Products* 43:169—234.

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2

Cannabinoids and Animal Physiology

INTRODUCTION

Much has been learned since the publication of the 1982 Institute of Medicine (IOM) report *Marijuana and Health*.[1] Although it was clear then that most of the effects of marijuana were due to its actions on the brain, there was little information about how THC acted on brain cells (neurons), which cells were affected by THC, or even what general areas of the brain were most affected by THC. Too little was known about cannabinoid physiology to offer any scientific insights into the harmful or therapeutic effects of marijuana. That is no longer true. During the past 16 years, there have been major advances in what basic science discloses about the potential medical benefits of cannabinoids, the group of compounds related to THC. Many variants are found in the marijuana plant, and other cannabinoids not found in the plant have been chemically synthesized. Sixteen years ago it was still a matter of debate as to whether THC acted nonspecifically by affecting the fluidity of cell membranes or whether a specific pathway of action was mediated by a receptor that responded selectively to THC (Table 2.1).

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

most likely to yield conclusive results.

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

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

- The most far reaching of the recent advances in cannabinoid biology are the identification of two types of cannabinoid receptors (CB_1 and CB_2) and of anandamide, a substance naturally produced by the body that acts at the cannabinoid receptor and has effects similar to those of THC. The CB_1 receptor is found primarily in the brain and mediates the psychological effects of THC. The CB_2 receptor is associated with the immune system; its role remains unclear.

- The physiological roles of the brain cannabinoid system in humans are the subject of much active research and are not fully known; however, cannabinoids likely have a natural role in pain modulation, control of movement, and memory.

- Animal research has shown that the potential for cannabinoid dependence exists, and cannabinoid withdrawal symptoms can be observed. However, both appear to be mild compared to dependence and withdrawal seen with other drugs.

- Basic research in cannabinoid biology has revealed a variety of cellular pathways through which potentially therapeutic drugs could act on the cannabinoid system. In addition to the known cannabinoids, such drugs might include chemical derivatives of plant-derived cannabinoids or of endogenous cannabinoids such as anandamide but would also include noncannabinoid drugs that act on the cannabinoid system.

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

The Value of Animal Studies

Much of the research into the effects of cannabinoids on the brain is based on animal studies. Many speakers at the public workshops associated with this study argued that animal studies of marijuana are not relevant to humans. Animal studies are not a substitute for clinical trials, but they are a necessary complement. Ultimately, every biologically active substance exerts its effects at the cellular and molecular levels, and the evidence has shown that this is remarkably consistent among mammals, even those as different in body and mind as rats and humans. Animal studies typically provide information about how drugs work that would not be obtainable in clinical studies. A the same time, animal studies can never inform us completely about the full range of psychological and physiological effects of marijuana or cannabinoids on humans.

The Active Constituents of Marijuana

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

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

The most important effect of CBD seems to be its interference with drug metabolism, including Δ^9-THC metabolism in the liver.[14,114] It exerts that effect by inactivating cytochrome P450s, which are the most important class of enzymes that metabolize drugs. Like many P450 inactivators, CBD can also induce P450s after repeated doses.[13] Experiments in which mice were treated with CBD followed by THC showed that CBD treatment was associated with a substantial increase in brain concentrations of THC and its major metabolites, most likely because it decreased the rate of clearance of THC from the body.[15]

In mice, THC inhibits the release of luteinizing hormone, the pituitary hormone that triggers the release of testosterone from the testes; this effect

is increased when THC is given with cannabinol or CBD.

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

The Pharmacological Toolbox

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

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

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

Another key tool involves identifying the receptor protein and determining how it works. That makes it possible to locate where a drug activates its receptor in the brain--both the general region of the brain and the cell type where the receptor is located. The way to find a receptor for a drug in the brain is to make the receptor "visible" by attaching a radioactive or fluorescent marker to the drug. Such markers show where in the brain a drug binds to the receptor, although this is not necessarily the part of the brain where the drug ultimately has its greatest effects.

Because drugs injected into animals must be dissolved in a water-based solution, it is easier to deliver water-soluble molecules than to deliver fat-

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

CANNABINOID RECEPTORS

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

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

CB_1 receptors are extraordinarily abundant in the brain. They are more abundant than most other G protein-coupled receptors and 10 times more abundant than *mu* opioid receptors, the receptors responsible for the effects of morphine.[148]

The cannabinoid receptor in the brain is a protein referred to as CB_1. The peripheral receptor (outside the nervous system), CB_2, is most abundant on cells of the immune system and is not generally found in the

brain. Although no other receptor subtypes have been identified, there is a genetic variant known as CB_1A (such variants are somewhat different proteins that have been produced by the same genes via alternative processing). In some cases, proteins produced via alternative splicing have different effects on cells. It is not yet known whether there are any functional differences between the two, but the structural differences raise the possibility.

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

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

THE ENDOGENOUS CANNABINOID SYSTEM

For any drug for which there is a receptor, the logical question is, "Why does this receptor exist?" The short answer is that there is probably an endogenous agonist (that is, a compound that is naturally produced in the brain) that acts on that receptor. The long answer begins with a search for such compounds in the area of the body that produces the receptors and ends with a determination of the natural function of those compounds. So far, the search has yielded several endogenous compounds that bind

selectively to cannabinoid receptors. The best studied of them are anandamide[37] and arachidonyl glycerol (2-AG).[108] However, their physiological roles are not yet known.

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

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

Anandamide

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

Anandamide appears to have both central (in the brain) and peripheral (in the rest of the body) effects. The precise neuroanatomical localization of anandamide and the enzymes that synthesize it are not yet known. This information will provide essential clues to the natural role of anan-damide and an understanding of the brain circuits in which it is a neurotransmitter. The importance of knowing specific brain circuits that involve anandamide (and other endogenous cannabinoid ligands) is that such circuits are the pivotal elements for regulating specific brain functions, such as mood, memory, and cognition. Anandamide has been found in numerous regions of the human brain: hippocampus (and parahippocampic cortex), striatum, and cerebellum; but it has not been precisely identified with specific neuronal circuits. CB_1 receptors are abundant in these regions, and this further implies a physiological role for endogenous cannabinoids in the brain functions controlled by these areas. But substantial concentrations of anandamide are also found in the thalamus, an area of the brain that has

relatively few CB_1 receptors.

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

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

The molecular structure of anandamide is relatively simple, and it can be formed from arachidonic acid and ethanolamine. Arachidonic acid is a common precursor of a group of biologically active molecules known as eicosanoids, including prostaglandins.[3] Although anandamide can be synthesized in a variety of ways, the physiologically relevant pathway seems to be through enzymatic cleavage of *N*-arachidonyl-phosphatidyl-ethanolamine (NAPE), which yields anandamide and phosphatidic acid (reviewed by Childers and Breivogel[27]).

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

Other Endogenous Agonists

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

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

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

Some effects of cannabinoid agonists are receptor independent. For

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

Novel Targets for Therapeutic Drugs

Drugs that alter the natural biology of anandamide or other endogenous cannabinoids might have therapeutic uses (Table 2.4). For example, drugs that selectively inhibit neuronal uptake of anandamide would increase the brain's own natural cannabinoids, thereby mimicking some of the effects of THC. A number of important psychotherapeutic drugs act by inhibiting neurotransmitter uptake. For example, antidepressants like fluoxetine (Prozac) inhibit serotonin uptake and are known as selective serotonin reuptake inhibitors, or SSRIs. Another way to alter levels of endogenous cannabinoids would be to develop drugs that act on the enzymes involved in anandamide synthesis. Some antihypertensive drugs work by inhibiting enzymes involved in the synthesis of endogenous hypertensive agents. For example, anti-converting enzyme (ACE) inhibitors are used in hypertensive patients to interfere with the conversion of angiotensin I, which is inactive, to the active hormone, angiotensin II.

SITES OF ACTION

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

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

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

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

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

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

CANNABINOID RECEPTORS AND BRAIN FUNCTIONS

Motor Effects

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

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

Cannabinoids decrease both the inhibitory and stimulatory inputs to the substantia nigra and therefore might provide dual regulation of movement at this nucleus. In the substantia nigra, cannabinoids decrease transmission from both the striatum and the subthalamic nucleus.[141] The globus pallidus

has been implicated in mediating the cataleptic effects of large doses of cannabinoids in rats.[126] (Catalepsy is a condition of diminished responsiveness usually characterized by trancelike states and waxy rigidity of the muscles.) Several other brain regions--the cortex, the cerebellum, and the neural pathway from cortex to striatum--are also involved in the control of movement and contain abundant cannabinoid receptors.[52,59,101] They are therefore possible additional sites that might underlie the effects of cannabinoids on movement.

Memory Effects

One of the primary effects of marijuana in humans is disruption of short-term memory.[68] That is consistent with the abundance of CB_1 receptors in the hippocampus, the brain region most closely associated with memory. The effects of THC resemble a temporary hippocampal lesion.[63] Deadwyler and colleagues have demonstrated that cannabinoids decrease neuronal activity in the hippocampus and its inputs.[23,24,83] *In vitro*, several cannabinoid ligands and endogenous cannabinoids can block the cellular processes associated with memory formation.[29,30,116,157,163] Furthermore, cannabinoid agonists inhibit release of several neurotransmitters: acetylcholine from the hippocampus,[49-51] norepinephrine from human and guinea pig (but not rat or mouse) hippocampal slices,[143] and glutamate in cultured hippocampal cells.[144] Cholinergic and noradrenergic neurons project into the hippocampus, but circuits within the hippo-campus are glutamatergic.[4] Thus, cannabinoids could block transmission both into and within the hippocampus by blocking presynaptic neurotransmitter release.

Pain

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

Behavioral Studies

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

Cannabinoids are also effective in rodent models of chronic pain. Herzberg and co-workers found that cannabinoids can block allodynia and hyperalgesia associated with neuropathic pain in rats.[62] This is an

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

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

Neural Sites of Altered Responsiveness to Painful Stimuli

The brain and spinal cord mediate cannabinoid analgesia. A number of brain areas participate in cannabinoid analgesia and support the role of descending pathways (neural pathways that project from the brain to the spinal cord).[103,104] Although more work is needed to produce a comprehensive map of the sites of cannabinoid analgesia, it is clear that the effects are limited to particular areas, most of which have an established role in pain.

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

Neurophysiology and Neurochemistry of Cannabinoid Analgesia

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

Endogenous Cannabinoids Modulate Pain

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

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

CHRONIC EFFECTS OF THC

Most substances of abuse produce tolerance, physical dependence, and withdrawal symptoms. *Tolerance* is the most common response to repetitive use of a drug and is the condition in which, after repeated exposure to a drug, increasing doses are needed to achieve the same effect. *Physical dependence* develops as a result of a resetting of homeostatic

mechanisms in response to repeated drug use. Tolerance, dependence, and withdrawal are not peculiar to drugs of abuse. Many medicines that are not addicting can produce these types of effects; examples of such medications include clonidine, propranolol, and tricyclic antidepressants. The following sections discuss what is known about the biological mechanisms that underlie tolerance, reward, and dependence; clinical studies about those topics are discussed in chapter 3.

Tolerance

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

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

Most studies have found that brain cannabinoid receptor concentrations usually decrease after prolonged exposure to agonists,[42,119,136,138] although some studies have reported increases[137] or no changes[2] in receptor binding in brain. Differences among studies could be due to the particular agonist tested, the assay used, the brain region examined, or the treatment time. For example, the THC analogue, levonantradol, produces a greater desensitization of adenylyl cyclase inhibition than does THC in cultured neuroblastoma cells.[40] This might be explained by differences in efficacy between these two agonists.[18,147] A time course study revealed differences among brain regins in the rates and magnitudes of receptor down regulation.[16] Those findings suggest that tolerance to different effects of cannabinoids develops at different rates.

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

It is difficult to extend the findings of short-term animal studies to

human marijuana use. To simulate long-term use, higher doses are used in animal studies than are normally achieved by smoking marijuana. For example, the average human will feel "high" after injection of THC at a level of 0.06 mg/kg,[118] compared with the 10—20 mg/kg per day used in many chronic rat studies. At the same time, doses of marijuana needed to observe behavioral changes in rats (usually changes in locomotor behavior) are substantially higher than doses at which people feel "high." The pharmacokinetics of THC distribution in the body are also dramatically different between rats and humans and depend heavily on whether it is inhaled, injected, or swallowed. It is likely that some of the same biochemical adaptations to chronic cannabinoid administration occur in laboratory animals and humans, but the magnitude of the effects in humans might be less than that in animals in proportion to the doses used.

Reward and Dependence

Experimental animals that are given the opportunity to self-administer cannabinoids generally do not choose to do so, which has led to the conclusion that they are not reinforcing and rewarding.[38] However, behavioral[95] and brain stimulation[64] studies have shown that THC can be rewarding to animals. The behavioral study used a "place preference" test, in which an animal is given repeated doses of a drug in one place, and is then given a choice between a place where it received the drug and a place where it did not. The animals chose the place where they received the THC. These rewarding effects are highly dose dependent. In all models studied, cannabinoids are only rewarding at midrange; doses that are too low are not rewarding; doses that are too high can be aversive. Mice will self-administer the cannabinoid agonist WIN 55,212-2 but only at low doses.[106] This effect is specifically mediated by CB_1 receptors and indicates that stimulation of those receptors is rewarding to the mice. Antagonism of cannabinoid receptors is also rewarding in rats; in conditioned place preference tests, animals show a preference for the place they receive the cannabinoid antagonist SR 141716A at both low and high doses.[140] Cannabinoids increase dopamine concentrations in the mesolimbic dopamine system of rats, a pathway associated with reinforcement.[25,30,161] However, the mechanism by which THC increases dopa-mine concentrations appears to be different from that of other abused drugs[51] (see chapter 3 for further discussion of reinforcement). THC-induced increases in dopamine are due to increases in the firing rate of dopamine cells in the ventral tegmental area by Δ^9-THC.[47] However, these increases in firing rate in the ventral tegmental area could not be explained by increases in the firing of the A10 dopamine cell group, where other abused drugs have been shown to act.[51]

Physical dependence on cannabinoids has been observed only under experimental conditions of "precipitated withdrawal" in which animals are first treated chronically with cannabinoids and then given the CB_1 antagonist SR 141716A.[3,166] The addition of the antagonist accentuates

any withdrawal effect by competing with the agonist at receptor sites; that is, the antagonist helps to clear agonists off and keep them off receptor sites. This suggests that, under normal cannabis use, the long half-life and slow elimination from the body of THC and the residual bioactivity of its metabolite, 11-OH-THC, can prevent substantial abstinence symptoms. The precipitated withdrawal produced by SR 141716A has some of the characteristics of opiate withdrawal, but it is not affected by opioid antagonists, and it affects motor systems differently. An earlier study with monkeys also suggested that abrupt cessation of chronic THC is associated with withdrawal symptoms.[8] Monkeys in that study were trained to work for food after which they were given THC on a daily basis; when the investigators stopped administering THC, the animals stopped working for food.

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

CANNABINOIDS AND THE IMMUNE SYSTEM

The human body protects itself from invaders, such as bacteria and viruses through the elaborate and dynamic network of organs and cells referred to as the immune system. Cannabinoids, especially THC, can modulate the function of immune cells in various ways--in some cases enhancing and in others diminishing the immune response[85] (summarized in Table 2.7). However, the natural function of cannabinoids in the immune system is not known. Immune cells respond to cannabinoids in a variety of ways, depending on such factors as drug concentration, timing of drug delivery to leukocytes in relation to antigen stimulation, and type of cell function. Although the chronic effects of cannabinoids on the immune system have not been studied, based on acute exposure studies in experimental animals it appears that THC concentrations that modulate immunological responses are higher than those required for psychoactivity.

The CB_2 receptor gene, which is not expressed in the brain, is particularly abundant in immune tissues, with an expression level 10—100 times higher than that of CB_1. In spleen and tonsils the CB_2 mRNA[5] content is equivalent to that of CB_1 mRNA in the brain.[48] The rank order, from high to low, of CB_2 mRNA levels in immune cells is B-cells > natural killer cells >> monocytes > polymorphonuclear neutrophil cells > T8 cells > T4 cells. In tonsils the CB_2 receptors appear to be restricted to B-lymphocyte-enriched areas. In contrast, CB_1 receptors are mainly expressed in the central nervous system and, to a lesser extent, in several peripheral tissues such as adrenal gland, heart, lung, prostate, uterus, ovary, testis, bone marrow, thymus, and tonsils.

Cannabinoid Receptors and Intracellular Action in Immune Cells

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

Ligand binding to either CB_1 or CB_2 inhibits adenylate cyclase, an enzyme that is responsible for cAMP production and is, thus, an integral aspect of intracellular signal transduction (see Figure 2-3).[53,79,91,122,139,151,167] Increases in intracellular cAMP concentrations lead to immune enhancement, and decreases lead to an inhibition of the immune response.[77] Cannabinoids inhibit the rise in intracellular cAMP that normally results from leukocyte activation, and this might be the pathway through which cannabinoids suppress immune cell functions.[28,74,167] In addition, cannabinoids activate other molecular pathways such as the nuclear factor-kB pathway, and therefore these signals might be modified in drug-treated immune cells.[53,74]

T and B Cells

When stimulated by antigen, lymphocytes (see Box 2-1) first proliferate and then mature or differentiate to become potent effector cells, such as B cells that release antibodies or T cells that release cytokines. The normal T-cell proliferation that is seen when human lymphocytes and mouse splenocytes (spleen cells) are exposed to antigens and mitogens[6] can be inhibited by THC, 11-OH-THC, cannabinol, and 2-AG, as well as synthetic cannabinoid agonists such as CP 55,940; WIN 55,212-2; and HU-210.[61,89,93,99,127,155] In contrast, one study testing anandamide

revealed little or no effect on T cell proliferation.

However, these drug effects are variable and depend on experimental conditions, such as the experimental drug dose used, the mitogen used, the percentage of serum in the culture, and the timing of cannabinoid drug exposure. In general, lower doses of cannabinoids increase proliferation and higher doses suppress proliferation. Doses that are effective in suppressing immune function are typically greater than 10 μM in cell culture studies and greater than 5 mg/kg in whole-animal studies.[85] By comparison, at 0.05 mg/kg, people will experience the full psychoactive effects of THC; however, because of their high metabolic rates, small rodents frequently require drug doses that are 100-fold higher than doses needed for humans to achieve comparable drug effects. Thus, the immune effects of doses of cannabinoids higher than those ever experienced by humans should be interpreted with caution.[93]

As with T cells, B cell proliferation can be suppressed by various cannabinoids, such as THC, 11-OH-THC, and 2-AG, but B cell proliferation is more inhibited at lower drug concentrations than T cell proliferation.[89,93] Conversely, low doses of THC, CP 55,940 and WIN 55,212-2 *increase* B cell proliferation in cultured human cells exposed to mitogen.[35] This effect possibly involves the CB_2 receptor, because the effect appears to be the same when the CB_1 receptor was blocked by the antagonist SR 141716A (which does not block the CB_2 receptor). The reason for the differences in B cell responsiveness to cannabinoids is probably due to differences in cell type and source; for example, B cells collected from mouse spleen might respond to cannabinoids somewhat differently than B cells from human tonsils

Natural Killer Cells

Repeated injections of relatively low doses of THC (3 mg/kg/day[121,7]) or two injections of a high dose (40 mg/kg[80]) suppress the ability of NK cells to destroy foreign cells in rats and mice. THC can also suppress cytolytic activity of the NK cells in cell cultures; 11-OH-THC is even more potent.[86] In contrast, THC concentrations below 10 μM had no effect on NK cell activity in mouse cell cultures.[98]

Macrophages

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

Cytokines

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

Some cytokines, such as interferon-γ and interleukin-2 (IL-2), are produced by T helper-1 (Th1) cells. These cytokines help to activate cell-mediated immunity and the killer cells that eliminate microorganisms from the body (see Box 2.1). When injected into mice, THC suppresses the production of those cytokines that modulate the host response to infection (see below).[115] Cannabinoids also modulate interferons induced by viral infection,[21] as well as other interferon inducers.[85] Furthermore, in human cell cultures, interferon production can be increased by low concentrations but decreased by high concentrations of either THC or CBD.[168] In addition to Th1 cytokines, cannabinoids modulate the production of cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and interleukin-6 (IL-6).[145,179] At 8 mg/kg, THC can increase the *in vivo* mobilization of serum acute-phase cytokines, including IL-1, TNF, and IL-6.[80] Finally, although these studies suggest that cannabinoids can induce an increase in cytokines, other studies suggest that they can also suppress cytokine production.[85] The different results might be due to different cell culture conditions or because different cell lines were studied.

Antibody Production

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

Resistance to Infection in Animals Exposed to Cannabinoids

Evaluation of bacterial infections in mice that received injections of THC can suppress resistance to infection, although the effect depends on the dose and timing of drug administration. Mice pretreated with THC (8 mg/kg) one day before infection with a sublethal dose of the pneumonia-causing bacteria *Legionella pneumophilia* and then treated again one day after the infection with THC developed symptoms of cytokine-mediated

septic shock and died; control mice that were not pretreated with THC became immune to repeated infection and survived the bacterial challenge.[90] If only one injection of THC was given or doses less than 5 mg/kg were used, all the mice survived the initial infection but failed to survive later challenge with a lethal dose of the bacteria; hence, these m failed to develop immune memory in response to the initial sublethal infection.[87] Note that these are very high doses and are considerably higher than doses experienced by marijuana users (see Figure 3.1).[115] In rats, doses of 4.0 mg/kg THC are aversive.[95]

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

Antiinflammatory Effects

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

It is interesting to note that two reports of cannabinoid-induced analgesia are based on the ability of the endogenous cannabinoids, anan-

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

Conclusions Regarding Effects on the Immune System

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

Cannabinoids affect multiple cellular targets in the immune system and a variety of effector functions. Many of the effects noted above appear to occur at concentrations over 5 μM *in vitro* and over 5 μg/kg *in vivo*.[8] By comparison, a 5-mg injection of THC into a person (about 0.06 mg/kg) is enough to produce strong psychoactive effects. It should be emphasized, however, that little is known about the immune effects of chronic low-dose exposure to cannabinoids.

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

CONCLUSIONS AND RECOMMENDATIONS

Given the progress of the past 15 years in understanding the effects of cannabinoids, research in the next decade is likely to reveal even more. It is interesting to compare how little we know about cannabinoids with how much we know about opiates. Table 2.8 suggests good reason for optimism about the future of cannabinoid drug development. Now that many of the basic tools of cannabinoid pharmacology and biology have been developed, one can expect to see rapid advances that can begin to match what is known of opiate systems in the brain.

Despite the tremendous progress in understanding the pharmacology and neurobiology of brain cannabinoid systems, this field is still in its early developmental stages. A key focus for future study is the neurobiology of endogenous cannabinoids; establishing the precise brain localization (in which cells and where) of cannabinoids, cellular storage and release mechanisms, and uptake mechanisms will be crucial in determining the biological role of this system. Technology needed to establish the

biological significance of these systems will be broad based and include such research tools as the transgenic or gene knockout mice, as has already been accomplished for various opioid-receptor types.[26] In 1997, both CB_1 and CB_2 knockout mice were generated by a team of scientists at the National Institutes of Health, and a group in France has developed another strain of CB_1 knockout mice.[92]

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

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

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

Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.

The natural role of cannabinoids in immune systems is likely multi-faceted and remains unclear.

The brain develops tolerance to cannabinoids.

Animal research has demonstrated the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.

Withdrawal symptoms can be observed in animals but appear mild compared with those of withdrawal from opiates or benzodiazepines, such as diazepam (Valium).

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

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

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

REFERENCES

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

[2] Abood ME, Sauss C, Fan F, Tilton CL, Martin BR. 1993. Development of behavioral tolerance to delta 9-THC without alteration of cannabinoid receptor binding or mRNA levels in whole brain. *Pharmacology, Biochemistry and Behavior* 46:575—579.

[3] Aceto MD, Scates SM, Lowe JA, Martin BR. 1995. Cannabinoid precipitated withdrawal by the selective cannabinoid receptor antagonist, SR 141716A. *European Journal of Pharmacology* 282:R1—R2.

[4] Adams IB, Martin BR. 1996. Cannabis: Pharmacology and toxicology in animals and humans. *Addiction* 91:1585—1614.

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

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

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

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

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

Journal of Pharmacology 353:23—31.

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

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

[12] Bloom AS, Dewey WL, Harris LS, Brosius KK. 1977. 9-nor-9b-hydroxyhexa-hydrocannabinol, a ca abinoid with potent antinociceptive activity: Comparisons with morphine. *Journal of Pharmacology and Experimental Therapeutics* 200:263—270.

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

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

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

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

[17] British Medical Association. 1997. *Therapeutic Uses of Cannabis*. Amsterdam, The Netherlands: Harwood Academic Publishers.

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

[19] Buxbaum DM. 1972. Analgesic activity of Δ^9-tetrahydrocannabinol in the rat and mouse. *Psychopharmacology* 25:275—280.

[20] Cabral GA , Dove Pettit DA. 1998. Drugs and immunity: Cannabinoids and their role in decreased resistance to infectious disease. *Journal of Neuroimmunology* 83:116—123.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[38] Dewey WL. 1986. Cannabinoid pharamacology. *Pharmacology Review* 38:151—178.

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

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

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

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

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

[44] Felder CC, Nielsen A, Briley EM, Palkovits M, Priller J, Axelrod J, Nguyen DN, Richardson JM, Riggin RM, Koppel GA, Paul SM, Becker GW. 1996. Isolation and measurement of the endogenous cannabinoid receptor agonist, anandamide, in brain and peripheral tissues of human and rat. *FEBS Letters* 393:231—235.

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

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

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

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

[49] Gessa GL, Mascia MS, Casu MA, Carta G. 1997. Inhibition of hippocampal acetylcholine release by cannabinoids: Reversal by SR 141716A. *European Journal of Pharmacology* 327:R1—R2.

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

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

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

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

[54] Hampson AJ, Grimaldi M, Axelrod J, Wink D. 1998. Cannabidiol and (-)delta-9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Acade of Sciences, USA* 95:8268—8273.

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

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

[57] Herkenham M. 1995. Localization of cannabinoid receptors in brain and periphery. In: Pertwee RG, Editor, *Cannabinoid Receptors*. New York: Academic Press. Pp. 145—166.

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

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

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

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

[62] Herzberg U, Eliav E, Bennett GJ, Kopin IJ. 1997. The analgesic effects of R(+)-WIN 55,212-2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. *Neuroscience Letters* 221:157—160.

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

[64] Hohmann AG, Briley EM, Herkenham M. 1999. Pre- and postsynaptic distribution of cannabinoid and mu opioid receptors in rat spinal cord. *Brain Research* 822:17—25.

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

[66] Hohmann AG, Herkenham M. 1999. Localization of central cannabinoid CB1 receptor mRNA in neuronal subpopulations of rat dorsal root ganglia: A double-label *in situ* hybridization study. *Neuroscience* 90:923—931.

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

[68] Hollister LE. 1986. Health aspects of cannabis. *Pharmacological Reviews* 38 —20.

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

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

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

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

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

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

[75] Johnson MR, Melvin LS. 1986. The discovery of non-classical cannabinoid analgesics. In: Mechoulam R, Editor, *Cannabinoids as Therapeutic Agents*. Boca Raton, FL: CRC Press, Inc. Pp. 121—145.

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

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

[78] Kaminski NE, Abood ME, Kessler FK, Martin BR, Schatz AR. 1992. Identification of a functionally relevant cannabinoid receptor on mouse spleen cells that is involved in cannabinoid-mediated immune modulation. *Molecular Pharmacology* 42:736—742.

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

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

[81] Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carli..i EA. 1975. Cannabidiol interferes with the effects of delta-9-tetrahydrocannbinol in man. *Eu.opean Journal of Pharmacology* 28:172—177.

[82] Kieffer BL, Befort K, Gaveriaux-Ruff C, Hirth CG. 1992. The delta-opioid receptor: Isolation of a cDNA by expression cloning and pharmacological characterization. *Proceedings of the National Academy of Sciences, USA* 89:12048—12052.

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

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

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

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

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

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

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

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

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

[92] Ledent C , Valverde O, Cossu G, Petitet F, Aubert JF, Beslot F, Bohme GA, Imperato A, Pedrazzini T, Roques BP, Vassart G, Fratta W, Parmentier M. 1999. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. *Science* 283:401—404.

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

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

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

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

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

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

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

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

[101] Mailleux P, Vanderhaeghen JJ. 1992. Distribution of neuronal cannabinoid receptor in the adult rat brain: A comparative receptor binding radioautography and *in situ* hybridization

histochemistry. *Neuroscience* 48:655—668.

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

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

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

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

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

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

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

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

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

[111] Miller AS, Walker JM. 1996. Electrophysiological effects of a cannabinoid on neural activity in the globus pallidus. *European Journal of Pharmacology* 304:29—35.

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

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

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

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

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

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

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

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

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

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

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

[123] Pert CB, Snyder SH. 1973. Opiate receptor: Demonstration in nervous tissue. *Science* 179:1011—1014.

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

[125] Pertwee RG, Stevenson LA, Griffin G. 1993. Cross-tolerance between delta-9-tetrahydrocannabinol and the cannabimimetic agents, CP 55,940, WIN 55,212-2 and anandamide [published erratum appears in *British Journal of Pharmacology*, 1994, 111(3):968]. *British Journal of Pharmacology* 110:1483—1490.

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

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

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

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

[130] Richardson JD, Aanonsen L, Hargreaves KM. 1998. Hypoactivity of the spinal

cannabinoid system results in NMDA-dependent hyperalgesia. *Journal of Neuroscience* 18:451—457.

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

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

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

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

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

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

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

[138] Romero J, Garcia-Palomero E, Castro JG, Garcia-Gil L, Ramos JA, Fernandez-Ruiz JJ. 1997. Effects of chronic exposure to delta-9-tetrahydrocannabinol on cannabinoid receptor binding and mRNA levels in several rat brain regions. *Molecular Brain Research* 46:100—108.

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

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

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

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

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

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

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

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

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

[148] Sim LJ, Xiao R, Selley DE, Childers SR. 1996. Differences in G-protein activation by mu- and delta-opioid, and cannabinoid, receptors in rat striatum. *European Journal of Pharmacology* 307:97—105.

[149] Simon EJ. 1973. In search of the opiate receptor. *American Journal of Medical Sciences* 266:160—168.

[150] Skaper SD, Buriani A, Dal Toso R, Petrelli L, Romanello S, Facci L, Leon A. 1996. The ALIAmide palmitoylethanolamide and cannabinoids, but not anandamide, are protective in a delayed postglutamate paradigm of excitotoxic death in cerebellar granule neurons. *Proceedings of the National Academy of Sciences, USA* 93:3984—3989.

[151] Smith JW, Steiner AL, Newberry WM, Parker CW. 1971. Cyclic adenosine 3',5'-monophosphate in human lymphocytes: Alteration after phytohemagglutinin. *Journal of Clinical Investigation* 50:432—441.

[152] Smith PB, Compton DR, Welch SP, Razdan RK, Mechoulam R, Martin BR. 1994. The pharmacological activity of anandamide, a putative endogenous cannabinoid, in mice. *Journal of Pharmacology and Experimental Therapeutics* 270:219—227.

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

[154] Sofia RD, Nalepa SD, Harakal JJ, Vassar HB. 1973. Anti-edema and analgesic properties of delta-9-tetrahydrocannabinol (THC). *Journal of Pharmacology and Experimental Therapeutics* 186:646—655.

[155] Specter S, Lancz G, Hazelden J. 1990. Marijuana and immunity: Tetrahydrocannabinol mediated inhibition of lymphocyte blastogenesis. *International Journal of Immunopharmacology* 12:261—267.

[156] Stefano G, Salzet B, Salzet M. 1997. Identification and characterization of the leech CNS cannabinoid receptor: Coupling to nitric oxide release. *Brain Research* 753:219—224.

[157] Stella N, Schweitzer P, Piomelli D. 1997. A second endogenous cannabinoid that modulates long term potentiation. *Nature* 388:773—778.

[158] Strangman NM, Patrick SL, Hohmann AG, Tsou K, Walker JM. 1998. Evidence for a role of endogenous cannabinoids in the modulation of acute and tonic pain sensitivity. *Brain Research* 813:323—328.

[159] Sulcova E, Mechoulam R, Fride E. 1998. Biphasic effects of anandamide. *Pharmacology, Biochemistry and Behavior* 59:347—352.

[160] Szabo B, Dorner L, Pfreundtner C, Norenberg W, Starke K. 1998. Inhibition of GABAergic inhibitory postsynaptic currents by cannabinoids in rat corpus striatum. *Neuroscience* 85:395—403.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[175] Yoshida H, Usami N, Ohishi Y, Watanabe K, Yamamoto I, Yoshimura H. 1995. Synthesis and pharmacological effects in mice of halogenated cannabinol derivatives. *Chemical and Pharmaceutical Bulletin* 42:355—337.

[176] Zhu W, N[illegible]ton C, Daaka Y, Friedman H, Klein TW. 1994. Delta 9-tetrahydrocan[illegible]binol enhances the secretion of interleukin 1 from endotoxin-stimulated macrophages. *Journal of Pharmacology and Experimental Therapeutics* 270:1334—1339.

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

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

Notes

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

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

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

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

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

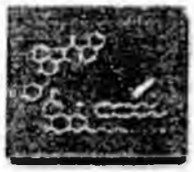
[6] Mitogens are substances that stimulate cell division (mitosis) and cell transformation.

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

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

3

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



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

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

THE MARIJUANA "HIGH"

The most commonly reported effects of smoked marijuana are a sense of well-being or euphoria and increased talkativeness and laughter alternating with periods of introspective dreaminess followed by lethargy and sleepiness (see reviews by Adams and Martin, 1996,[1] Hall and Solowij,[59] and Hall et al. [60]). A characteristic feature of a marijuana "high" is a distortion in the sense of time associated with deficits in short-term memory and learning. A marijuana smoker typically has a sense of enhanced physical and emotional sensitivity, including a feeling of greater interpersonal closeness. The most obvious behavioral abnormality displayed by someone under the influence of marijuana is difficulty in carrying on an intelligible conversation, perhaps because of an inability to remember what was just said even a few words earlier.

The high associated with marijuana is not generally claimed to be integral to its therapeutic value. But mood enhancement, anxiety reduction,

and mild sedation can be desirable qualities in medications--particularly for patients suffering pain and anxiety. Thus, although the psychological effects of marijuana are merely side effects in the treatment of some symptoms, they might contribute directly to relief of other symptoms. They also must be monitored in controlled clinical trials to discern which effect of cannabinoids is beneficial. These possibilities are discussed later under the discussions of specific symptoms in chapter 4.

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

Adverse Mood Reactions

Although euphoria is the more common reaction to smoking marijuana, adverse mood reactions can occur. Such reactions occur most frequently in inexperienced users after large doses of smoked or oral marijuana. They usually disappear within hours and respond well to reassurance and a supportive environment. Anxiety and paranoia are the most common acute adverse reactions;[59] others include panic, depression, dysphoria, depersonalization, delusions, illusions, and hallucinations.[1,40,66,69] Of regular marijuana smokers, 17% report that they have experienced at least one of the symptoms, usually early in their use of marijuana.[145] Those observations are particularly relevant for the use of medical marijuana in people who have not previously used marijuana.

DRUG DYNAMICS

There are many misunderstandings about drug abuse and dependence (see reviews by O'Brien[114] and Goldstein[54]). The terms and concepts used in this report are as defined in the most recent *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*),[3] the most influential system in the United States for diagnoses of mental disorders, including substance abuse (see Box 3.1). Tolerance, dependence, and withdrawal are often presumed to imply abuse or addiction, but this is not the case. Tolerance and dependence are *normal* physiological adaptations to repeated use of any drug. The correct use of prescribed medications for pain, anxiety, and even hypertension commonly produces tolerance and some measure of physiological dependence.

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

Because it is an illegal substance, some people consider any use of

marijuana as substance abuse. However, this report uses the medical definition; that is, substance abuse is a maladaptive pattern of repeated substance use manifested by recurrent and significant adverse consequences.[3] Substance abuse and dependence are both diagnoses of pathological substance use. Dependence is the more serious diagnosis and implies compulsive drug use that is difficult to stop despite significant substance-related problems (see Box 3.2).

Reinforcement

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

As an argument to dispute the abuse potential of marijuana, some have cited the observation that animals do not willingly self-administer THC, as they will cocaine. Even if that were true, it would not be relevant to human use of marijuana. The value in animal models of drug self-administration is not that they are necessary to show that a drug is reinforcing but rather that they provide a model in which the effects of a drug can be studied. Furthermore, THC is indeed rewarding to animals at some doses but, like many reinforcing drugs, is aversive at high doses (4.0 mg/kg).[93] Similar effects have been found in experiments conducted in animals outfitted with intravenous catheters that allow them to self-administer WIN 55,212, a drug that mimics the effects of THC.[100]

A specific set of neural pathways has been proposed to be a "reward system" that underlies the reinforcement of drugs of abuse and other pleasurable stimuli.[51] Reinforcing properties of drugs are associated with their ability to increase concentrations of particular neurotransmitters in areas that are part of the proposed brain reward system. The median forebrain bundle and the nucleus accumbens are associated with brain reward pathways.[88] Cocaine, amphetamine, alcohol, opioids, nicotine, and THC[144] all increase extracellular fluid dopamine in the nucleus accumbens region (reviewed by Koob and Le Moal[88] and Nestler and Aghajanian[130] in 1997). However, it is important to note that brain reward systems are not strictly "drug reinforcement centers." Rather, their biological role is to respond to a range of positive stimuli, including sweet foods and sexual attraction.

Tolerance

The rate at which tolerance to the various effects of any drug develops is an important consideration for its safety and efficacy. For medical use, tolerance to some effects of cannabinoids might be desirable. Differences in the rates at which tolerance to the multiple effects of a drug develops can be dangerous. For example, tolerance to the euphoric effects of heroin develops faster than tolerance to its respiratory depressant effects, so heroin users tend to increase their daily doses to reach their desired level of euphoria, thereby putting themselves at risk for respiratory arrest. Because tolerance to the various effects of cannabinoids might develop at different rates, it is important to evaluate independently their effects on mood, motor performance, memory, and attention, as well as any therapeutic use under investigation.

Tolerance to most of the effects of marijuana can develop rapidly after only a few doses, and it also disappears rapidly. Tolerance to large doses has been found to persist in experimental animals for long periods after cessation of drug use. Performance impairment is less among people who use marijuana heavily than it is among those who use marijuana only occasionally,[29,104,124] possibly because of tolerance. Heavy users tend to reach higher plasma concentrations of THC than light users after similar doses of THC, arguing against the possibility that heavy users show less performance impairment because they somehow absorb less THC (perhaps due to differences in smoking behavior).[95]

There appear to be variations in the development of tolerance to the different effects of marijuana and oral THC. For example, daily marijuana smokers participated in a residential laboratory study to compare the development of tolerance to THC pills and to smoked marijuana.[61,62] One group was given marijuana cigarettes to smoke four times per day for four consecutive days; another group was given THC pills on the same schedule. During the four-day period, both groups became tolerant to feeling "high" and what they reported as a "good drug effect." In contrast, neither group became tolerant to the stimulatory effects of marijuana or THC on appetite. "Tolerance" does not mean that the drug no longer produced the effects but simply that the effects were less at the end than at the beginning of the four-day period. The marijuana smoking group reported feeling "mellow" after smoking and did not show tolerance to this effect; the group that took THC pills did not report feeling "mellow." The difference was also reported by many people who described their experiences to the IOM study team.

The oral and smoked doses were designed to deliver roughly equivalent amounts of THC to a subject. Each smoked marijuana dose consisted of five 10-second puffs of a marijuana cigarette containing 3.1% THC; the pills contained 30 mg of THC. Both groups also received placebo drugs during other four-day periods. Although the dosing of the two groups was comparable, different routes of administration resulted in different patterns of drug effect. The peak effect of smoked marijuana is usually felt within

minutes and declines sharply after 30 minutes ; the peak effect of oral THC is usually not felt until about an hour and lasts for several hours.[118]

Withdrawal

A distinctive marijuana and THC withdrawal syndrome has been identified, but it is mild and subtle compared with the profound physical syndrome of alcohol or heroin withdrawal.[31,74] The symptoms of marijuana withdrawal include restlessness; irritability, mild agitation, insomnia, sleep EEG disturbance, nausea, and cramping (Table 3.2). In addition to those symptoms, two recent studies noted several more. A group of adolescents under treatment for conduct disorders also reported fatigue and illusions or hallucinations after marijuana abstinence (this study is discussed further in the section on "Prevalence and Predictors of Dependence on Marijuana and Other Drugs").[31] In a residential study of daily marijuana users, withdrawal symptoms included sweating and runny nose, in addition to those listed above.[62] A marijuana withdrawal syndrome, however, has been reported only in a group of adolescents in treatment for substance abuse problems[31] and in a research setting where subjects were given marijuana or THC daily.[62,74]

Withdrawal symptoms have been observed in carefully controlled laboratory studies of people after use of both oral THC and smoked marijuana.[61,62] In one study, subjects were given very high doses of oral THC: 180—210 mg per day for 10—20 days, roughly equivalent to smoking 9—10 2% THC cigarettes per day.[74] During the abstinence period at the end of the study, the study subjects were irritable and showed insomnia, runny nose, sweating, and decreased appetite. The withdrawal symptoms, however, were short lived. In four days they had abated. The time course contrasts with that in another study in which lower doses of oral THC were used (80—120 mg/day for four days) and withdrawal symptoms were still near maximal after four days.[61,62]

In animals, simply discontinuing chronic heavy dosing of THC does not reveal withdrawal symptoms, but the "removal" of THC from the brain can be made abrupt by another drug that blocks THC at its receptor if administered when the chronic THC is withdrawn. The withdrawal syndrome is pronounced, and the behavior of the animals becomes hyperactive and disorganized.[153] The half-life of THC in brain is about an hour.[16,24] Although traces of THC can remain in the brain for much longer periods, the amounts are not physiologically significant. Thus, the lack of a withdrawal syndrome when THC is abruptly withdrawn without administration of a receptor-blocking drug is probably not due to a prolonged decline in brain concentrations.

Craving

Craving, the intense desire for a drug, is the most difficult aspect of

addiction to overcome. Research on craving has focused on nicotine, alcohol, cocaine, and opiates but has not specifically addressed marijuana.[115] Thus, while this section briefly reviews what is known about drug craving, its relevance to marijuana use has not been established.

Most people who suffer from addiction relapse within a year of abstinence, and they often attribute their relapse to craving.[58] As addiction develops, craving increases even as maladaptive consequences accumulate. Animal studies indicate that the tendency to relapse is based on changes in brain function that continue for months or years after the last use of the drug.[115] Whether neurobiological conditions change during the manifestation of an abstinence syndrome remains an unanswered question in drug abuse research.[88] The "liking" of sweet foods, for example, is mediated by opioid forebrain systems and by brain stem systems, whereas "wanting" seems to be mediated by ascending dopamine neurons that project to the nucleus accumbens.[109]

Anticraving medications have been developed for nicotine and alcohol. The antidepressant, bupropion, blocks nicotine craving, while naltrexone blocks alcohol craving.[115] Another category of addiction medication includes drugs that block other drugs' effects. Some of those drugs also block craving. For example, methadone blocks the euphoric effects of heroin and also reduces craving.

MARIJUANA USE AND DEPENDENCE

Prevalence of Use

Millions of Americans have tried marijuana, but most are not regular users. In 1996, 68.6 million people--32% of the U.S. population over 12 years old--had tried marijuana or hashish at least once in their lifetime, but only 5% were current users.[132] Marijuana use is most prevalent among 18- to 25-year-olds and declines sharply after the age of 34 (Figure 3.1).[77,132] Whites are more likely than blacks to use marijuana in adolescence, although the difference decreases by adulthood.[132]

Most people who have used marijuana did so first during adolescence. Social influences, such as peer pressure and prevalence of use by peers, are highly predictive of initiation into marijuana use.[9] Initiation is not, of course, synonymous with continued or regular use. A cohort of 456 students who experimented with marijuana during their high school years were surveyed about their reasons for initiating, continuing, and stopping their marijuana use.[9] Students who began as heavy users were excluded from the analysis. Those who did not become regular marijuana users cited two types of reasons for discontinuing. The first was related to health and well-being; that is, they felt that marijuana was bad for their health or for their family and work relationships. The second type was based on age-related changes in circumstances, including increased responsibility and

decreased regular contact with other marijuana users. Among high school students who quit, parental disapproval was a stronger influence than peer disapproval in discontinuing marijuana use. In the initiation of marijuana use, the reverse was true. The reasons cited by those who continued to use marijuana were to "get in a better mood or feel better." Social factors were not a significant predictor of continued use. Data on young adults show similar trends. Those who use drugs in response to social influences are more likely to stop using them than those who also use them for psychological reasons.[80]

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

Prevalence and Predictors of Dependence on Marijuana and Other Drugs

Many factors influence the likelihood that a particular person will become a drug abuser or an addict; the user, the environment, and the drug are all important factors (Table 3.3).[114] The first two categories apply to potential abuse of any substance; that is, people who are vulnerable to drug abuse for individual reasons and who find themselves in an environment that encourages drug abuse are initially likely to abuse the most readily available drug--regardless of its unique set of effects on the brain.

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

The proportion of people who become addicted varies among drugs. Table 3.4 shows estimates for the proportion of people among the general population who used or became dependent on different types of drugs. The proportion of users that ever became dependent includes anyone who was *ever* dependent--whether it was for a period of weeks or years--and thus includes more than those who are currently dependent. Compared to most other drugs listed in this table, dependence among marijuana users is relatively rare. This might be due to differences in specific drug effects, the availability of or penalties associated with the use of the different drugs, or some combination.

Daily use of most illicit drugs is extremely rare in the general population. In 1989, daily use of marijuana among high school seniors was less than that of alcohol (2.9% and 4.2%, respectively).[76]

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

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

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

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

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

disorders than is any use of illicit substances, it does not follow that this comparison is true for every amount of cigarette smoking.[79]

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

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

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

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

Although parents often state that marijuana caused their children to be rebellious, the troubled adolescents in the study by Crowley and co-workers developed conduct disorders *before* marijuana abuse. That is consistent with reports that the more symptoms of conduct disorders children have, the younger they begin drug abuse,[127] and that the earlier

they begin drug use, the more likely it is to be followed by abuse or dependence.[125]

Genetic factors are known to play a role in the likelihood of abuse for drugs other than marijuana,[7,129] and it is not unexpected that genetic factors play a role in the marijuana experience, including the likelihood of abuse. A study of over 8,000 male twins listed in the Vietnam Era Twin Registry indicated that genes have a statistically significant influence on whether a person finds the effects of marijuana pleasant.[97] Not surprisingly, people who found marijuana to be pleasurable used it more often than those who found it unpleasant. The study suggested that, although social influences play an important role in the initiation of use, individual differences--perhaps associated with the brain's reward system--influence whether a person will continue using marijuana. Similar results were found in a study of female twins.[86] Family and social environment strongly influenced the likelihood of ever using marijuana but had little effect on the likelihood of heavy use or abuse. The latter were more influenced by genetic factors. Those results are consistent with the finding that the degree to which rats find THC rewarding is genetically based.[92]

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

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

Progression from Marijuana to Other Drugs

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

There are strikingly regular patterns in the progression of drug use from adolescence to adulthood. Because it is the most widely used illicit drug, marijuana is predictably the first illicit drug that most people encounter. Not surprisingly, most users of other illicit drugs used marijuana first.[81,82] In fact, most drug users do not begin their drug use with marijuana--they begin with alcohol and nicotine, usually when they are too young to do so legally.[82,90]

The gateway analogy evokes two ideas that are often confused. The first, more often referred to as the "stepping stone" hypothesis, is the idea that progression from marijuana to other drugs arises from pharmacological properties of marijuana itself.[82] The second is that marijuana serves as a gateway to the world of illegal drugs in which youths have greater opportunity and are under greater social pressure to try other illegal drugs. The latter interpretation is most often used in the scientific literature, and it is supported, although not proven, by the available data.

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

Whereas the stepping stone hypothesis presumes a predominantly physiological component of drug progression, the gateway theory is a social theory. The latter does not suggest that the pharmacological qualities of marijuana make it a risk factor for progression to other drug use. Instead, the legal status of marijuana makes it a gateway drug.[82]

Psychiatric disorders are associated with substance dependence and are probably risk factors for progression in drug use. For example, the troubled adolescents studied by Crowley and co-workers[31] were dependent on an average of 3.2 substances, and this suggests that their conduct disorders were associated with increased risk of progressing from one drug to another. Abuse of a single substance is probably also a risk factor for later multiple drug use. For example, in a longitudinal study that examined drug use and dependence, about 26% of problem drinkers reported that they first used marijuana after the onset of alcohol-related problems (R. Pandina, IOM workshop). The study also found that 11% of marijuana users

developed chronic marijuana problems; most also had alcohol problems.

Intensity of drug use is an important risk factor in progression. Daily marijuana users are more likely than their peers to be extensive users of other substances (for review, see Kandel and Davies[78]). Of 34- to 35-year-old men who had used marijuana 10—99 times by the age 24—25, 75% never used any other illicit drug; 53% of those who had used it more than 100 times did progress to using other illicit drugs 10 or more times.[78] Comparable proportions for women are 64% and 50%.

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

Data on the gateway phenomenon are often overinterpreted. For example, one study reports that "marijuana's role as a gateway drug appears to have increased."[55] It was a retrospective study based on interviews of drug abusers who reported smoking crack or injecting heroin daily. The data from the study provide no indication of what proportion of marijuana users become serious drug abusers; rather, they indicate that serious drug abusers usually use marijuana before they smoke crack or inject heroin. Only a small percentage of the adult population uses crack or heroin daily; during the five-year period from 1993 to 1997, an average of three people per 1,000 used crack and about two per 1,000 used heroin in the preceding month.[132]

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

In the sense that marijuana use typically precedes rather than follows initiation into the use of other illicit drugs, it is indeed a gateway drug. However, it does not appear to be a gateway drug to the extent that it is the *cause* or even that it is the most significant predictor of serious drug abuse; that is, care must be taken not to attribute cause to association. The most consistent predictors of serious drug use appear to be the intensity of marijuana use and co-occurring psychiatric disorders or a family history of psychopathology (including alcoholism).[78,85]

An important caution is that data on drug use progression pertain to *nonmedical* drug use. It does not follow from those data that if marijuana were available by prescription for *medical* use, the pattern of drug use would be the same. Kandel and co-workers also included nonmedical use of prescription psychoactive drugs in their study of drug use progression.[82] In contrast with the use of alcohol, nicotine, and illicit drugs, there was not a clear and consistent sequence of drug use involving the abuse of prescription psychoactive drugs. The current data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse among medical marijuana users. Whether the medical use of marijuana might encourage drug abuse among the general community--not among medical marijuana users themselves but among others simply because of the fact that marijuana would be used for medical purposes--is another question.

LINK BETWEEN MEDICAL USE AND DRUG ABUSE

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

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

Medical Use and Abuse of Opiates

Two highly influential papers published in the 1920s and 1950s led to widespread concern among physicians and medical licensing boards that liberal use of opiates would result in many addicts (reviewed by Moulin and co-workers[106] in 1996). Such fears have proven unfounded; it is now recognized that fear of producing addicts through medical treatment resulted in needless suffering among patients with pain as physicians needlessly limited appropriate doses of medications.[27,44] Few people begin

their drug addiction problems with misuse of drugs that have been prescribed for medical use.[114] Opiates are carefully regulated in the medical setting, and diversion of medically prescribed opiates to the black market is not generally considered to be a major problem.

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

Marijuana Decriminalization

Monitoring the Future, the annual survey of values and lifestyles of high school seniors, revealed that high school seniors in decriminalized states reported using no more marijuana than did their counterparts in states where marijuana was not decriminalized.[72] Another study reported somewhat conflicting evidence indicating that decriminalization had increased marijuana use.[105] That study used data from the Drug Awareness Warning Network (DAWN), which has collected data on drug-related emergency room (ER) cases since 1975. There was a greater increase from 1975 to 1978 in the proportion of ER patients who had used marijuana in states that had decriminalized marijuana in 1975–1976 than in states that had not decriminalized it (Table 3.6). Despite the greater increase among decriminalized states, the proportion of marijuana users among ER patients by 1978 was about equal in states that had and states that had not decriminalized marijuana. That is because the non-decriminalized states had higher rates of marijuana use *before* decriminalization. In contrast with marijuana use, rates of other illicit drug use among ER patients were substantially higher in states that did not decriminalize marijuana use. Thus, there are different possible reasons for the greater increase in marijuana use in the decriminalized states. On the one hand, decriminalization might have led to an increased use of marijuana (at least among people who sought health care in hospital ERs). On the other hand, the lack of decriminalization might have encouraged greater use of drugs that are even more dangerous than marijuana.

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

In 1976, the Netherlands adopted a policy of toleration for possession of up to 30 g of marijuana. There was little change in marijuana use during the seven years after the policy change, which suggests that the change itself had little effect; however, in 1984, when Dutch "coffee shops" that sold marijuana commercially spread throughout Amsterdam, marijuana use began to increase.[98] During the 1990s, marijuana use has continued to increase in the Netherlands at the same rate as in the United States and Norway--two countries that strictly forbid marijuana sale and possession. Furthermore, during this period, approximately equal percentages of American and Dutch 18 year olds used marijuana; Norwegian 18 year olds were about half as likely to have used marijuana. The authors of this study conclude that there is little evidence that the Dutch marijuana depenalization policy led to increased marijuana use, although they note that commercialization of marijuana might have contributed to its increased use. Thus, there is little evidence that decriminalization of marijuana use necessarily leads to a substantial increase in marijuana use.

The Medical Marijuana Debate

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

PSYCHOLOGICAL HARMS

In assessing the relative risks and benefits related to the medical use of marijuana, the psychological effects of marijuana can be viewed both as unwanted side effects and as potentially desirable end points in medical treatment. However, the vast majority of research on the psychological effects of marijuana has been in the context of assessing the drug's intoxicating effects when it is used for nonmedical purposes. Thus, the literature does not directly address the effects of marijuana taken for medical purposes.

There are some important caveats to consider in attempting to extrapolate from the research mentioned above to the medical use of marijuana. The circumstances under which psychoactive drugs are taken are an important influence on their psychological effects. Furthermore, research protocols to study marijuana's psychological effects in most

instances were required to use participants who already had experience with marijuana. People who might have had adverse reactions to marijuana either would choose not to participate in this type of study or would be screened out by the investigator. Therefore, the incidence of adverse reactions to marijuana that might occur in people with no marijuana experience cannot be estimated from such studies. A further complicating factor concerns the dose regimen used for laboratory studies. In most instances, laboratory research studies have looked at the effects of single doses of marijuana, which might be different from those observed when the drug is taken repeatedly for a chronic medical condition.

Nonetheless, laboratory studies are useful in suggesting what psychological functions might be studied when marijuana is evaluated for medical purposes. Results of laboratory studies indicate that acute and chronic marijuana use has pronounced effects on mood, psychomotor, and cognitive functions. These psychological domains should therefore be considered in assessing the relative risks and therapeutic benefits related to marijuana or cannabinoids for any medical condition.

Psychiatric Disorders

A major question remains as to whether marijuana can produce lasting mood disorders or psychotic disorders, such as schizophrenia. Georgotas and Zeidenberg[52] reported that smoking 10—22 marijuana cigarettes per day was associated with a gradual waning of the positive mood and social facilitating effects of marijuana and an increase in irritability, social isolation, and paranoid thinking. Inasmuch as smoking *one* cigarette is enough to make a person feel "high" for about 1—3 hours,[68,95,118] the subjects in that study were taking very high doses of marijuana. Reports have described the development of apathy, lowered motivation, and impaired educational performance in heavy marijuana users who do not appear to be behaviorally impaired in other ways.[121,122] There are clinical reports of marijuana-induced psychosis-like states (schizophrenia-like, depression, and/or mania) lasting for a week or more.[112] Hollister suggests that, because of the varied nature of the psychotic states induced by marijuana, there is no specific "marijuana psychosis." Rather, the marijuana experience might trigger latent psychopathology of many types.[60] More recently, Hall and colleagues[60] concluded that "there is reasonable evidence that heavy cannabis use, and perhaps acute use in sensitive individuals, can produce an acute psychosis in which confusion, amnesia, delusions, hallucinations, anxiety, agitation and hypomanic symptoms predominate." Regardless of which of those interpretations is correct, the two reports agree that there is little evidence that marijuana alone produces a psychosis that persists after the period of intoxication.

Schizophrenia

The association between marijuana and schizophrenia is not well understood. The scientific literature indicates general agreement that heavy

marijuana use can precipitate schizophrenic episodes but not that marijuana use can cause the underlying psychotic disorder.[59,96,151] As noted earlier, drug abuse is common among people with psychiatric disorders. Estimates of the prevalence of marijuana use among schizophrenics vary considerably but are in general agreement that it is at least as great as that among the general population.[134] Schizophrenics prefer the effects of marijuana to those of alcohol and cocaine,[35] which they seem to use less often than does the general population.[134] The reasons for this are unknown, but it raises the possibility that schizophrenics might obtain some symptomatic relief from moderate marijuana use. But overall, compared with the general population, people with schizophrenia or with a family history of schizophrenia are likely to be at greater risk for adverse psychiatric effects from the use of cannabinoids.

Cognition

As discussed earlier, acutely administered marijuana impairs cognition.[60,66,112] Positron emission tomography (PET) imaging allows investigators to measure the acute effects of marijuana smoking on active brain function. Human volunteers who perform auditory attention tasks before and after smoking a marijuana cigarette show impaired performance while under the influence of marijuana; this is associated with substantial reduction in blood flow to the temporal lobe of the brain, an area that is sensitive to such tasks.[116,117] Marijuana smoking increases blood flow in other brain regions, such as the frontal lobes and lateral cerebellum.[101,155] Earlier studies purporting to show structural changes in the brains of heavy marijuana users[22] have not been replicated with more sophisticated techniques.[28,89]

Nevertheless, recent studies[14,122] have found subtle defects in cognitive tasks in heavy marijuana users after a brief period (19—24 hours) of marijuana abstinence. Longer term cognitive deficits in heavy marijuana users have also been reported.[140] Although these studies have attempted to match heavy marijuana users with subjects of similar cognitive abilities before exposure to marijuana use, the adequacy of this matching has been questioned.[133] The complex methodological issues facing research in this area are well reviewed in an article by Pope and colleagues.[121] Care must be exercised so that studies are designed to differentiate between changes in brain function caused the effects of marijuana and by the illness for which marijuana is being given. AIDS dementia is an obvious example of this possible confusion. It is also important to determine whether repeated use of marijuana at therapeutic dosages produces any irreversible cognitive effects.

Psychomotor Performance

Marijuana administration has been reported to affect psychomotor

performance on a number of tasks. The review by Chait and Pierri not only details the studies that have been done but also points out the inconsistencies among studies, the methodological shortcomings of many studies, and the large individual differences among the studies attributable to subject, situational, and methodological factors. Those factors must be considered in studies of psychomotor performance when participants are involved in a clinical trial of the efficacy of marijuana. The types of psychomotor functions that have been shown to be disrupted by the acute administration of marijuana include body sway, hand steadiness, rotary pursuit, driving and flying simulation, divided attention, sustained attention, and the digit-symbol substitution test. A study of experienced airplane pilots showed that even 24 hours after a single marijuana cigarette their performance on flight simulator tests was impaired.[163] Before the tests, however, they told the study investigators that they were sure their performance would be unaffected.

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

Amotivational Syndrome

One of the more controversial effects claimed for marijuana is the production of an "amotivational syndrome." This syndrome is not a medical diagnosis, but it has been used to describe young people who drop out of social activities and show little interest in school, work, or other goal-directed activity. When heavy marijuana use accompanies these symptoms, the drug is often cited as the cause, but no convincing data demonstrate a causal relationship between marijuana smoking and these behavioral characteristics.[25] It is not enough to observe that a chronic marijuana user lacks motivation. Instead, relevant personality traits and behavior of subjects must be assessed before and after the subject becomes a heavy marijuana user. Because such research can only be done on subjects who become heavy marijuana users on their own, a large population study--such as the Epidemiological Catchment Area study described earlier in this chapter--would be needed to shed light on the relationship between motivation and marijuana use. Even then, although a causal relationship between the two could, in theory, be dismissed by an epidemiological study, causality could not be proven.

Summary

Measures of mood, cognition, and psychomotor performance should be incorporated into clinical trials evaluating the efficacy of marijuana or cannabinoid drugs for a given medical condition. Ideally, participants would complete mood assessment questionnaires at various intervals throughout the day for a period before; every week during; and, where appropriate, after marijuana therapy. A full psychological screening of research participants should be conducted to determine whether there is an

interaction between the mood-altering effects of chronic marijuana use and the psychological characteristics of the subjects. Similarly, the cognitive and psychomotor functioning should be assessed before and regularly during the course of a chronic regimen of marijuana or cannabinoid treatment to determine the extent to which tolerance to the impairing effects of marijuana develops and to monitor whether new problems develop.

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

> **Conclusion:** The psychological effects of cannabinoids, such as anxiety reduction, sedation, and euphoria, can influence their potential therapeutic value. Those effects are potentially undesirable in some patients and situations and beneficial in others. In addition, psychological effects can complicate the interpretation of other aspects of the drug's effect.
>
> **Recommendation: Psychological effects of cannabinoids, such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.**

PHYSIOLOGICAL HARMS: TISSUE AND ORGAN DAMAGE

Many people who spoke to the IOM study team in favor of the medical use of marijuana cited the absence of marijuana overdoses as evidence that it is safe. Indeed, epidemiological data indicate that in the general population marijuana use is not associated with increased mortality.[138] However, other serious health outcomes should be considered, and they are discussed below.

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

Immune System

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

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

Human Studies

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

Assays of Leukocytes from Marijuana Smokers. One of the more common approaches has been to isolate peripheral blood leukocytes from people who have smoked marijuana in order to evaluate the immune response of those cells in vitro--most often by measuring mitogen-induced cell proliferation, a normal immune response. Almost without exception, this approach has failed to demonstrate any reduction in leukocyte function. The major problem with the approach is that after blood samples are drawn from the study subjects the leukocytes must be isolated from whole blood before they are tested. That is done by high-speed centrifugation followed by extensive washing of the cells, which removes the cannabinoid; perhaps for this reason no adverse effects have been demonstrated in peripheral blood leukocytes from marijuana smokers.[75,91,123,160]

Leukocyte Responses to THC. Another approach is to isolate peripheral blood leukocytes from healthy control subjects who do not smoke marijuana and then to measure the effect of THC on the ability of these cells to proliferate in response to mitogenic stimulation *in vitro*. One important difference between leukocytes isolated from a marijuana smoker, as described above, and leukocyte cell cultures to which THC has been added directly is in the cannabinoid composition. Marijuana smoke contains many distinct cannabinoid compounds of which THC is just one. Moreover, the immunomodulatory activity of many of the other cannabinoid compounds has never been tested, and it is now known that at least one of those--cannabinol (CBN)--has greater activity on the immune system than on the central nervous system,[64] so it is unclear whether the profile of activity observed with THC accurately represents the effects of marijuana smoke on immune competence. Likewise, the extent to which different cannabinoids in combination exhibit additive, synergistic, or antagonistic effects with respect to immunomodulatory activity is unclear. The issue is complicated by the fact that leukocytes express both types of cannabinoid receptors: CB_1 and CB_2.

An additional factor that might affect the immunomodulatory activity of cannabinoids in leukocytes is metabolism. Leukocytes have very low levels of the cytochrome P-450 drug-metabolizing enzymes,[20] so the metabolism of cannabinoids is probably different between *in vivo* and *in vitro* exposure. That last point is pertinent primarily to investigations of chronic,

not acute, cannabinoid exposure.

Human-Derived Cell Lines. A third approach for investigating the effects of cannabinoids on human leukocytes has been to study human-derived cell lines.[2] As described above, the cell lines are treated *in vitro* with cannabinoids to test their responses to different stimuli. Although cell lines are a convenient source of human cells, the problems described above apply here as well. In addition, the cell lines might not be the same as the original cells. For example, cell lines do not necessarily have the same number of cannabinoid receptors as the original human cells.

Rodent Studies

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

Summary

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

Marijuana Smoke

Tobacco is the predominant cause of such lung diseases as cancer and emphysema, and marijuana smoke contains many of the components of tobacco smoke.[69] Thus, it is important to consider the relationship between habitual marijuana smoking and some lung diseases.

Given a cigarette of comparable weight, as much as four times the amount of tar can be deposited in the lungs of marijuana smokers as in the lungs of tobacco smokers.[162] The difference is due primarily to the differences in filtration and smoking technique between tobacco and marijuana smokers. Marijuana cigarettes usually do not have filters, and marijuana smokers typically develop a larger puff volume, inhale more deeply, and hold their breath several times longer than tobacco smokers.[119]

However, a marijuana cigarette smoked recreationally typically is not packed as tightly as a tobacco cigarette, and the smokable substance is about half that in a tobacco cigarette. In addition, tobacco smokers generally smoke considerably more cigarettes per day than do marijuana smokers.

Cellular Damage

Lymphocytes: T and B Cells. Human studies of the effect of marijuana smoking on immune cell function are not all consistent with cannabinoid cell culture and animal studies. For example, antibody production was decreased in a group of hospitalized patients who smoked marijuana for four days (12 cigarettes/day), but the decrease was seen in only one subtype of humoral antibody (IgG), whereas two other subtypes (IgA and IgM) remained normal and one (IgE) was increased.[108] In addition, T cell proliferation was normal in the blood of a group of marijuana smokers, although closer evaluation showed an increase in one subset of T cells[161] and a decrease in a different subset (CD8).[157] It appears that marijuana use is associated with intermittent disturbances in T and B cell function, but the magnitude is small and other measures are often normal.[87]

Macrophages. Alveolar macrophages are the principal immune-effector cells in the lung and are primarily responsible for protecting the lung against infectious microorganisms, inhaled foreign substances, and tumor cells. They are increased during tissue inflammation. In a large sample of volunteers, habitual marijuana smokers had twice as many alveolar macrophages as nonsmokers, and smokers of both marijuana and tobacco had twice as many again.[11] Marijuana smoking also reduced the ability of alveolar macrophages to kill fungi, such as *Candida albicans*;[3] pathogenic bacteria, such as *Staphylococcus aureus*; and tumor target cells. The reduction in ability to destroy fungal organisms was similar to that seen in tobacco smokers. The inability to kill pathogenic bacteria was not seen in tobacco smokers.[10] Furthermore, marijuana smoking depressed production of proinflammatory cytokines, such as TNF-I and IL-6, but not of immunosuppressive cytokines.[10] Cytokines are important regulators of macrophage function, so this marijuana-related decrease in inflammatory cytokine production might be a mechanism whereby marijuana smokers are less able to destroy fungal and bacterial organisms, as well as tumor cells.

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

Bronchial and Pulmonary Damage

Animal Studies. A number of animal studies have revealed respiratory tract changes and diseases associated with marijuana smoking, but others have not. Extensive damage to the smaller airways, which are the major site of chronic obstructive pulmonary disease (COPD),[4] and acute and chronic pneumonia have been observed in various species exposed to different doses of marijuana smoke.[41,42,128] In contrast, rats exposed to increasing doses of marijuana smoke for one year did not show any signs of COPD, whereas rats exposed to tobacco smoke did.[67]

Chronic Bronchitis and Respiratory Illness. Results of human studies suggest that there is a greater chance of respiratory illness in people who smoke marijuana. In a survey of outpatient medical visits at a large health maintenance organization (HMO), marijuana users were more likely to seek help for respiratory illnesses than people who smoked neither marijuana or tobacco.[120] However, the incidence of seeking help for respiratory illnesses was not higher in those who smoked marijuana for 10 years or more than in those who smoked for less than 10 years. One explanation for this is that people who experience respiratory symptoms are more likely to quit smoking and that people who continue to smoke constitute a set of survivors who do not develop or are indifferent to such symptoms. One limitation of this study is that no data were available on the use of cocaine, which when used with marijuana could contribute to the observed differences. Another limitation is that the survey relied on self-reporting; tobacco, alcohol, and marijuana use might have been under-reported (S. Sidney, IOM workshop).

When marijuana smokers were compared with nonsmokers and tobacco smokers in a group of 446 volunteers, 15—20% of the marijuana smokers reported symptoms of chronic bronchitis, including chronic cough and phlegm production,[146] and 20—25% of the tobacco smokers reported symptoms of chronic bronchitis. Despite a marked disparity in the amount of each substance smoked per day (three or four joints of marijuana versus more than 20 cigarettes of tobacco), the difference in the percentages of tobacco smokers and marijuana smokers experiencing symptoms of chronic bronchitis was statistically insignificant.[146] Similar findings were reported by Bloom and co-workers,[15] who noted an additive effect of smoking both marijuana and tobacco.

Bronchial Tissue Changes. Habitual marijuana smoking is associated with changes in the lining of the human respiratory tract. Many marijuana or tobacco smokers have increased redness (erythema) and swelling (edema) of the airway tissues and increased mucous secretions.[43,50] In marijuana smokers the number and size of small blood vessels in the bronchial wall are increased, tissue edema is present, and the normal ciliated cells[5] lining the inner surface of the bronchial wall are largely replaced by mucous-secreting goblet cells. The damage is greater in people who smoke both marijuana and tobacco.[130] Overproduction of mucus by the increased

numbers of mucous-secreting cells in the presence of decreased numbers of ciliated cells tends to leave coughing as the only major mechanism to remove mucus from the airways; this might explain the relatively high proportion of marijuana smokers who complain of chronic cough and phlegm production.[148]

A 1998 study has shown that both marijuana and tobacco smokers have significantly more cellular and molecular abnormalities in bronchial epithelium cells than nonsmokers; these changes are associated with increased risk of cancer.[12] The tobacco-only smokers in that study smoked an average of 25 cigarettes per day, whereas the marijuana-only smokers smoked an average of 21 marijuana cigarettes per week. Although the marijuana smokers smoked far fewer cigarettes, their cellular abnormalities were equivalent to or greater than those seen in tobacco smokers. This and earlier studies have shown that such abnormalities are greatest in people who smoke both marijuana and tobacco; hence, marijuana and tobacco smoke might have additive effects on airway tissue.[12,45,56] Tenant[150] found similar results in U.S. servicemen who suffered from respiratory symptoms and were heavy hashish smokers. (Hashish is the resin from the marijuana plant.)

Chronic Obstructive Pulmonary Disease. In the absence of epidemiological data, indirect evidence, such as nonspecific airway hyperresponsiveness and measures of lung function, offers an indicator of the vulnerability of marijuana smokers to COPD.[154] For example, the methacholine provocative challenge test, used to evaluate airway hyperresponsiveness, showed that tobacco smokers develop more airway hyperresponsiveness. But no such correlation has been shown between marijuana smoking and airway hyperresponsiveness.

There is conflicting evidence on whether regular marijuana use harms the small airways of the lungs. Bloom and co-workers found that an average of one joint smoked per day significantly impaired the function of small airways.[15] But Tashkin and co-workers[146] did not observe such damage among heavier marijuana users (three to four joints per day for at least 10 years), although they noted a narrowing of large central airways. Tashkin and co-workers' long-term study, which adjusted for age-related decline in lung function (associated with an increased risk for developing COPD), showed an accelerated rate of decline in tobacco smokers but not in marijuana smokers.[147] Thus, the question of whether usual marijuana smoking habits are enough to cause COPD remains open.

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

HIV/AIDS Patients

The relationship between marijuana smoking and the natural course of AIDS is of particular concern because HIV patients are the largest group who report using marijuana for medical purposes. Marijuana use has been linked both to increased risk of progression to AIDS in HIV-seropositive patients and to increased mortality in AIDS patients.

For unknown reasons, marijuana use is associated with increased mortality among men with AIDS but not among the general population.[138] (The relative risk of AIDS mortality for current marijuana users in this 12-year study was 1.90, indicating that almost twice as many marijuana users died of AIDS as did noncurrent marijuana users.) Never-married men used twice as much marijuana as married men and accounted for 83% of the AIDS deaths in the study. The authors of the study note that, while marital status is insufficient to adjust for lifestyle factors--particularly, homosexual behavior--a substantial proportion of the never-married men with AIDS were probably homosexuals or bisexuals. That raises the possibility that the association of marijuana use with AIDS deaths might be related to indirect factors, such as use of other drugs or high-risk sexual behavior, both of which increase risks of infection to which AIDS patients are more susceptible. The higher mortality of AIDS patients who were current marijuana users also raises the question of whether this was because patients increased their use of marijuana at the endstages of the disease to treat their symptoms. However, the association between marijuana use and AIDS deaths was similar even when the subjects who died earliest in the first five years of this 12-year study, and who were presumably the most sick, were excluded from the analysis. In summary, it is premature to conclude what the underlying causes of this association might be.

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

Marijuana use has been associated with a higher prevalence of HIV seropositivity in cross-sectional studies,[84] but the relationship of marijuana to the progression to AIDS in HIV-seropositive patients is a reasonable question. It remains unclear whether marijuana smoking is an independent risk factor in the progression of AIDS in HIV-seropositive men. Marijuana use did not increase the risk of AIDS in HIV-seropositive men in the Multicenter AIDS Cohort Study, in which 1,795 HIV-seropositive men were studied for 18 months,[84] or in the San Francisco Men's Health Study, in which 451 HIV-seropositive men were studied for six years.[34] In contrast, the Sydney AIDS Project in Australia, in which 386 HIV-seropositive men were studied for 12 months,[152] reported that marijuana use was associated with increased risk of progression to AIDS. The results of the Sydney study are less reliable than those of the other two studies noted; it was the shortest of the studies and, according to the 1993

definition of AIDS, many of the subjects probably already had AIDS at the beginning of the study.[6]

The most compelling concerns regarding marijuana smoking in HIV/AIDS patients are the possible effects of marijuana on immunity.[111] Reports of opportunistic fungal and bacterial pneumonia in AIDS patients who used marijuana suggest that marijuana smoking either suppresses the immune system[33] or exposes patients to an added burden of pathogens.[21] In summary, patients with preexisting immune deficits due to AIDS should be expected to be vulnerable to serious harm caused by smoking marijuana. The relative contribution of marijuana smoke versus THC or other cannabinoids is not known.

Carcinogenicity

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

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

Case Studies. Results of several case series suggest that marijuana might play a role in the development of human respiratory cancer. Reports indicate an unexpectedly large proportion of marijuana users among people with lung cancer[141,149] and cancers of the upper aerodigestive tract--that is, the oral cavity, pharynx, larynx, and esophagus--that occur before the age of 45.[36,39,149] Respiratory tract cancers associated with heavy tobacco and alcohol consumption are not usually seen before the age of 60,[154] and the occurrence of such cancers in marijuana users younger than 60 suggests that long-term marijuana smoking potentiates the effects of other risk factors, such as tobacco smoking, and is a more potent risk factor than tobacco and alcohol use in the early development of respiratory cancers. Most studies lack the necessary comparison groups to calculate the isolated effect of marijuana use on cancer risk. Many marijuana smokers also smoke tobacco, so when studies lack information regarding cigarette smoking status, there is no way to separate the effects of marijuana smoke and tobacco smoke.

Epidemiological Evidence. As of this writing, Sidney and co-workers[139] had conducted the only epidemiological study to evaluate the association

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

Cellular and Molecular Studies. In contrast with clinical studies, cellular and molecular studies have provided strong evidence that marijuana smoke is carcinogenic. Cell culture studies implicate marijuana smoke in the development of cancer. Prolonged exposure of hamster lung cell cultures to marijuana smoke led to malignant transformations,[94] and exposure of human lung explants to marijuana smoke resulted in chromosomal and DNA alterations.[154] The tar from marijuana smoke also induced mutations similar to those produced by tar from the same quantity of tobacco in a common bacterial assay for mutagenicity.[158]

Molecular studies also implicate marijuana smoke as a carcinogen. Proto-oncogenes and tumor suppressor genes are a group of genes that affect cell growth and differentiation. Normally, they code for proteins that control cellular proliferation. Once mutated or activated, they produce proteins that cause cells to multiply rapidly and out of control, and this results in tumors or cancer.[7] When the production of these proteins was evaluated in tissue biopsies taken from marijuana, tobacco, and marijuana plus tobacco smokers, and nonsmokers, two of them (EGFR and Ki-67) were markedly higher in the marijuana smokers than in the nonsmokers and the tobacco smokers. Moreover, the effects of marijuana and tobacco were additive.[131] Thus, in relatively young smokers of marijuana, particularly those who smoke both marijuana and tobacco, marijuana is implicated as a risk factor for lung cancer.

DNA alterations are known to be early events in the development of cancer, and have been observed in the lymphocytes of pregnant marijuana smokers and in those of their newborns.[4] This is an important study because the investigators were careful to exclude tobacco smokers--a problem in previous studies that cited mutagenic effects of marijuana smoke.[26,53,63,142] The same investigators found similar effects in previous studies among tobacco smokers,[5,6] so the effects cannot be attributed solely to THC or other cannabinoids. Although it can be determined only by experiment, it is likely that the smoke contents--other than cannabinoids--are responsible for a large part of the mutagenic effect.

Preliminary findings suggest that marijuana smoke activates cytochrome P4501A1 (CYP1A1), the enzyme that converts PAHs, such as benz[α]pyrene, into active carcinogens.[99] Bronchial epithelial cells in tissue biopsies taken from marijuana smokers show more binding to CYP1A1 antibodies than do comparable cells in biopsies from nonsmokers (D. Tashkin, IOM workshop). That suggests that there is more of CYP1A1 itself in the bronchial cells of marijuana smokers, but different experimental methods will be needed to establish that possibility.

Conclusions

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

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

1. **Case control studies to determine whether marijuana use is associated with an increased risk of respiratory cancer.** Despite the lack of compelling epidemiological evidence, findings from the biochemical, cellular, immunological, genetic, tissue, and animal studies cited above strongly suggest that marijuana is a risk factor for human cancer. What is required to address that hypothesis more convincingly is a population-based case control study of sufficiently large numbers of people with lung cancer and upper aerodigestive tumors (cancers of the oral cavity and pharynx, larynx, and esophagus), as well as noncancer controls, to demonstrate a statistically significant association, if one exists. Because of the long period required for induction of human carcinomas and the infrequent use of marijuana in the general U.S. population before 1966, no epidemiological studies so far have been extensive enough to measure the association between marijuana and cancer adequately. However, epidemiological investigation of this association is probably possible now in that some 30 years have elapsed since the star[illegible] widespread marijuana use in the United States among teenagers and young adults.

2. **Molecular markers of respiratory cancer progression in marijuana smokers.** If an epidemiological association between marijuana use and risk of respiratory cancer is demonstrated, studies would be warranted to explore the presence of molecular markers--such as TP53, p16, NAT2, and GSTM1--that could be predictive of genetically increased risk of carcinogenesis in marijuana users.

3. **Prospective epidemiological studies of populations with HIV**

seropositivity or at high risk for HIV infection. Because HIV/AIDS patients constitute the largest group that reports smoking marijuana for medical purposes and they are particularly vulnerable to immunosuppressive effects, there is a pressing need for a better understanding of the relative risk posed by and the rewards of smoking marijuana. Such studies should include history of marijuana use in the analysis of potential risk factors for seroconversion and acquisition of opportunistic infections or progression to AIDS. The studies could be carried out in the context of any federally approved clinical trials of medical marijuana in immuno-compromised patients and should provide a follow-up period long enough to capture potential adverse events.

4. **Regularized recording of marijuana use by patients**. Although marijuana is the most commonly used illicit drug, medical providers often do not question patients about marijuana use and rarely document its use.[102] Among 452 Kaiser Permanente patients who reported daily or almost daily marijuana use, physicians recorded marijuana use in only 3% of their medical records (S. Sidney, IOM workshop).

5. **Additional cellular, animal, and human studies to investigate the effects of THC and marijuana on immune function.** The effects studied should include effects on proinflammatory versus immunosuppressive cytokines and on the function of leukocytes that present antigen to T cells.

The question that needs to be addressed is whether THC or marijuana is a risk factor for HIV infection, for progression to more severe stages of AIDS, or for opportunistic infection among HIV-positive patients. Studies are needed to determine the effects of marijuana use on the function of alveolar macrophages. It would be important to compare the HIV infectivity and replication of alveolar macrophages harvested from habitual marijuana users with those harvested from nonusers or infrequent marijuana users. Cell culture studies could be used to compare the susceptibility of HIV-infected alveolar macrophages to additional infection with opportunistic pathogens. Similarly, further studies on cell cultures of peripheral blood mononuclear cells could be used to assess the effects of exposure to THC on HIV infectivity and replication.

Cardiovascular System

Marijuana smoke and oral THC can cause tachycardia (rapid heart beat) in humans, 20—100% above baseline.[57,85] The increase in heart rate is greatest in the first 10—20 minutes after smoking and decreases sharply and steadily; depending on whether smoked marijuana or oral THC is used, this can last three or five hours, respectively.[68,95] In some cases, blood pressure increases while a person is in a reclining position but decreases inordinately on standing, resulting in postural hypotension (decreased blood pressure due to changing posture from a lying or sitting position to a standing position, which can cause dizziness and faintness). In contrast with acute administration of THC, chronic oral ingestion of THC reduces heart rate in humans.[13]

In animals, THC decreases heart rate and blood pressure.[57,156] However, most of the animal studies have been conducted in anesthetized animals, and anesthesia causes hypertension. Thus, those studies should be interpreted as reports on the effects of cannabinoids in hypertensive subjects. The results of the animal and human studies are consistent with the conclusion that cannabinoids are hypotensive at high doses in animals, as well as humans.[156]

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

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

Reproductive System

Animal Studies. Marijuana and THC can inhibit many reproductive functions on a short-term basis. In both male and female animals, THC injections suppress reproductive hormones and behavior.[107,150] Studies have consistently shown that injections of THC result in rapid, dose-dependent suppression of serum luteinizing hormone (LH).[70] (LH is the pituitary hormone that stimulates release of the gonadal hormones, testosterone and estrogen.) Embryo implantation also appears to be inhibited by THC. But it does not necessarily follow that marijuana use will interfere with human reproduction. With few exceptions, the animal studies are based on acute treatments (single injections) or short-term treatments (THC injections given over a series of days). The results are generally observed for only several hours or in females sometimes for only one ovulatory cycle.

Acute treatments with cannabinoids--including THC, CBD, cannabinol, and anandamide--can decrease the fertilizing capacity of sea urchin

sperm. The sea urchin is only a distant relative of humans, but the cellular processes that regulate fertilization are similar enough that one can expect a similar effect in humans. However, the effect of cannabinoids on the capacity of sperm to fertilize eggs is reversible and is observed at concentrations of 6—100 μM,[136,137] which are higher than those likely to be experienced by marijuana smokers. The presence of cannabinoid receptors in sperm suggests the possibility of a natural role for anandamide in modulating sperm function during fertilization. However, it remains to be determined whether smoked marijuana or oral THC taken in prescribed doses has a clinically significant effect on the fertilizing capacity of human sperm.

Exposure to THC *in utero* can result in long-term changes. Many *in utero* effects interfere with embryo implantation (see review by Wenger and co-workers[159]). Exposure to THC shortly before or after birth can result in impaired reproductive behavior in mice when they reach adulthood: females are slower to show sexual receptivity, and males are slower to mount.[107]

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

Human Studies. The few human studies are consistent with the acute animal studies: THC inhibits reproductive functions. However, studies of men and women who use marijuana regularly have yielded conflicting results and show either depression of reproductive hormones, no effect, or only a short-term effect. Overall, the results of human studies are consistent with the hypothesis that THC inhibits LH on a short-term basis but not in long-term marijuana users. In other words, long-term users develop tolerance to the inhibitory effect of THC on LH. The results in men and women are similar, with the added consideration of the menstrual cycle in women: the acute effects of THC appear to vary with cycle stage. THC appears to have little effect during the follicular phase (the phase after menses and before ovulation) and to inhibit the LH pulse during the luteal phase (the phase after ovulation and before menses).[103] In brief, although there are no data on fertility itself, marijuana or THC would probably decrease human fertility--at least in the short term--for both men and women. And it is reasonable to predict that THC can interfere with early pregnancy, particularly with implantation of the embryo. Like tobacco smoke, marijuana smoke is highly likely to be harmful to fetal development and should be avoided by pregnant women and those who might become pregnant in the near future. Nevertheless, although fertility and fetal development are important concerns for many, they are unlikely to be of much concern to people with seriously debilitating or life-threatening diseases. The well-documented inhibition of reproductive functions by THC is thus not a serious concern for evaluating the short-term medical use of marijuana or specific cannabinoids.

The results of studies of the relationship between prenatal marijuana exposure and birth outcome have been inconsistent (reviewed in 1995 by Cornelius and co-workers[30]). Except for adolescent mothers, there is little evidence that gestation is shorter in mothers who smoke marijuana.[30] Several studies of women who smoked marijuana regularly during pregnancy show that they tend to give birth to lower weight babies.[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.

REFERENCES

[1] Adams IB, Martin BR. 1996. Cannabis: Pharmacology and toxicology in animals and humans. *Addiction* 91:1585—1614.

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

[3] American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th ed. Washington, DC: American Psychiatric Association.

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

[5] Ammenheuser MM, Berenson NJ, Stiglich EB, Whorton Jr EB, Ward Jr JB. 1994.

Elevated frequencies of *hprt* mutant lymphocytes in cigarette-smoking mothers and their newborns. *Mutation Research* 304:285—294.

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

[7] Anthenelli RM, Schuckit MA. 1992. Genetics. In: Lowinson JH, Ruiz P, Millman RB, Editors, *Substance Abuse: A Comprehensive Textbook*. 2nd ed. Baltimore, MD: Williams & Wilkins. Pp. 39—50.

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

[9] Bailey SL, Flewelling RL, Rachal JV. 1992. Predicting continued use of marijuana among adolescents: The relative influence of drug-specific and social context factors. *Journal of Health and Social Behavior* 33:51—66.

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

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

[12] Barsky SH, Roth MD, Kleerup EC, Simmons M, Tashkin DP. 1998. Histopathologic and molecular alterations in bronchial epithelium in habitual smokers of marijuana, cocaine, and/or tobacco. *Journal of the National Cancer Institute* 90:1198—1205.

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

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

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

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

[17] British Medical Association. 1997. *Therapeutic Uses of Cannabis*. Amsterdam, The Netherlands: Harwood Academic Publishers.

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

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

[20] Burns LA, Meade BJ, Munson AE. 1996. Toxic responses of the immune system. In: CD Klaassen, MO Amdur, and J Doul, Editors, *Casarett and Doul, Toxicology: The Basic*

Science of Poisons.

[21] Caiaffa WT, Vlahov D, Graham N, Astemborski J, Solomon L, Nelson KE, Muem. In: CD Klaassen, MO A*Pneumocystis carinii* pneumonia, and immunosuppression increase risk of bacterial pneumonia in human immunodeficiency virus-seropositive injection drug users. *American Journal of Respiratory and Critical Care Medicine* 150:1493—1498.

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

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

[24] Charalambous A, Marciniak G, Shiue CY, Dewey SL, Schlyer DJ, Wolf AP, Makriyannis A. 1991. PET studies in the primate brain and biodistribution in mice using (—)-5'-18F-delta 8-THC. *Pharmacology Biochemistry and Behavior* 40:503—507.

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

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

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

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

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

[30] Cornelius MD, Taylor PM, Geva D, Day NL. 1995. Prenatal tobacco and marijuana use among adolescents: Effects on offspring gestational age, growth, and morphology. *Pediatrics* 95(5):738—743.

[31] Crowley TJ, Macdonald MJ, Whitmore EA, Mikulich SK. 1998. Cannabis dependence, withdrawal, and reinforcing effects among adolescents with conduct symptoms and substance use disorders. *Drug and Alcohol Dependence* 50:27—37.

[32] Crowley TJ, Rhine MW. 1985. The substance use disorders. In: Simons RC, Editor. *Understanding Human Behavior in Health and Illness*. 3rd ed. Baltimore, MD: Williams & Wilkins. Pp. 730—746.

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

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

[35] Dixon L, Haas G, Weiden PJ, Sweeney J, Frances AJ. 1991. Drug abuse in schizophrenic patients: Clinical correlates and reasons for use. *American Journal of Psychiatry* 148:224—

230.

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

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

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

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

[40] Fehr K, Kalant H. 1981. Cannabis and health hazards. *Proceedings of an ARF/WHO Scientific Meeting on Adverse Health and Behavioral Consequences of Cannabis Use*. Fehr K, Kalant H, Editors, Toronto, Canada: Addiction Research Foundation.

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

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

[43] Fligiel SEG, Roth MD, Kleerup EC, Barsky SH, Simmons M, Tashkin DP. 1997. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco. *Chest* 112:319—326.

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

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

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

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

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

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

[50] Fried PA, Watkinson B, Gray K. 1998. Differential effects on cognitive functioning in 9- to 12-year-olds prenatally exposed to cigarettes and marihuana. *Neurotoxicology and Teratology* 20:293—306.

[51] Gardner EL. 1992. Brain reward mechanisms. In: Lowinson JH, Ruiz P, Millman RB, Editors, *Substance Abuse: A Comprehensive Textbook*. 2nd ed. Baltimore, MD: Williams

and Wilkins. Pp. 70—99.

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

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

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

[55] Golub A, Johnson BD. 1994. The shifting importance of alcohol and marijuana as gateway substances among serious drug abusers. *Journal of Studies on Alcohol* 55:607—614.

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

[57] Graham JDP. 1986. The cardiovascular action of cannabinoids. In: Mechoulam R, Editor, *Cannabinoids as Therapeutic Agents*. Boca Raton, FL: CRC Press. Pp. 159—166.

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

[59] Hall W, Solowij N. 1998. Adverse effects of cannabis. *The Lancet* 352:1611—1616.

[60] Hall W, Solowij N, Lemon J. 1994. *The Health and Psychological Consequences of Cannabis Use*. Department of Human Services and Health, Monograph Series, No. 25. Canberra, Australia: Australian Government Publishing Service.

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

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

62a. Heishman SJ, Huestis MA, Henningfield JE, Cone EJ. 1990. Acute and residual effects of marijuana: Profiles of plasma THC levels, physiological, subjective, and performance measures. *Pharmacology, Biochemistry, and Behavior* 37:561-565.

[63] Herha J, Obe G. 1974. Chromosomal damage in caronical users of cannabis: In vivo investigation with two-day lymphocyte cultures. *Pharmakopsychiatrie* 7:328—337.

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

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

[66] Hollister LE. 1986. Health aspects of cannabis. *Pharmacological Reviews* 38:1—20.

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

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

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

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

[71] Johnson V. 1995. The relationship between parent and offspring comorbid disorders. *Journal of Substance Abuse* 7:267—280.

[72] Johnston LD, O'Malley PM, Bachman JG. 1989. Marijuana decriminalization. The impact on youth, 1975—1980. *Journal of Public Health Policy* 10:456.

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

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

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

[76] Kandel DB. 1992. Epidemiological trends and implications for understanding the nature of addiction. In: O'Brien CP, Jaffe JH, Editors, *Addictive States*. New York: Raven Press, Ltd. Pp. 23—40.

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

[78] Kandel DB, Davies M. 1992. Progression to regular marijuana involvement: phenomenology and risk factors for near-daily use. In: Glantz M, Pickens R, Editors, *Vulnerability to Drug Abuse*. Washington, DC: American Psychological Association. Pp. 211—253.

[79] Kandel DB, Johnson JG, Bird HR, Canino G, Goodman SH, Lahey BB, Regier DA, Schwab-Stone M. 1997. Psychiatric disorders associated with substance use among children and adolescents: Findings from the Methods for the Epidemiology of Child and Adolescent Mental Disorders (MECA) Study. *Journal of Abnormal Child Psychology* 25:121—132.

[80] Kandel DB, Raveis VH. 1989. Cessation of illicit drug use in young adulthood. *Archives of General Psychiatry* 46:109—116.

[81] Kandel DB, Yamaguchi K. 1993. From beer to crack: developmental patterns of drug involvement. *American Journal of Public Health* 83:851—855.

[82] Kandel DB, Yamaguchi K, Chen K. 1992. Stages of progression in drug involvement

from adolescence to adulthood: Further evidence for the gateway theory. *Journal of Studies in Alcohol* 53:447—457.

[83] Kaplan HB, Martin SS, Johnson RJ, Robbins CA. 1996. Escalation of marijuana use: Application of a general theory of deviant behavior. *Journal of Health and Social Behavior* 27:44—61.

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

[85] Kelly TH, Foltin RW, Fischman MW. 1993. Effects of smoked marijuana on heart rate, drug ratings and task performance by humans. *Behavioural Pharmacology* 4:167—178.

[86] Kendler KS, Prescott CA. 1998. Cannabis use, abuse, and dependence in a population-based sample of female twins. *American Journal of Psychiatry* 155:1016.

[87] Klein TW, Friedman H, Specter SC. 1998. Marijuana, immunity and infection. *Journal of Neuroimmunology* 83:102—115.

[88] Koob GF, Le Moal M. 1997. Drug abuse: Hedonic homeostatic dysregulation. *Science* 278:52—58.

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

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

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

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

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

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

[95] Lindgren JE, Ohlsson A, Agurell S, Hollister LE, Gillespie H. 1981. Clinical effects and plasma levels of delta 9-tetrahydrocannabinol (delta 9-THC) in heavy and light users of cannabis. *Psychopharmacology (Berlin)* 74:208—212.

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

[97] Lyons MJ., Toomey R, Meyer JM, Green AI, Eisen SA, Goldberg J, True WR, Tsuang

MT. 1997. How do genes influence marijuana use? The role of subjective effects. *Addiction* 92:409—417.

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

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

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

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

[102] Mathre ML. 1998. A survey on disclosure of marijuana use to health care professionals. *Journal of Psychoactive Drugs* 20:117—120.

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

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

[105] Model KE. 1993. The effect of marijuana decriminalization on hospital emergency room drug episodes: 1975—1978. *Journal of the American Statistical Association* 88:737—747.

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

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

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

[109] Nesse RM, Berridge KC. 1997. Psychoactive drug use in evolutionary perspective. *Science* 278:63—66.

[110] Nestler EJ, Aghajanian GK. 1997. Molecular and cellular basis of addiction. *Science* 278:58—63.

[111] Newell GR, Mansell PW, Wilson MB, Lynch HK, Spitz MR, Hersh EM. 1985. Risk factor analysis among men referred for possible acquired immune deficiency syndrome. *Preventive Medicine* 14:81—91.

[112] NIH (National Institutes of Health). 1997. Workshop on the Medical Utility of Marijuana. Report to the Director, National Institutes of Health by the Ad Hoc Group of Experts. Bethesda, MD, February 19—20, 1997. Bethesda, MD: National Institutes of Health.

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

[114] O'Brien CP. 1996. Recent developments in the pharmacotherapy of substance abuse. *Journal of Consulting and Clinical Psychology* 64:677—686.

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

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

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

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

[119] Peterson RC. 1979. Importance of inhalation patterns in determining effects of marijuana use. *Lancet* 1:727—728.

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

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

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

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

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

[125] Robins LN. 1980. The natural history of drug abuse. *Acta Psychiatrica Scandinavica Supplement* 284:7—20.

[126] Robins LN. 1998. The intimate connection between antisocial personality and substance abuse. *Social Psychiatry and Psychiatric Epidemiology* 33:393—399.

[127] Robins LN, McEvoy LT. 1990. Conduct problems as predictors of substance abuse. In: Robins L, Rutter M, Editors, *Straight and Devious Pathways from Childhood to Adulthood*. New York: Cambridge University Press. Pp. 182—204.

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

[129] Rosenzweig MR, Leiman AL, Breedlove SM. 1996. *Biological Psychology*. Sunderland, MA: Sinauer Associates.

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

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

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

[133] Scheier LM, Botvin GJ. 1996. Cognitive effects of marijuana. *Journal of the American Medical Association* 275:JAMA Letters.

[134] Schneier FR, Siris SG. 1987. A review of psychoactive substance use and abuse in schizophrenia: Patterns of drug choice. *Journal of Nervous and Mental Disease* 175:641—652.

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

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

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

[138] Sidney S, Beck JE, Tekawa IS, Quesenberry CP Jr, Friedman GD. 1997a. Marijuana use and mortality. *American Journal of Public Health* 87:585—590.

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

[140] Solowij N. 1995. Do cognitive impairments recover following cessation of cannabis use? *Life Sciences* 56:2119—2126.

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

[142] Stenchever MA, Kunysz TJ, Allen MA. 1974. Chromosome breakage in users of marijuana. *American Journal of Gynecology* 118:106—113.

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

[144] Tanda G, Pontieri FE, Di Chiara G. 1997. Cannabinoid and heroin activation of

mesolimbic dopamine transmission by a common μ1 opioid receptor mechanism. *Science* 276:2048—2049.

[145] Tart CT. 1971. *On Being Stoned: A Psychological Study of Marijuana Intoxication*. Palo Alto, CA: Science and Behavior Books.

[146] Tashkin DP, Coulson AH, Clark VA, Simmons M, Bourque LB, Duann S, Spivey GH, Gong H. 1987. Respiratory symptoms and lung function in habitual, heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. *American Review of Respiratory Disease* 135:209—216.

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

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

[149] Taylor FM. 1988. Marijuana as a potential respiratory tract carcinogen: A retrospective analysis. *Southern Medical Journal* 81:1213—1216.

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

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

[152] Tindall B, Cooper D, Donovan B, Barnes T, Philpot C, Gold J, Penny R. 1988. The Sydney AIDS Project: Development of acquired immunodeficiency syndrome in a group of HIV seropositive homosexual men. *Australian and New Zealand Journal of Medicine* 18:8—15.

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

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

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

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

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

[158] Wehner FC, Van Rensburg SJ, Theil PF. 1980. Mutagenicity of marijuana and transkei tobacco smoke condensates in the salmonella/microsome assay. *Mutation Research* 77:135—142.

[159] Wenger T, Croix D, Tramu G, Leonardelli J. 1992. Effects of delta-9-tetrahydrocannabinol on pregnancy, puberty, and the neuroendocrine system. In: Murphy L, Bartke A, Editors. *Marijuana/Cannabinoids: Neurobiology and Neurophysiology*. Boca

Raton, FL: CRC Press.

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

[161] Whitfield RM, Bechtel LM, Starich GH. 1997. The impact of ethanol and marinol/marijuana usage on HIV+/AIDS patients undergoing azidothymidine, azidothymidine/dideoxycytidine, ordideoxyinosine therapy. *Alcoholism Clinical and Experimental Research* 21:122—127.

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

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

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

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 α_2 adrenoreceptor in cannabinoid analgesia.[111] Perhaps a combination of a CB_1 agonist and an α_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 Δ^9-THC and Δ^8-THC) and the synthetic cannabinoids nabilone and levonantradol. Smoked marijuana has also been examined.

Antiemetic Properties of THC

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

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

In a carefully controlled double-blind study comparing THC with the

antiemetic drug metoclopramide, in which no patient had previously received chemotherapy and in which anticipatory emesis was therefore not a factor, all patients received the same dose of cisplatin and were randomly assigned to the THC group or the metoclopramide group. Complete control of emesis occurred in 47% of those treated with metoclopramide and 13% of those treated with THC.[58] Major control (two or fewer episodes) occurred in 73% of the patients given metoclopramide compared to 27% of 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. Δ^8-THC is less psychoactive than THC[151] but was found to completely block both acute and delayed chemotherapy-induced emesis in a study of eight children, ages 3—13 years.[2] Two hours before the start of each cancer treatment and every six hours thereafter for 24 hours, the children were given Δ^8-THC as oil drops on the tongue or in a bite of bread (18 mg/m^2 body surface area). The children received a total of 480 treatments. The only side effects reported were slight irritability in two of the youngest children (3.5 and 4 years old). Based on the prediction that the THC-induced anxiety effects would be less in children than in adults, the authors used doses that were higher than those recommended for adults (5 — 10 mg/m^2 body surface area).

Antiemetic Properties of Synthetic THC Analogues

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

Antiemetic Properties of Marijuana

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

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 Δ^9-THC, Δ^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 Δ^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]

REFERENCES

[1] Alm A, Camras CB, Watson PG. 1997. Phase III latanoprost studies in Scandanavia, the United Kingdom and the United States. *Survey of Ophthalmology* 41:S105—S110.

[2] Alward WL. 1998. Medical management of glaucoma. *The New England Journal of Medicine* 339:1298—1307.

[3] AMA (American Medical Association Council on Scientific Affairs). 1997. *Report to the AMA House of Delegates*. Chicago: AMA.

[4] Ames FR. 1986. Anticonvulsant effect of cannabidiol. *South African Medical Journal* 69:14.

[5] Andreoli TE, Carpenter CC, Bennet CJ, Plum F, eds. 1997. *Cecil Essentials of Medicine*. Fourth Edition. Philadelphia: W.B. Saunders Co.

[6] Andrews PL, Davis CJ. 1995. The physiology of emesis induced by anti-cancer therapy. In: Reynolds DJ, Andrews PL, Davis CJ, Editors, *Serotonin and the Scientific Basis of Anti-Emetic Therapy*. Oxford: Oxford Clinical Communications. Pp. 25—49.

[7] Bayer R, O'Connell TJ, Lapey JD. 1997. Medicinal uses of marijuana (Letter to the Editor). *Annals of Internal Medicine* 127:1134—1135.

[8] Beal JE, Olson RLL, Morales JO, Bellman P, Yangco B, Lefkowitz L, Plasse TF, Shepard KV. 1995. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *Journal of Pain and Symptom Management* 10:89—97.

[9] Beal JE, Olson R, Lefkowitz L, Laubenstein L, Bellman P, Yangco B, Morales JO, Murphy R, Powderly W, Plasse TF, Mosdell KW, Shepard KV. 1997. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *Journal of Pain and Symptom Management* 14:7—14.

[10] Bhasin S, Storer TW, Asbel-Sethi N, Kilbourne A, Hays R, Sinha-Hikim I, Shen R, Arver S, Beall G. 1998. Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. *Journal Clinical of Endocrinology and Metabolism* 83:3155—3162.

[11] Billingsley KG, Alexander HR. 1996. The pathophysiology of cachexia in advanced cancer and AIDS. In: Bruera E, Higginson I, Editors, *Cachexia-Anorexia in Cancer Patients*. New York: Oxford Universtiy Press. Pp. 1—22.

[12] Borison HL, McCarthy LE. 1983. Neuropharmacology of chemotherapy-induced emesis. *Drugs* 25:8—17.

[13] British Medical Association. 1997. *Therapeutic Uses of Cannabis*. Amsterdam, The Netherlands: Harwood Academic Publishers.

[14] Bruera E. 1998. Pharmacological treatment of cachexia: Any progress? *Supportive Care of Cancer* 6:109—113.

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

[16] Camras CB, Alm A, Watson P, Stjernschantz J. 1996. Latanoprost, a prostaglandin analog, for glaucoma therapy: Efficacy and safety after 1 year of treatment in 198 patients. Latanoprost Study Groups. *Ophthalmology* 103:1916—1924.

[17] (CDC) Centers for Disease Control. 1992. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR (Morbidity Mortality Weekly Report)* 41(RR-17):1—19.

[18] Chang AE, Shiling DJ, Stillman RC, et al. 1979. Delta-9-tetrahydrocannabinol as an antiemetic in patients receiving high-dose methotrexate: A prospective, randomized evaluation. *Annals of Internal Medicine* 91:819—824.

[19] Chang AE, Shiling DJ, Stillman RC, Goldberg NH, Seipp CA, Barofsky I, Rosenberg SA. 1981. A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and cytoxan chemotherapy. *Cancer* 47:1746—1751.

[20] Chauhan BC, Drance SM. 1992. The relationship between intraocular pressure and visual field progression in glaucoma. *Graefe's Archives for Clinical and Experimental Ophthalmology* 230:521—526.

[21] Clark RA, Tyson LB, Frisone M. 1985. A correlation of objective and subjective parameters in assessing antiemetic regimens. *Proceedings of the Tenth Anniversary Congress of the Oncology Nursing Society* 2:96.

[22] Clark WC, Janal MN, Zeidenberg P, Nahas GG. 1981. Effects of moderate and high doses of marihuana on thermal pain: A sensory decision theory analysis. *Journal of Clinical Pharmacology* 21:299S—310S.

[23] Clarke RC. 1995. *Marijuana Botany--An Advanced Study: The Propagation and Breeding of Distinctive Cannabis*. Berkeley, CA: Ronin Publishing.

[24] Clifford DB. 1983. Tetrahydrocannabinol for tremor in multiple sclerosis. *Annals of Neurology* 13:669—671.

[25] Consroe P. 1998a. Clinical and experimental reports of marijuana and cannabinoids in spastic disorders. In: Nahas GG, Sutin KM, Harvey DJ, Agurell S, Editors, *Marijuana and Medicine*. Totowa, NJ: Humana Press.

[26] Consroe P. 1998b. Brain cannabinoid systems as target for the treatment of neurological disorders. *Neurobiology of Disease* 5:534—551.

[27] Consroe P, Laguna J, Allender J, Snider S, Stern L, Sandyk R, Kennedy K, Schram K. 1991. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacology, Biochemistry and Behavior (New York)* 40:701—708.

[28] Consroe P, Musty R, Rein J, Tillery W, Pertwee RG. 1997. The perceived effects of smoked cannabis on patients with multiple sclerosis. *European Neurology* 38:44—48.

[29] Consroe P, Sandyk R. 1992. Potential role of cannabinoids for therapy of neurological disorders. In: Bartke A, Murphy LL, Editors, *Marijuana/Cannabinoids: Neurobiology and Neurophysiology*. Boca Raton, FL: CRC Press. Pp. 459—524.

[30] Consroe P, Sandyk R, Snider SR. 1986. Open label evaluation of cannabidiol in dystonic movement disorders. *International Journal of Neuroscience* 30:277—282.

[31] Cooler P, Gregg JM. 1977. Effect of delta—9—tetrahydrocannabinol on intraocular pressure in humans. *Southern Medical Journal* 70:951—954.

[32] Crawford WJ, Merritt JC. 1979. Effects of tetrahydrocannabinol on arterial and-intraocular hypertension. *International Journal of Clinical Pharmacology and Biopharmacy* 17:191—196.

[33] Crow S. 1997. Investigational drugs for eating disorders. *Expert Opinion on Investigational Drugs* 6:427—436.

[34] Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, Sanvito WL, Lander N, Mechoulam R. 1980. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology* 21:175—185.

[35] Davis CJ. 1995. Emesis research: A concise history of the critical concepts and experiments. In: Reynolds DJ, Andrews PL, Davis CJ, Editors, *Serotonin and the Scientific Basis of Anti-Emetic Therapy*. Oxford : Oxford Clinical Communications. Pp. 9—24.

[36] DeLong MR, Georgopoulos AP, Crutcher MD, Mitchell S J, Richardson RT, Alexander GE. 1984. Functional organization of the basal ganglia: Contributions of single-cell recording studies. *CIBA Foundation Symposium* 107:64—82.

[37] DeMulder PH, Seynaeve C, Vermorker JB, et al. 1990. Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting: A multicenter, randomized, double-blind, crossover study. *Annals of Internal Medicine* 113:834—840.

[38] Doblin R, Kleiman MA. 1995. The medical use of marijuana: The case for clinical trials [editorial; comment]. *Journal of Addictive Diseases* 14:5—14; Comment in *Journal of Addictive Diseases* 1994, 13(1):53—65.

[39] Doblin R, Kleiman M. 1991. Marijuana as antiemetic medicine: A survey of oncologists' experiences and attitudes. *Journal of Clinical Oncology* 9:1314—1319.

[40] Dunlop R. 1996. Clinical epidemiology of cancer cachexia. In: Bruera E, Higginson I, Editors, *Cachexia-Anorexia in Cancer Patients*, Vol. 5. Oxford: Oxford University Press. Pp. 76—82.

[41] Dunn M, Davis R. 1974. The perceived effects of marijuana on spinal cord injured males. *Paraplegia* 12:175.

[42] Eidelberg D, Moeller JR, Antonini A, Kazumata K, Dhawan V, Budman C, Feigin A. 1997. The metabolic anatomy of Tourette's syndrome. *Neurology* 48:927—934.

[43] El-Mallakh RS. 1987. Marijuana and migraine. *Headache* 27:442—443.

[44] Engelson ES, Rabkin JG, Rabkin R, Kotler DP. 1996. Effects of testosterone upon body composition. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* 11:510—511.

[45] Enoch M, Kaye WH, Rotondo A, Greenberg BD, Murphy DL, Goldman D. 1998. 5-HT2A promoter polymorphism-1438G/A, anorexia nervosa, and obsessive-compulsive disorder. *The Lancet* 351:1785—1786.

[46] Follmann P, Paltotas C, Suveges I, Petrovits A. 1996—1997. Nocturnal blood pressure and intraocular pressure measurement in glaucoma patients and healthy controls.

International Ophthalmology 20:83—87.

[47] Foltin RW, Fischman MW, Byrne MF. 1988. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite* 11:1—14.

[48] Frankel JP, Hughes A, Lees AJ, Stern GM. 1990. Marijuana for Parkinsonian tremor. *Journal of Neurology, Neurosurgery and Psychiatry* 53:436.

[49] French J. 1998. The art of antiepileptic trial design. *Advances in Neurology* 76:113—123.

[50] Frytak S, Moertel CG, O'Fallon J, et al. 1979. Delta-9-tetrahydrocannabinol as an antiemetic in patients treated with cancer chemotherapy: A double comparison with prochloperazine and a placebo. *Annals of Internal Medicine* 91:825—830.

[51] Glass M, Dragunow M, Faull RLM. 1997. Cannabinoid receptors in the human brain: A detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience* 77:299—318.

[52] Goadsby PJ, Gundlach AL. 1991. Localization of [3H]-dihydroergotamine binding sites in the cat central nervous system: Relevance to migraine. *Annals of Neurology* 29:91—94.

[53] Gonzalez EC, Brownlee HJ. 1998. Movement disorders. In: Taylor RB, Editor, *Family Medicine: Principles and Practice*. 5th Edition. New York: Springer-Verlag. Pp. 565—573.

[54] Gorter R. 1991. Management of anorexia-cachexia associated with cancer and HIV infection. *Oncology (Supplement)* 5:13—17.

[55] Gralla RJ, Itri LM, Pisko SE, et al. 1981. Antiemetic efficacy of high dose metoclopramide: Randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. *New England Journal of Medicine* 305:905—909.

[56] Gralla RJ, Navari RM, Hesketh PJ, et al. 1998. Single-dose oral granisetron has equivalent antiemetic efficacy to intravenous ondansetron for highly emetogenic cisplatin-based chemotherapy. *Journal of Clinical Oncology* 16:1—7.

[57] Gralla RJ, Rittenberg CN, Lettow LA, et al. 1995. A unique all-oral, single-dose, combination antiemetic regimen with high efficacy and marked cost saving potential. *Proceedings of the American Society for Clinical Oncology* 14:526.

[58] Gralla RJ, Tyson LB, Borden LB, et al. 1984. Antiemetic therapy: A review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. *Cancer Treatment Reports* 68:163—172.

[59] Grandara DR, Roila F, Warr D, Edelman MJ, Perez EA, Gralla RJ. 1998. Consensus proposal for 5HT3 antagonists in the prevention of acute emesis related to highly emetogenic chemotherapy: Dose, schedule, and route of administration. *Supportive Care in Cancer* 6:237—243.

[60] Green K, Roth M. 1982. Ocular effects of topical administration of delta-9-tetrahydrocannabinol in man. *Archives of Ophthalmology* 100:265—267.

[61] Greenberg HS, Werness SA, Pugh JE, Andrus RO, Anderson DJ, Domino EF. 1994. Short-term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers. *Clinical Pharmacology and Therapeutics* 55:324—328.

[62] Grinspoon L, Bakalar JB. 1993. *Marijuana: The Forbidden Medicine*. New Haven: Yale

University Press.

[63] Grinspoon L, Bakalar JB, Zimmer L, Morgan JP. 1997. Marijuana addiction [Letter]. *Science* 277:749; discussion. 750—752.

[64] Grinspoon S, Corcoran C, Askari H, Schoenfeld D, Wolf L, Burrows B, Walsh M, Hayden D, Parlman K, Anderson E, Basgoz N, Klibanski A. 1998. Effects of androgen administration in men with the AIDS wasting syndrome. *Annals of Internal Medicine* 129:18—26.

[65] Gross H, Egbert MH, Faden VB, Godberg SC, Kaye WH, Caine ED, Hawks R, Zinberg NE. 1983. A double-blind trial of delta-9-THC in primary anorexia nervosa. *Journal of Clinical Psychopharmacology* 3:165—171.

[66] Guyatt GH, Keller JL, Jaeschke R, Rosenbloom D, Adachi JD, Newhouse MT. 1990. The N-of-1 randomized controlled trial--clinical usefulness: Our three-year experience. *Annals of Internal Medicine* 112:293—299.

[67] Guyatt GH, Sackett D, Taylor DW, Chong J, Roberts R, Pugsley S. 1986. Determining optimal therapy: Randomized trials in individual patients. *New England Journal of Medicine* 314:889—892.

[68] Guyton AC. 1986. *Textbook of Medical Physiology*. 7th ed. Philadelphia: WB Saunders Company.

[69] Hall W. 1997. An ongoing debate. *Science* 278:75.

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

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

[72] Hanigan WC, Destree R, Truong XT. 1986. The effect of delta-9-THC on human spasticity. *Clinical Pharmacology and Therapeutics* 39:198.

[73] Hardin TC. 1993. Cytokine mediators of malnutrition: Clinical implications. *Nutrition in Clinical Practice* 8:55—59.

[74] Hayreh SS, Zimmerman MB, Podhajsky P, Alward W. 1994. Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. *American Journal of Ophthalmology* 117:603—624.

[75] Hemming M, Yellowlees PM. 1993. Effective treatment of Tourette's syndrome with marijuana. *Journal of Psychopharmacology* 7:389—391.

[76] Hepler RS, Frank IM, Petrus R. 1976. Ocular effects of marijuana smoking. In: Braude MC, Szara S, Editors, *The Pharmacology of Marijuana*. New York: Raven Press. Pp. 815—824.

[77] Hepler RS, Frank IR. 1971. Marihuana smoking and intraocular pressure. *Journal of the American Medical Association* 217(10):1392.

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

[79] Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC. 1991b.

Characterization and localization of cannabinoid receptors in rat brain: A quantitative *in vitro* autoradiographic study. *Journal of Neuroscience* 11:563—583.

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

[81] Herrstedt J, Aapro MS, Smyth JF, Del Favero A. 1998. Corticosteroids, dopamine antagonists and other drugs. *Supportive Care in Cancer* 6:204—214.

[82] Hesketh PJ, Gralla RJ, duBois A, Tonato M. 1998. Methodology of antiemetic trials: Response assessment, evaluation of new agents and definition of chemotherapy emetogenicity. *Supportive Care in Cancer* 6:221—227.

[83] Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, Aapro MS, Gandara D, Lindley CM. 1997. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *Journal of Clinical Oncology* 15:103—109.

[84] Hill SY, Schwin R, Goodwin DW, Powell BJ. 1974. Marihuana and pain. *Journal of Pharmacology and Experimental Therapeutics* 188:415—418.

[85] Holdcroft A, Smith M, Jacklin A, Hodgson H, Smith B, Newton M, Evans F. 1997. Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia* 5:483—486.

[86] Homesley HD, Gainey JM, Jobson VN, et al. 1982. Double-blind placebo-controlled study of metoclopramide in cisplatin-induced emesis. *New England Journal of Medicine* 307:250—251.

[87] Huestis MA, Henningfield JE, Cone EJ. 1992. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. *Journal of Analytical Toxicology* 16:276—282.

[88] Italian Group for Antiemetic Trials. 1995. Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. *New England Journal of Medicine* 332:332—337.

[89] Jain AK, Ryan JR, McMahon FG, Smith G. 1981. Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *Journal of Clinical Pharmacology* 21:320S—326S.

[90] Jay WM, Green K. 1983. Multiple-drop study of topically applied 1% Δ^9-tetrahydrocannabinol in human eyes. *Archives of Ophthalmology* 101:591—593.

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

[92] Kass MA, Gordon MO, Hoff MR, Pardinson JM, Kolker AE, Hart WM, Becker B. 1989. Topical timolol administration reduces the incidence of glaucomatous damage in ocular hypertensive individuals: A randomized, double-masked, long-term clinical trial. *Archives of Ophthalmology* 107:1590—1598.

[93] Kaufman P, Mittag TW. 1994. Medical therapy of glaucoma. In: Kaufman P, Mittag TW, Editors, *Textbook of Ophthalmology*. Volume 7. London: Mosby-Yearbook.

[94] Kotler DP. 1997. Wasting Syndrome Pathogenesis and Clinical Markers. *Institute of Medicine Workshop*. Irvine, CA, December 15, 1997. Pp. 56—66. Washington, DC: Institute of Medicine.

[95] Kotler DP, Gaetz HP, Klein EB, Lange M, Holt PR. 1984. Enteropathy associated with the acquired immunodeficiency syndrome. *Annals of Internal Medicine* 101:421—428.

[96] Kotler DP, Tierney AR, Culpepper-Morgan JA, Wang J, Peirson RN. 1990. Effect of home total parental nutrition on body composition in patients with acquired immunodeficiency syndrome. *Journal of Parenteral Nutrition* 14:454—458.

[97] Kotler DP, Tierney AR, Dilmanian FA, Kamen Y, Wang J, Pierson Jr RN, Weber D. 1991. Correlation between total body potassium and total body nitrogen in patients with acquired immunodeficiency syndrome. *Clinical Research* 39:649A.

[98] Kotler DP, Tierney AR, Ferraro R, et al. 1991. Enteral alimentation and repletion of body cell mass in malnourished patients with acquired immunodeficiency syndrome. *American Journal of Clinical Nutrition* 53:149—154.

[99] Kotler DP, Tierney AR, Wang J, Pierson RN. 1989. Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. *American Journal of Clinical Nutrition* 50:444—447.

[100] Kotler DP, Wang J, Pierson RN. 1985. Studies of body composition in patients with the acquired immunodeficiency syndrome. *American Journal of Clinical Nutrition* 42:1255—1265.

[101] Kris MG, Gralla RJ, Clark RA, et al. 1987. Antiemetic control and prevention of side effects of anticancer therapy with lorazepam or diphenhydramine when used in combination with metoclopramide plus dexamethasone: A double-blind randomized trial. *Cancer* 60:2816—2822.

[102] Kris MG, Radford JE, Pizzo BA, et al. 1997. Use of an NK-1 receptor antagonist to prevent delayed emesis following cisplatin. *Journal of the National Cancer Institute* 89:817—818.

[103] Kris MG, Roila F, De Mulder PH, Marty M. 1998. Delayed emesis following anticancer chemotherapy. *Supportive Care in Cancer* 6:228—232.

[104] Lang IM, Sarna SK. 1989. Motor and myoelectric activity associated with vomiting, regurgitation, and nausea. In: Wood JD, Editor, *Handbook of Physiology: The Gastrointestinal System*. 1, Motility and Circulation. Bethesda, MD: American Physiological Society. Pp. 1179—1198.

[105] Larson EB, Ellsworth AJ, Oas J. 1993. Randomized clinical trials in single patients during a 2-year period. *Journal of the American Medical Association* 270:2708—2712.

[106] Leske MC, Connell AM, Schachat AP, Hyman L. 1994. The Barbados Eye Study: Prevalence of open angle glaucoma. *Archives of Ophthalmology* 112:821—829.

[107] Levitt M, Faiman C, Hawks R, et al. 1984. Randomized double-blind comparison of delta-9-THC and marijuana as chemotherapy antiemetics. *Proceedings of the American Society for Clinical Oncology* 3:91.

[108] Libman E, Stern MH. 1985. The effects of delta-9-tetrahydrocannabinol on cutaneous sensitivity and its relation to personality. *Personality, Individuality and Difference* 6:169—174.

[109] Lichter PR. 1988. A wolf in sheep's clothing. *Ophthalmology* 95:149—150.

Lichtman AH, Cook SA, Martin BR. 1996. Investigation of brain sites mediating cannabinoid-induced antinociception in rats: Evidence supporting periaqueductal gray involvement. *Journal of Pharmacology and Experimental Therapeutics* 276:585—593.

[111] Lichtman AH, Martin BR. 1991. Cannabinoid-induced antinociception is mediated by a spinal alpha-noradrenergic mechanism. *Brain Research* 559:309—314.

[112] Lindgren JE, Ohlsson A, Agurell S, Hollister LE, Gillespie H. 1981. Clinical effects and plasma levels of delta 9-tetrahydrocannabinol (delta 9-THC) in heavy and light users of cannabis. *Psychopharmacology (Berlin)* 74:208—212.

[113] Macallan DC, Noble C, Baldwin C, Foskett M, McManus T, Griffin GE. 1993. Prospective analysis of patterns of weight change in stage IV human immunodeficiency virus infection. *American Journal of Clinical Nutrition* 58:417—424.

[114] Malec J, Harvey RF, Cayner JJ. 1982. Cannabis effect on spasticity in spinal cord injury. *Archives of Physical Medicine and Rehabilitation* 63:116—118.

[115] Mao LK, Stewart WC, Shields M. 1991. Correlation between intraocular pressure control and progressive glaucomatous damage in primary open-angle glaucoma. *American Journal of Ophthalmology* 111:51—55.

[116] Marotta JT. 1995. Spinal injury. In: Rowland LP, Editor. *Merrit's Textbook of Neurology*. 9th Edition. Philadelphia: Lea and Febiger. Pp. 440—447.

[117] Martyn CN, Illis LS, Thom J. 1995. Nabilone in the treatment of multiple sclerosis [Letter]. *Lancet* 345:579.

[118] Mathew NT. 1997. Serotonin 1D (5-HT 1D) agonists and other agents in acute migraine. *Neurologic Clinics* 15:61—83.

[119] Mattes RD, Engelman K, Shaw LM, Elsohly MA. 1994. Cannabinoids and appetite stimulation. *Pharmacology, Biochemistry and Behavior* 49:187—195.

[120] Maurer M, Henn V, Dittrich A, Hoffman A. 1990. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. *European Archives of Psychiatry and Clinical Neuroscience* 240:1—4.

[121] McCarthy LE, Flora KP, Vishnuvajjala BR. 1984. Antiemetic properties and plasma concentrations of delta-9-tetrahydrocannabinol against cisplatin vomiting in cats. In: Agurell S, Dewey WL, Willette RE, Editors, *The Cannabinoids: Chemical, Pharmacologic and Therapeutic Aspects*. Orlando, FL: Academic Press. Pp. 859—870.

[122] McQuay H, Carroll D, Moore A. 1996. Variation in the placebo effect in randomised controlled trials of analgesics: All is as blind as it seems. *Pain* 64:331—335.

[123] Meinck HM, Schonle PW, Conrad B. 1989. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. *Journal of Neurology* 236:120—122.

[124] Merritt JC, Cook CE, Davis KH. 1982. Orthostatic hypotension after delta 9-tetrahydrocannabinol marihuana inhalation. *Ophthalmic Research* 14:124—128.

[125] Merritt JC, Crawford WJ, Alexander PC, Anduze AL, Gelbart SS. 1980. Effect of marihuana on intraocular and blood pressure in glaucoma. *Ophthalmology* 87:222—228.

[126] Mertens TE, Low-Beer D. 1996. HIV and AIDS: Where is the epidemic going? *Bulletin of the World Health Organization* 74:121—129.

[127] Miller AD. 1998. Nausea and vomiting: Underlying mechanisms and upcoming treatments. *Journal of the Japanese Broncho-Esophagological Society* 49:57—64.

[128] Miller AD, Nonaka S, Siniaia MS, Jakus J. 1995. Multifunctional ventral respiratory group: Bulospinal expiratory neurons play a role in pudendal discharge during vomiting. *Journal of the Autonomic Nervous System* 54:253—260.

[129] Miller AS, Walker JM. 1995. Effects of a cannabinoid on spontaneous and evoked neuronal activity in the substantia nigra pars reticulata. *European Journal of Pharmacology* 279:179—185.

[130] Miller AS, Walker JM. 1996. Electrophysiological effects of a cannabinoid on neural activity in the globus pallidus. *European Journal of Pharmacology* 304:29—35.

[131] Moertel CG, Taylor WF, Roth A, Tyce FA. 1976. Who responds to sugar pills? *Mayo Clinic Proceedings* 51:96—100.

[132] Moldawer LL, Andersson C, Gelin J, Lundholm KG. 1988. Regulation of food intake and hepatic protein synthesis by recombinant-derived cytokines. *American Journal of Physiology* 254:G450—G456.

[133] Mulligan K, Tai VW, Schambelan M. 1997. Cross-sectional and longitudinal evaluation of body composition in men with HIV infection. *Journal of Acquired Immunodeficiency Syndrome* 15:43—48.

[134] Murray CJL, Lopez AD. 1996. *Global Health Statistics: A Compendium of Incidence, Prevalence, and Mortality Estimates for Over 200 Conditions*. Global Burden of Disease and Injury Series, Volume II. Boston, MA: The Harvard School of Public Health.

[135] Navari RM, Reinhardt RR, Gralla RJ, Kris MG, Hesketh PJ, et al. 1999. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. *The New England Journal of Medicine* 340:190—195.

[136] Newell FW, Stark P, Jay WM, Schanzlin DJ. 1979. Nabilone: A pressure-reducing synthetic benzopyran in open-angle glaucoma. *Ophthalmology* 86:156—160.

[137] Ng SKC, Brust JCM, Hauser WA, Susser M. 1990. Illicit drug use and the risk of new-onset seizures. *American Journal of Epidemiology* 132:47—57.

[138] NIH. 1997. Spinal cord injury: Emerging concepts: An NIH workshop. *Proceedings of an NIH Workshop on Spinal Cord Injury*. Bethesda, MD, September 30—October 1, 1996. Bethesda, MD: National Institute of Neurological Disorders and Stroke.

[139] Noyes R, Jr, Brunk SF, Avery DH, Canter A. 1975b. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clinical Pharmacology and Therapeutics* 18:84—89.

[140] Noyes Jr R, Brunk SF, Baram DA, Canter A. 1975a. Analgesic effect of delta-9-tetrahydrocannabinol. *Journal of Clinical Pharmacology* 15:139—143.

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

[142] Orgul S, Kaiser HJ, Flammer J, Gasser P. 1995. Systemic blood pressure and capillary blood-cell velocity in glaucoma patients: A preliminary study. *European Journal of*

Ophthalmology 5:88—91.

[143] Orr LE, McKernan JF, Bloome B. 1980. Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. *Archives of Internal Medicine* 140:1431—1433.

[144] Ott M, Lambke B, Fischer H, Jagre R, Polat H, Geier H, Rech M, Staszeswki S, Helm EB, Caspary WF. 1993. Early changes of body composition in human immunodeficiency virus-infected patients: Tetrapolar body impedance analysis indicates significant malnutrition. *American Journal of Clinical Nutrition* 57:15—19.

[145] Perez EA, Chawla SP, Kaywin PK, et al. 1997. Efficacy and safety of oral granisetron versus IV ondansetron in prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. *Proceedings of the American Society for Clinical Oncology* 16:43.

[146] Perez-Reyes M, Wagner D, Wall ME, Davis KH. 1976. Intravenous administration of cannabinoids and intraocular pressure. In: *The Pharmacology of Marihuana*, New York: Raven Press. Pp. 829—832.

[147] Peroutka SJ. 1996. Drugs effective in the therapy of migraine. In: Hardman JG, Limbird LE, Editors, *Goodman and Gilman's The Pharmacological Basis of Therapeutics* 9th Edition. New York: McGraw-Hill. Pp. 488—502.

[148] Petro D, Ellenberger Jr C. 1981. Treatment of human spasticity with delta 9-tetrahydrocannabinol. *Journal of Clinical Pharmacology* 21:413S—416S.

[149] Quigley HA. 1996. Number of people with glaucoma worldwide. *British Journal of Ophthalmology* 80:389—393.

[150] Raft D, Gregg J, Ghia J, Harris L. 1977. Effects of intravenous tetrahydrocannabinol on experimental and surgical pain: Psychological correlates of the analgesic response. *Clinical Pharmacology and Therapeutics* 21:26—33.

[151] Razdan RK. 1986. Structure-activity relationships in cannabinoids. *Pharmacology Review* 38:75—149.

[152] Richfield EK, Herkenham M. 1994. Selective vulnerability in Huntington's disease: Preferential loss of cannabinoid receptors in lateral globus pallidus. *Annals of Neurology* 36:577—584.

[153] Richter A, Loscher W. 1994. (+)-WIN55,212-2 A novel cannabinoid receptor agonist, exerts antidystonic effects in mutant dystonic hamsters. *European Journal of Pharmacology* 264:371—377.

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

[155] Roila F, Tonato M, Cognetti F, et al. 1991. Prevention of cisplatin-induced emesis: A double-blind multicenter randomized crossover study comparing ondansetron and ondansetron plus dexamethasone. *Journal of Clinical Oncology* 9:674—678.

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

[157] Roth RI, Owen RL, Keren DF, Volberding PA. 1985. Intestinal infection with Mycobacterium avium in acquired immune deficiency syndrome (AIDS): Histological and

clinical comparison with Whipple's disease. *Digestive Disease Science* 30:497—504.

[158] Süttmann U, Ockenga J, Selberg O, Hoogestraat L, Deicher H, Müller MJ. 1995. Incidence and prognostic value of malnutrition and wasting in human immunodeficiency virus--infected outpatients. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* 8:239—246.

[159] Sackett D, Rosenberg W, Haynes B, Richardson S. 1997. *Evidence-Based Medicine: How to Practice and Teach EBM*. New York: Churchhill Livingston.

[160] Sallan SE, Cronin CM, Zelen M, et al. 1980. Antiemetics in patients receiving chemotherapy for cancer: A randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *New England Journal of Medicine* 302:135—138.

[161] Sallan SE, Zinberg NE, Frei E. 1975. Antiemetic effect of delta-9-THC in patients receiving cancer chemotherapy. *New England Journal of Medicine* 293:795—797.

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

[163] Sandyk R, Awerbuch G. 1988. Marijuana and Tourette's syndrome. *Journal of Clinical Psychopharmacology* 8:444—445.

[164] Sandyk R, Consroe P, Stern P, Biklen D. 1988. Preliminary trial of cannabidiol in Huntington's disease. Chesher G, Consroe P, Musty R., Editors. *Marijuana: An International Research Report*. Canberra: Australian Government Publishing Service.

[165] Sanudo-Pena MC, Patrick SL, Patrick RL, Walker JM. 1996. Effects of intranigral cannabinoids on rotational behavior in rats: Interactions with the dopaminergic system. *Neuroscience Letters* 206:21—24.

[166] Sanudo-Pena MC, Tsou K, and Walker JM. Cannabinoid dopamine interactions in the basal ganglia in an animal model of Parkinson disease. (in preparation).

[167] Sanudo-Pena MC, Tsou K, and Walker JM. Superior colliculus and turning: Dopamine and cannabinoids. (in preparation).

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

[169] Sanudo-Pena MC, Walker JM. 1998. Effects of intrastriatal cannabinoids on rotational behavior in rats: Interactions with the dopaminergic system. *Synapse* 30:221—226.

[170] Schambelan M, Mulligan K, Grunfeld C, Daar ES, LaMarca A, Kotler DP. 1996. Recombinant human growth hormone in patients with HIV-associated wasting: A randomized, placebo-controlled trial: Serostim Study Group. *Annals of Internal Medicine* 125:873—882.

[171] Schwartz RH, Beveridge RA. 1994. Marijuana as an antiemetic drug: How useful is it today? Opinions from clinical oncologists [see Comments]. *Journal of Addictive Diseases* 13:53—65.

[172] Schwartz RH, Voth EA. 1995. Marijuana as medicine: Making a silk purse out of a sow's ear. *Journal of Addictive Diseases* 14:15—21.

[173] Shields MB. 1998. *Textbook of Glaucoma*. 4th Edition. Baltimore, MD: Williams &

Wilkins.

[174] Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt J, Singh K. 1991. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans: The Baltimore Eye Survey. *Archives of Ophthalmology* 109:1090—1095.

[175] Staquet M, Gantt C, Machin D. 1978. Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. *Clinical Pharmacology and Therapeutics* 23:397—401.

[176] Steele N, Gralla RJ, Braun Jr DW. 1980. Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. *Cancer Treatments Report* 64:219—224.

[177] Stimmel B. 1995. Medical marijuana: To prescribe or not to prescribe, that is the question [Editorial]. *Journal of Addictive Diseases* 14:1—3.

[178] Strassman RJ. 1998. *Marijuana: The Forbidden Medicine* (book review). *Journal of the American Medical Association* 279:963—964.

[179] Struwe M, Kaempfer SH, Geiger CJ, Pavia AT, Plasse TF, Shepard KV, Ries K, Evans TG. 1993. Effect of dronabinol on nutritional status in HIV infection. *Annals of Pharmacotherapy* 27:827—831.

[180] Swift RM. 1994. *Marijuana: The Forbidden Medicine* (book review). *The New England Journal of Medicine* 331:749—750.

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

[182] Tiedeman JS, Shields MB, Weber PA, Crow JW, Cocchetto DM, Harris WA, Howes JF. 1981. Effect of synthetic cannabinoids on elevated intraocular pressure. *Ophthalmology* 88:270—277.

[183] Timpone JG, Wright DJ, Li N, Egorin MJ, Enama ME, Mayers J, Galetto G, DATRI 004 Study Group. 1997. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome: The DATRI 004 study group. *AIDS Research and Human Retroviruses* 13:305—315.

[184] Trembly B, Sherman M. 1990. Double-blind clinical study of cannabidiol as a secondary anticonvulsant. Unpublished manuscript presented at the Marijuana '90 International Conference on Cannabis and Cannabinoids. Kolympari, Crete, July 8—11.

[185] Tyson LB, Gralla RJ, Clark RA, et al. 1985. Phase I trial of levonantradol in chemotherapy-induced emesis. *American Journal of Clinical Oncology* 8:528—532.

[186] UNAIDS, WHO. 1998. *Report on the Global HIV/AIDS Epidemic, June 1998.*

[187] Ungerleider JT, Andrysiak TA, Fairbanks L, Ellison GW, My LW. 1987. Delta-9-THC in the treatment of spasticity associated with multiple sclerosi *Advances in Alcohol and Substance Abuse* 7:39—50.

[188] Vinciguerra V, Moore T, Brennan E. 1988. Inhalation marijuana as an antiemetic for cancer chemotherapy. *New York State Journal of Medicine* 88:525—527.

Volicer L, Smith S, Volicer BJ. 1995. Effect of seizures on progression of dementia of the Alzheimer type. *Dementia* 6:258—263.

[190] Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. 1997. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry* 12:913—919.

[191] Voth EA, Schwartz RH. 1997. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. *Annals of Internal Medicine* 126:791—798.

[192] Wall PD, Melzack R. 1994. *Textbook of Pain*. Edinburgh: Churchill Livingstone

[193] Walters TR. 1996. Development and use of brimonidine in treating acute and chronic elevations of intraocular pressure: A review of safety, efficacy, dose response, and dosing studies. *Survey of Ophthalmology* 41(Suppl. 1):S19—S26.

[194] Wang ZM, Visser M, Ma R, Baumgartner RN, Kotler DP, Gallagher D, Heymsfield SB. 1996. Skeletal muscle mass: Validation of neutron activation and dual energy X-ray absorptiometry methods by computerized tomography. *Journal of Applied Physiology* 80:824—831.

[195] Whitney EN, Cataldo CB, Rolfes SR. 1994. *Understanding Normal and Clinical Nutrition*. 4th Edition. Minneapolis, MN: West Publishing Co.

[196] Wood. 1998. HIV-protease inhibitors. *Drug Therapy* 338:1281—1292.

[197] Yoles E, Belkin M, Schwartz M. 1996. HU-211, a nonpsychotropic cannabinoid, produces short- and long-term neuroprotection after optic nerve axotomy. *Journal of Neurotrauma* 13:49—57.

[198] Zimmer L, Morgan JP. 1997. *Marijuana Myths, Marijuana Facts*. New York: The Lindesmith Center.

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

[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 Δ^8-THC were demonstrated in a clinical trial in children who were undergoing cancer chemotherapy,[1] but no sponsor was interested in developing Δ^8-THC for commercial purposes (R. Mechoulam, Hebrew University, personal communication, 1998). The absence of plant cannabinoids under development implies that the specter of automatic placement in Schedule I under the CSA is an important deterrent, even though rescheduling would occur before marketing.[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.

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

REGULATION OF AND MARKET OUTLOOK FOR MARIJUANA

Marijuana is not legally marketed in the United States.[12] No sponsor has ever sought marketing approval from the FDA for medical use of marijuana. One sponsor has an IND for a clinical safety study on HIV anorexia (D. Abrams, University of California at San Francisco, personal communication, 1998). Another has an IND pending for the treatment of migraine headaches (E. Russo, Western Montana Clinic, personal communication, 1998). Since 1970, marijuana's manufacture and distribution have been tightly restricted under the CSA, which places marijuana in Schedule I, which is reserved for drugs or other substances with "a high potential for abuse," "no currently accepted medical use," and "lack of accepted safety for use . . . under medical supervision" (21 U.S.C. § 812 (b)(1)).

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

Availability for Research

To use marijuana for research purposes, researchers must register with the DEA, as well as adhere to other relevant requirements of the CSA and other federal statutes, such as the FD&C act. The National Institute on Drug Abuse (NIDA), one of the institutes of NIH, is the only organization in the United States licensed by the DEA to manufacture and distribute marijuana for research purposes. NIDA performs this function under its Drug Supply Program.[14] Through this program, NIDA arranges for marijuana to be grown and processed through contracts with two organizations: the University of Mississippi and the Research Triangle Institute. The University of Mississippi grows, harvests, and dries marijuana; and the institute processes it into cigarettes. A researcher can obtain marijuana free of charge from NIDA through an NIH-approved research grant to investigate marijuana, or through a separate protocol review.[39] Research grant approvals are handled through the conventional NIH peer review process for extramural research, a highly competitive process with a success rate in 1997 of 32% of approved NIDA grants.[41]

Through the separate protocol review, in which a researcher funds research independently of an NIH grant, NIDA submits the researcher's protocol to several external reviewers who evaluate the protocol on the basis of scientific merit and relevance to the mission of NIDA and NIH.

Through those two avenues marijuana has been supplied to several research groups--most of those that apply. While there has been much discussion of NIDA's alleged failure to supply marijuana for research purposes, we are unaware of recent cases in which they failed to supply marijuana to an investigator with an NIH-approved grant for research on marijuana. Donald Abrams's difficulty in obtaining research funding and marijuana from NIDA has been much discussed,[2] but the case of a single individual should not be presumed to be representative of the community of marijuana researchers. Failure of investigators who apply to NIH for marijuana research grants to receive funding is hardly exceptional: in 1998 less than 25% of *all* first time investigator-initiated grant applications (known as RO1s) to the NIH were funded.[35]

To import marijuana under the CSA for research purposes, the procedures are more complex. Under DEA regulations, marijuana can be imported, provided that the researcher is registered with the DEA, has approval for marijuana research (21 CFR § 1301.11, .13, and .18), and has a DEA-approved permit for importation (21 CFR § 1312.11, .12, and .13), and that the exporter in the foreign country has appropriate authorization by the country of exportation. Importation would enable U.S. researchers to conduct research on marijuana grown by HortaPharm, a company that has developed unique strains of marijuana. However, no U.S. researcher has imported HortaPharm's marijuana because Dutch authorities have refused to issue an export permit, despite the issuance of an import permit by the DEA (D. Pate, HortaPharm, personal communication, 1998).[15]

HortaPharm, which is in the Netherlands, grows marijuana as a raw material for the manufacture of pharmaceuticals. Through selective breeding and controlled production, HortaPharm has developed marijuana strains that feature single cannabinoids, such as THC or cannabidiol. The plants contain a consistently "clean" phytochemical profile and a higher concentration of THC (16%) or other desired cannabinoids than seized marijuana. Marijuana seized in the United States in 1996 had a THC content averaging about 5%.[16] Consistency of THC content is desirable because it overcomes the natural variability due to latitude, weather, and soil conditions. Product consistency is a basic tenet of pharmacology because it enables standardized dosing for regulatory and treatment purposes.

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

Regulatory Hurdles to Market

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

Under the FD&C act, a botanical product like marijuana *theoretically* might be marketed in oral form as a dietary supplement;[16] however, as a practical matter, only a new drug approval is likely to satisfy the provisions of the CSA, which require prescribing and distribution controls on drugs of abuse that also have an "accepted medical use." (The final paragraphs of this section clarify the criteria for "accepted medical use.")

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

A handful of botanical preparations are on the market, but none received formal approval as a new drug by today's standards of safety and efficacy (FDA, Center for Drug Evaluation and Research, personal communication, 1998). The three marketed botanical preparations are older drugs that came to market years before safety and efficacy studies were required by legislative amendments in 1938 and 1962, respectively. One of the botanical preparations is the prescription product digitalis. Because it came to market before 1938, it is available today, having been "grandfathered" under the law; but it does not necessarily meet contemporary standards for safety and effectiveness.[20] Two other botanical preparations, psyllium and senna, came to market between 1938 and 1962. Drugs entering the market during that period were later required to be evaluated by the FDA in what is known as the over-the-counter drug review process,[20] through which psyllium and senna were found to be generally recognized as safe and effective and so were allowed to remain on the market as over-the-counter drugs.[17] Although no botanical preparations have been approved as new drugs, it is important to point out that a number of individual plant constituents, either extracted or synthesized *de novo*, have been approved (for example, taxol and morphine). But these drug approvals were for single constituents rather than botanical preparations themselves. The FDA is developing guidance for industry to explain how botanicals are reviewed as new drugs, but the final document might not be available before 1999.

That marijuana is smoked might pose an even greater regulatory challenge. The risks associated with smoking marijuana are described in chapter 2. The FDA would have to weigh those risks with marijuana's

therapeutic benefits to arrive at a judgment about whether a sponsor's NDA for marijuana met the requirements for safety and efficacy under the FD&C act. Marijuana delivered in a novel way that avoids smoking would overcome some, but not all, of the regulatory concerns. Vaporization devices that permit inhalation of plant cannabinoids without the carcinogenic combustion products found in smoke are under development by several groups; such devices would also require regulatory review by the FDA.

The regulatory hurdles to market posed by the CSA are formidable but not insurmountable. If marijuana received market approval as a drug by the FDA, it would most likely be rescheduled under the CSA, as was the case for dronabinol. That is because a new drug approval satisfies the "accepted medical use" requirement under the CSA for manufacture and distribution in commerce.[13] But a new drug approval is not the *only* means to reschedule marijuana under the CSA.[14] For years advocates for rescheduling have argued that marijuana does enjoy "accepted medical use," even in the absence of a new drug approval. Although advocates have been unsuccessful in rescheduling efforts, their actions prompted the DEA to specify the criteria by which it would determine whether a substance had "accepted medical use." In the DEA's 1992 denial of a rescheduling petition, it listed these elements as constituting "accepted medical use": the drug's chemistry must be known and reproducible, there must be adequate safety studies, there must be adequate and well-controlled studies proving efficacy, the drug must be accepted by qualified experts, and the scientific evidence must be widely available.[14]

Assuming that all of those criteria were satisfied, marijuana could be rescheduled--but into which schedule? The level of scheduling would be dictated primarily by a medical and scientific recommendation to the DEA made by the secretary of DHHS.[18] As noted earlier, this recommendation is determined by the five scheduling criteria listed in the CSA. However, scheduling in a category less restrictive than Schedule II might be prohibited by international treaty obligations. The Single Convention on Narcotic Drugs, a treaty ratified by the United States in 1967, restricts scheduling of the plant and its resin to at least Schedule II (the more restrictive Schedule I is another option).[13]

Market Outlook

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

to be safe. Depending on the route of administration, an additional overlay of regulatory requirements might have to be satisfied.

From a commercial point of view, uncertainties abound. The often-cited cost of new drug development, about $200—$300 million, might not apply, but there are probably additional costs needed to satisfy the FDA's requirements for a botanical product. As noted above, no botanical products have ever been approved as new drugs by the FDA under today's stringent standards for safety and efficacy. Satisfying the legal requirements of the CSA also will add substantially to the cost of development. On the positive side, so much research already has been done that some development costs will be lower. The cost of bringing dronabinol to market, for example, was reduced dramatically as a result of clinical trials supported with government funding. Nevertheless, it is impossible to estimate the cost of developing marijuana as a new drug. Estimating return on investment is similarly difficult. A full-fledged market analysis would be required for the indication being sought. Such an analysis would take into account the market limitations resulting from drug scheduling restrictions, stigma, and patentability.

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

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

CONCLUSIONS

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

history, and its small market.

There appear to be only two novel cannabinoids actively being developed for human use, but they have yet to be tested in humans in the United States. Their experience is likely to be more predictive of the marketing prospects for other cannabinoids. It is too early to forecast the prospects for cannabinoids, other than to note that their development at this point is considered to be especially risky, to judge by the paucity of products in development and the small size of the pharmaceutical firms sponsoring them.

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

REFERENCES

[1] Abrahamov A, Abrahamov A, Mechoulam R. 1995. An efficient new cannabinoid antiemetic in pediatric oncology. *Life Sciences* 56:2097—2102.

[2] Abrams DI. 1998. Medical marijuana: Tribulations and trials. *Journal of Psychoactive Drugs* 30:163—169.

[3] AMA (American Medical Association Council on Scientific Affairs). 1997. *Report to the AMA House of Delegates*. Chicago: AMA.

[4] Annas GJ. 1997. Reefer madness--the federal response to California's medical-marijuana law. *The New England Journal of Medicine* 337:435—439.

[5] Arno PS, Bonuck K, Davis M. 1995. Rare diseases, drug development, and AIDS: The impact of the Orphan Drug Act. *Milbank Quarterly* 73:231—252.

[6] Asbury C. 1991. The Orphan Drug Act: The first seven years. *Journal of the American Medical Association* 265:893—897.

[7] Atlantic Pharmaceuticals. 1997. Atlantic Pharmaceuticals' proprietary compound shows promising anti-inflammatory effects in pre-clinical trials [WWW document]. URL http://www.atlan.com/pr_11_10_97et2/prtier.htm (accessed September 1998).

[8] Beal JE, Olson RLL, Morales JO, Bellman P, Yangco B, Lefkowitz L, Plasse TF, Shepard KV. 1995. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *Journal of Pain and Symptom Management* 10:89—97.

[9] Beal JE, Olson R, Lefkowitz L, Laubenstein L, Bellman P, Yangco B, Morales JO, Murphy R, Powderly W, Plasse TF, Mosdell KW, Shepard KV. 1997. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *Journal of Pain and Symptom Management* 14:7—14.

Boseley S. 1998. Multiple sclerosis victims to test medicinal effects of marijuana [WWW document]. URL http://www.anomalous.images/news/news227.HTML (accessed September 8, 1998).

[11] Bouaboula M, Perrachon S, Milligan L, Canat X, Rinaldi-Carmona M, Portier MB, Calandra B, Pecceu F, Lupker J, Maffrand JP, Le Fur G, Casellas P. 1997. A selective inverse agonist for central cannabinoid receptor inhibits mitogen-activated protein kinase activation stimulated by insulin or insulin-like growth factor 1. Evidence for a new model of receptor/ligand interactions. *Journal of Biological Chemistry* 272:22330—22339.

[12] Calhoun, SR, Galloway GP, Smith DE. 1998. Abuse potential of dronabinol (Marinol). *Journal of Psychoactive Drugs* 30:187—196.

[13] Cooper RM. 1980. Therapeutic use of marijuana and heroin: The legal framework. *Food Drug Cosmetic Law Journal* 35:68—82.

[14] DEA (Drug Enforcement Administration). 1992. Marijuana scheduling petition; denial of petition; remand. *Federal Register* 57:10499—10508.

[15] DEA. 1998. Drugs of abuse [WWW document]. URL http://www.usdoj.gov/dea/pubs/abuse/concern.htm (accessed September 1998).

[16] DEA. 1996. The National Narcotics Intelligence Consumers Committee (NNICC) report [WWW document]. URL www.usdoj.gov/dea/pubs/intelmnic97.htm (accessed September 1998).

[17] DEA. 1998b. Rescheduling of synthetic dronabinol from Schedule II to Schedule III. *Federal Register* 63:59751—59753.

[18] DiMasi JA, Brown JS, Lasagna L. 1996. An analysis of regulatory review times of supplemental indications for already approved drugs: 1989—1994. *Drug Information Journal* 30:315—337.

[19] DiMasi JA, Hanson RW, Grabowski HG, Lasagna L. 1995. Research and development costs for new drugs by therapeutic category: A study of the U.S. pharmaceutical industry. *PharmacoEconomics* 7:152—169.

[20] FDA (Food and Drug Administration). 1990. *From Test Tube to Patient: New Drug Development in the United States*. Rockville, MD: U.S. Department of Health and Human Services.

[21] FDA. 1997b. *Draft Guidelines for Research Involving the Abuse Liability Assessment of New Drugs*. Rockville, MD: U.S. Department of Health and Human Services, Division of Anesthetic, Critical Care and Addiction Drug Products.

[22] FDA. 1997a. Center for Drug Evaluation and Research Fact Book [WWW document]. URL http://www.fda.gov/cder/fbhomepage (accessed September 1998).

[23] FDA. 1998a. Center for Drug Evaluation and Research Handbook [WWW document] URL http://www.fda.cder/handbook.htm (accessed September 1998).

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

[24] FDA. 1998c. Guidance for industry: Providing clinical evidence of effectiveness for human drugs and biological products. Center for Drug Evaluation and Research, Center for

Biologics Evaluation and Research. May 1998 [WWW document]. URL http://www.fda.gov/cder/guidance/1397fnl.pdf (accessed September 1998).

[25] FDA. 1998d. Office of Orphan Products Development Program Overview [WWW document]. URL http://www.fda.gov/orphan/DESIGNA1recent.htm (accessed October 14, 1998).

[26] Felder CC, Glass M. 1998. Cannabinoid receptors and their endogenous agonists. *Annual Reviews of Pharmacology and Toxicology* 38:179—200.

[27] Glain SJ. 1998. I. *Wall Street Journal*.

[28] Gollin MA. 1994. Patenting recipes from nature's kitchen: How can a naturally occurring chemical like taxol be patented? *Biotechnology (NY)* 12:406—407.

[29] Hampson AJ, Grimaldi M, Axelrod J, Wink D. 1998. Cannabidiol and (—)delta-9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences USA* 95:8268—8273.

[30] Howlett AC. 1995. Pharmacology of cannabinoid receptors. *Annual Review of Pharmacology and Toxicology* 35:607—634.

[31] IOM (Institute of Medicine). 1990. *Medical Utilization of Clinical Investigations*. Washington, DC: National Academy Press.

[32] IOM. 1991. *Expanding Access to Investigational Therapies for HIV Infection and AIDS*. Washington, DC: National Academy Press.

[33] IOM. 1995. *The Development of Medications for the Treatment of Opiate and Cocaine Addictions: Issues for the Government and Private Sector*. Washington, DC: National Academy Press.

[34] IOM. 1996. *Pathways of Addiction: Opportunities in Drug Abuse Research*. Washington, DC: National Academy Press.

[35] Knoller N, Levi L, Israel Z, Razon N, Reichental E, Rappaport Z, Ehrenfreund N, Biegon A. Safety and outcome in a Phase II clinical trail of dexanabinol in severe head trauma. Congress of Neurological Surgeons Annual Meeting. Seattle, WA, Oct. 7, 1998.

[36] Mechoulam R, Hanus L, Fride E. 1998. Towards cannabinoid drugs--revisited. In: Ellis GP, Luscombe DK, Oxford AW, Editors, *Progress in Medicinal Chemistry*, vol. 35. Amsterdam: Elsevier Science. Pp. 199—243.

[37] Nainggolan L. 1997. Marijuana--a missed market opportunity? *Scrip Magazine*.

[38] National Institutes of Health (NIH). 1999. http://www.nih.gov/grants/oer/clinguid/.

[39] NIDA (National Institute on Drug Abuse). 1996. *Research Resources: Drug Supply System, 10th Edition*. Rockville, MD.

[40] NIH (National Institutes of Health). 1997. Workshop on the Medical Utility of Marijuana. Report to the Director, National Institutes of Health by the Ad Hoc Group of Experts. Bethesda, MD, February 19—20, 1997. Bethesda, MD: National Institutes of Health.

[41] NIH. 1998. FY (1970—1997 NIH (Preliminary) competing research project applications [WWW document]. URL http://silk.nih.gov/public/cby2r1m.@www.comic.dsice (accessed

October 1998).

[42] Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. 1980. Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clinical Pharmacology and Therapeutics* 28:409—416.

[43] OTA (Office of Technology Assessment). 1991. *Biotechnology in a Global Economy*. OTA-BA-494. Washington, DC: U.S. Government Printing Office.

[44] OTA. 1993. *Pharmaceutical R&D: Costs, Risks and Rewards*. OTA-H-522. Washington, DC: U.S. Government Printing Office.

[45] PDR (Physicians' Desk Reference). 1996. *Physicians' Desk Reference*. 50th ed. Montvale, NJ: Medical Economics Co.

[46] Pertwee RG. 1997. Cannabis and cannabinoids: Pharmacology and rationale for clinical use. *Pharmaceutical Science* 3:539—545.

[47] Plasse TF, Gorter RW, Krasnow SH, Lane M, Shepard KV, Wadleigh RG. 1991. Recent clinical experience with dronabinol. *Pharmacology Biochemistry and Behavior* 40:695—700.

[48] Randall IV B. 1993. *Medical Use of Marijuana: Policy and Regulatory Issues*. 93-308 SPR. Washington, DC: Congressional Research Service.

[49] Schmidt WK. 1998. Overview of current investigational drugs for the treatment of chronic pain. National Managed Health Care Congress, Second Annual Conference on Therapeutic Developments in Chronic Pain. Annapolis, MD, May 18, 1998.

[50] Shapiro RS. 1994. Legal bases for the control of analgesic drugs. *Journal of Pain and Symptom Management* 9:153—159.

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

[52] Shohami E, Weidenfeld J, Ovadia H, Vogel Z, Hanus L, Fride E, Breuer A, Ben-Shabat S, Sheskin T, Mechoulam R. 1996. Endogenous and synthetic cannabinoids: Recent advances. *CNS Drug Reviews* 2:429—451.

[53] Spilker B. 1989. *Multinational Drug Companies: Issues in Drug Discovery and Development*. New York: Raven Press.

[54] Standaert DG, Young AB. 1996. Treatment of central nervous system degenerative disorders. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RR, Gilman AG, Editors. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. 9th ed. New York: McGraw-Hill. Pp. 503—519.

[55] Striem S, Bar-Joseph A, Berkovitch Y, Biegon A. 1997. Interaction of dexanabinol (HU-211), a novel NMDA receptor antagonist, with the dopaminergic system. *European Journal of Pharmacology* 388:205—213.

[56] Timpone JG, Wright DJ, Li N, Egorin MJ, Enama ME, Mayers J, Galetto G, DATRI 004 Study Group. 1997. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. The DATRI 004 study group. *AIDS Research and Human Retroviruses* 13:305—315.

Turk DC, Brody MC, Akiko OE. 1994. Physicians' attitudes and practices regarding the long-term prescribing of opioids for non-cancer pain. *Pain* 59:201—208.

[58] Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. 1997. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry* 12:913—919.

[59] Voth EA, Schwartz RH. 1997. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. *Annals of Internal Medicine* 126:791—798.

[60] Wall ME, Sadler BM, Brine D, Taylor H, Perez-Reyes M. 1983. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. *Clinical Pharmacology and Therapeutics* 34:352—363.

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

Notes

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

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

[3] Marijuana cigarettes were available under a special FDA-sponsored Compassionate Investigational New Drug Program for desperately ill patients until March 1992, when the program was closed to new participants.[45]

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

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

[6] Technically, the CSA and the regulations use the term "tetrahydrocannabinols."

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

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

[9] The DEA did not provide an estimate of the weight of marijuana per bag.

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

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

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

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

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

[15] It might eventually be possible to import HortaPharm's marijuana from England, where HortaPharm is growing its marijuana strains for research use in clinical trials for multiple sclerosis (Boseley, 1998).[49] England, as the country of origin, would have to provide appropriate authorization for export of the strains to the United States. Permission to export for research purposes is part of the basis for HortaPharm's participation in this project with GW Pharmaceuticals through a special set of licenses with the British Home Office (David Pate, HortaPharm, personal communication, 1998).

[16] Inhaled products may not lawfully be marketed as dietary supplements.

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

[18] At present, there is no practical mechanism for generating such a recommendation outside the new drug approval process, although such a mechanism could, theoretically, be developed.[19]

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Appendix A

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

Donald I. Abrams
University of California at San Francisco

Jill Aguilera
Colorado Federation of Parents

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

Roger D. Anderson
Anderson Clinical Research

M. Douglas Anglin
UCLA Drug Abuse Research Center

Dave Baleria
Jackson County Sheriff's Office

Joe Barker

Frank Bartosic
Minister of Universal Life Church

Dana Beal
Cures Not Wars

J. Bellam
Center for Drug Information

Sandra S. Bennett
Northwest Center for Health and Safety

Anna T. Boyce
California Senior Legislature (Prop 215)

William Britt

Richard Brookhiser
National Review

Ronald Brooks
California Narcotic Officers Association

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

Al Byrne
Patients Out of Time

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

Steven Childers
Bowman Gray School of Medicine
Wake Forest University

Barb Christensen
Prevention Partners

Gale Cincotta
National People's Action

Carol Coburn
Prevention Partners

Chris Conrad
Author of *Hemp for Health*

Paul Consroe
University of Arizona

J. Richard Crout
Private Consultant

Judy Cushing
Oregon Partnership, National Family Partnership

John De Miranda
Peninsula Health Concepts

Mahendra Dedhiya
Roxane Laboratories, Inc.

Robert Deitch
Cannabis Freedom Fund

Philip Diaz
Physicians for Prevention

Stephen L. Dilts

American Academy of Addiction Psychiatry

Rick Doblin
MAPS and Kennedy School of Government

Del Dolton

Barbara Douglass

Drug-Free Youth--USA

Robert Dudley
UNIMED

Victoria Duran
National Parents and Teachers Association

David Edwards

Edward Ehman
Certified Prevention Specialist

Mahmoud ElSohly
University of Mississippi

Mouncey Ferguson

Howard L. Fields
University of California at San Francisco

Jody Fitt

Richard W. Foltin
Columbia University

Etienne Fontan
Cannabis Alliance of Veterans, 1st CAV

Meg Foster

Phyllis Gardner
ALZA Corporation

Charles V. Giannasio
American Academy of Addiction Psychiatry

Dale Gieringer
California NORML, Friends of 215

Mark Gold
University of Florida Brain Institute

Richard Gralla
OCHSNER Cancer Institute

Linda Hall

Pride, Omaha, Inc.

Margaret Haney
Columbia University

Ann Hansen
Michigan Communities in Action for Drug-Free Youth

Jim Hardin

Terry Hensley
Drug-Free America Foundation

Kimberly Hessel
American Cancer Society and Muscatine General Hospital

Michele Hodak
National Education Association

Leo Hollister
Harris County Psychiatric Center

Jennifer Hudson
Oregonians Against Dangerous Drugs

Paul Isford

Becki Jelinek
Family Service/South Omaha Counseling

Jeffery Jones
Oakland Cannabis Buyers' Cooperative

Linda R. Wolf Jones
Therapeutic Communities of America

Norbert E. Kaminski
Michigan State University

Robert Kampia
Marijuana Policy Project

Paul L. Kaufman
University of Wisconsin Medical School

Andrew Kinnon

Thomas Klein
University of South Florida College of Medicine

Audra Koerber
Orange County Patient, Doctor, Nurse Support Group

Ellen Komp
San Luis Obispo Citizens for Medical Marijuana

George Koob
Scripps Research Institute

Thomas R. Kosten
American Academy of Addiction Psychiatry

Donald Kotler
St. Luke's-Roosevelt Hospital

Michael Krawitz
Disabled American Veterans, American Legion

Kiyoshi Kuromiya
Critical Path AIDS Project

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

Eric Larson
University of Washington Medical Center

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

Carla Lowe

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

Patrick Magee
Orange County Hemp Council

Robert L. Maginnis
Family Research Council

Billy R. Martin
Virginia Commonwealth University

Mary Lynn Mathre
Patients Out of Time

Jeane McCarty
West Coast Neonatology

Todd McCormick

JoAnna McKee
Green Cross Patient Co-Op

Manon McKinnon
Empower America

George McMahon

Peter McWilliams

John Edward Mendelson
University of California at San Francisco

Bonnie Metcalf
Yuba County Compassionate Use Co-Op

R. Mikin
American Academy of Addiction Psychiatry

Alan D. Miller
The Rockefeller University

Jim Montgomery

John P. Morgan
City University of New York Medical School

Arlene Munoz
Office of Substance Abuse, San Joaquin County

Elvy Musikka

Richard E. Musty
University of Vermont

Edgar P. Nace
American Academy of Addiction Psychiatry

Joyce Nalepka
America Cares

Tammera Nauts
Great Falls Public Schools

Dan Noelle
Multnomah County Sheriff

Stephen O'Brien
East Bay Aids Center

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

Lynn Osburn
Access Unlimited

Robert Pandina
Rutgers, The State University of New Jersey

David Pate
HortaPharm B.V.

Maggie Petito
Drug Watch International

Stephen Popolizio

The International Association of Lions Clubs

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

Beny Primm
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Carol Reeves
Greenville Family Partnership

Irvin Rosenfeld
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National Families in Action

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Marin Alliance for Medical Marijuana

John Sheridan
New York City Marijuana Buyers' Club

Cathy Shipp
PRIDE-Omaha, Inc.

Stephen Sidney
Kaiser Permanente

Brian Slater

Kenneth Smuland
Women's Alliance for Medical Marijuana

Mark Stone
Washington, D.C., Police Department

Barb Sweeney
Flower Therapy

Donald Tashkin
University of California at Los Angeles School of Medicine

Dana Taub

Chuck Thomas
Marijuana Policy Project Foundation

Bill Tiuen
Gainesville Family Partnership

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

Jeanne Trumble
American Academy of Addiction Psychiatry

Barbara Urist-Fenton
OCHC

Eric A. Voth
International Drug Strategy Institute

Michelle Voth
Kansas Family Partnership

C. Gary Wainwright
American Civil Liberties Union

J. Michael Walker
Brown University

Gene Weeks
Southern California Medical Cannabis Consumers' Co-Op

Sandra Welch
Medical College of Virginia

Tracy Wells
Family Service—Healthy Alternatives for Little Ones

Sgt. Larry L. Welty

Oregon State Police

Sis Wenger
National Association of Children of Alcoholics

Lennice Werth
Virginians Against Drug Violence

Casey Wilbanks
Green Cross

Carol Wortman
Drug Watch Pennsylvania

Kevin Zeese
Common Sense for Drug Policy

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UNITED STATES DEPARTMENT OF JUSTICE
Drug Enforcement Administration

In The Matter Of)
) Docket No. 86-22
MARIJUANA RESCHEDULING PETITION)

OPINION AND RECOMMENDED RULING, FINDINGS OF FACT, CONCLUSIONS OF LAW AND DECISION OF Administrative LAW JUDGE.

FRANCIS L. YOUNG, Administrative Law Judge

DATED: SEP 6 1988

UNITED STATES DEPARTMENT OF JUSTICE
Drug Enforcement Administration

In The Matter Of)
) Docket No. 86-22
MARIJUANA RESCHEDULING PETITION)

OPINION AND RECOMMENDED RULING, FINDINGS OF FACT, CONCLUSIONS OF LAW AND DECISION OF ADMINISTRATIVE LAW JUDGE.

FRANCIS L. YOUNG, Administrative Law Judge

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DATED: SEP 6 1988

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UNITED STATES DEPARTMENT OF JUSTICE
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In The Matter Of)
) Docket No. 86-22
MARIJUANA RESCHEDULING PETITION)

OPINION AND RECOMMENDED RULING, FINDINGS OF FACT, CONCLUSIONS OF LAW AND DECISION OF ADMINISTRATIVE LAW JUDGE.

I.

INTRODUCTION

This is a rulemaking pursuant to the Administrative Procedure Act, 5 U.S.C. § 551, et seq., to determine whether the marijuana plant (Cannabis sativa L) considered as a whole may lawfully be transferred from Schedule I to Schedule II of the schedules established by the Controlled Substances Act (the Act), 21 U.S.C. § 801, et seq. None of the parties is seeking to "legalize" marijuana generally or for recreational purposes. Placement in Schedule II would mean, essentially, that physicians in the United States would not violate Federal law by prescribing marijuana for their patients for legitimate therapeutic purposes. It is contrary to Federal law for physicians to do this as long as marijuana remains in Schedule I. This proceeding had its origins on May 18, 1972 when the National Organization for the Reform of Marijuana Laws (NORML) and two other groups submitted a petition to the Bureau of Narcotics and Dangerous Drugs (BNDD) [footnote 1], predecessor

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1 The powers and authority granted by the Act to the Attorney General were delegated to the Director of BNDD and subsequently to the Administrator of DEA. 28 C.F.R. § 0.100, et seq.

agency to the Drug Enforcement Administration (DEA or the Agency), asking that marijuana be removed from Schedule I and freed of all controls entirely, or be transferred from Schedule I to Schedule V where it would be subject to only minimal controls. The Act by its terms had placed marijuana in Schedule I thereby declaring, as a matter of law that it had no legitimate use in therapy in the United States and subjecting the substance to the strictest level of controls. The Act had been in effect for just over one year when NORML submitted its 1972 petition.

On September 1, 1972 the Director of BNDD announced his refusal to accept the petition for filing, stating that he was not authorized to institute proceedings for the action requested because of the provisions of the Single Convention on Narcotic Drugs, 1961. NORML appealed this action to the United States Court of Appeals for the District of Columbia Circuit. The court held that the Director had erred in rejecting the petition without "a reflective consideration and analysis," observing that the Director's refusal "was not the kind of agency action that promoted the kind of interchange and refinement of views that is the lifeblood of a sound administrative process." NORML v. Ingersoll, 162 U.S. App. D.C. 67, 497 F.2d 654, 659 (1974). The court remanded the matter in January 1974 for further proceedings not inconsistent with its

opinion, "to be denominated a consideration on the merits." Id.

A three-day hearing was held at DEA [footnote 2] by Administrative Law Judge Lewis Parker in January 1975. The judge found in NORML's favor on several issues but the Acting Administrator of DEA entered a final order denying NORML's petition "in all respects." NORML again petitioned the court for review. Finding fault

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2 DEA became the successor agency to BNDD in a reorganization carried out pursuant to Reorganization Plan No. 2 of 1973, eff. July 1, 1973. 38 Fed Reg. 15932 (1973).

with DEA's final order the court again remanded for further proceedings not inconsistent with its opinion. NORML v. DEA, 182 U.S. App. D.C. 114, 559 F.2d 735 (1977). The Court directed the then-Acting Administrator of DEA to refer NORML's petition to the Secretary of the Department of Health, Education and Welfare (HEW) for findings and, thereafter, to comply with the rulemaking procedures outlined in the Act at 21 U.S.C. § 811 (a) and (b).

On remand the Administrator of DEA referred NORML's petition to HEW for scientific and medical evaluation. On June 4, 1979 the Secretary of HEW advised the Administrator of the results of the HEW evaluation and recommended that marijuana remain in Schedule I. Without holding any further hearing the Administrator of DEA proceeded to issue a final order ten days later denying NORML's petition and declining to initiate proceedings to transfer marijuana from Schedule I. 44 Fed. Reg. 36123 (1979). NORML went back to the Court of Appeals.

When the case was called for oral argument there was discussion of the then-present status of the matter. DEA had moved for a partial remand. The court found that "reconsideration of all the issues in this case would be appropriate" and again remanded it to DEA, observing: "We regrettably find it necessary to remind respondents [DEA and HEW] of an agency's obligation on remand not to 'do anything which is contrary to either the letter or spirit of the mandate construed in the light of the opinion of [the] court deciding the case.'" (Citations omitted.) NORML v. DEA, et al., No. 79.1660, United States Court of Appeals for the District of Columbia Circuit, unpublished order filed October 16, 1980. DEA was directed to refer all the substances at issue to the Department of Health and Human Services (HHS), successor agency to HEW, for scien-

tific and medical findings and recommendations on scheduling. DEA did so and HHS has responded. In a letter dated April 1, 1986 the then-Acting Deputy Administrator of DEA requested this administrative law judge to commence hearing procedures as to the proposed rescheduling of marijuana and its components.

After the Judge conferred with counsel for NORML and DEA, a notice was published in the Federal Register on June 24, 1986 announcing that hearings would be held on NORML's petition for the rescheduling of marijuana and its components commencing on August 21, 1986 and giving any interested person who desired to participate the opportunity to do so. 51 Fed. Reg. 22946 (1986).

Of the three original petitioning organizations in 1972 only NORML is a party to the present proceeding. In addition the following entities responded to the Federal Register notice and have become parties, participating to varying degrees: the Alliance for Cannabis Therapeutics (ACT), Cannabis Corporation of America (CCA) and Carl Eric Olsen, all seeking transfer of marijuana to Schedule II; the Agency, National Federation of Parents for Drug free Youth (NFP) and the International Association of Chiefs of Police (IACP), all contending that marijuana should remain in Schedule I.

Preliminary prehearing sessions were held on August 21 and December 5, 1986 and on February 20, 1987. [footnote 3] During the preliminary stages, on January 20, 1987, NORML filed an amended petition for rescheduling. This new petition abandoned NORML's previous requests for the complete descheduling of marijuana or rescheduling to Schedule V. It asks only that marijuana be placed in Schedule II.

At a prehearing conference on February 20, 1987 this amended petition was

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3 Transcripts of these three preliminary prehearing sessions are included in the record.

discuss. [footnote 4] All Parties present stipulated, for the purpose of this proceeding, that marijuana has a high potential for abuse and that abuse of the marijuana plant may lead to severe psychological or physical dependence. They then agreed that the principal issue in this proceeding would be stated thus:

> Whether the marijuana plant, considered as a whole, [footnote 5] may

4 The transcript of this prehearing conference and of the subsequent hearing session comprise 15 volumes numbered as follows:

Vol. I - Prehearing Conference, October 16, 1987

Vol. II - Cross Examination, November 19, 1987

Vol. III - Cross Examination, December 8, 1987

Vol. IV - Cross Examination, December 9, 1987

Vol. V - Cross Examination, January 5, 1988

Vol. VI - Cross Examination, January 6, 1988

Vol. VII - Cross Examination, January 7, 1988

Vol. VIII - Cross Examination, January 26, 1988

Vol. IX - Cross Examination, January 27, 1988

Vol. X - Cross Examination, January 28, 1988

Vol. XI - Cross Examination, January 29, 1988

Vol. XII - Cross Examination, February 2, 1988

Vol. XIII - Cross Examination, February 4, 1988

Vol. XIV - Cross Examination, February 5, 1988

Vol. XV - Oral Argument, June 10, 1988

Pages of the transcript are cited herein by volume and page, e.g. "Tr. V-96"; "G-" identifies an Agency exhibit.

5 Throughout this opinion the term marijuana" refers to "the marijuana plant, consider as a whole".

lawfully be transferred from Schedule I to Schedule II of the schedules established by the Controlled Substances Act.

Two subsidiary issues were agreed on, as follows:

1. Whether the marijuana plant has a currently accepted medical use in treatment in the United States, or a currently accepted medical use with severe restrictions.

2. Whether there is a lack of accepted safety for use of the marijuana plant under medical supervision.

As stated above, the parties favoring transfer from Schedule I to Schedule II are NORML, ACT, CCA and Carl Eric Olsen. Those favoring retaining marijuana in Schedule I are the Agency, NFP and IACP.

During the Spring and Summer of 1987 the parties identified their witnesses and put the direct examination testimony of each witness in writing in affidavit form. Copies of these affidavits were exchanged. Similarly, the parties assembled their proposed exhibits and exchanged copies. Opportunity was provided for each party to submit objections to the direct examination testimony and exhibits proffered by the others. The objections submitted were considered by the administrative law judge and ruled on. The testimony and exhibits not excluded were admitted into the record. Thereafter hearing sessions were held at which witnesses were subjected to cross-examination. These sessions were held in New Orleans, Louisiana on November 18 and 19, 1987; in San Francisco, California on December 8 and 9, 1987; and in Washington, D.C. on January 5 through 8 and 26 through 29, and on February 2, 4 and 5, 1988. The parties have submitted proposed findings and conclusions and briefs. Oral arguments were heard by the judge on June 10, 1988 in Washington.

II.

RECOMMENDED RULING

It is recommended that the proposed findings and conclusions submitted by the parties to the administrative law judge be rejected by the Administrator except to the extent they are included in those hereinafter set forth; for the reason that they are irrelevant or unduly repetitious or not supported by a preponderance of the evidence. 21 C.F.R. § 1316.65(a)(1).

III.

ISSUES

As noted above, the agreed issues are as follows:

Principle issue:

Whether the marijuana plant, considered as a whole, may lawfully be transferred from Schedule I to Schedule II of the schedules established by the Controlled Substances Act.

Subsidiary issues:

1. Whether the marijuana plant has a currently accepted medical use in treatment in the United States, or a currently accepted medical use with severe restrictions.

2. Whether there is a lack of accepted safety for use of the marijuana plant under medical supervision.

IV.

STATUTORY REQUIREMENTS FOR SCHEDULING

The Act provides (21 U.S.C. § 812(b)) that a drug or other substance may not be placed in any schedule unless certain specified findings are made with respect to it. The findings required for Schedule I and Schedule II are as follows:

Schedule I. -

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

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

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

Schedule II. -

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

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

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

As noted above the parties have stipulated, for the purpose of this proceeding, that marijuana has a high potential for abuse and that abuse of it may lead to severe psychological or physical dependence. Thus the dispute between the two sides in this proceeding is narrowed to whether or not marijuana has a currently accepted medical use in treatment in the United States, and whether or not there is a lack of accepted safety for use of marijuana under medical supervision.

The issues as framed here contemplate marijuana's being placed only in

Schedule I or Schedule II. The criteria for placement in any of the other three schedules established by the Act are irrelevant to this proceeding.

V.

ACCEPTED MEDICAL USE IN TREATMENT

- CHEMOTHERAPY

With respect to whether or not marijuana has a "currently accepted medical use in treatment in the United States" for chemotherapy patients, the record shows the following facts to be uncontroverted.

Findings Of Fact

1. One of the most serious problems experienced by cancer patients undergoing chemotherapy for their cancer is severe nausea and vomiting caused by their reaction to the toxic (poisonous) chemicals administered to them in the course of this treatment. This nausea and vomiting at times becomes life threatening. The therapy itself creates a tremendous strain on the body. Some patients cannot tolerate the severe nausea and vomiting and discontinue treatment. Beginning in the 1970's

there was considerable doctor-to-doctor communication in the United States concerning patients known by their doctors to be surreptitiously using marijuana with notable success to overcome or lessen their nausea and vomiting.

2. Young patients generally achieve better control over nausea and vomiting from smoking marijuana than do older patients, particularly when the older patient has not been provided with detailed information on how to smoke marijuana.

3. Marijuana cigarettes in many cases are superior to synthetic THC capsules in reducing chemotherapy-induced nausea and vomiting. Marijuana

cigarettes have an important, clear advantage over synthetic THC capsules in that the natural marijuana is inhaled and generally takes effect more quickly than the synthetic capsule which is ingested and must be processed through the digestive system before it takes effect.

4. Attempting to orally administer the synthetic THC capsule to a vomiting patient presents obvious problems - it is vomited right back up before it can have any effect.

5. Many physicians, some engaged in medical practice and some teaching in medical schools, have accepted smoking marijuana as effective in controlling or reducing the severe nausea and vomiting (emesis) experienced by some cancer patients undergoing chemotherapy for cancer.

6. Such physicians include board-certified internists, oncologists and psychiatrists. (Oncology is the treatment of cancer through the use of highly toxic chemicals, or chemotherapy.)

7. Doctors who have come to accept the usefulness of marijuana in controlling or reducing emesis resulting from chemotherapy have dose so as the result of reading reports of studies and anecdotal reports in their professional literature, and as the result of observing patients and listening to reports directly from patients.

8. Some cancer patients who have acknowledged to doctors that they smoke marijuana for emesis control have indicated in their discussions that, although they may have first smoked marijuana recreationally, they accidentally found that doing so helped reduce the emesis resulting from their chemotherapy. They consistently indicated that they felt better and got symptomatic relief from the intense nausea

and vomiting caused by the chemotherapy. These patients

were no longer simply getting high, but were engaged in medically treating their illness, albeit with an illegal substance. Other chemotherapy patients began smoking marijuana to control their emesis only after hearing reports that the practice had proven helpful to others. Such patients had not smoked marijuana recreationally.

9. This successful use of marijuana has given many cancer chemotherapy patients a much more positive outlook on their overall treatment, once they were relieved of the debilitating, exhausting and extremely unpleasant nausea and vomiting previously resulting from their chemotherapy treatment.

10. In about December 1977 the previously underground patient practice of using marijuana to control emesis burst into the public media in New Mexico when a young cancer patient, Lynn Pearson, began publicly to discuss his use of marijuana. Mr. Pearson besought the New Mexico legislature to pass legislation making marijuana available legally to seriously ill patients whom it might help. As a result, professionals in the public health sector in New Mexico more closely examined how marijuana might be made legally available to assist in meeting what now openly appeared to be a widely recognized patient need.

11. In many cases doctors have found that, in addition to suppressing nausea and vomiting, smoking marijuana is a highly successful appetite stimulant. The importance of appetite stimulation in cancer therapy cannot be overstated. Patients receiving chemotherapy often lose tremendous amounts of weight. They endanger their lives because they lose interest in food and in eating. The resulting sharp reduction in weight may well affect their prognosis. Marijuana smoking induces some patients to eat. The benefits are obvious, doctors have found. There is no significant loss of weight. Some patients will gain weight.

This allows them to retain strength and makes them better able to fight the cancer. Psychologically, patients who can continue to eat even while receiving chemotherapy maintain a balanced outlook and are better able to cope with their disease and its treatment, doctors have found.

12. Synthetic anti-emetic agents have been in existence and utilized for a number of years. Since about 1980 some new synthetic agents have been developed which appear to be more effective in

controlling and reducing chemotherapy-induced nausea and vomiting than were some of those available in the 1970's. But marijuana still is found more effective for this purpose in some people than any of the synthetic agents, even the newer ones.

13. By the late 1970's in the Washington, D.C. area there was a growing recognition among health care professionals and the public that marijuana had therapeutic value in reducing the adverse effects of some chemotherapy treatments. With this increasing public awareness came increasing pressure from patients on doctors for information about marijuana and its therapeutic uses. Many patients moved into forms of unsupervised self-treatment. While such self-treatment often proved very effective, it has certain hazards, ranging from arrest for purchase or use of an illegal drug to possibly serious medical complications from contaminated sources or adulterated materials. Yet, some patients are willing to run these risks to obtain relief from the debilitating nausea and vomiting caused by their chemotherapy treatments.

14. Every oncologist known to one Washington, D.C. practicing internist and board-certified oncologist has had patients who used marijuana with great success to prevent or diminish chemotherapy-induced nausea and vomiting. Chemotherapy patients reporting directly to that Washington doctor that they

have smoked marijuana medicinally vomit less and eat better than patients who do not smoke it. By gaining control over their severe nausea and vomiting these patients undergo a change of mood and have a better mental outlook than patients who, using the standard anti-emetic drugs, are unable to gain such control.

15. The vomiting induced by chemotherapeutic drugs may last up to four days following the chemotherapy treatment. The vomiting can be intense, protracted and, in some instances, is unendurable. The nausea which follows such vomiting is also deep and prolonged. Nausea may prevent a patient from taking regular food or even much water for periods of weeks at a time.

16. Nausea and vomiting of this severity degrades the quality of life for these patients, weakening them physically, and destroying the will to fight the cancer. A desire to end the chemotherapy treatment in order to escape the emesis can supersede the will to live. Thus the emesis, itself, can truly be considered a life-threatening consequence of many cancer treatments. Doctors have known such cases to occur. Doctors have known other cases where marijuana smoking has enabled the patient to

endure, and thus continue, chemotherapy treatments with the result that the cancer has gone into remission and the patient has returned to a full, active satisfying life.

17. In San Francisco chemotherapy patients were surreptitiously using marijuana to control emesis by the early 1970's. By 1976 virtually every young cancer patient receiving chemotherapy at the University of California in San Francisco was using marijuana to control emesis with great success. The use of marijuana for this purpose had become generally accepted by the patients and increasingly by their physicians as a valid and effective form of treatment. This was particularly true for younger cancer patients, somewhat less common for

older ones. By 1979 about 25% to 30% of the patients seen by one San Francisco oncologist were using marijuana to control emesis, about 45 to 50 patients per year. Such percentages and numbers vary from city to city. A doctor in Kansas City who sees about 150 to 200 new cancer patients per year found that over the 15 years 1972 to 1987 about 5% of the patients he saw, or a total of about 75, used marijuana medicinally.

18. By 1987 marijuana no longer generated the intense interest in the world of oncology that it had previously, but it remains a viable tool, commonly employed, in the medical treatment of chemotherapy patients. There has evolved an unwritten but accepted standard of treatment within the community of oncologists in the San Francisco, California area which readily accepts the use of marijuana.

19. As of the Spring of 1987 in the San Francisco area, patients receiving chemotherapy commonly smoked marijuana in hospitals during their treatments. This in-hospital use, which takes place in rooms behind closed doors, does not bother staff, is expected by physicians and welcomed by nurses who, instead of having to run back and forth with containers of vomit, can treat patients whose emesis is better controlled than it would be without marijuana. Medical institutions in the Bay area where use of marijuana obtained on the streets is quite common, although discrete, include the University of California at San Francisco Hospital, the Mount Zion Hospital and the Franklin Hospital. In effect, marijuana is readily accepted throughout the oncologic community in the bay area for its benefits in connection with chemotherapy. The same situation exists in other large metropolitan areas of the United States.

20. About 50% of the patients seen by one San Francisco oncologist

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during the year 1987 were smoking marijuana medicinally. This is about 90 to 95 individuals. This number is higher than during the previous ten years due to the nature of this physician's practice which includes patients from the "tenderloin" area of San Francisco, many of whom are suffering from AIDS-related lymphosarcoma. These patients smoke marijuana to control their nausea and vomiting, not to "get high." They self-titrate, i.e., smoke the marijuana only as long as needed to overcome the nausea, to prevent vomiting.

21. The State of New Mexico set up a program in 1978 to make marijuana available to cancer patients pursuant to an act of the State legislature. The legislature had accepted marijuana as having medical use in treatment. It overwhelmingly passed this legislation so as to make marijuana available for use in therapy, not just for research. Marijuana and synthetic THC were given to patients, administered under medical supervision, to control or reduce emesis. The marijuana was in the form of cigarettes obtained from the Federal government. The program operated from 1979 until 1986, when funding for it was terminated by the State. During those seven years about 250 cancer patients in New Mexico received either marijuana cigarettes or THC. Twenty or 25 physicians in New Mexico sought and obtained marijuana cigarettes or THC for their cancer patients during that period. All of the oncologists in New Mexico accepted marijuana as effective for some of their patients. At least ten hospitals involved in this program in New Mexico, in which cancer patients smoked their marijuana cigarettes. The hospitals accepted this medicinal marijuana smoking by patients. Voluminous reports filed by the participating physicians make it clear that marijuana is a highly effective anti-emetic substance. It was found in the New Mexico program to be far superior to the best available conventional

anti-emetic drug, compazine, and clearly superior to synthetic THC pills. More than 90% of the patients who received marijuana within the New Mexico program reported significant or total relief from nausea and vomiting. Before the program began cancer patients were surreptitiously smoking marijuana in New Mexico to lessen or control their emesis resulting from chemotherapy treatments. They reported to physicians that it was successful for this purpose. Physicians were aware that this was going on.

22. In 1978 the Louisiana legislature became one of the first-State legislatures in the nation to recognize the efficacy of marijuana in controlling emesis by enacting legislation intended to make marijuana available by prescription for therapeutic use by chemotherapy patients. This enactment shows that there was widespread acceptance in Louisiana of the therapeutic value of marijuana. After a State Marijuana Prescription Review Board was established, pursuant to that legislation, it became apparent that, because of Federal restrictions, marijuana could be obtained legally only for use in cumbersome, formal research programs. Eventually a research program was entered into by the State, utilizing synthetic THC, but without much enthusiasm, since most professionals who had wanted to use marijuana clinically, to treat patients, had neither the time, resources nor inclination to get involved in this limited, formal study. The original purpose of the Louisiana legislation was frustrated by the Federal authorities. Some patients, who had hoped to obtain marijuana for medical use legally after enactment of the State legislation, went outside the law and obtained it illicitly. Some physicians in Louisiana accept marijuana as having a distinct medical value in the treatment of the nausea and vomiting associated with certain types of chemotherapy treatments.

23. In 1980 the State of Georgia enacted legislation authorizing a therapeutic research program for the evaluation of marijuana as a medically recognized therapeutic substance. Its enactment was supported by letters from a number of Georgia oncologist and other Georgia physician, including the Chief of oncology at Grady Hospital and staff oncologist at Emory University Medical Clinic. Sponsors of the legislation originally intended the enactment of a law making marijuana available for clinical, therapeutic use by patients. The bill was referred to as the "Marijuana-as-Medicine" bill. The final legislation was crafted, however, of necessity, merely to set up a research program in order to obtain marijuana from the one legitimate source available - the Federal Government, which would not make the substance available for any other purpose other than conducting a research program. The act was passed by an overwhelming majority in the lower house of the legislature and unanimously in the Senate. In January 1983 an evaluation of the program, which by then had 44 evaluable marijuana smoking patient-participants, accepted marijuana smoking as being an effective anti-emetic agent.

24. In Boston, Massachusetts in 1977 a nurse in a hospital suggested to a chemotherapy patient, suffering greatly from the therapy and at the point of refusing further treatment, that smoking marijuana

might help relieve his nausea and vomiting. The patient's doctor, when asked about it later, stated that many of his younger patients were smoking marijuana. Those who did so seemed to have less trouble with nausea and vomiting. The patient in question obtained some marijuana and smoked it, in the hospital, immediately before his next chemotherapy treatment. Doctors, nurses, and orderlies coming into the room as he finished smoking realized what the patient had been doing. None of them

made any comment. The marijuana was completely successful with this patient, who accepted it as effective in controlling his nausea and vomiting. Instead of being sick for weeks following chemotherapy, and having trouble going to work, as had been the case, the patient was ready to return to work 48 hours after that chemotherapy treatment. The patient thereafter always smoked marijuana, in the hospital, before chemotherapy. The doctors were aware of it, openly approved of it and encouraged him to continue. The patient resumed eating regular meals and regained lost eight, his mood improved markedly, he became more active and outgoing and began doing things together with his wife that he had not done since beginning chemotherapy.

25. During the remaining two years of this patient's life, before his cancer ended it, he came to know other cancer patients who were smoking marijuana to relieve the adverse effects of their chemotherapy. Most of these patients had learned about using marijuana medically from their doctors who, having accepted its effectiveness, subtly encouraged them to use it.

26. A Boston psychiatrist and professor, who travels about the country, has found a minor conspiracy to break the law among oncologists and nurses in every oncology center he has visited to let patients smoke marijuana before and during cancer chemotherapy. He has talked with dozens of these health care oncologists who encourage their patients to do this and who regard this as an accepted medical usage of marijuana. He has known nurses who have obtained marijuana for patients unable to obtain it for themselves.

27. A cancer patient residing in Beaverton, Michigan smoked marijuana medicinally in the nearby hospital where he was undergoing chemotherapy from early 1979 until he died of his cancer in October of that year. He smoked it in

his hospital room after his parents made arrangements with the hospital

for him to do so. Smoking marijuana controlled his post-chemotherapy nausea and vomiting, enabled him to eat regular-meals again with his family, and he became outgoing and talkative. His parents accepted his marijuana smoking as effective and helpful. Two clergymen, among others, brought marijuana to this patient's home. Many people at the hospital supported the patient's marijuana therapy, none doubted its helpfulness or discouraged it. This patient was asked for help by other patients. He taught some who lived nearby how to form the marijuana cigarettes and properly inhale the smoke to obtain relief from nausea and vomiting. When an article about this patient's smoking marijuana appeared in a local newspaper, he and his family heard from many other cancer patients who were doing the same. Most of them made an effort to inform their doctors. Most Physicians who knew their patients smoked marijuana medicinally approved, accepting marijuana's therapeutic helpfulness in reducing nausea and vomiting.

28. In October 1979 the Michigan legislature enacted legislation whose underlying purpose was to make marijuana available therapeutically for cancer patients and others. The State Senate passed the bill 29-5, the House of Representatives 100-0. In March 1982 the Michigan legislature passed a resolution asking the Federal Congress to try to alter Federal policies which prevent physicians from prescribing marijuana for legitimate medical applications and prohibit its use in medical treatments.

29. In Denver, Colorado a teenage cancer patient has been smoking marijuana to control nausea and vomiting since 1986. He has done this in his hospital room both before and after chemotherapy. His doctor and hospital staff know he does this. The doctor has stated that he would prescribe marijuana for

this patient if it were legal to do so. Other patients in the Denver area smoke marijuana for the same purpose. This patient's doctor, and nurses with whom he comes in contact, understand that cancer patients smoke marijuana to reduce or control emesis. They accept it.

30. In late 1980 a three year old boy was brought by his parents to a hospital in Spokane, Washington. The child was diagnosed as having cancer. Surgery was performed. Chemotherapy was begun. The child became extremely nauseated and vomited for days after each chemotherapy treatment. He could not eat regularly. He lost strength. He lost weight. His body's ability to ward off common infections, other life-threatening infections, significantly decreased. Chemotherapy's after-effects caused the child great suffering. They caused his watching

parents great suffering. Several standard, available anti-emetic agents were tried by the child's doctors. None of them succeeded in controlling his nausea or vomiting. Learning of the existence of research studies with THC or marijuana the parents asked the child's doctor to arrange for their son to be the subject of such a study so that he might have access to marijuana. The doctor refused, citing the volume of paperwork and record-keeping detail required in such programs and his lack of administrative personnel to handle it.

31. The child's mother read an article about marijuana smoking helping chemotherapy patients. She obtained some marijuana from friends. She baked cookies for her child with marijuana in them. She made tea for him with marijuana in it. When the child ate these cookies or drank this tea in connection with his chemotherapy, he did not vomit. His strength returned. He regained lost weight. His spirits revived. The parents told the doctors and nurses at the hospital of their giving marijuana to their child. None objected.

They all accepted smoking marijuana as effective in controlling chemotherapy induced nausea and vomiting. They were interested to see the results of the cookies.

32. Soon this child was riding a tricycle in the hallways of the Spokane hospital shortly after his chemotherapy treatments while other children there were still vomiting into pans, tied to intravenous bottles in an attempt to re-hydrate them, to replace the liquids they were vomiting up. Parents of some of the other patients asked the parents of this "lively" child how he seemed to tolerate his chemotherapy so well. They told of the marijuana use. Of those parents who began giving marijuana to their children, none ever reported back encountering any adverse side effects. In the vast majority of these cases, the other parents reported significant reduction in their children's vomiting and appetite stimulation as the result of marijuana. The staff, doctors and nurses at the hospital knew of this passing on of information about marijuana to other parents. They approved. They never told the first parents to hide their son's medicinal use of marijuana. They accepted the effectiveness of the cookies and the tea containing marijuana.

33. The first child's cancer went into remission. Then it returned and spread. Emotionally drained, the parents moved the family back to San Diego, California to be near their own parents. Their son was admitted to a hospital in San Diego. The parents informed the doctors, nurses and social workers there of their son's therapeutic use of marijuana. No one objected. The child's doctor in San Diego strongly

supported the parent's giving marijuana to him. Here in California, as in Spokane, other parents noticed the striking difference between their children after chemotherapy and the first child.

Other parents asked the parents of the first child about it, were told of the use of marijuana, tried it with their children, and saw dramatic improvement. They accepted its effectiveness. In the words of the mother of the first child: ". . . When your kid is riding a tricycle while his other hospital buddies are hooked up to IV needles, their heads hung over vomiting buckets, you don't need a federal agency to tell you marijuana is effective. The evidence is in front of you, so stark it cannot be ignored." [footnote 6]

34. There is at least one hospital in Tucson, Arizona where medicinal use of marijuana by chemotherapy patients is encouraged by the nursing staff and some physicians.

35. In addition to the physicians mentioned in the Findings above, mostly oncologists and other practitioners, the following doctors and health care professionals, representing several different areas of expertise, accept marijuana as medically useful in controlling or reducing emesis and testified to that effect in these proceedings:

a. George Goldstein, Ph.D., psychologist, Secretary of Health for the State of New Mexico from 1978 to 1983 and chief administrator in the implementation of the New Mexico program utilizing marijuana;

b. Dr. Daniel Danzak, psychiatrist and former head of the New Mexico program utilizing marijuana;

c. Dr. Tod Mikuriya, psychiatrist and editor of Marijuana: Medical Papers, a book presenting an historical perspective of marijuana's medical use;

d. Dr. Norman Zinberg, general psychiatrist and Professor of Psychiatry at Harvard Medical School since 1951;

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6 Affidavit of Janet Andrews, ACT rebuttal witness, par. 98.

e. Dr. John Morgan, psychopharmacologist, Board-certified in Internal Medicine, full Professor and Director of Pharmacology at the

City University of New York;

f. Dr. Phillip Jobe, neuropsychopharmacologist with a practice in Illinois and former Professor of Pharmacology and Psychiatry at the Louisiana State University School of Medicine in Shreveport, Louisiana, from 1974 to 1984;

g. Dr. Arthur Kaufman, formerly a general practitioner in Maryland, currently Vice-President of a private medical consulting group involved in the evaluation of the quality of care of all the U.S. military hospitals throughout the world, who has had extensive experience in drug abuse treatment and rehabilitation programs;

h. Dr. J. Thomas Ungerleider, a full Professor of Psychiatry at the University of California in Los Angeles with extensive experience in research on the medical use of drugs;

i. Dr. Andrew Weil, ethnopharmacologist, Associate Director of Social Perspectives in Medicine at the College of Medicine at the University of Arizona, with extensive research on medicinal plants; and

j. Dr. Lester Grinspoon, a practicing psychiatrist and Associate Professor at Harvard Medical School.

36. Certain law enforcement authorities have been outspoken in their acceptance of marijuana as an antiemetic agent. Robert T. Stephan, Attorney General of the State of Kansas, and himself a former cancer patient, said of chemotherapy in his affidavit in this record: "The treatment becomes a terror." His cancer is now in remission. He came to know a number of health care professionals whose medical judgment he respected. They had accepted marijuana

as having medical use in treatment. He was elected Vice President of the National Association of Attorneys General (NAAG) in 1983. He was instrumental in the adoption by that body in June 1983 of a resolution acknowledging the efficacy of marijuana for cancer and glaucoma patients. The resolution expressed the support of NAAG for legislation then pending in the Congress to make marijuana available on prescription to cancer and glaucoma patients. The resolution was adopted by an overwhelming margin. NAAG's President, the Attorney General of Montana, issued a statement that marijuana does have accepted medical uses and is improperly classified at present. The Chairman of NAAG's Criminal Law and Law Enforcement Committee, the Attorney General of Pennsylvania, issued a

statement emphasizing that the proposed rescheduling of marijuana would in no way affect or impede existing efforts by law enforcement authorities to crack down on illegal drug trafficking.

37. At least one court has accepted marijuana as having medical use in treatment for chemotherapy patients. On January 23, 1978 the Superior Court of Imperial County, California issued orders authorizing a cancer patient to possess and use marijuana for therapeutic purposes under the direction of a physician. Another order authorized and directed the Sheriff of the county to release marijuana from supplies on hand and deliver it to that patient in such form as to be usable in the form of cigarettes.

38. During the period 1978-1980 polls were taken to ascertain the degree of public acceptance of marijuana as effective in treating cancer and glaucoma patients. A poll in Nebraska brought slightly over 1,000 responses - 83% favored making marijuana available by prescription, 12% were opposed, 5% were undecided. A poll in Pennsylvania elicited 1,008 responses - 83.1% favored availability by prescription, 12.2% were opposed, 4.7% were undecided. These

two surveys were conducted by professional polling companies. The Detroit Free Press conducted a telephone poll in which 85.4% of those responding favored access to marijuana by prescription. In the State of Washington the State Medical Association conducted a poll in which 80% of the doctors belonging to the Association favored controlled availability of marijuana for medical purposes.

Discussion

From the foregoing uncontroverted facts it is clear beyond any question that many people find marijuana to have, in the words of the Act, an "accepted medical use in treatment in the United States" in effecting relief for cancer patients. Oncologists, physicians treating cancer patients, accept this. Other medical practitioners and researchers accept this. Medical faculty professors accept it. Nurses performing hands-on patient care accept it.

Patients accept it. As counsel for CCA perceptively pointed out at oral argument, acceptance by the patient is of vital importance. Doctors accept a therapeutic agent or process only if it "works" for the patient. If the patient does not accept, the doctor cannot administer the treatment. The patient's informed consent is vital. The doctor

ascertains the patient's acceptance by observing and listening to the patient. Acceptance by the doctor depends on what he sees in the patient and hears from the patient. Unquestionably, patients in large numbers have accepted marijuana as useful in treating their emesis. They have found that it "works". Doctors, evaluating their patients, can have no basis more sound than that for their own acceptance.

Of relevance, also, is the acceptance of marijuana by state attorneys-

general, officials whose primary concern is law enforcement. A large number of them have no fear that placing marijuana in Schedule II, thus making it available for legitimate therapy, will in any way impede existing efforts of law enforcement authorities to crack down on illegal drug trafficking.

The Act does not specify by whom a drug or substance must be "accepted [for] medical use in treatment" in order to meet the Act's "accepted" requirement for placement in Schedule II. Department of Justice witnesses told the Congress during hearings in 1970 preceding passage of the Act that "the medical Profession" would make this determination, that the matter would be "determined by the medical community." The Deputy Chief Counsel of BNDD, whose office had written the bill with this language in it, told the House subcommittee that "this basic determination . . . is not made by any part of the federal government. It is made by the medical community as to whether or not the drug has medical use or doesn't". [footnote 7]

No one would seriously contend that these Justice Department witnesses meant that the entire medical community would have to be in agreement on the usefulness of a drug or substance. Seldom, if ever, do all lawyers agree on a point of law. Seldom, if ever, do all doctors agree on a medical question. How many are required here? A majority of 51%? It would be unrealistic to attempt a plebiscite of all doctors in the country on such a question every time it arises, to obtain a majority vote.

In determining whether a medical procedure utilized by a doctor is actionable as malpractice the courts have adopted the rule what it is acceptable

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7 Drug Abuse Control Amendments - 1970: Hearings on H.R. 11701 and H.R. 13743 Before the Subcommittee on Public Health and Welfare of the House Committee on Interstate and Foreign Commerce, 91st

Congress, 2d Sess. 678, 696, 718 (1970) (Statement of John E. Ingersoll, Director, BNDD).

for a doctor to employ a method of treatment supported by a respectable minority of physicians.

In Hood v. Phillips, 537 S.W. 2d 291 (1976) the Texas Court of Civil Appeals was dealing with a claim of medical malpractice resulting from a surgical procedure claimed to have been unnecessary. The court quoted from an Arizona court decision holding that

> a method of treatment, as espoused and used by . . . a respectable minority of physicians in the United States, cannot be said to be an inappropriate method of treatment or to be malpractice as a matter of law even though it has not been accepted as a proper method of treatment by the medical profession generally.

Ibid. at 294. Noting that the Federal District court in the Arizona case found a "respectable minority" composed of sixty-five physicians throughout the United States, the Texas court adopted as "the better rule" to apply in its case, that

> a physician is not guilty of malpractice where the method of treatment used is supported by a respectable minority of physicians.

Ibid.

In Chumbler v. McClure, 505 F.2d 489 (6th Cir. 1974) the Federal courts were dealing with a medical malpractice case under their diversity jurisdiction, applying Tennessee law. The Court of Appeals said:

> . . . The most favorable interpretation that may be placed on the testimony adduced at trial below is that there is a division of opinion in the medical profession regarding the use of Premarin in the Treatment of cerebral vascular insufficiency, and that Dr. McClure was alone among neurosurgeons in Nashville in using such therapy. The test for malpractice and for community standards is not to be determined solely by a plebiscite. Where two or more schools of thought exist among competent members of the medical profession concerning proper medical treatment for a given

ailment, each of which is supported by responsible

> medical authority, it is not malpractice to be among the minority in a given city who follow: one of the accepted schools.

505 F.2d at 492 (Emphasis added). See, also, Leech v. Bralliar, 275 F.Supp. 897 (D.Ariz., 1967).

How do we ascertain whether there exists a school of thought supported by responsible medical authority, and thus "accepted"? We listen to the physicians.

> The court and jury must have a standard measure which they are to use in measuring the acts of a doctor to determine whether he exercised a reasonable degree of care and skill; they are not permitted to set up and use any arbitrary or artificial standard of measurement that the jury may wish to apply. The proper standard of measurement is to be established by testimony of physicians, for it is a medical question.

Hayes v. Brown, 133 S.E. 2d. 102 (Ga., 1963) at 105.

As noted above, there is no question but that this record shows a great many physicians, and others, to have "accepted" marijuana as having a medical use in the treatment of cancer patients' emesis. True, all physicians have not "accepted" it. But to require universal, 100% acceptance would be unreasonable. Acceptance by "a respectable minority" of physicians is all that can reasonably be required. The record here establishes conclusively that at least "a respectable minority" of physicians has "accepted" marijuana as having a "medical use in treatment in the United states." That others may not makes no difference.

The administrative law judge recommended this same approach for determining whether a drug has an "accepted medical use in treatment" in The Matter Of MDMA Scheduling, Docket No. 84-48. The Administrator, in his first final rule in that proceeding, issued on October 8, 1986 [footnote 8], declined to adopt this approach. He

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8 51 Fed. Reg. 36552 (1986).

ruled, instead, that DEA's decision on whether or not a drug or other substance had an accepted medical use in treatment in the United States would be determined simply by ascertaining whether or not "the drug or other substance is lawfully marketed in the United States pursuant to the Federal Food, Drug and Cosmetic Act of 1938 . . . ." [footnote 9]

The United States Court of A eals for the First Circuit held that the Administrator erred in so ruling. [footnote 10] That court vacated the final order of October 8, 1986 and remanded the matter of MDMA's scheduling for further consideration. The court directed that, on remand, the Administrator would not be permitted to treat the absence of interstate marketing approval by FDA as conclusive evidence on the question of accepted medical use under the Act.

In his third final rule [footnote 11] of the matter of the scheduling of MDMA the Administrator made a series of findings of fact as to MDMA, the drug there under consideration, with respect to the evidence in that record. On those findings he based his last final rule in the case. [footnote 12]

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9 Ibid., at 36558.

10 Grinspoon v. Drug Enforcement Administration, 828 F.2d 881 (1st. Cir., 1987).

11 53 Fed. Reg. 5156 (1988). A second final rule had been issued on January 20, 1988. It merely removed MDMA from Schedule I pursuant to the mandate of the Court of Appeals which had voided the first final rule placing it there. Subsequently the third final rule was issued, without any further hearings, again placing MDMA in Schedule I. There was no further appeal.

12 In neither the first nor the third final rule in the MDMA case does the Administrator take any cognizance of the statements to the Congressional committee by predecessor Agency officials that the determination as to "accepted medical use in treatment" is to be made by the medical community and not by any part of the federal government. See page 27, above. It is curious that the administrator makes no effort whatever to show how the BNDD representatives were mistaken or to explain why he now has abandoned their interpretation. They wrote that language into the original bill.

That third final rule dealing with MDMA is dealing with a synthetic, "simple", "single-action" drug. What might be appropriate criteria for a "simple" drug like MDMA may not be appropriate for a "complex" substance with a number of active components. The criteria applied to MDMA, a synthetic drug, are not appropriate for application to marijuana, which is a natural plant substance.

The First Circuit Court of Appeals in the MDMA case told the Administrator that he should not treat the absence of FDA interstate marketing approval as conclusive evidence of lack of currently accepted medical use. The court did not forbid the Administrator from considering the absence of FDA approval as a factor when determining the existence of accepted medical use. Yet on remand, in his third final order, the Administrator adopted by reference 18 of the numbered findings he had made in the first final order. Each of these findings had to do with requirements imposed by FDA for approval of a new drug application (NDA) or of an investigational new drug exemption (IND). These requirements deal with data resulting from controlled studies and scientifically conducted investigations and test.

Among those findings incorporated into the third final MDMA order from the first, and relied on by the Administrator, was the determination and recommendation of the FDA that the drug there in question was not "accepted". In relying on the FDA's action the Administrator apparently overlooked the fact that the FDA clearly stated that it was interpreting "accepted medical use" in the Act as being equivalent to receiving FDA approval for lawful marketing under the FDCA. Thus the Administrator accepted as a basis for his MDMA third final rule the FDA recommendation which was based upon a statutory interpretation which the Court

of Appeals had condemned.

The Administrator in that third final rule made a series of further findings. Again, the central concern in these findings was the content of test results and the sufficiency or adequacy of studies and scientific reports. A careful reading of the criteria considered in the MDMA third final order reveals that the Administrator was really considering the question: Should the drug be accepted for medical use?; rather than the question: Has the drug been accepted for medical use? By considering little else but scientific test results and reports the Administrator was making a determination as to whether or not, in his opinion, MDMA ought to be accepted for medical use in treatment.

The Agency's arguments in the present case are to the same effect.

In a word, they address the wrong question. It is not for this Agency to tell doctors whether they should or should not accept a drug or substance for medical use. The statute directs the Administrator merely to ascertain whether, in fact, doctors have done so.

The MDMA third final order mistakenly looks to FDA criteria for guidance in choosing criteria for DEA to apply. Under the Food, Drug and Cosmetic Act the FDA is deciding - properly, under that statute - whether a new drug should be introduced into interstate commerce. Thus it is appropriate for the FDA to rely heavily on test results and scientific inquiry to ascertain whether a drug is effective and whether it is safe. The FDA must look at a drug and pass judgment on its intrinsic qualities. The DEA, on the other hand, is charged by 21 U.S.C. § 812(b)(1)(B) and (2)(B) with ascertaining what it is that other people have done with respect to a drug or substance: "Have they accepted it?," not "Should they accept it?"

In the MDMA third final order DEA is actually making the decision that doctors have to make, rather than trying to ascertain the decision which doctors have made. Consciously or not, the Agency is undertaking to tell doctors what they should or should not accept. In so doing the Agency is acting beyond the authority granted in the Act.

It is entirely proper for the Administrator to consider the pharmacology of a drug and scientific test results in connection with determining abuse potential. But abuse potential is not in issue in this marijuana proceeding.

There is another reason why DEA should not be guided by FDA criteria in ascertaining whether or not marijuana has an accepted medical use in treatment. These criteria are applied by FDA pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act (FDCA), as amended. [footnote 13] When the FDA is making an inquiry pursuant to that legislation it is looking at a synthetically formed new drug. The marijuana plant is anything but a new drug. Uncontroverted evidence in this record indicates that marijuana was being used therapeutically by mankind 2000 years before the Birth of Christ. [footnote 14]

Uncontroverted evidence further establishes that in this country today "new drugs" are developed by pharmaceutical companies possessing resources sufficient to bear the enormous expense of testing a new drug, obtaining FDA approval of its efficacy and safety, and marketing it successfully. No company undertakes the investment required unless it has a patent on the drug, so it can recoup its development costs and make

a profit. At oral argument Government counsel conceded that "the FDA system is constructed for pharmaceutical companies. I won't

13 21 U.S.C. § 355.

14 Alice M. O'Leary, direct, par. 9.

deny that." [footnote 15]

Since the substance being considered in this case is a natural plant rather than a synthetic drug, it is unreasonable to make FDA-type criteria determinative of the issue in this case, particularly so when such criteria are irrelevant to the question posed by the act: does the substance have an accepted medical use in treatment?

Finally, the Agency in this proceeding relies in part on the FDA's recommendation that the Administrator retain marijuana in Schedule I. But, as in the MDMA case, that recommendation is based upon FDA's equating "accepted medical use" under the Act with being approved for marketing by FDA under the Food, Drug and Cosmetic Act, the interpretation condemned by the First Circuit in the MDMA case. See Attachment A, p.24, to exhibit G-1 and exhibit G-2.

The overwhelming preponderance of the evidence in this record establishes that marijuana has a currently accepted medical use in treatment in the United States for nausea and vomiting resulting from chemotherapy treatments in some cancer patients. To conclude otherwise, on this record, would be unreasonable, arbitrary and capricious.

15 Tr. XV-37.

Click here for Part 3

VI.

ACCEPTED MEDICAL USE IN TREATMENT
- GLAUCOMA

Findings of Fact

The preponderance of the evidence establishes the following facts with respect to the accepted medical use of marijuana in the treatment of glaucoma.

1. Glaucoma is a disease of the eye characterized by the excessive accumulation of fluid causing increased intraocular pressure, distorted vision and, ultimately, blindness. In its early stages this pressure can sometimes be relieved by the administration of drugs. When such medical treatment fails adequately to reduce the intraocular pressure (IOP), surgery is generally resorted to. Although useful in many cases, there is a high incidence of failure with some types of surgery. Further, serious complications can occur as a result of invasive surgery. Newer, non-invasive procedures such as laser trabeculoplasty are thought by some to offer much greater efficacy with fewer complications. Unless the IOP is relieved and brought to a satisfactory level by one means or another, the patient will go blind.

2. Two highly qualified and experienced ophthalmologists in the United States have accepted marijuana as having a medical use in treatment for glaucoma. They are John C. Merritt, M.D. and Richard D. North, M.D. Each of them is both a clinician, treating patients, and a researcher. Dr. Merritt is also a professor of ophthalmology. Dr. North has served as a medical officer in ophthalmology for the Department of Health, Education and Welfare and has worked with the Public Health Service and FDA.

3. Dr. Merritt's experience with glaucoma patients using marijuana medicinally includes one Robert Randall and, insofar as the evidence here establishes per petitioners' briefs, an unspecified number of other patients, something in excess of 40.

4. Dr. North has treated only one glaucoma patient using marijuana medicinally - the same Robert Randall mentioned immediately above. Dr. North had monitored Mr. Randall's medicinal use of marijuana for nine years as of May 1987

5. Dr. Merritt has accepted marijuana as having an important place in the treatment of "End Stage" glaucoma. "End Stage" glaucoma, essentially, defines a patient who has already lost substantial amounts of vision; available glaucoma control drugs are no longer able adequately to reduce the intraocular pressure (IOP) to prevent further, progressive sight loss; the patient, lacking additional IOP reductions, will go blind.

6. Robert S. Hepler, M.D., is a highly qualified and

experienced ophthalmologist. He has done research with respect to the effect of smoking marijuana on glaucoma. In December 1975 he prescribed marijuana for the same Robert Randall mentioned above as a research subject. Dr. Hepler found that large dosages of smoked marijuana effectively reduced Robert Randall's IOP into the safe range over an entire test day. He concluded that the only known alternative to preserve Randall's sight which would avoid the significant risks of surgery is to include marijuana as part of Randall's prescribed medical regimen. He further concluded in 1977 that, if marijuana could have been legally prescribed, he would have prescribed it for Randall as part of Randall's regular glaucoma maintenance program had he been Randall's personal physician.

Nonetheless, in 1987 Dr. Hepler was of the opinion that marijuana did not have a currently accepted medical use in the United States for the treatment of glaucoma.

7. Four glaucoma patients testified in these proceedings. Each has found marijuana to be of help in controlling IOP.

8. In 1984 the treatment of glaucoma with Cannabis was the subject of an Ophthalmology Grand Rounds at the University of California, San Francisco. A questionnaire was distributed which queried the ophthalmologists on cannabis therapy for glaucoma patients refractory to standard treatment. Many of them have glaucoma patients who have asked about marijuana. Most of the responding ophthalmologists believed that THC capsules or smoked marijuana need to be available for patients who have not benefited significantly from standard treatment.

9. In about 1978 an unspecified number of persons in the public health service sector in New Mexico, including some physicians, accepted marijuana as having medical use in treating glaucoma.

10. A majority of an unspecified number of ophthalmologists known to Arthur Kaufman, M.D., who was formerly in general practice but now is employed as a medical program administrator, accept marijuana as having medical use in treatment of glaucoma.

11. In addition to the physicians identified and referred to in the findings above, the testimony of patients in this record establishes that no more than three or four other physicians consider marijuana to be medically useful in the treatment of glaucoma in the United States. One of those Physicians actually wrote a prescription for marijuana for a patient, which, of course, she was unable to have filled.

12. There are test results showing that smoking marijuana has reduced the IOP in some glaucoma patients. There is continuing research underway in the United States as to the therapeutic effect of marijuana on glaucoma.

Discussion

Petitioners' briefs fail to show that the preponderance of the evidence in the record with respect to marijuana and glaucoma establishes that a respectable minority of physicians accepts marijuana as being useful in the treatment of glaucoma in the United States.

This conclusion is not to be taken in any way as criticism of the opinions of the ophthalmologists who testified that they accept marijuana for this purpose. The failure lies with petitioners. In their briefs they do not point out hard, specific evidence in this record sufficient to establish that a respectable minority of physicians has accepted their position.

There is a great volume of evidence here, and much discussion in the briefs, about the protracted case of Robert Randall. But when all is said and done, his experience presents but one case. The record contains sworn testimony of three ophthalmologists who have treated Mr. Randall. One of them tells us of a relatively small number of other glaucoma patients whom he has treated with marijuana and whom he knows to have responded favorably. Another of these three doctors has successfully treated only Randall with marijuana. The third testifies, despite his successful experience in treating Randall, that marijuana does not have an accepted use in such treatment.

In addition to Robert Randall, Petitioners point to the testimony of three other glaucoma patients. Their case histories are impressive, but they contribute

little to the carrying of Petitioner's burden of showing that marijuana is accepted for medical treatment of glaucoma by a respectable minority of physicians. See pages 26-29, above.

Petitioners have in evidence copies of a number of newspaper clippings reporting statements by persons claiming that marijuana has helped their glaucoma. The administrative law judge is unable to give

significant weight to this evidence. Had these persons testified so as to have been subject to cross-examination, a different situation would be presented. But these newspaper reports of extra-judicial statements, neither tested by informed inquiry nor supported by a doctor's opinion, are not entitled to much weight. They are of little, if any, materiality.

Beyond the evidence referred to above there is a little other "hard" evidence, pointed out by petitioners, of Physicians accepting marijuana for treatment of glaucoma. Such evidence as that concerning a survey of a group of San Francisco ophthalmologists is ambiguous, at best. The relevant document establishes merely that most of the doctors on the grand round, who responded to an inquiry, believed that the THC capsules or marijuana ought to be available.

In sum, the evidence here tending to show that marijuana is accepted for treatment of glaucoma falls far, far short of quantum of evidence tending to show that marijuana is accepted for treatment of emesis in cancer patients. The preponderance of the evidence here, identified by petitioners in their briefs, does not establish that a respectable minority of physicians has accepted marijuana for glaucoma treatment.

VII.

ACCEPTED MEDICAL USE IN TREATMENT - MULTIPLE SCLEROSIS, SPASTICITY AND HYPERPARATHYROIDISM

Findings Of Fact

The preponderance of the evidence clearly establishes the following facts with respect to marijuana's use in connection with multiple sclerosis, spasticity and hyperparathyroidism.

1. Multiple sclerosis is the major cause of neurological disability among young and middle-aged adults in the United States today. It is a life-long disease. It can be extremely debilitating to some of its victims but it does not shorten the life span of most of them. Its cause is yet to be determined. It attacks the myelin sheath, the coating or insulation surrounding the message-carrying nerve fibers in the brain and spinal cord. Once the myelin sheath is destroyed, it is replaced by plaques of hardened tissue known as sclerosis. During the initial stages of the disease nerve impulses are transmitted with only minor

interruptions. As the disease progresses, the plaques may completely obstruct the impulses along certain nerve systems. These obstructions produce malfunctions. The effects are sporadic in most individuals and the effects often occur episodically, triggered either by malfunction of the nerve impulses or by external factors.

2. Over time many patients develop spasticity, the involuntary and abnormal contraction of muscle or muscle fibers. (Spasticity can also result from serious injuries to the spinal cord, not related to multiple sclerosis.)

3. The symptoms of multiple sclerosis vary according to the area of

the nervous system which is affected and according to the severity of the disease. The symptoms can include one or more of the following: weakness, tingling, numbness, impaired sensation, lack of coordination, disturbances in equilibrium, double vision, loss of vision, involuntary rapid movement of the eyes (nystagmus), slurred speech, tremors, stiffness, spasticity, weakness of limbs, sexual dysfunction, paralysis, and impaired bladder and bowel functions.

4. Each person afflicted by multiple sclerosis is affected differently. In some persons, the symptoms of the disease are barely detectable, even over long periods of time. In these cases, the persons can live their lives as if they did not suffer from the disease. In others, more of the symptoms are present and acute, thereby limiting their physical capabilities. Moreover, others may experience sporadic, but acute, symptoms.

5. At this time, there is no known prevention or cure for multiple sclerosis. Instead, there are only treatments for the symptoms of the disease. There are very few drugs specifically designed to treat spasticity. These drugs often cause very serious side effects. At the present time two drugs are approved by FDA as "safe" and "effective" for the specific indication of spasticity. These drugs are Dantrium and Lioresal baclofen.

6. Unfortunately, neither Dantrium nor Lioresal is a very effective spasm control drug. Their marginal medical utility, high toxicity and potential for serious adverse effects make these drugs difficult to use in spasticity therapy.

7. As a result, many physicians routinely prescribe

tranquilizers, muscle relaxants, mood elevators and sedatives such as Valium to patients experiencing spasticity. While these drugs do not directly reduce spasticity

they may weaken the patient's muscle tone, thus making the spasms less noticeable. Alternatively, they may induce sleep or so tranquilize the patient that normal mental and physical functions are impossible.

8. A healthy, athletic young woman named Valerie Cover was stricken with multiple sclerosis while in her early twenties. She consulted several medical specialists and followed all the customary regimens and prescribed methods for coping with this debilitating disease over a period of several years. None of these proved availing. Two years after first experiencing the symptoms of multiple sclerosis her active, productive life - as an athlete, Navy officer's wife and mother - was effectively over. The Social Security Administration declared her totally disabled. To move about her home she had to sit on a skateboard and push herself around. She spent most of her time in bed or sitting in a wheelchair.

9. An occasional marijuana smoker in her teens, before her marriage, she had not smoked it for five years as of February 1986. Then a neighbor suggested that marijuana just might help Mrs. Cover's multiple sclerosis, having read that it had helped cancer patient's control their emesis. Mrs. Cover acceded to the suggestion.

10. Just before smoking the marijuana cigarette produced by her neighbor, Mrs. Cover had been throwing up and suffering from spasms. Within five minutes of smoking part of the marijuana cigarette she stopped vomiting, no longer felt nauseous and noticed that the intensity of her spasms was significantly reduced. She stood up unaided.

11. Mrs. Cover began smoking marijuana whenever she felt nauseated. When she did so it controlled her vomiting, stopped the nausea and increased her

appetite. It helped ease and control her spasticity. Her limbs were much easier to control. After three months of smoking marijuana she could walk unassisted, had regained all of her lost weight, her seizures became almost nonexistent. She could again care for her children. She could drive an automobile again. She regained the ability to lead a normal life.

12. Concerned that her use of this illegal substance might jeopardize the career of her Navy officer husband, Mrs. Cover stopped smoking marijuana several times. Each time she did so, after about a month, she had retrogressed to the point that her multiple sclerosis again had her confined to bed and wheelchair or skateboard. As of the Spring of 1987 Mrs. Cover had resumed smoking marijuana regularly on an "as needed" basis. Her multiple sclerosis symptoms are under excellent control. She has obtained a full-time job. She still needs a wheelchair on rare occasions, but generally has full use of her limbs and can walk around with relative ease.

13. Mrs. Cover's doctor has accepted the effectiveness of marijuana in her case. He questioned her closely about her use of it, telling her that it is the most effective drug known in reducing vomiting. Mrs. Cover and her doctor are now in the process of filing an Investigational New Drug (IND) application with FDA so that she can legally obtain the marijuana she needs to lead a reasonably normal life.

14. Martha Hirsch is a young woman in her mid-thirties. She first exhibited symptoms of multiple sclerosis at age 19 and it was diagnosed at that time. Her condition has grown progressively worse. She has been under the care of physicians and hospitalized for treatment. Many drugs have been prescribed for her by her doctors. At one point in 1983 she listed the drugs that had been

prescribed for her. There were 17 on the list. None of them has given her the relief from her multiple sclerosis symptoms that marijuana has.

15. During the early stages in the development of her illness Ms. Hirsch found that smoking marijuana improved the quality of her life, keeping her spasms under control. Her balance improved. She seldom needed to use her cane for support. Her condition lately has deteriorated. As of May 1987 she was experiencing severe, painful spasms. She had an indwelling catheter in her bladder. She had lost her locomotive abilities and was wheelchair bound. She could seldom find marijuana on the illegal market and, when she did, she often could not afford to purchase it. When she did obtain some, however, and smoked it, her entire body seemed to relax, her spasms decreased or disappeared, she slept better and her dizzy spells vanished. The relaxation of her leg muscles after smoking marijuana has been confirmed by her personal care attendant's examination of them.

16. The personal care attendant has told Ms. Hirsch that she,

the attendant, treats a number of patients who smoke marijuana for relief of multiple sclerosis symptoms. In about 1980 another patient told Ms. Hirsch that he knew many patients who smoke marijuana to relieve their spasms. Through him she met other patients and found that marijuana was commonly used by many multiple sclerosis patients. Most of these persons had told their doctors about their doing so. None of those doctors advised against the practice and some encouraged it.

17. Among the drugs prescribed by doctors for Ms. Hirsch was ACTH. This failed to give her any therapeutic benefit or to control her spasticity. It did produce a number of adverse effects, including severe nausea and vomiting which, in turn, were partly controlled by rectally administered anti-emetic

drugs.

18. Another drug prescribed for her was Lioresal, intended to reduce her spasms. It was not very effective in doing. But it did cause Ms. Hirsch to have hallucinations. On two occasions, while using this drug, Ms. Hirsch "saw" a large fire in her bedroom and called for help. There was no fire. She stopped using that drug. Ms. Hirsch has experienced no adverse reactions with marijuana.

19. Ms. Hirsch's doctor has accepted marijuana as beneficial for her. He agreed to write her a prescription for it, if that would help her obtain it. She has asked him if he would file an IND application with the FDA for her. He replied that the paperwork was "overwhelming". He indicated willingness to put the paper work together.

20. When Greg Paufler was in his early twenties, employed by Prudential Insurance Company, he began to experience the first symptoms of multiple sclerosis. His condition worsened as the disease intensified. He had to be hospitalized. He lost the ability to walk, to stand. Diagnosed as having multiple sclerosis, a doctor prescribed ACTH for him, an intensive form of steroid therapy. He lost all control over his limbs and experienced severe, painful spasms. His arms and legs became numb.

21. ACTH had no beneficial effects. The doctor continued to prescribe it many months. ACTH made Paufler ravenously hungry and he began gaining a great deal of weight. ACTH caused fluid retention and Paufler became bloated, rapidly gaining weight. His doctor thought Paufler should continue this steroid therapy, even though it caused the adverse effects mentioned plus the possibility of sudden heart attack or

Physical, Mental, and Moral Effects of Marijuana: The Indian Hemp Drugs Commission Report

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The Indian Hemp Drugs Commission Report (1894), comprising some seven volumes and 3,281 pages, is by far the most complete and systematic study of marijuana undertaken to date. Because of the rarity and, perhaps, the formidable size of this document, the wealth of information contained in it has not found its way into contemporary writings on this subject. This is indeed unfortunate, as many of the issues concerning marijuana being argued in the United States today were dealt with in the Indian Hemp Drugs Commission Report.

It is both surprising and gratifying to note the timeless and lucid quality of the writings of these British colonial bureaucrats. It would be fortunate if studies undertaken by contemporary commissions, task force committees, and study groups could measure up to the standards of thoroughness and general objectivity embodied in this report. In the current context of violently polarized attitudes toward marijuana, the prospect of a study of similar stature is bleak.

The scope of this paper is necessarily limited to the issues of physical, mental, and moral effects of hemp drugs as discussed in the report, although the topics of cultivation, processing, and administrative control schemes make up significant portions of the work itself.

History of British Involvement

The British government in India had substantial knowledge of intoxicants other than alcohol because of active involvement in regulation, taxation, and actual trafficking in these substances for over a hundred years prior to the Hemp Drugs Commission investigation and report.

In 1790 duties on alcohol and other intoxicant drugs were first levied by the British on landlords in India. The regulation of cannabis preparations was further specified in 1793 in Regulation XXXIV of that year. "No person shall manufacture or vend any such drugs (bhang,2 ganja,3 charas,4 and other intoxicating drugs) without a license from the collector of the zillah5" (3:16).

This system of regulations was instituted "with a view to check immoderate consumption, and at the same time to augment the public revenue" (3:16).

In 1800 in a further modification of regulation, the manufacture and sale of charas was prohibited as "being of a most noxious quality" (3:16), while daily rates of duty were declared as the basis for taxing procedures. Curiously, in 1824 the restriction on charas was rescinded "as this drug was found on examination to be not more prejudicial to health than ganja or other intoxicating drugs" (3:16).

In 1849 limits on retail sale of cannabis drugs were fixed "for better securing the abkari6 revenue of Calcutta," and later extended to the whole of Bengal (3:16). Four years later the daily tax method was abandoned and a fee charged on a per weight basis, and in 1860 an additional set of dealers fees' imposed (3:16).

It should be noted, however, that the system of the state of Bengal was only one of several schemes among the many provinces. Variations on this approach existed in the other states, a function of the differing local administrations, reflecting the degree of administrative and fiscal controls exerted by the Imperial government.

There had apparently been controversies as to the possible noxious effects of cannabis drugs at least from the time of the inception of British controls on these products, unless we assume that the initial stated reasons for regulation were merely cynical rationalizations for obtaining additional sources of revenue. Within a country of several hundred millions of inhabitants, divided into hundreds of regions, and with only rudimentary "homogenizing" forces of effective transportation and mass media, it is perhaps reasonable to infer that wide variations in opinions and beliefs would be encountered.

1 *Report of the Indian Hemp Drugs Commission, 1893-94*. Simla, India: Government Central Printing House, 1894, 7 vols. All references in this paper are to volumes of the Report.

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2 Leaves and flowers of wild growing or inferior cultivated cannabis plants.

3 Flowering tops of the cannabis plant.

4 Resin from the mature cannabis plant.

5 A county-sized district or administrative division.

6 Manufacture or sale of intoxicating liquors or drugs: hence, an excise or internal revenue tax on such manufacture or sale (Ankara: A wine seller; distiller. Also, one whose trade is subject to abkari tax).

FORMATION OF THE COMMISSION

On 2 March 1893 (1:1,n) a question was raised in the British House of Commons concerning the effects of the production and consumption of hemp drugs in the province of Bengal, India. In response, the Government of India convened a seven-member commission to look into these questions on 3 July 1893 (1:1). Upon the suggestion of Lord Kimberley the scope of the investigation was expanded to include all of India.

PROCEDURES

The Commission actually met for the first time in Calcutta on 3 August 1893 (1:4). Between this date and 6 August of the following year, when the study was finished (1:361), the Commission received evidence from

1,193 witnesses (1:12). Field trips were made to thirty cities in eight provinces and Burma from the end of October 1893 through the latter part of April 1894 (1:9-10). Eighty-six meetings for examination of witnesses transpired during the inquiry. Actual participation of the members of the Commission was duly noted and reported - a custom that it might be worthwhile to revive.

[redacted] statement on the previous page shows the attendance of the members of the Commission during the period occupied in inquiry (3rd August 1893 to 25th April 1894).

Witnesses whose evidence was received by the Commission were divided into three categories:

(1) Official witnesses able to give information regarding hemp drugs, based on their official and local experience.

(2) Non-official witnesses of all ranks able to give information regarding the drugs generally or in connection with certain classes of the people.

(3) Other persons or associations having facts or holding opinions which they desired to communicate to the Commission (1:11).

Categories and numbers of the witnesses were (1:12):

Civil Officers 197

Medical Officers 214

Private Practitioners (European methods) 34

[redacted]vate Practitioners (Native methods) 87

Cultivators 144

Professional Men 55

Missionaries 34

Associations 24

Persons engaged in Trade 75

Others 59

Total 1,193

To facilitate collection of information, seventy questions framed by the Commission were given to the witnesses. The written answers to these questions constituted the bulk of the evidence before the Commission (1:13). Where appropriate, witnesses were examined orally for further clarification or explanation. In addition, witnesses who had not submitted written statements were examined orally. It was duly noted in the record which forms of testimony had been provided by the individual witnesses. The following were the questions dealing with effects of hemp drugs with regard to adverse physical [redacted]nsequences, insanity, and the causation of crime (4:iii):

45. (a) Does the habitual moderate use of any of these drugs produce any noxious effects - physical, mental, or moral?

(b) Does it impair the constitution in any way?

(c) Does it injure the digestion or cause loss of appetite?

Does it cause dysentery, bronchitis, or asthma?

(e) Does it impair the moral sense or induce laziness or habits of immortality or debauchery?

(f) Does it deaden the intellect or produce insanity?

If it produces insanity, then of what type, and is it temporary or permanent?

If temporary, may the symptoms be re-induced by use of the drug after liberation from restraint?

Are there any typical symptoms?

Do insanes, who have no recorded ganja history, confess to the use of the drug?

(g) In such cases of the alleged connection between insanity and the use of hemp as are known to you, are you of opinion that the use of the drug by persons suffering from mental anxiety or brain disease to obtain relief his been sufficiently considered in explaining that connection?

And do you think there is any evidence to indicate that insanity may often tend to indulgence in the use of hemp drugs by a person who is deficient in self-control through weakened intellect?

Give an account under each of these points of any cased with which you are acquainted.

. Discuss the same questions in regard to the habitual excessive use of any of these drugs.

51. (a) Are any large proportion of bad characters habitual moderate consumers of any of these drugs?

(b) What connection, if any, has the moderate use with crime in general or with crime of any special character?

52. Discuss the same question in regard to the excessive use of any of these drugs.

53. Does excessive indulgence in any of these drugs incite to unpremeditated crime, violent or otherwise? Do you know of any case in which it has led to temporary homicidal frenzy?

1. Are these drugs used by criminals to fortify themselves to commit a premeditated act of violence or other crime?

Physical Effects of Chronic Cannabis Use

The Commission sought to evaluate alleged connections of hemp drug use with disorders other than mental. Popular opinion held that the use of hemp drugs led to the physical disorders of dysentery, bronchitis, and asthma:

regard to these definite physical results, the only evidence to which much weight can be attached is the evidence of the medical witnesses. From their training and opportunities of observation they are the only witnesses qualified to give reliable evidence. It is proposed to examine this medical evidence in detail

(1:205).

The Commission reviewed and discussed medical evidence given by 335 physicians7 throughout India from Bengal, Assam, North-Western Provinces, Punjab, Central Provinces, Madras, Bombay, Sind, Burma, and Behar. The testimony from the array of medical witnesses from Bengal illustrates the confusion and the lack of knowledge among the members of our profession:

In Bengal eight commissioned medical officers were examined on the effect of the ...oderate use of the drugs. Surgeon-Lieutenant-Colonel Russell (witness No. 105), 20 years in civil employ in Bengal and Assam, a witness whose evidence has frequently been quoted by the Commission, stated that the use of the drug does not cause bronchitis, dysentery, or asthma, and that scarcely any other noxious effects are induced. Surgeon-Lieutenant-Cclonel Russiel Lall Dutt (witness No. 107) an officer of over 20 years' experience, stated "Very moderate smoking of Ganja or charas or moderate drinking of siddhi in infusion do not produce any appreciable effects. . . but these moderate cases are seldom long-lived. There is in them a slow and insidious undermining process going on in their digestive, respiratory, and nervous system, which predispose them to acute diseases and cut their lives short." Surgeon-Lieutenant-Colonel Price (witness No. 108), of 21 years' service, who had frequently come across consumers of hemp drugs, was unable to answer the question regarding effects. Surgeon-Captain Prain (witness No. 113) stated: "I do not believe that the habitual moderate use of any of these drugs produces any noxious effects - physical, mental, or moral. I think that perhaps the use of bhang does injure the digestion and impair appetite even when used moderately, but I am convinced that it neither causes dysentery, bronchitis, or asthma." Surgeon-Major Cobb (witness No. 110) stated that the drugs did not cause asthma, bronchitis, or dysentery; and in cross-examination he stated: "I have no experience that the excessive use of the drug produces dysentery and bowel complaints." Surgeon-Lieutenant-Colonel Flood Murray (witness No. 102),

five years in military service and nineteen years in civil employ, quoted the opinion of a pandit8 whom he consulted regarding the ill effects of the drugs. In cross-examination he stated: "The general statement as contained in my written answer is a statement made to me by this hakim9 and others to whom I applied for information. *My own experience in no way corroborates it.*" Surgeon-Lieutenant-Colonel Bovill (witness No. 109), of 21 years' service, stated that the habitual moderate use of bhang does not produce any ill effects, and in many cases that of ganja is equally harmless. He added; "I know of no case where it has caused bronchitis, dysentery, or asthma, but I have noted hoarseness of the voice probably due to some laryngeal irritation among ganja smokers." Surgeon-Lieutenant-Colonel Crombie (witness No. 104), of over 20 years' service, is not aware of any ill effects being produced by the moderate use of the drugs; but he added: "If any were produced, the use would no longer be moderate, but excessive." In cross-examination Dr. Crombie stated: "I have had no experience of any diseases attributable to ganja. My experience has been chiefly in Eastern Bengal, where ganja is largely consumed."

Twenty-three assistant surgeons were examined. Assistant Surgeon Devendranath Roy (witness No. 123), of over 20 years' service, and who has had service in Rajputana, the North-Western Provinces, Behar, and Bengal, where hemp drugs are used by a large portion of the people, is of opinion that those who smoke ganja not more than twice or thrice a day do not suffer in general health; bhang does not impair the digestion, whereas ganja does. "Those of my patients," he remarks "who admitted having been habitual ganja smokers suffered from dysentery or diarrhoea, but they have been exposed to conditions which produce these ailments. Hence I do not draw any conclusion as to ganja being a primary cause of those diseases." Assistant Surgeon Preonath Bose (witness No. 122), Teacher of Materia Medica and Pharmacy in the Dacca Medical School, clearly has no personal knowledge of the effects, as he remarked: "Evidence on these points is conflicting. Some of the consumers maintain, others deny, that evil effects are produced." Another teacher at the same school (witness No. 121) stated: "Evidence on these points is conflicting. The general consensus of opinion is that the habitual moderate use of bhang and ganja does not impair the constitution." Assistant Surgeon Soorjee Narain Singh, of 28 years' service, now Teacher of Materia Medica,

Patna Medical School (witness No. 125), stated that "habitual moderate consumers of bhang, ganja or charas do not apparently suffer from any injurious effects." Assistant Surgeon Narendra Nath Gupta (witness No. 120), as Deputy Superintendent of Vaccination and as Deputy Sanitary Commissioner and as Civil Medical Officer has had considerable opportunities for noting the effects of the drugs. His opinion is that the [illegible]erate use of ganja and bhang does not produce any noxious effects. Durga Dass Lahiri, L.M.S. (witness [illegible] 132), a private medical practitioner, said: "I have not seen any evil results mentioned when taken moderately, but it is very difficult to keep to moderation." Assistant Surgeon Taraprosanna Roy (witness No. 116) is Chemical Examiner to the Government of Bengal. He stated that the habitual moderate use of the three drugs is not known to produce any noxious effects. Assistant Surgeon Bosonto Kumar Sen (witness No. 119) has had service in ganja producing districts. He stated that the use of ganja and bhang products noxious effects, and "generally produce dysentery, asthma, and bronchitis." The cross examination of this witness is of interest. "I have seen more than one person, about half a dozen, in my village. . . suffering from dysentery, bronchitis, and asthma who were also ganja smokers. *They were all excessive smokers.* These effects do not follow the moderate, but the excessive, use. It is a mistake to have put them under the moderate use. . . . The fact that they were ganja smokers led me to believe that these effects were due to ganja . . I have no recollection of ever treating any case of dysentery, bronchitis, or asthma caused by ganja. *These cases are the basis of my remarks.* I do not remember any case of dysentery, bronchitis, or asthma in a ganja smoker which I attributed to any other cause. In other words, when I saw ganja smokers suffering from these diseases, I attributed them to ganja. *This was twenty years ago,* before I was a medical student." Pyari Sankar Dass Gupta, L.M.S. (witness No. 134), is a private medical practitioner, Secretary to the Bogra Medical Society of ten members, and a member of a temperance association founded by the late Keshub Chunder Sen. The witness is pledged against the use of all intoxicants. The witness submitted three papers to the Commission which seem to illustrate the development of tradition into opinion. In one paper the witness states: "The smokers of ganja often suffer from hoarseness of voice produced by the continual inhalation of its fumes, giving rise to sore-throat, bronchitis, and carbonaceous phthisis. It has long been a [illegible]*dition* in our country that the *ganja-khors always* die of dysentery, their intestines gradually sloughing [illegible]ay." In his second paper the witness states "Ganja smokers generally die of bloody dysentery, asthma and phthisis, and haemoptysis." And in his last paper he says: "It produces bloody dysentery and chest diseases, blood spitting, bronchitis, asthma, and phthisis." Kailas Chundra Bose, L.M.S. (witness No. 135), is a private medical practitioner in Calcutta with an extensive practice. He states that no ill effects are produced by the moderate use, and that, instead of causing bronchitis, dysentery, or asthma, it relieves these afflictions. The witness, however, states in his oral examination: "My experience is not to any large extent what I have gathered in my practice, but rather what I have learnt from smokers." Assistant Surgeon Akbar Khan (witness No. 124) is another Teacher in the Patna Medical School. He states the habitual moderate use of any of the drugs does not produce noxious effects, but that charas and ganja cause dysentery, bronchitis, and asthma if the consumers are not well fed. Witnesses Nos. 126 and 138 consider that no ill effects are produced. Assistant Surgeon Upendra Nath Sen (witness No. 118) states that bronchitis, and asthma are common complaints of ganja smokers. Madhab Krishna Dass, L.M.S. (witness No. 158) a private practitioner in Calcutta, considers that smoking may cause dysentery, bronchitis, or asthma. Assistant Surgeon Durga

Nath Chakravarti (witness No. 150) considers that "ganja causes dysentery after a long run." Annoda Prasanna Ghatak, M.B. (witness No. 149), a private medical practitioner, considers that digestive complaints are caused when good food is not procurable. Rakhal Das Ghosh, L.M.S., (witness No. 149) a private practitioner in Calcutta, had apparently seen no ill effects caused by the drug. The remaining witnesses in this class clearly failed to discriminate between the moderate and excessive use and their evidence has not been considered.

Three hospital assistants were examined. One gave no reply regarding moderate use. The other stated: "The habitual moderate use of ganja or charas does not produce any noxious effects - physical, mental, or moral, but the use of ganja impairs the constitution in some way or other . . . and has a tendency toward bronchitis

and asthma." Witness No. 145 is a vernacular class hospital assistant, but not now in Government employ. According to this witness, moderate use of ganja leads to excessive use. "The habitual moderate consumers, as well as the excessive consumers, suffer in their lungs and become insane . . . No intoxicant can be taken in moderation except when administered medicinally."

Seven native practitioners were examined. Bijoya Ratna Son (witness No. 151), a kabiraj10 practising in Calcutta, considers that the habitual moderate use of ganja or charas, but not siddhi, may in some cases cause bronchitis, dysentery or asthma. Witness No. 152, also of Calcutta, gives the same reply couched in the same language. Witness No. 126, of Nattore, in the Rajsha-hi district, and witness No. 153, of Calcutta, both consider the moderate use harmless. Piyari Mohan (witness No. 154), a kabiraj states: "I know it causes dysentery and I believe owing to its healing power it can cause bronchitis and asthma." Kedareswar Acharjya (Witness No. 137) remarks: "Those ganja smokers who cannot command abundant wholesome food suffer from dysentery, but it is difficult to determine how far it is due to ganja or to improper food. As to asthma, I have not seen any typical case originating from ganja smoking. I know that a chronic catarrhal condition of the air passages with a certain amount of spasm is the misfortune of many old ganja smokers. I know a friend who suffered from chronic bronchitis, and in whom asthmatic fits were induced by attempts to smoke ganja." The witness refers also to another case in which a habitual ganja smoker had an asthmatic attack which subsided on breaking off the habit and reappeared on resuming it." This witness lays stress in personal idiosyncrasy as modifying the effects of the drugs, and on the importance of a diet rich in fat. Witness No. 155, another kabiraj, states that, while no ill effects are produced, occasionally it entices dysentery, bronchitis, and asthma. Witness No. 128, also a kabiraj, states that, according to the Aurveda Shastra, smoking these drugs causes bronchitis and asthma, and in his opinion "even the moderate use of any of these drugs, not according to the rules of Shastra, is injurious in its effects." This witness does not appear to have any personal knowledge of ill effects, but to base his views on the teachings of the Shastras. Witness No. 139 states: "Certainly they produce effects on the moral and physical constitution," but as the witness is silent as to the effects of excessive use, probably he has not discriminated between the two uses of the drugs. Witness No. 157, a valid11, considers that even the habitual moderate use of these drugs produces noxious effects. This is the pandit who was consulted by Dr. Flood Murray (witness No. 102), and who produced two cases of hemp drug asthma and weakened heart for Dr. Murray's inspection. These seem to have been the only cases in any way connected with hemp drug that he had. Witness No. 146 is a zamindar12 and medical practitioner, and does not reply as to effects. Witness No. 147 studied two and half years at the Calcutta Medical College, but took no degree. He states that no noxious effects are produced without giving details (1·205-8).

After reviewing similar conflicting testimony from the other states, the Commission concluded:

The medical evidence which has thus been analyzed very clearly indicates in the opinion of the Commission that when the basis of the opinions as to the alleged evil effects of the moderate use of the drugs is subjected to careful examination, the grounds on which the allegations are founded, prove to be in the highest degree defective. A large number of medical witnesses of all classes, ascribe dysentery, bronchitis, and asthma to the moderate use of the drugs. An equally representative number give a diametrically opposite opinion. The most, striking feature of the medical evidence is perhaps the large number of practitioners of long experience who have seen no evidence of any connection between hemp drugs and disease, and when witnesses who speak to these ill effects from the moderate use are cross-examined it is found that (a) their opinions are based on popular ideas on the subject; (b) they have not discriminated between the effects of moderate and excessive use of the drugs; (c) they have accepted the disease as being induced by hemp drugs because the patients confessed to the habit; and (d) the fact has been overlooked that the smoking of hemp drugs is recognized as a remedial agent in asthma and bronchitis. A few witnesses incidentally refer to personal idiosyncrasy as perhaps being a factor in rendering some consumers of the drugs less tolerant and more liable to be affected by them even when used in moderate quantity. This view the Commission are prepared to accept; but for the vast majority of consumers, the Commission consider that the evidence

shows the moderate use of ganja or charas not to be appreciably harmful, while in the case of moderate bhang drinking the evidence shows the habit to be quite harmless. As in long continued and excessive cigarette smoking considerable bronchial irritation and chronic catarrhal laryngitis may he induced, so, too, may a similar condition be caused by excessive ganja or charas smoking; and to the oetiology of bronchial catarrh and asthma in ganja smokers the Commission have already referred. The direct connection alleged between dysentery and the use of hemp drugs the Commission consider to be wholly without any foundation. In the case of bhang there is nothing in the physiological action of the drug which could in any way set up an acute inflammation of the large intestine resulting in ulceration. On the contrary, it is well known that hemp resin is a valuable remedial agent in dysentery. As regards ganja or charas smoking inducing dysentery, even assuming that the products of the destructive distillation of the drugs directly reached the intestines, there is evidence that those products, when condensed and injected into a cat's stomach, failed to induce any inflammatory process. The connection, therefore, between hemp drug smoking and dysentery appears even remoter than in the case of bhang drinking and that disease and cannot be accepted by any stretch of the imagination as even a possible direct cause of dysentery (1: 223).

7 214 Medical Officers, 34 Practitioners of European medicine and 87 Practitioners of native methods.

8 Learned man, teacher; esp., a Brahman versed in Sanskrit, and in the science, laws, and religion of the Hindus; in Kashmir, any clerk or native official.

9 In Moslem countries, a ruler or a judge.

10 A member of a Unitarian reform sect of India based upon the teachings of Kabir (Hindu mystic and poet, c. 1450-1518).

11 A native practitioner.

12 A land owner; also: Formerly, under the Mohammedan administration, a collector of the land revenue of a specified district for the government. Now, usually a kind of feudatory recognized as an actual proprietor so long as he pays the government a fixed revenue averaging in different provinces less than one-half the net revenue (India).

Cannabis and Insanity

Because many people believed that the use of hemp drugs led to insanity, especially in the case of prolonged use of large amounts of charas and perhaps ganja, the Commission addressed a significant amount of effort to the study of this topic (1: 225 and all of Vol. 2). In addition to the testimony received from physicians, the Commission set about to evaluate all cases admitted to the Indian mental hospitals for the year 1892 that were listed as being caused by hemp drugs (1:227).

Initial inquiry into the Dullunda Asylum at Calcutta led the Commission to distrust the asylum statistics. Because of incomplete figures, frequent absence of supporting data and outright errors, the Commission decided to take up each of the cases of 1892 separately and to inquire as fully as possible into its history (1:227).

In the course of its inquiry into the 24 asylums in India and Burma, the Commission sharply criticized the testimony of the reporting superintendents:

They have known nothing of the effects of the drugs at all, though the consumption is so extensive, except that cases of insanity have been brought to them attributed with apparent authority to hemp drugs. They have generalized from this limited and one-sided experience. They have concluded that hemp drugs produce

insanity in every case, or in the great majority of cases, of consumption. They have had no idea that in the vast majority of cases this result does not follow the use. They have accordingly without sufficient inquiry assisted, by the statistics they have supplied and by the opinions they have expressed, in stereotyping the popular opinion and giving it authority and permanence (1:226).

With such hindrances to the inquiry into the connection between hemp drugs and insanity, the Commission, after careful inquiry into the 222 cases allegedly attributed to hemp drugs, from among the total of 2,344 patients admitted during the year 1892 to asylums, concluded, with reservation, that some 61 cases might have been caused by hemp drugs alone:

Even in regard to the remaining 61 cases, it must be borne in mind that it is impossible to say that the use of hemp drugs was in all the sole cause of insanity, or indeed any part of the cause. The following considerations combine to demand caution and reserve in pronouncing an opinion on this point.

Firstly, there are twelve cases in which it has been found impossible to obtain any further information by local inquiry. In these cases we are thrown back on the original papers and the asylum history. Besides these, there are ten more cases in which the patients are beggars and foreign laborers about whose past history no satisfactory information is obtainable. Thus there remain only 39 of these 61 cases about which anything like a satisfactory inquiry has been possible. Further, a great majority of these cases come from the lower orders of cultivators and laborers, from whom information of any value is very difficult to obtain as to other than the most apparent causes. The fact of the existence of the hemp habit is easy enough to ascertain, but that it is the cause, or one of the causes of the insanity, or that it even preceded the insanity, is much more difficult to establish.

Secondly, the method of inquiry has not been satisfactory in regard to all the cases referred for local inquiry. In regard to the great majority, the instructions issued by the Commission as to the agency by which this further inquiry should be conducted have been carried out. But in some, it will be observed, even this further inquiry has been left to the police. Then again there are cases, such as those of the Hyderabad (Sind) Asylum, in which the Superintendent has necessarily been the principal agent in the inquiry, and has, perhaps, not unnaturally but certainly unfortunately, evinced a strong tendency to defend the old asylum entries regarding cause. The series of questions framed by the Civil Surgeon of Delhi for use in the further inquiry also illustrates a tendency to assume that the cases were hemp drug cases, and thus to limit the scope of the inquiry.

Thirdly, it may be noted that excess in the use of hemp drugs is very frequently only one of several vices in which a dissipated man indulges. Further inquiry has proved this in several cases. There is strong probability that had information been complete, it would have been established in many more cases. It is impossible in such cases to say definitely to what form of excess insanity may be mainly due. Further, it is an accepted and established fact that intemperance of any kind may sometimes be not the cause of insanity, but an early manifestation of mental instability. Dr. Conolly Norman (Hack Tuke's Dictionary of Psychological Medicine: article "Mania") says: "The patient also indulges in intoxicants with very undue or unwonted freedom, and thereby precipitates the course and aggravates the symptoms of his disease." One or two cases have been rejected by the Commission on the ground that the evidence merely showed that the habit of use of hemp began at the same time as the mental aberration, or even later. There may have been other cases in which this would have been shown had the information been complete. It is possible therefore that more complete information might have shown in some cases, not only that other causes contributed to the insanity, but also that hemp drugs had nothing whatever to do with inducing it.

These and similar considerations already indicated demand caution in the expression of any judgment as to the causation of insanity in this country. If in England opinion, based on inquiries such as are there possible, has to be stated with caution, this is much more necessary here. In many or the cases in which the hemp

drug habit has been established, it is impossible to feel certain in view of the defective character of the information that the drugs have been the sole cause, or perhaps indeed a cause at all, of the insanity (1:241-2).

Summing up, the Commission indicates the difficulties that prevent conclusive answers to the question of causality between the use of hemp drugs and insanity:

In answering the question therefore, on what the evidence rests that hemp drugs may induce mental aberration, the Commission would offer the following remarks: The evidence may he considered under two heads - (a) popular; (b) scientific. The popular idea that the use of hemp drugs may induce insanity can be traced back for many centuries, and the present day views on the subject are no doubt the outcome of old popular ideas which have been handed down and become concrete. With non-medical wit the mere use of the drug along with the fact of insanity, as the evidence shows, has as a rule been accepted as cause and effect. Of the large number of medical witnesses who have given evidence before the Commission, probably not a single one has ever observed the inception of the habit and the use giving rise to mental aberration, and been in a position to gauge the value of other contributory causes if present. With practically no modern literature on the subject, with no special knowledge apart from the popular idea, with a very slight or no clinical experience of insanity in England, with the experience derived from perhaps having had half a dozen insanes in the course of two years under observation as Civil Surgeons, officers have been placed in charge of asylums, and have had to differentiate between cases of hemp drug insanity and ordinary mania. The careful inquiry which has been made by the Commission into all the alleged hemp drug cases admitted in one year into asylums in British India demonstrates conclusively that the usual mode of differentiating between hemp drug insanity and ordinary mania was in the highest degree uncertain, and therefore fallacious. Even after the inquiry which has been conducted, it cannot be denied that in some of the cases at least the connection between hemp drugs and insanity has not been conclusively established (1:250).

Thus, final answers to this pressing but complex question of the causal relation between hemp drugs use and insanity, as such, remain obscured.

With their usual thoroughness, the Commission sought to explore the possible structural changes to the brain caused by chronic hemp drugs use. Because data from neuropathologic studies based on postmortem examinations was wholly lacking, Brigade-Surgeon-Lieutenant-Colonel D.D. Cunningham, F.R.S., C.I.E., undertook three experiments at the Biological Laboratory attached to the Zoological Garden in Calcutta to evaluate the effects following the continued administration of hemp drugs to monkeys (3:192-6).

The first study dealt with the chronic smoking of ganja in a 16 lb. male rhesus monkey. By means of a smoking chamber, the animal was administered 181 inhalations of ganja smoke over a period of about 8 1/3 months. The daily dose was supplied by a habitué, the amount administered being proportional by weight to that consumed daily by the chronic user. An autopsy performed after sacrificing the animal, including gross examination of the brain, revealed an absence of any pathology.

The second experiment examined the effects of chronic oral ingestion of charas, with the daily dose again obtained from a chronic user on a comparative weight basis. The animals used this time were two smaller *cynomolgus* monkeys, weighing 5 lb. 7 oz. and 4 lb. 1oz. The study lasted 67 days, the animals receiving the drug mixed in milk on 62 days. Because either minimal or no effects were noted, the dose was increased from the usual 1/2 grain to 2 and then 3 grains about a week before termination of the study. Although no behavioral effects were noted with this higher dose schedule, the animals refused to eat the charas-treated milk after three days, bringing the study to a premature end. These animals were not sacrificed.

The third investigation evaluated the effects on a rhesus monkey of the smoking of dhatura daily, for six weeks. The same inhalation chamber was used as in the first experiment. Unfortunately the size of the dose

is not specified. Post-mortem examination of the central nervous system revealed the following effects:

On opening the cranium the dura-mater was found to be somewhat thickened and, especially in the neighbourhood of the superior longitudinal sinus, very conspicuously congested. In this region, too, the membrane in the occipital region was fixed to the cranial walls by soft, very vascular adhesions. The pia-mater was thickened and so highly injected throughout that the cerebral surface had a generally diffused pink tint. The cerebral substance was everywhere abnormally soft and so friable as to render any immediate removal of the membranes impossible without the occurrence of much destruction of the nervous tissue. Like the surface, although in minor degree, it was of a pinkish tinge owing to abnormal accumulation of blood. Conditions or this kind appeared to be universally diffused throughout the whole of the cerebral centres, the texture of the hemispheres, of the cerebellum and of the basal ganglia being alike soft, and the evidence of abnormal congestion universally distributed. In spite of this, however, the spinal cord and its membranes were to all appearance perfectly healthy.

In so far as a single experiment goes the results in this case would, then, seem in show that the habitual inhalation of the smoke of dhatura, even when only practised for a relatively brief period, is sufficient to establish serious morbid changes in the cerebral nervous centres, and that it therein differs from the habitual inhalation of the smoke of ganja extending over a much more prolonged period. This clearly indicates the necessity of distinguishing between cases in which ganja alone is employed from those in which a mixture of ganja and dhatura is substituted for it, as otherwise certain prejudicial effects which are really due to the use of the latter drug may be erroneously credited to the former one" (3:195-6).

Comparisons made concerning organic brain pathology caused by alcohol (whose effects were well known from other studies) and dhatura left the Commission with the impression that these other Intoxicants were far more hazardous than hemp drugs:

So far as the information from all sources before the Commission is concerned there is no evidence of any brain lesions being directly caused by hemp drugs, as they have been found to be caused by alcohol and dhatura; and there is evidence that the coarse brain lesions produced by alcohol and dhatura are not produced by hemp drugs (1.251).

The complex phenomenon of intoxication, as such, was noted by the Commission:

The individual factor with its idiosyncrasies plays here, as everywhere, a very important part. There are other factors, too, which have to be considered, the degree of education, reason, locality, dosage, and mode of preparation of the drug, all of which may modify the symptoms. Thus the hallucinations of the Western people under the influence of hashish are not identical with the voluptuous dreams of the Orientals (1:253).

Of more functional import is the discussion of medico-legal questions involved in the confusion between intoxication and insanity:

A more serious result of this confusion is that there are cases in which men who have committed offenses, especially crimes of violence, under the influence of hemp drugs have been acquitted on the ground of insanity, although the circumstances have been such that had the intoxicant been alcohol, they would have been convicted. It is undoubtedly more difficult in the case of ganja than in the case of alcohol to recognize the line drawn for social and legal purposes between intoxication and insanity. But the difficulty is not insuperable. The main reason for the confusion that has existed is probably the ignorance that has prevailed regarding hemp drugs. When they are recognized as a common intoxicant, it is to be hoped that the practice of the Courts will be freed from the occasional blemishes above indicated. It is not expedient nor is it just that intoxication from hemp drugs should secure immunity from punishment which is not allowed to alcohol (1:254).

Cannabis and Crime

The use of hemp drugs had been implicated as a cause of crime:

Discussing the connection of hemp drugs with crime, it is necessary to discriminate between any effect which they may be supposed to produce of crime in general and the unpremeditated crimes of violence to which intoxication may give rise. Thus there are those who allege that the habitual use of alcohol, at all events if carried to excess, degrades the mind and character of the consumer and predisposes him to crime in general, or to crimes of particular character, especially to offenses against property. Drink is thus so down sometimes as one of the most efficient agencies for increasing the criminal classes. On the other hand, there are well known cases in which intoxication from alcohol has led to crimes of an occasional and exceptional character generally to unpremeditated crimes of violence or other unpremeditated offenses against the person. These two classes of cases should be carefully distinguished and treated separately (1:253-6).

In addition to hearing testimony of numerous enforcement and county officials, the Commission examined the 81 case records of crimes of violence alleged to have been caused by cannabis drugs in the whole of India over the prior 20 years. The Commission immediately excluded 5 of these cases, ascertaining either that data included in abstracts of the court records did not support the assertion that hemp drugs were causative factor, or that the records were unavailable.

In each of the remaining 23 cases, the Commission reviewed the court transcripts and examined, where possible, individuals who were connected, with the case (1:259-60; 3:262-6). The Commission concluded:

Of these twenty-three cases, then, the records in not less than eighteen show that the crimes cannot be connected with hemp drugs. There is one case of which doubt is thrown by subsequent discoveries. The connection between drugs and crime is only established in the remaining four. It is astonishing to find how defective and misleading are the recollections which man witnesses retain even of cases with which they have had special opportunities of being well acquainted. It is instructive to see how preconceived notion based on rumour and tradition tend to preserve the impression of certain particulars, while the impressions of far more important features of the case are completely forgotten.

In some cases these preconceived notions seem to prevail to distort the incident altogether and to create a picture in the mind of the witness quite different from the recorded facts. Some of the witnesses whose me have thus failed them are men who might have been expected to be careful and accurate. Their failure must tend to increase the distrust with which similar evidence, which there has been no opportunity of testing must be received (1:263).

On the topic of crime, the Commission concluded:

In respect to his relations to society, however, even the excessive consumer of hemp drugs is ordinarily inoffensive. His excesses may indeed bring him to degraded poverty which may lead him to dishonest practices; and occasionally, but apparently very rarely indeed, excessive indulgence in hemp drugs may lead to violent crime. But for all practical purposes it may be laid down that there is little or no connection between the use of hemp drugs and crime (1:264).

Conclusions

The Commission have now examined all the evidence before them regarding the effects attributed to hemp drugs. It will be well to summarize briefly the conclusions to which they come. It has been clearly established that the occasional use or hemp in moderate doses may be beneficial: but this use may be

regarded as medicinal in character. It is rather to the popular and common use of the drugs that the Commission will now confine their attention. It is convenient to consider the effects separately as affecting the physical, mental, or moral nature.

Physical Effects

In regard to the physical effects, the Commission have come to the conclusion that the moderate use of hemp drugs is practically attended by no evil results at all. There may be exceptional cases in which, owing to idiosyncrasies of constitution, the drugs in even moderate use may be injurious. There is probably nothing the use of which may not possibly be injurious in cases of exceptional intolerance. There are also many cases where in tracts with a specially malarious climate, or in circumstances of hard work and exposure, the people attribute beneficial effects to the habitual moderate use of these drugs; and there is evidence to show that the popular impression may have some basis in fact. Speaking generally, the Commission are of opinion that the moderate use of hemp drugs appears to cause no appreciable physical injury of any kind. The excessive use does cause injury. As in the case of other intoxicants, excessive use tends to weaken the constitution and to render the consumer more susceptible to disease. In respect to the particular diseases which according to a considerable number of witnesses should be associated directly with hemp drugs, it appears to be reasonably established that the excessive use of these drugs does not cause asthma; that it may indirectly cause dysentery by weakening the constitution as above indicated; and that it may cause bronchitis mainly through the action of the inhaled smoke on the bronchial tubes (1:263-4).

Mental Effects

In respect to the alleged mental effects of the drugs, the Commission have come to the conclusion that the moderate use of hemp drugs produces no injurious effects on the mind. It may indeed be accepted that in the case of specially marked neurotic diathesis, even the moderate use may produce mental injury. For the slightest mental stimulation or excitement may have that effect in such cases. But putting aside these quite exceptional cases, the moderate use of these drugs produces no mental injury. It is otherwise with the excessive use. Excessive use indicates and intensifies mental instability (1:264).

Moral Effects

In regard to the moral effects of the drugs, the Commission are of opinion that their moderate use produces no moral injury whatever. There is no adequate ground for believing that it injuriously affects the character of the consumer. Excessive consumption, on the other hand, both indicates and intensifies moral weakness or depravity (1:264).

Discussion

Viewing the subject generally, it may be added that the moderate use of these drugs is the rule, and that the excessive use is comparatively exceptional. The moderate use practically produces no ill effects. In all but the most exceptional cases, the injury from habitual moderate use is not appreciable. The excessive use may certainly be accepted as very injurious, though it must be admitted that in many excessive consumers the injury is not clearly marked. The injury done by the excessive use is, however, confined almost exclusively to the consumer himself; the effect on society is rarely appreciable. It has been the most striking feature in this inquiry to find how little the effects of hemp drugs have obtruded themselves on observation. The large number of witnesses of all classes who professed never to have seen these effects, the vague statements

made by many who professed to have observed them, the very few witnesses who could so recall a case as to give any definite account of it, and the manner in which a large proportion of these cases broke down on the first attempt to examine them, are facts which combine to show most clearly how little injury society has hitherto sustained from hemp drugs (1:264).

REPORT OF THE INDIAN HEMP DRUGS COMMISSION, 1893-94.

President:

The Hon'ble W. MACKWORTH YOUNG, M.A., C.S.I., First Financial Commissioner, Punjab.

Members:

1. Mr. H.T. OMMANNEY, Collector, Panch Mahals, Bombay.

2. Mr. A. H. L. FRASER, M.A., Commissioner, Chhattisgah Division, Central Provinces.

3. Surgeon-Major C.J.H. WARDEN, Professor of Chemistry, Medical College, and Chemical Examiner to Government, Calcutta; Officiating Medical Storekeeper to Government, Calcutta.

4. Raja SOSHI SIKHARESWAR ROY, of Tahirpur, Bengal.

5. KAHWAR HARNAN SINGH, Ahluwalia, C.I.E., Punjab.

6. LALA NIHAL CHAND, of Muzaffarnagar, North-Western Provinces.

Secretary:

Mr. H.J. McINTOSH, Under-Secretary to the Government of Bengal, Financial and Municipal Departments.

SIMLA:

PRINTED AT THE GOVERNMENT CENTRAL PRINTING OFFICE.

1894.

Price Rs. 3.

Period of Attendance with the Commission

Name

(a) During the first tour

(b) During the second tour

(c) Number of meetings for examination of witnesses attended

- **President**

(a) 83 days

(b) 183 days

(c) 86

- **Mr. Ommanney**

(a) 83 days

(b) 183 days

(c) 85

- **Mr. Fraser**

(a) 83 days

(b) 193 days

(c) 85

- **Dr. Warden**

(a) 83 days

(b) 183 days

(c) 86

- **Raja Soshi Sikhareswar Roy**

(a) From 3rd August to 15th September, 44 days

(b) From 30th October to 24th January, from 14th to 16th February, from 22nd to 24th February, and from 7th to 25th March, 112 days

(c) 44

- **Kanwar Harnam Singh**

(a) 83 days

(b) From 13th November to 5th January, 22nd February to 2nd April, and from 12th to 25th April, 78 days

(c) 48

Lala Nihal Chand

(a) 3rd August to 20th September, 49 days

(b) From 30th October to 18th November and from 17th to 25th April, 29 days

(c) 5

The attendance of Raja Soshi Sikhareswar Roy was broken by occasional absence caused by ill-health and other reasons. The absence of Kanwar Harnam Singh during two short periods was due to ill-health. The prolonged absence of Lala Nihal Chand was due to the fact that he suffered from continued ill-health, and was able to be with the Commission only at Calcutta at the first; then for some part of their preliminary tour and at a few meetings for the examination of witnesses during the second tour. All the members were present at Simla during the preparation of the report (1:11).

POLICY FOR THE NEW MILLENNIUM:

WORKING TOGETHER TO REDEFINE CANADA'S DRUG STRATEGY

REPORT OF THE SPECIAL COMMITTEE ON NON-MEDICAL USE OF DRUGS

Paddy Torsney, M.P.
Chair

December 2002

CHAPTER 9: CANNABIS

1. MANDATE OF THE SPECIAL COMMITTEE ON NON-MEDICAL USE OF DRUGS

As explained in Chapter 1, the Special Committee on Non-Medical Use of Drugs was initially mandated to study "the factors underlying or relating to the non-medical use of drugs in Canada" and to bring forward recommendations aimed at reducing "the dimensions of the problem involved in such use." That mandate was expanded on 17 April 2002 when the House of Commons, by order of reference, added the subject matter of Private Member's Bill C-344, *An Act to amend the Contraventions Act and the Controlled Drugs and Substances Act (marihuana)*.[299] This chapter will consider the provisions of the *Controlled Drugs and Substances Act* (CDSA) only as it relates to the criminal prosecution of cannabis offences.[300]

Bill C-344 proposed to amend the *Controlled Drugs and Substances Act* and the *Contraventions Act*, to make the offences of possession, possession for the purposes of trafficking and trafficking in small amounts of cannabis (one gram or less of cannabis resin and thirty grams or less of cannabis (marijuana)) "ticketable" offences. The available penalties would be a $200 fine for a first conviction, $500 for a second and $1,000 for a third. At present, possession of those amounts is a summary conviction offence with a maximum penalty of a $1,000 fine or six months in jail, or both. Today, trafficking of anything less than 3 kg of cannabis resin or marijuana is exclusively indictable and carries a maximum penalty of 5 years less a day imprisonment.[301] In support of his bill, Dr. Martin argued that it would unburden the courts, save money, and free up police resources to combat more serious offences.

2. LEGISLATIVE OPTIONS

The Committee heard a wide variety of suggestions respecting the legal treatment of cannabis. Some recommended legalization, either regulated or unregulated. Others favoured some form of decriminalization that would create a non-criminal offence of possession, while still others preferred a more cautious approach that would retain present prohibitions, while introducing more and better diversion options as a way of avoiding some of the harms associated with prosecution. There were also those who favoured increased penalties, at least for trafficking offences, and a renewed commitment to the goal of abstinence. For their part, some health care professionals thought that more research into the effects of cannabis should be undertaken before amending the law, in order to bring better information to the debate, while others pointed out that the illegal status of cannabis has contributed to "a real resistance to conducting those sorts of studies."[302]

For the purposes of this discussion, the Committee defines *legalization* as the removal of all criminal sanctions prohibiting the production, sale or possession of a given substance. Legalization need not be accompanied by the removal of all regulatory controls. In fact, the ability to regulate production and supply, to tax, and to limit access by age, are often cited as major advantages of legalization. The Committee uses the term *decriminalization* to refer to the removal of *criminal* sanctions for certain activity while retaining legal prohibitions. Decriminalization would allow continued criminal prosecution of many or most actions relating to an illicit substance like cannabis, while allowing possession of small amounts of the same substance for personal use to be treated as a regulatory offence, with consequences not unlike those attached to minor motor vehicle infractions under provincial legislation. Under such a scheme, prosecution of the new regulatory offence could be initiated by issuance of a ticket, fines could be paid without a court appearance, and enforcement would not result in a criminal conviction.

The Committee heard from witnesses who expressed the view that the prosecution of cannabis-related offences takes up too much of our scarce criminal justice resources. The potentially negative impact of a criminal conviction was often given as another reason for changing the law. The possibility of uneven or inconsistent enforcement of existing laws may also lend support for legislative changes, to ensure that some individuals don't end up with a large fine and a criminal conviction for possession of a small amount, while others are simply warned and/or have their cannabis confiscated. Although some witnesses argued that enforcement agencies no longer target cannabis possession, preferring instead to pursue more serious CDSA charges, recent crime statistics make clear that possession still constitutes the majority of cannabis incidents reported. For example, Statistics Canada noted that cannabis accounted for about three-quarters of all 91,920 drug-related incidents reported by Canadian police services in 2001. Moreover, 70 percent of those cannabis incidents were for possession.[303]

The following arguments are often made in support of legalization:

- criminal sanctions that do not have the support of a strong majority of the population lead to a loss of respect for the law and those responsible for enforcing it;
- the illicit status of cannabis results in users being exposed to traffickers who also deal in more harmful substances (the need for "separation of markets" has been cited as a principle reason for the existing cannabis policy in the Netherlands);[304]
- legalization also permits regulation and taxation, along with the ability to limit access on the basis of age.

On the other hand, the following reasons are most commonly cited by those who are opposed to legalizing cannabis;

- removing prohibitions would send the wrong message by normalizing use, especially for young people.[305] As an example, many argue that the current publicity around medical use of marijuana has already been perceived by some as an endorsement of the healthful effects of the drug;
- cannabis acts as a "gateway" to the use of other more harmful drugs, if not directly through dependency, then indirectly, through the social milieu and risk-taking aspects of the behaviour.[306]

A majority of members of the Committee are persuaded that there is a need to reform the legislation respecting cannabis, for a variety of reasons. We agree, for example, that because enforcement of the law appears to be sporadic, uneven, and subject to regional discrepancies, its application is likely to be inconsistent and unfair. We further agree that the consequences of a criminal conviction for simple possession of a cannabis product are disproportionate to the potential harms associated with personal use. This is especially true when one considers the harm caused every day by the use of licit substances like tobacco, alcohol, and some common non-prescription medications.

However, the Committee shares the concern expressed by many educators, treatment providers, and law enforcement officers to name only a few, that many Canadians, and youth in particular, might misperceive legalization as evidence that Parliament is not concerned about the widespread use of cannabis. At least as far as this Committee is concerned, nothing could be further from the truth. Indeed, the Committee was told by various health care professionals, addictions specialists and treatment providers that frequent and prolonged use of cannabis can lead to dependence as well as social problems for certain users. In addition, Dr. Mark Zoccolillo expressed concern about the frequency of marijuana use among students he studied, the resulting potential for the disruption of short-term or "working memory," and the long-term consequences for that particular age group. Furthermore, the Committee is not convinced that legalization accompanied by regulation would remove the profit from the illegal production and sale of cannabis or in any significant way discourage criminals currently involved in distribution.

For those reasons, the Committee would prefer to see cannabis offences retained in the

Controlled Drugs and Substance Act, but with simple possession decriminalized by designation as a "contravention," much like the scheme proposed in Bill C-344.[307] However, unlike the amendments proposed in Bill C-344, we do not support a lessening of the penalties for any form of trafficking or possession for the purposes of trafficking. Thus, our preference would be to mandate proceeding against incidents of possession and/or cultivation for personal use by ticketing, except where the offence is committed in the presence of specified aggravating circumstances. For example, in recognition of the safety and policing concerns expressed by law enforcement agencies, the Committee believes that possession charges linked to impaired driving offences should continue to be prosecuted as a criminal offence under the CDSA.[308] Implementation of these proposals may require a redrafting of the possession offences in the CDSA, in order to retain present penalties for 'aggravated' possession charges.

The Committee deliberated at considerable length over the question of whether criminal sanctions should be retained for simple possession of cannabis in relation to schools and other places frequented by youth. However, most Committee members were reluctant to propose a scheme that operates more onerously against youth than it does against their adult counterparts. Furthermore, trafficking, or possession for the purposes of trafficking, in or near a school or other place frequented by those under eighteen, and trafficking to persons under eighteen, are already "aggravating factors" to be considered at the time of sentencing. Because trafficking-related offences and penalties will not be affected by the decriminalization scheme we propose, those provisions will continue to apply. Therefore, the Committee proposes that possession of a small amount of cannabis for personal use, even on school property, should also be a "ticketable" offence under the new scheme. The Committee expects that school boards will continue to impose their own administrative controls, as necessary, to further deter students from bringing cannabis onto school property in much the same way as they do now with other substances.

By designating as contraventions, those offences relating to the possession or cultivation of small amounts of cannabis for personal use, the proposed decriminalization scheme would leave existing criminal sanctions in place to allow the full force of the law to continue to be brought to bear against anyone who traffics in or cultivates cannabis products for profit. Retaining a criminal offence for possession of cannabis in association with an impaired driving offence would do the same for those individuals whose substance use risks grave and substantial harm to others. Finally, decriminalization would have the added benefit of maintaining Canada's compliance with the International Conventions discussed in Chapter 7.

3. COMMITTEE OBSERVATIONS — CANNABIS

The Committee observed the following:

- *Smoking any amount of marijuana is unhealthy, because of its high concentration of tar and benzopyrene.*
- *The consequences of conviction for possession of a small amount of cannabis for personal use are disproportionate to the potential harm associated with that behaviour.*
- *DECRIMINALIZING the possession of small amounts of cannabis for personal use would not affect the penalties or consequences for trafficking, or for the possession of any other controlled substance.*
- *All orders of government must undertake to inform Canadians about the potential harms associated with cannabis use and, in particular, the heightened risk to young persons.*

RECOMMENDATION 40

The Committee recommends that the possession of cannabis continue to be illegal and that trafficking in any amount of cannabis remain a crime.

RECOMMENDATION 41

The Committee recommends that the Minister of Justice and the Minister of Health establish a comprehensive strategy for decriminalizing the possession and cultivation of not more than thirty grams of cannabis for personal use. This strategy should include:

- **Prevention and education programs outlining the risks of cannabis use and, in particular, the heightened risk it poses to young persons; and**
- **The development of more effective tools to facilitate the enforcement of existing *Criminal Code* prohibitions against driving while impaired by a drug.**

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299 Introduced on 4 May 2001 by Dr. Keith Martin, M.P. (Esquimalt—Juan de Fuca). An earlier version of the bill was given first reading on 26 October 1999; see Bill C-266, 2nd Session, 36th Parliament.

300 Because this is a study of the non-medical use of drugs, the adequacy and operation of the *Medical Marijuana Access Regulations* will not be included in the discussion.

301 Trafficking or possession for the purposes of trafficking, in amounts in excess of 3 kg, is a purely indictable offence, punishable by a maximum of life imprisonment; see sections 5(1), (2) and (3) of the *Controlled Drugs and Substances Act*.

302 Eugene Oscapella, Canadian Foundation for Drug Policy and Harm Reduction Network, Testimony before the Committee, February 28, 2001.

303 Josée Savoie, "Crime Statistics in Canada, 2001," *Juristat*, Statistics Canada, Canadian Centre for Justice Statistics, Catalogue no. 85-002-XIE Vol. 22 no.6, p. 11.

304 This theory rests on the argument that, given legal access to a substance like cannabis, would-be purchasers are no longer forced to consort with criminals, many of whom may also be involved in the sale of much more harmful substances.

305 Ernie Howe, Addictions Services-Outpatient, Testimony before the Committee, May 23, 2002.

306 Corporal Ken Murray, RCMP, Testimony before the Committee, April 15, 2002.

307 To be logically consistent, it may also be advisable to deal with cultivation for personal use in the same manner if that is practically and administratively possible.

308 Chief Superintendent Bob Lesser, Drug Enforcement Branch, Federal Services Directorate, RCMP, Testimony before the Committee, October 3, 2001.

ORIGINAL ARTICLE

Risk Factors Predicting Changes in Marijuana Involvement in Teenagers

Marianne B. M. van den Bree, PhD; Wallace B. Pickworth, PhD

Background: Marijuana use during adolescence has various adverse psychological and health outcomes. It is poorly understood whether the same risk factors influence different stages in the development of marijuana involvement.

Objective: To establish which risk factors best explain different stages of marijuana involvement.

Design: Data were collected at 2 points using computer-assisted personal interview (wave 1 and wave 2 were separated by 1 year). Twenty-one well-established risk factors of adolescent substance use/abuse were used to predict 5 stages of marijuana involvement: (1) initiation of experimental use, (2) initiation of regular use, (3) progression to regular use, (4) failure to discontinue experimental use, and (5) failure to discontinue regular use. Data were analyzed using logistic regression analysis.

Participants: Middle school and high school students (N=13718, aged 11-21 years) participating in the National Longitudinal Study of Adolescent Health (Add Health).

Results: Three risk factors (own and peer involvement with substances, delinquency, and school problems) were the strongest predictors of all stages. Their combined presence greatly increased risk of initiation of experimental (odds ratio, 20) and regular (odds ratio, 87) marijuana use over the next year. Personality, family, religious, and pastime factors exerted stage-specific, sex-specific, and age-specific influences.

Conclusions: Assessment of substance, school, and delinquency factors is important in identifying individuals at high risk for continued involvement with marijuana. Prevention and/or intervention efforts should focus on these areas of risk.

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MARIJUANA IS THE MOST commonly used illicit drug. Approximately 50% of secondary-school students in the United States indicate having used marijuana.[1] It is one of the leading substances reported in arrests, emergency department and treatment admissions, and autopsies.[2] Short-term risks of marijuana use include traffic accidents[3] and unprotected sex.[4] In addition, marijuana use is associated with lack of motivation; greater involvement with and inability to quit other substances; psychiatric problems, including depression, schizophrenia, anxiety, suicide, conduct problems, antisocial behavior, and criminal behavior; and reduced chances of participation and stability in adult roles (eg, not graduating from high school, abortion, unemployment, and divorce).[5-13]

Experimentation with substances usually takes place during adolescence when tolerance is lower and risk of dependence is greater than in adulthood.[14] Although most adolescents use marijuana infrequently, without adverse health consequences, a minority progress to harmful use.[15] A better understanding of the risk factors that put adolescents at increased risk for experimentation with marijuana, progression to regular use, and failure to discontinue use can make important contributions to the evidence-based development of prevention and intervention programs.

Previously published studies have indicated that marijuana involvement is associated with a multitude of risk factors, including psychological, family, peer, and school variables.[16] However, most risk factor studies conducted to date have focused on a single aspect of the development of marijuana involvement, usually lifetime use or initiation of experimentation.[16] It is poorly understood to what extent well-established risk factors are associated with different stages of marijuana involvement.[17] The primary aim of our study was to establish and compare the contributions of risk factors to the stages

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Table 1. Marijuana Use Development From Wave 1 to Wave 2[a]

Wave 1		Wave 2			
		Experimental Use		Regular Use	
		No	Yes	No	Yes
Experimental use					
No	10 331 (83)	9090 (88), group A	981 (10), group B		260 (3), group C
Yes	2123 (17)	955 (45), group D	786 (37), group E		382 (18), group F
Regular use					
No	12 454 (91)			11 812 (95)	642 (5)
Yes	1264 (9)			640 (47), group G	664 (53), group H

[a] Values are expressed as number (percentage) of subjects. Experimental user, 1-10 times; regular user, >10 times. Five stages were assessed based on comparisons of groups who changed their marijuana use since wave 1 vs those who did not. Stages were initiation of experimental marijuana use (compared groups A and B), initiation of regular marijuana use (compared groups A and C), progression to regular use (compared groups E and F), failure to discontinue experimental use (compared groups E and D), and failure to discontinue regular use (compared groups H and G).

of initiation, progression, and failure to discontinue experimental and regular marijuana use. Most previous studies have focused on 1 or a few risk factors. Our second aim was to evaluate a wide range of relevant risk factors to provide well-funded evidence for their relative importance in predicting development of marijuana involvement. Third, most previous studies have been cross-sectional in nature. Our study uses a longitudinal design, enabling us to predict developments in marijuana involvement based on risk factors assessed in the previous year.

METHODS

The National Longitudinal Study of Adolescent Health (Add Health) was established to determine the causes of health-related behaviors of adolescents and their outcomes in young adulthood. The primary sampling frame included all high schools in the United States with an 11th grade and at least 30 enrollees. From this, a systematic random sample of high schools was selected. Overall, 79% of schools contacted agreed to participate (final sample of 134 schools). Among students, a random sample was selected to take part in in-home interviews. Sixteen thousand seven hundred six subjects were selected to be interviewed at 2 points, wave 1 in 1995 (response rate, 78.9%) and wave 2 in 1996 (response rate, 88.2%). Estimates in this sample were not significantly biased by missing data from dropouts and graduates.[18] The Add Health study and sampling procedures are described in detail elsewhere.[19] For the present study (N = 13 718), we excluded any nonrandomly selected subsamples, duplicates, and students with missing data on marijuana use. Subjects were aged 11 to 21 years, with a mean (SD) age of 15.4 (1.6) years.

Data were gathered by computer-assisted interview, which yields higher reported prevalences of high-risk behaviors than regular interviews.[20] Interviews took 1 to 2 hours and were administered in the presence of trained assistants. Subjects responded to questions by typing in answers on a laptop computer. Sensitive questions, including those on marijuana involvement, were given on headphones. This avoided the problem of underreporting, which may occur in situations where subjects are face to face with the interviewer.[20] At wave 1, adolescents indicated how many times they had used marijuana during their lives; 1 year later, during wave 2, they reported on their use since wave 1. For both waves, we established the following groups: nonusers, experimental users (used 1-10 times), and regular users (used >10 times). We subsequently assessed changes in marijuana involvement between the 2 waves according to 5 stages: (1) initiation of experimental use (we selected nonusers at wave 1 and compared those who started experimental use at wave 2 with those who had remained nonusers), (2) initiation of regular use (we selected nonusers at wave 1 and compared those who started regular use at wave 2 with those who had remained nonusers), (3) progression to regular use (we selected experimental users at wave 1 and compared those who progressed to regular use at wave 2 with those who had remained experimental users), (4) failure to discontinue experimental use (we selected experimental users at wave 1 and compared those who had discontinued experimental use at wave 2 with those who had remained experimental users), and (5) failure to discontinue regular use (we selected regular users at wave 1 and compared those who had discontinued regular use at wave 2 with those who had remained regular users) (**Table 1**).

Risk factors were established at wave 1 and were used to predict these 5 stages of marijuana involvement. To establish these risk factors, 8 major risk factor domains were first established a priori from the literature, and variables (total of 238) were selected from the Add Health data set to best represent these domains. Next, factor analysis was used to identify within each domain the presence of subdomains (21 identified altogether). Factor solutions were rotated orthogonally (Varimax rotation) to make individual risk factors within each domain independent from each other. For each subject, for each risk factor, summed risk factor scores were obtained by adding those items with relatively high loadings on a factor (≥0.30) and discarding items with lower factor scores. The great majority of the sample had no missing responses for all items making up each risk factor (ie, ≥95% of the sample had 0 missing values for each of the 21 risk factors). Individuals with 10% or more of the responses to a summed score missing were excluded from further analyses. For those with fewer than 10% missing values, an imputation formula was used, based on replacing the missing items by the mean of the nonmissing responses. Prior to further analysis, the scored risk factors were normalized using the Blom transformation.[21] The correlation coefficients between the factors as obtained by factor analysis and normalized summed risk factors were equal to or exceeded 0.90 for 18 of 21 subdomains, illustrating the legitimacy of the procedures used to obtain summed risk factors (ie, excluding items with factor scores >0.30, imputation of missing values, and normalization of the summed scores). We conducted 2 sets of logistic regression analyses. First, in analyses including 1 risk factor at a time, we evaluated their association with each of the stages

of marijuana involvement. Subsequently, we performed stepwise logistic regression analyses to select the subset of risk factors best predicting the 5 stages of marijuana involvement. Included as independent variables were all risk factors that were significant in the first set of analyses. For all regression analyses, a conservative significance level of $P \leq .03$ for factors to enter and remain in the model was specified a priori. The influences of age,[7] race,[22] urbanicity,[23] and socioeconomic status[24] (parental educational and occupational status) on the relations between the risk factors and marijuana involvement were taken into account in all analyses. These variables were force-entered into each model before the introduction of the risk factors. Therefore, the associations between the stages of marijuana involvement and the risk factors were corrected for the influences of these 5 variables. Socioeconomic status was assessed by 2 variables: parental level of education and occupation. In the case of a single residential parent, these were the only 2 indicators of socioeconomic status used. In the case of 2 residential parents, the mean level of education and of occupational level was used in regression analyses. Since sex differences have been established in substance use,[25,26] we performed regression analyses including sex as a covariate and, if significant, the analysis was repeated for males and females separately. Data were missing for 29% of the subjects on the items assessing the relationship and activities undertaken with the father. Therefore, regression analyses were run twice, first, including these 2 factors and establishing their significance on the marijuana variables, and next, on having established that these influences were not significant, the regression analyses were repeated excluding these 2 variables, allowing us to include more subjects in the analysis. The results of the latter analyses are presented. The significance of mean differences between groups was assessed by *t* test (level of $P \leq .05$ used). All analyses were performed using SAS (SAS Institute Inc, Cary, NC).[27]

RESULTS

The majority of adolescents had not tried marijuana, and among those who had, experimental use was more common than regular use. However, most adolescents who had used marijuana at wave 1 continued to do so 1 year later (Table 1).

All risk factor information was gathered at wave 1, allowing us to establish the influences on the development of marijuana involvement over the next year. Boys had significantly higher mean scores on most risk factors, except somatic symptoms, depressive symptoms, self-doubt, irrational decision making, activities with mother, and religious involvement, for which girls scored higher (**Table 2**). There were no significant sex differences for activities with father and extent to which the parents allow the adolescent to make independent decisions.

Most risk factors contributed significantly to at least some of the stages of marijuana involvement (**Table 3**). However, 3 risk factors were stronger predictors than others and influenced all stages of marijuana development: own and peer involvement with substances; delinquency; and school-related problems. Other risk factors had smaller effects and tended to be stage and/or sex specific. Considerably more risk factors significantly influenced initiation of experimental and regular marijuana use than progression to regular use or failure to discontinue experimental and regular use.

Stepwise regression analyses were performed to establish the set of variables best predicting each stage of marijuana involvement. The results (**Table 4**) further confirmed the importance and global influence of these 3 risk factors. "Own and peer involvement with substances" predicted initiation of experimental marijuana use (odds ratio [OR], 1.79 for boys and 2.94 for girls), initiation of regular use (OR, 2.72 for boys and girls combined), failure to discontinue experimental use (OR, 0.65 for girls), and failure to discontinue regular marijuana use (OR, 0.62 for boys and girls combined). Delinquency predicted initiation of experimental marijuana use (OR, 1.30 for boys and 1.34 for girls), initiation of regular use (OR, 1.36 for boys and girls combined), progression to regular use (OR, 1.35 for boys), failure to discontinue experimental use (OR, 0.71 for boys), and failure to discontinue regular use (OR, 0.77 for boys and girls combined). School variables predicted initiation of experimental marijuana use (OR, 1.17 for boys and 1.21 for girls), initiation of regular use (OR, 1.57 for boys and girls combined), and progression to regular use for girls (OR, 1.60). Other risk factors exerted stage-specific and sex-specific influences: low religiosity predicted initiation of experimental marijuana use in girls (OR, 0.78) and initiation of regular use in boys and girls combined (OR, 0.83); independent decision making predicted progression to regular use in boys (OR, 1.30), and activities with the mother predicted failure to discontinue regular marijuana use for boys and girls combined (OR, 1.17).

We divided the sample into age groups 11 to 15 years (n = 7334) and 16 to 21 years (n = 6999) and conducted age-specific analyses for the 3 stages of marijuana involvement in Table 3 for which significant age differences were found. For initiation of experimental use in girls, 4 risk factors were significant for the younger age group (own and peer involvement with substances, OR, 3.12 [95% confidence interval (CI), 2.50-3.90]; delinquency, OR, 1.39 [95% CI, 1.15-1.67]; unhappy in school, OR, 1.25 [95% CI, 1.08-1.44]; and religion, OR, 0.76 [95% CI, 0.66-0.87]), while only own and peer involvement with substances (OR, 3.12 [95% CI, 2.42-4.02]) and religion (OR, 0.81 [95% CI, 0.68-0.97]) were significant in the older group. For initiation of regular use for boys and girls combined, own and peer involvement with substances and trouble in school were significant in both the younger (OR, 2.94 [95% CI, 2.11-4.09] and OR, 1.61 [95% CI, 1.20-2.16], respectively) and older age groups (OR, 2.87 [95% CI, 2.10-3.94] and OR, 1.63 [95% CI, 1.20-2.23], respectively). In addition, delinquency (OR, 1.42 [95% CI, 1.06-1.89]) and irrational decision making (OR, 1.36 [95% CI, 1.08-1.71]) were significant in the younger age group, while inactive pastimes was significant for the older age group (OR, 1.35 [95% CI, 1.05-1.75]). Finally, failure to discontinue experimental use for girls was explained by religion only in the younger age group (OR, 1.34 [95% CI, 1.05-1.72]) and own and peer involvement with substances only in the older age group (OR, 0.54 [95% CI, 0.36-0.82]).

To further establish the influences of the 3 strongest risk factors on marijuana involvement (combining the factors "trouble in school" and "happy in school"), we divided the sample in a high-risk group who scored in the upper 33% for each of the 3 risk factors (n = 1386) and a low-risk group who scored in the lower 33%

Table 2. Means, Standard Deviations, and *P* Values Associated With *t* Tests for Sex Differences for the Risk Factors*

Domain	Boys, Mean (SD)	Girls, Mean (SD)	*P* Value
Daily activities†			
Active pastime	7.72 (2.90)	6.91 (2.77)	<.001
Passive pastime	6.31 (2.78)	5.34 (2.69)	<.001
Psychological health‡			
Somatic symptoms	14.67 (7.59)	17.73 (8.92)	<.001
Positive emotions	8.15 (2.63)	7.84 (2.75)	<.001
Depressive symptoms	6.41 (5.30)	7.97 (6.40)	<.001
Personality§			
Self-doubt	21.99 (5.80)	24.14 (6.37)	<.001
Irrational decision making	10.85 (2.86)	10.95 (2.91)	.047
Problem avoidance	11.44 (2.58)	10.98 (2.46)	<.001
School situation‖			
Dissatisfaction with school	21.38 (6.48)	20.82 (6.32)	<.001
Trouble in school	10.91 (5.16)	9.20 (4.62)	<.001
Family functioning¶			
Relations with mother	31.47 (3.80)	30.82 (4.69)	<.001
Activities with mother	3.84 (1.70)	4.44 (1.71)	<.001
Relations with father	22.34 (3.53)	21.59 (4.12)	<.001
Activities with father	12.19 (2.67)	12.14 (2.62)	.28
Family relations	24.91 (4.53)	24.47 (4.92)	<.001
Independent decision making	5.02 (1.61)	5.04 (1.54)	.43
"Rough living"#			
Substance involvement, substance involvement of peers	8.85 (10.11)	7.75 (8.91)	<.001
Violence	2.04 (2.92)	0.91 (1.81)	<.001
Delinquency	3.85 (4.77)	3.03 (3.71)	<.001
Religion**	13.60 (4.85)	14.39 (4.74)	<.001
Neighborhood††	13.69 (2.40)	13.50 (2.56)	<.001

*Analyses are based on the full sample regardless of the status of marijuana use. To facilitate interpretation, the means are given for the nonnormalized risk factors. However, the *t* tests are based on the normalized risk factors. In the case of unequal variances for the 2 groups, *t* tests are based on the Satterthwaite method.[27]

†Active pastimes include active sports, exercise, hobbies, rollerblading, cycling, working around the house, and chores. Passive pastimes include hours watching television and videos, playing video and computer games, and listening to the radio.

‡Somatic symptoms include feeling tired, weak, moody, and/or dizzy, having trouble relaxing, frequent crying, insomnia; waking up tired; feeling very sick, feeling hot, frequent stomachaches, feeling fearful, poor appetite, chest pains, headaches, aches and/or pains, cold sweats; painful urination, too sick for social activities, sore throat and/or cough; acne; and being too sick for school. Positive emotions include feeling hopeful about the future, enjoying life, and feeling happy and just as good as others. Depressive symptoms include feeling depressed, sad, the blues, lonely, bothered by things, people dislike you, life is a failure, fearful, too tired to do things, it's hard to get going, life is not worth living, people are unfriendly to you, poor appetite, and talking less than usual.

§Self-doubt includes not feeling proud of self, not liking self, having no good qualities, feeling unloved and unwanted, not fitting in, having low energy, having poor coordination, ill sick, not recovering quickly, and often sick. Irrational decision making includes not seeing many approaches to problems, not researching solutions, irrational decision making, not evaluating outcome of decision, and not believing in accomplishment through hard work. Problem avoidance includes never arguing with anyone, never criticizing others, never feeling sad, avoiding confronting problems, and relying on gut feelings.

‖Dissatisfaction with school includes being happy at school, part of school, and close to people at school; feeling teachers treat students fairly, safe in school, students prejudiced, and teachers care about me, and having no trouble with homework. Trouble in school includes having trouble with teachers, having trouble paying attention, frequently skipping school, being suspended, repeating a grade, having trouble with homework, being expelled, not wanting to attend college, having a low grade point average, and being unlikely to attend college.

¶Relations with mother includes having a good relationship with mother, good communication with mother, mother is warm and loving, discusses ethics with mother, mother encourages independence, having few arguments about behavior, feeling mother cares, and being close to mother. Activities with mother includes talking about grades, school issues, personal problems, and life; working on school projects; going shopping; to the movies, concerts, plays, or sporting events; and doing things. Relations with father includes a good relationship with father, good communication with father, father is warm and loving, feeling father cares, and being close to father. Activities with father includes talking about grades and school issues; working on school projects; talking about life; having few arguments about behavior; discussing personal problems; father would be disappointed if didn't graduate from college; going to the movies, concerts, plays, or sporting events; father disappointed if didn't graduate from high school; and doing things. Family relations includes family paying attention to you, having fun together, understanding you, caring about you, and not wanting you to leave home. Independent decision making includes making own choices on television amount and television programs, clothing, diet, weekday bedtime, friends, and weekend curfew.

#Substance involvement, substance involvement of peers includes frequent alcohol consumption, drunkenness, 5 or more drinks on a single occasion, alcohol use outside family, being hung over, throwing up after drinking, best friends drink alcohol, alcohol use more than 2 to 3 times, regretting actions because of alcohol, best friends smoke marijuana, regular cigarette smoking, best friends smoke cigarettes, regretting sex because of alcohol, having parental trouble because of alcohol, having dating problems because of alcohol, ever smoking cigarettes, driving while drunk, having problems with friends because of alcohol, being drunk at school, getting into physical fights because of alcohol, having first sex at an early age, having school problems because of alcohol, and spending nights away from home without permission. Violence includes pulling a knife or gun on someone, having a knife or gun pulled on you, being shot, stabbing someone, using a weapon in a fight, seeing a shooting or stabbing, being jumped or stabbed, carrying a weapon to school, getting into physical fights, and being seriously injured from a fight. Delinquency includes shoplifting, stealing worth more than $50, causing property damage, painting graffiti, burglary, selling drugs, being loud or rowdy in public, lying to parents about whereabouts, joyriding, and running away from home.

**Religion includes attending religious services, religion is important to you, prayer, participating in youth groups, and believing scriptures are the word of God.

††Neighborhood includes neighbors looking out for others, being unhappy to move, knowing most neighbors, stopping and talking to neighbors, feeling safe in neighborhood, and being happy in neighborhood.

Table 3. Associations of the Risk Factors With Marijuana Involvement*

	Initiation of Experimental Use		Initiation of Regular Use		Progression to Regular Use		Failure to Discontinue Experimental Use		Failure to Discontinue Regular Use	
Risk Factor	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Active pastimes										
Inactive pastimes	1.14	1.14								
Somatic symptoms	1.15	1.28		1.48						
Positive emotions		0.80		0.73						
Depressive symptoms	1.16	1.33		1.44						
Self-doubt		1.20		1.44						
Irrational decision making		1.14	1.24	1.46		1.34			0.82	
Problem avoidance					0.79					
Dissatisfaction with school	1.34	1.62†	1.58†	2.03†					0.78	
Trouble in school	1.51†	1.83†	2.16†	2.32†		1.60†			0.76	
Relations with mother	0.86	0.80		0.73						
Activities with mother										1.40
Relations with father	0.79	0.74		0.57†						
Activities with father										
Family relations	0.78	0.69	0.68	0.66†						
Independent decision making		1.20	1.30		1.29					
Substance involvement	2.15†	3.77†	2.63†	6.08†	1.51†	1.49	0.76	0.64†	0.54†	0.64†
Violence	1.49	1.55†	1.68†	2.10†						
Delinquency	1.71†	2.21†	1.77†	3.54†	1.32		0.72	0.80	0.68	0.75
Religion	0.73	0.70	0.76	[illegible]73				1.20		
Neighborhood										

*Values are expressed as odds ratios. Analyses are based on normalized, summed risk factor scores. Significant odds ratios were obtained from regression analyses run for each of the individual risk factors separately. Covariates age, race, urban status, and parental educational and occupational status were force-entered into each model before the introduction of the risk factors. A significance level of $P \leq .05$ for factors to enter and remain in the model was specified a priori. See Table 2 for explanation of risk factors.

†Odds ratios of highest value (≤0.67 or ≥1.50).

(n = 1696), while excluding the middle 33%, and repeated the regression analyses. In the high-risk group, 28% of adolescents initiated marijuana use in the next year compared with 2% in the low-risk group (OR, 19.90 [95% CI, 12.02-32.95]). Regular marijuana use was initiated by 16% in the high-risk group compared with 0.3% in the low-risk group (OR, 78.40 [95% CI, 26.40-232.85]). In the low-risk group, no individual progressed to regular use (39% in high-risk group) or continued using marijuana experimentally or regularly (52% and 60% in high-risk group, respectively), so no ORs could be calculated for these 3 stages.

COMMENT

In this large population-based sample, 13% of nonusers at wave 1 had become involved with marijuana 1 year later (at wave 2, 10% experimentally and 3% regularly). More than half (55%) of adolescents who had experimented with marijuana at wave 1 continued to use marijuana either experimentally (37%) or regularly (18%). The great majority of regular users at wave 1 remained involved with marijuana (53% on a regular basis and 20% experimentally). These numbers indicate that initiation tends to result in continuation.

The risk factors that have been most consistently related to marijuana use in the literature include the following: (1) Daily activities. Low levels of engagement in prosocial activities are associated with marijuana use[28,29]; (2) Psychological health. Marijuana use is associated with intrapersonal difficulty,[30] poor control of emotions,[31] and depression and anxiety[31,32]; (3) Personality. Risk of marijuana use may be increased in those with limited inner resources to cope with psychological stress[33] and poor self-concept.[34-36] Other personality traits associated with increased risk include deviance,[37] rebelliousness,[35] being unempathetic,[38] and unconventionality[30,38]; (4) School situation. School-related risk factors include poor academic performance,[39-41] low connectedness to school,[44] truancy, and school dropout[43-47]; (5) Family functioning. Risk factors within the family environment include poor, inconsistent family management practices; family conflict; low bonding[48,49]; poor parental monitoring; and lack of structure and rules[35,42,50]; (6) Rough living. Risk of marijuana use is increased in those with greater use of other substances[6,51] and substance-using friends.[49,51-53] Marijuana use has also been associated with a maladaptive conflict style,[54,55] aggression,[56] delinquency,[6,7,57] violence,[23,58] and precocious and risky sexual behavior[59,60]; (7) Religiosity and conservative beliefs may protect against adolescent substance use[61]; and (8) Risk of substance use may be greater in disadvantaged neighborhoods.[62,63]

Our analyses indicated that, when analyzed individually, most of these risk factors predicted at least some stages of marijuana involvement. However, the strongest predictors were substance use by adolescents themselves and their peers; delinquency; and school-related problems. These factors also influenced most stages of marijuana involvement, suggesting that intervention efforts aimed at these risk factors may be broadly applicable. In addition, when

Table 4. Stepwise Logistic Regression Analysis on the Development of Marijuana Use Between Waves 1 and 2*

Significant Factor	OR (95% CI) Boys	Girls
Initiation of Experimental Marijuana Use		
Substance involvement, substance involvement of peers	1.79 (1.53-2.10)	2.94 (2.48-3.49)
Delinquency	1.30 (1.17-1.54)	1.34 (1.16-1.55)
Trouble in school	1.17 (1.02-1.35)	
Unhappy in school		1.21 (1.08-1.36)
Religion		0.78 (0.70-0.87)
	R, E*	A*
Initiation of Regular Marijuana Use†		
Substance involvement, substance involvement of peers	2.72 (2.21-3.34)	2.72 (2.21-3.34)
Trouble in school	1.57 (1.31-1.88)	1.57 (1.31-1.88)
Delinquency	1.36 (1.13-1.64)	1.36 (1.13-1.64)
Religion	0.83 (0.71-0.97)	0.83 (0.71-0.97)
	A, E*	A, E*
Progression to Regular Marijuana Use		
Delinquency	1.26 (1.09-1.68)	
Independent decision making	1.30 (1.05-1.60)	
Trouble in school		1.60 (1.28-2.01)
	R*	
Failure to Discontinue Experimental Marijuana Use		
Delinquency	0.71 (0.61-0.84)	
Substance involvement, substance involvement of peers		0.65 (0.50-0.84)
		A*
Failure to Discontinue Regular Marijuana Use†		
Substance involvement, substance involvement of peers	0.62 (0.50-0.77)	0.62 (0.50-0.77)
Delinquency	0.77 (0.66-0.90)	0.77 (0.66-0.90)
Activities with mother	1.17 (1.02-1.34)	1.17 (1.02-1.34)
	E, O*	E, O*

Abbreviations: A, age of the subject at wave 1; CI, confidence interval; E, parental education; O, parental occupation; OR, odds ratio; R, race; U, urban status.

*Analyses based on normalized, summed risk factor scores. In all regression analyses, the following factors were specified to be entered into the model: the age of the subject at wave 1 (A), race (R), urban status (U), parental education (E), and parental occupation (O). In case any of these factors were significant, their abbreviation is included in the table. The χ^2 test for the combined effect of the independent variables is based on the −2 log likelihood method. A significance level of $P = .03$ was specified for the χ^2 score for entering a factor in the model and for the factor to remain in the model.

†Sex differences were nonsignificant; therefore, boys and girls were combined in analyses on this variable.

we performed analyses on the younger (11-15 years) and older (16-21 years) age groups separately, these risk factors remained the strongest predictors.

Our results confirm previous reports of the importance of the risk factors "substance use by self and peers"[20,15,31,33,64] and "delinquency."[20,7,65] Use of alcohol or drugs during adolescence increases the risk of substance dependence in adulthood.[8] Marijuana use has been related to failure to quit other substances.[11] Peers may influence adolescent substance use by changing personal attitudes, serving as role models, and being a source of information and providing access, encouragement, and a social setting for experimentation with substances.[64,66,68] Deviant peer affiliations pose a risk to retention rates during substance abuse treatment and may need to be dealt with specifically during treatment.[69] The combination of the risk factors "substance abuse" and "delinquency" may lead to a career of crime.[16] High rates of substance use, involvement with delinquent activities, and being part of deviant peer groups seem to reflect low concern with the future or perceived future perspectives. Indeed, illicit drug use is associated with reduced chances of successful participation in adult roles.[12]

School-related variables presented the third strong risk factor. Poor academic achievement[13,41,62,45,47] has been previously associated with marijuana involvement. The present study used a broader assessment of the school situation. Risk factor "trouble in school" included, in addition to an indicator of test results (grade point average), information on problems with teachers, trouble paying attention, frequently skipping school, suspension, repeating a grade, expulsion, and no desire or intention to attend college. "Dissatisfaction with school" assessed being happy in school, part of school, safe in school, close to people in school, whether teachers care about students and treat them fairly, and whether other students are prejudiced. The few previous studies that have used similar broader evaluations of the school environment have also found that the broader school context is an important risk factor in marijuana involvement.[36,44] Interestingly, one of these studies found that school bonding is closely related to self-efficacy.[36] Our findings are not limited to marijuana use; we have previously found that school-related problems predict experimentation with cigarettes and progression to regular smoking.[70] It has been previously reported that remedial academic classes can improve not only school performance but also reduce smoking rates.[71]

Adolescents spend a major part of their lives in school. Certain school characteristics (eg, high turnover of staff and pupils, pupil-staff ratio, absenteeism, and indices of low socioeconomic status in pupils) have been associated with childhood disorder and deviance[72] and may also increase risk of marijuana involvement. Schools can play a role in shaping the development of socially approved conduct,[73] and active discouragement of substance use in schools can be effective.[74] Positive results achieved with classroom-based programs aimed at increasing academic and social competence as well as school-bonding[75] become particularly relevant in the light of the present results.

Other significant predictors in our study exerted stage-specific, sex-specific, and age-specific influences. Religion reduced risk of initiation of experimental marijuana use for girls (both age cohorts), initiation of regular use for boys and girls combined (but not in age-specific analyses), and continuation of experimental marijuana use in younger girls. It has previously been reported that religiosity and conservative beliefs are protective factors for adolescent substance use.[45,70] Possibly, the protective effects of religiosity may exert themselves through the family environment[76] or by enhancing ability to cope with stress.[76]

Family-related variables have been previously reported to be important in the development of adolescent substance use involvement. We found that 2 family-

related risk factors influenced marijuana involvement, independent decision making (eg, freedom in choosing what to wear, eat, when to go to bed, television time and programs) predicted progression to regular use for boys, and activities with the mother (eg, discussing school grades and personal problems) predicted discontinuation of regular marijuana use for boys and girls combined. Both parental monitoring and parent-child attachment have been previously related to adolescent substance involvement.[77,78] In our study, these influences were found to exert stage-specific and sex-specific influences. Possibly, family-related factors become less influential once the impact of other mediating factors (for example, socioeconomic status) and peer influences have been statistically accounted for, as in the analysis used in this study.

Two other factors were only significant in age-specific analyses: irrational decision making predicted initiation of regular marijuana use for boys and girls combined and inactive pastimes predicted the same variable for the older age cohort. Irrational decision making is characterized by the inability to make rational decisions, to research solutions, to evaluate outcomes of decisions, and to believe things can be accomplished through hard work. It reflects a lack of responsibility and self-efficacy, personality traits that have been previously related to marijuana involvement.[79] Inactive pastimes (hours spent watching television, playing computer and video games, listening to the radio) have also been related to risk of substance use.[28,29]

Most risk factor studies have focused on the initiation of marijuana use. The few studies that have also focused on discontinuation of use have indicated that use of other licit and illicit drugs, deviance, selection of social settings favorable for use, increased risk of victimization, and self-medicating to improve mood are important risk factors.[80-82] These findings are in agreement with our results. In addition, we found the progression and failure to discontinue (ie, of experimental and regular use) stages were influenced by considerably fewer risk factors than the initiation stages, and the 3 risk factors with the strongest associations with marijuana use were also the strongest predictors of failure to discontinue.

Adolescents with the highest scores on all 3 risk factors had considerably increased risks of initiating experimental (20 times) and regular marijuana use (87 times). When selecting the highest and lowest scoring groups for each risk factor individually, rather than combined, ORs ranged between 1.6 and 4.0, strongly indicating that the presence of multiple risk factors makes adolescents especially vulnerable for marijuana use and abuse. Therefore, directing intensive prevention and intervention efforts at those groups at greatest risk may be more successful than programs aimed at all students in a school, many of whom will never consider trying marijuana. The percentages of adolescents who were increasingly involved with marijuana were in the high-risk group more frequently than the low-risk group (28% vs 2% for experimental initiation; 16% vs 0.3% for regular initiation; 39% vs 0% for progression; 52% vs 0% for continued experimental use; and 60% vs 0% for continued regular use). This indicates that successful prevention and/or intervention efforts based on these combined risk factors may have an effect on a large proportion of adolescents at risk.

Identification of individuals at risk should take place in any setting where the 3 most important risk factors can be assessed, for example, in schools, medical practices, the judicial system, and substance treatment centers. Prevention and intervention should incorporate strategies to address other substance use and the peer group, delinquent activities, and the school situation. In addition, our finding of fewer risk factors influencing the progression and failure to discontinue use stages suggests that the greatest opportunities for intervention are during earlier stages of marijuana involvement. During later stages, genetic and other biological factors involved in habituation and dependence may become increasingly important[83] and treatment, more difficult.

Although we evaluated many carefully selected risk factors, not all relevant aspects of risk were assessed (for example, genetic factors[26,83] or attitudes toward drug use[84]). Despite the advantages of a longitudinal design, we cannot rule out the possibility that other factors at wave 1 influenced both risk factors as well as marijuana involvement. In addition, the analytical methods used cannot account for complex interactions between risk factors. Sample sizes were lower for analyses of the progression and failure to discontinue use stages. This could have influenced our finding of fewer significant risk factors and should be taken into account when evaluating our conclusions. Many comparisons between behaviors and marijuana involvement were made in this study, and it is therefore possible that significant findings have arisen owing to chance. Reassuringly, however, all associations were in the expected directions and agree with results obtained in previous studies. In addition, a conservative approach was adopted by presenting the results in terms of the strongest findings (P values of $\leq .03$ for the regression analyses). Additional research, also including clinical populations, is needed to confirm the results and to further enhance their practical implications.

Our study indicates that the assessment of licit substance use, information on peers, delinquency, and how adolescents experience their school environment strongly predict risk of involvement with marijuana. Therefore, these risk factors can be used to identify adolescents who may require early and intensive prevention efforts and to address these factors in efforts to help them.

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REFERENCES

1 Johnston LD, O'Malley PM, Bachman JG. *Monitoring the Future National Survey Results on Adolescent Drug Use. Overview of Key Findings*. Bethesda, Md: National Institute on Drug Abuse, US Dept of Health and Human Services; 2003.
2 Dennis M, Babor TF, Roebuck MC, Donaldson J. Changing the focus: the case for recognizing and treating cannabis use disorders. *Addiction*. 2002;97(suppl 1):4-15.
3 Williams AF, Peat MA, Crouch DJ, Wells JK, Finkle BS. Drugs in fatally injured young male drivers. *Public Health Rep*. 1985;100:19-25.
4 Kingree JB, Braithwaite R, Woodring T. Unprotected sex as a function of alcohol and marijuana use among adolescent detainees. *J Adolesc Health*. 2000;27:179-185.
5 Tunving K. Psychiatric effects of cannabis use. *Acta Psychiatr Scand*. 1985;72:209-217.
6 Rey JM, Sawyer MG, Raphael B, Patton GC, Lynskey M. Mental health of teenagers who use cannabis: results of an Australian survey. *Br J Psychiatry*. 2002;180:216-221.
7 Fergusson DM, Horwood LJ, Swain-Campbell N. Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction*. 2002;97:1123-1135.
8 Brook DW, Brook JS, Zhang C, Cohen P, Whiteman M. Drug use and the risk of major depressive disorder, alcohol dependence, and substance use disorders. *Arch Gen Psychiatry*. 2002;59:1039-1044.
9 Tunving K. Psychiatric aspects of cannabis use in adolescents and young adults. *Pediatrician*. 1987;14:83-91.
10 Weiser M, Reichenberg A, Rabinowitz J, Kaplan Z, Caspi A, Yasvizky R, Mark M, Knobler HY, Nahon D, Davidson M. Self-reported drug abuse in male adolescents with behavioral disturbances, and follow-up for future schizophrenia. *Biol Psychiatry*. 2003;54:655-660.
11 Ford DE, Vu HT, Anthony JC. Marijuana use and cessation of tobacco smoking in adults from a community sample. *Drug Alcohol Depend*. 2002;67:243-248.
12 Kandel DB, Davies M, Karus D, Yamaguchi K. The consequences in young adulthood of adolescent drug involvement: an overview. *Arch Gen Psychiatry*. 1986;43:746-754.
13 Brook JS, Balka EB, Whiteman M. The risks for late adolescence of early adolescent marijuana use. *Am J Public Health*. 1999;89:1549-1554.
14 Chen K, Kandel DB, Davies M. Relationships between frequency and quantity of marijuana use and last year proxy dependence among adolescents and adults in the United States. *Drug Alcohol Depend*. 1997;46:53-67.
15 Johnston LD, O'Malley PM, Bachman JG. *Monitoring the Future National Survey Results on Drug Use, 1975-2002. Volume I: Secondary School Students*. Bethesda, Md: National Institute on Drug Abuse, National Institutes of Health, Dept of Health and Human Services; 2002.
16 Clayton RR. Transitions in drug use: risk and protective factors. In: Glantz MD, Pickens RW, eds. *Vulnerability to Drug Abuse*. Washington, DC: American Psychological Association; 1992:15-51.
17 Warner LA, Kessler RC, Hughes M, Anthony JC, Nelson CB. Prevalence and correlates of drug use and dependence in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry*. 1995;52:219-229.
18 Udry JR, Chantala K. Missing school dropouts in surveys does not bias risk estimates. *Soc Sci Res*. 2003;32:294-311.
19 Resnick MD, Bearman PS, Blum RW, Bauman KE, Harris KM, Jones J, Tabor J, Beuhring T, Sieving RE, Shew M, Ireland M, Bearinger LH, Udry JR. Protecting adolescents from harm: findings from the National Longitudinal Study on Adolescent Health. *JAMA*. 1997;278:823-832.
20 Turner CF, Ku L, Rogers SM, Lindberg LD, Pleck JH, Sonenstein FL. Adolescent sexual behavior, drug use, and violence: increased reporting with computer survey technology. *Science*. 1998;280:867-873.
21 Rice G. *Statistical Estimates and Transformed Beta Variables*. New York, NY: John Wiley & Sons; 1958.
22 Reardon SF, Buka SL. Differences in onset and persistence of substance abuse and dependence among whites, blacks, and Hispanics. *Public Health Rep*. 2002;117(suppl 1):S51-S59.
23 Finke L, Williams J. Alcohol and drug use of inter-city versus rural school age children. *J Drug Educ*. 1999;29:279-291.
24 von Sydow K, Lieb R, Pfister H, Holler M, Wittchen HU. What predicts incident use of cannabis and progression to abuse and dependence? a 4-year prospective examination of risk factors in a community sample of adolescents and young adults. *Drug Alcohol Depend*. 2002;68:49-64.
25 Block J, Block JH, Keyes S. Longitudinally foretelling drug usage in adolescence: early childhood personality and environmental precursors. *Child Dev*. 1988;59:336-355.
26 Miles DR, van den Bree MB, Pickens RW. Sex differences in shared genetic and environmental influences between conduct disorder symptoms and marijuana use in adolescents. *Am J Med Genet*. 2002;114:159-168.
27 SAS Institute Inc. *SAS OnlineDoc, Version 8*. Cary, NC: SAS Institute Inc; 1999.
28 Pate RR, Heath GW, Dowda M, Trost SG. Associations between physical activity and other health behaviors in a representative sample of US adolescents. *Am J Public Health*. 1996;86:1577-1581.
29 Harrison PA, Narayan G. Differences in behavior, psychological factors, and environmental factors associated with participation in school sports and other activities in adolescence. *J Sch Health*. 2003;73:113-120.
30 Brook JS, Whiteman M, Gordon AS, Cohen P. Changes in drug involvement: a longitudinal study of childhood and adolescent determinants. *Psychol Rep*. 1989;65:707-726.
31 Christie KA, Burke JD Jr, Regier DA, Rae DS, Boyd JH, Locke BZ. Epidemiologic evidence for early onset of mental disorders and higher risk of abuse in young adults. *Am J Psychiatry*. 1988;145:971-975.
32 Robertson JR, Miller P, Anderson R. Cannabis use in the community. *Br J Gen Pract*. 1996;46:671-674.
33 Nicholi AM Jr. The nontherapeutic use of psychoactive drugs: a modern epidemic. *N Engl J Med*. 1983;308:925-933.
34 Kaplan HB, Martin SS, Johnson RJ, Robbins CA. Escalation of marijuana use: application of a general theory of deviant behavior. *J Health Soc Behav*. 1986;27:44-61.
35 Miller P, Plant M. Heavy cannabis use among UK teenagers: an exploration. *Drug Alcohol Depend*. 2002;65:235-242.
36 Kumpfer KL, Turner CW. The social ecology model of adolescent substance abuse: implications for prevention—special issue: preventive interventions for children at risk. *Int J Addict*. 1990;25:435-463.
37 Hays RD, Ellickson PL. Associations between drug use and deviant behavior in teenagers. *Addict Behav*. 1990;21:291-302.
38 Wills TA, Vaccaro D, McNamara G. Novelty seeking, risk taking, and related constructs as predictors of adolescent substance use: an application of Cloninger's theory. *J Subst Abuse*. 1994;6:1-20.
39 Newcomb MD, Maddahian E, Bentler PM. Risk factors for drug use among adolescents: concurrent and longitudinal analyses. *Am J Public Health*. 1986;76:525-531.
40 Wills TA, Cleary S, Filer M, Shinar O, Manani J, Spera K. Temperament related to early-onset substance use: test of a developmental model. *Prev Sci*. 2001;2:145-163.
41 Stevens MM, Freeman DH Jr, Mott J, Youells F. Three-year results of prevention

programs on marijuana use: the New Hampshire study. *J Drug Educ*. 1996;26:257-273.
42. Duncan SC, Duncan TE, Biglan A, Ary D. Contributions of the social context to the development of adolescent substance use: a multivariate latent growth modeling approach. *Drug Alcohol Depend*. 1998;50:57-71.
43. Hops H, Davis B, Lewin LM. The development of alcohol and other substance use: a gender study of family and peer context. *J Stud Alcohol Suppl*. 1999;13:22-31.
44. Sale E, Sambrano S, Springer JF, Turner CW. Risk, protection, and substance use in adolescents: a multi-site model. *J Drug Educ*. 2003;33:91-105.
45. Bachman JG, Johnston LD, O'Malley PM. Smoking, drinking, and drug use among American high school students: correlates and trends, 1975-1979. *Am J Public Health*. 1981;71:59-69.
46. Mensch BS, Kandel DB. Dropping out of high school and drug involvement. *Sociol Educ*. 1988;61:95-113.
47. Bray JW, Zarkin GA, Ringwalt C, Qi J. The relationship between marijuana initiation and dropping out of high school. *Health Econ*. 2000;9:9-18.
48. Hawkins JD, Catalano RF, Miller JY. Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: implications for substance abuse prevention. *Psychol Bull*. 1992;112:64-105.
49. Brook JS, Whiteman M, Finch S, Cohen P. Longitudinally foretelling drug use in the late twenties: adolescent personality and social-environmental antecedents. *J Genet Psychol*. 2000;161:37-51.
50. Kosterman R, Hawkins JD, Guo J, Catalano RF, Abbott RD. The dynamics of alcohol and marijuana initiation: patterns and predictors of first use in adolescence. *Am J Public Health*. 2000;90:360-366.
51. Hofler M, Lieb R, Perkonigg A, Schuster P, Sonntag H, Wittchen HU. Covariates of cannabis use progression in a representative population sample of adolescents: a prospective examination of vulnerability and risk factors. *Addiction*. 1999;94:1679-1694.
52. Brook JS, Kessler RC, Cohen P. The onset of marijuana use from preadolescence and early adolescence to young adulthood. *Dev Psychopathol*. 1999;11:901-914.
53. Prinstein MJ, Boergers J, Spirito A. Adolescents' and their friends' health-risk behavior: factors that alter or add to peer influence. *J Pediatr Psychol*. 2001;26:287-298.
54. Colsman M, Wuttke E. Conflict resolution style as an indicator of adolescents' substance use and other problem behaviors. *Addict Behav*. 2002;27:633-648.
55. Siqueira L, Diab M, Bodian C, Rolnitzky L. The relationship of stress and coping methods to adolescent marijuana use. *Subst Abus*. 2001;22:157-166.
56. Brook JS, Whiteman M, Cohen P, Tanaka JS. Childhood precursors of adolescent drug use: a longitudinal analysis. *Genet Soc Gen Psychol Monogr*. 1992;118:195-213.
57. Coffey C, Carlin JB, Lynskey M, Li N, Patton GC. Adolescent precursors of cannabis dependence: findings from the Victorian Adolescent Health Cohort Study. *Br J Psychiatry*. 2003;182:330-336.
58. Arseneault L, Moffitt TE, Caspi A, Taylor PJ, Silva PA. Mental disorders and violence in a total birth cohort: results from the Dunedin Study. *Arch Gen Psychiatry*. 2000;57:979-986.
59. Ary DV, Duncan TE, Biglan A, Metzler CW, Noell JW, Smolkowski K. Development of adolescent problem behavior. *J Abnorm Child Psychol*. 1999;27:141-150.
60. Orr DP, Beiter M, Ingersoll G. Premature sexual activity as an indicator of psychosocial risk. *Pediatrics*. 1991;87:141-147.
61. Wills TA, Yaeger AM, Sandy JM. Buffering effect of religiosity for adolescent substance use. *Psychol Addict Behav*. 2003;17:24-31.
62. Crum RM, Lillie-Blanton M, Anthony JC. Neighborhood environment and opportunity to use cocaine and other drugs in late childhood and early adolescence. *Drug Alcohol Depend*. 1996;43:155-161.
63. Barnett JR. Does place of residence matter? contextual effects and smoking in Christchurch. *N Z Med J*. 2000;113:433-435.
64. Kandel DB. On processes of peer influences in adolescent drug use: a developmental perspective. *Adv Alcohol Subst Abuse*. 1985;4:139-163.
65. Kandel DB, Davies M. High school students who use crack and other drugs. *Arch Gen Psychiatry*. 1996;53:71-80.
66. Kaplan HB, Martin SS, Robbins C. Pathways to adolescent drug use: self-derogation, peer influence, weakening of social controls, and early substance use. *J Health Soc Behav*. 1984;25:270-289.
67. Johnson BD. *Marijuana Users and Drug Subcultures*. New York, NY: John Wiley & Sons; 1973.
68. Adler PT, Lotecka L. Drug use among high school students: patterns and correlates. *Int J Addict*. 1973;8:537-548.
69. Battjes RJ, Gordon MS, O'Grady KE, Kinlock TW. Predicting retention of adolescents in substance abuse treatment. *Addict Behav*. 2004;29:1021-1027.
70. van den Bree MB, Whitmer MD, Pickworth WB. Predictors of smoking development in a population-based sample of adolescents: a prospective study. *J Adolesc Health*. 2004;35:172-161.
71. Hu TW, Lin Z, Keeler TE. Teenage smoking, attempts to quit, and school performance. *Am J Public Health*. 1998;88:940-943.
72. Rutter M, Yule B, Quinton D, Rowlands O, Yule W, Berger M. Attainment and adjustment in two geographical areas: III: some factors accounting for area differences. *Br J Psychiatry*. 1975;126:520-533.
73. Rutter M. Family and school influences on behavioural development. *J Child Psychol Psychiatry*. 1985;26:349-368.
74. Kumar R, O'Malley PM, Johnston LD, Schulenberg JE, Bachman JG. Effects of school-level norms on student substance use. *Prev Sci*. 2002;3:105-124.
75. Webster-Stratton C, Taylor T. Nipping early risk factors in the bud: preventing substance abuse, delinquency, and violence in adolescence through interventions targeted at young children (0-8 years). *Prev Sci*. 2001;2:165-192.
76. Kendler KS, Gardner CO, Prescott CA. Religion, psychopathology, and substance use and abuse: a multimeasure, genetic-epidemiologic study. *Am J Psychiatry*. 1997;154:322-329.
77. Chilcoat HD, Anthony JC. Impact of parent monitoring on initiation of drug use through late childhood. *J Am Acad Child Adolesc Psychiatry*. 1996;35:91-100.
78. Brook JS, Brook DW, Gordon AS, Whiteman M, Cohen P. The psychosocial etiology of adolescent drug use: a family interactional approach. *Genet Soc Gen Psychol Monogr*. 1990;116:111-267.
79. Kaplan HB. Self-esteem and self-derogation theory of drug abuse. *NIDA Res Monogr*. 1980;30:128-131.
80. Chen K, Kandel DB. Predictors of cessation of marijuana use: an event history analysis. *Drug Alcohol Depend*. 1998;50:109-121.
81. Kandel DB, Ravens VH. Cessation of illicit drug use in young adulthood. *Arch Gen Psychiatry*. 1989;46:109-116.
82. Sussman S, Dent CW. One-year prospective prediction of marijuana use cessation among youth at continuation high schools. *Addict Behav*. 1999;24:411-417.
83. van den Bree MB, Johnson EO, Neale MC, Pickens RW. Genetic and environmental influences on drug use and abuse/dependence in male and female twins. *Drug Alcohol Depend*. 1998;52:231-241.
84. Bachman JG, Johnson LD, O'Malley PM. Explaining recent increases in students' marijuana use: impacts of perceived risks and disapproval, 1976 through 1996. *Am J Public Health*. 1998;88:887-892.