Effects of Smoked Marijuana on the Lung and Its Immune Defenses: Implications for Medicinal Use in HIV-Infected Patients

Donald P. Tashkin

SUMMARY. Habitual marijuana smoking may cause a number of potentially harmful effects on the lung, including the following: (1) acute and chronic bronchitis; (2) extensive histopathologic alterations in the cells lining the bronchial passages that could impair mucociliary clearance or predispose to malignancy; (3) increased accumulation of inflammatory cells (alveolar macrophages) in the lung; and (4) impairment in the function of these important immune-effector cells, including their ability to kill microorganisms and to produce protective pro-inflammatory cytokines. The major potential pulmonary consequences of habitual marijuana use are pulmonary infection and respiratory cancer. Infectious complications could be due to smoking-related damage to the mucociliary clearance mechanism, marijuana-related impairment in the antimicrobial function of alveolar macrophages and/or fungal or bacterial contamination of marijuana. Patients with pre-existing immune deficits

Donald P. Tashkin, MD, is affiliated with the Division of Pulmonary and Critical Care Medicine, UCLA School of Medicine.

Address correspondence to: Donald P. Tashkin, MD, Professor of Medicine, Department of Medicine, UCLA School of Medicine, 10833 Le Conte Avenue, Los Angeles, CA 90095-1690 (E-mail: dtashkin@mednet.ucla.edu).

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due to AIDS could be particularly susceptible to pulmonary infectious complications of marijuana use.

KEYWORDS. Pulmonary function, cannabis, medical marijuana, HIV, AIDS

INTRODUCTION

In view of the continuing interest in the medical application of marijuana for treatment of AIDS-related symptoms, it is important to re-examine the effects of marijuana smoking on the lung and its biologic defenses against infection. This issue is of practical importance in assessing the risk-benefit ratio of cannabis therapy in the immune-suppressed patient, i.e., the relative risk of pneumonia and other potential, serious infectious complications of marijuana in relation to its possible benefits in stimulating appetite, combating nausea, relieving pain, etc. The present review will focus mainly on human observational and epidemiological studies conducted within the past two decades pertaining to the impact of marijuana smoking on lung structure and function and on respiratory illness. The reader is referred to a recent review article that also addresses the airway effects of illicit smoked substances (Tashkin 2001).

EFFECTS ON RESPIRATORY SYMPTOMS

Three separate community-based studies reported within the past 15 years have shown that habitual daily or near-daily use of marijuana is associated with both chronic and acute respiratory symptoms, indicative of chronic and acute bronchitis.

In a Los Angeles-based convenience sample of 144 daily smokers of marijuana only (MS, mean age 32 yrs), 135 smokers of both marijuana and tobacco (MTS, mean age 34 yrs), 70 smokers of tobacco only (TS, mean age 37 yrs) and 97 nonsmokers (NS, mean age 32 yrs), MS had a significantly higher prevalence than NS ($P < 0.05$) of chronic cough (18% vs. 0%, respectively), chronic sputum production (20% vs. 0%), wheeze (25% vs. 3.5%) and episodes of acute bronchitis (13% vs. 2%) (Tashkin et al. 1987). Chronic cough was defined as cough on most days for at least three months a year for two or more consecutive years and conforms to the accepted definition of "chronic bronchitis" (American Thoracic Society 1987). In contrast, the prevalence of

symptoms of chronic and acute bronchitis did not differ significantly between MS and TS, and no additive effects of marijuana and tobacco were found.

In a parallel Tucson-based study of young (mean 27 yrs) MS (n = 54), MTS (n = 56), TS (n = 20) and NS (n = 502) recruited from a random stratified cluster of households in the community, significantly more MS than NS reported cough, sputum, wheeze and shortness of breath ($p \leq 0.05$) (Bloom et al. 1987). Moreover, an additive effect of marijuana and tobacco on chronic respiratory symptoms was noted, in contrast to the findings from the Los Angeles study (Tashkin et al. 1987).

In a more recent study of 91 cannabis-dependent subjects selected from a total of 943 young adults 21 yrs of age who comprised a birth cohort born in Dunedin, New Zealand, respiratory symptoms were significantly more frequent in cannabis-dependent, nonsmokers of tobacco compared to non-tobacco smoking controls, including early morning sputum production (144% higher prevalence); wheezing apart from colds (61%); exertional dyspnea (65%); and night-time awakenings with chest tightness (72%) (Taylor et al. 2000). Interestingly, the prevalence of respiratory symptoms in cannabis-dependent subjects was similar to that in smokers of ≤ 1/2 pack of tobacco cigarettes/day.

EFFECTS ON LUNG FUNCTION

Findings from the three community-based studies of the pulmonary status of regular marijuana users cited above have revealed conflicting effects of habitual marijuana use on lung function. In the Tucson study, MS, compared to NS, showed significantly lower values for the ratio of forced expired volume in one second (FEV_1) to forced vital capacity (FVC), a sensitive and specific indicator of airflow obstruction (Bloom et al. 1987). Even lower values for FEV_1/FVC ratio were observed in MS than TS, although the mean values for this measure were still within statistically normal limits. From these observations the authors concluded that regular marijuana smoking among young individuals may be an important risk factor for the subsequent development of obstructive airways disease. A follow-up study of the same cohort demonstrated a significant reduction in FEV_1 and FEV_1/FVC ratio in relation to previous use of marijuana, a finding that was interpreted as suggesting that continuing marijuana smoking may lead to a progressive decline in lung function (Sherrill et al. 1991).

In the more recent study from New Zealand, 36% of 21-yr-old cannabis-dependent subjects (two-thirds of whom had developed cannabis dependence since age 18), demonstrated a reduced FEV_1/FVC ratio (< 0.80), compared to only 20% of the nonsmokers from the same birth cohort ($p = 0.04$) (Taylor et al. 2000). The authors concluded that only a relatively short duration of heavy

cannabis use can lead to early airways obstruction in young individuals. It is not clear, however, whether adequate adjustment was made for the possible confounding of these findings by concomitant tobacco use.

The above findings are not supported by the results of the Los Angeles study of 124 MS, 56 TS, 113 MTS and 92 NS (Tashkin et al. 1987). In the latter study, no association was observed between heavy, habitual use of marijuana (mean of > 3 joints/day for > 15 yrs) and abnormalities not only in FEV_1 or FEV_1/FVC ratio, but also in even more sensitive measures of early obstructive ventilatory impairment, including forced expiratory flow rates at low lung volumes and indices derived from single-breath nitrogen washout. Abnormalities in the latter tests are commonly found in tobacco cigarette smokers, some of who are destined to develop clinically significant chronic obstructive pulmonary disease. In addition, regular use of marijuana was not associated with any abnormality in the single-breath diffusing capacity for carbon monoxide ($D_L CO$), a sensitive physiologic indicator of emphysema (Tashkin et al. 1987). On the other hand, regular tobacco smoking was associated with abnormalities in most of the tests of airways function, as well as in $D_L CO$, and heavy habitual marijuana use did not potentiate any of the adverse effects of concomitant tobacco smoking on lung function in dual smokers of marijuana and tobacco.

More recently, the Los Angeles investigators sought to determine whether regular marijuana smoking might lead to a progressive decline in lung function with age and continuing smoking that was not evident in the earlier analysis of the cross-sectional data for lung function (Tashkin et al. 1997). They measured FEV_1 sequentially at intervals of $\geq$ 1 yr for up to 8 yrs in 87 MS, 42 TS, 63 MTS and 63 NS. While they noted that tobacco smoking was associated with a significant age-related decline in FEV_1 compared to the change in NS, they were unable to detect an effect of even heavy marijuana smoking (3 joints/d) on FEV_1 decline, nor did they observe any additive effect of marijuana and tobacco. Since chronic obstructive pulmonary disease (chronic obstructive bronchitis and/or emphysema) is characterized by an excessive age-related decline in FEV_1, these findings argue against an association between regular marijuana smoking and the development of chronic obstructive pulmonary disease. This conclusion is supported by the results of earlier studies in rats exposed to progressively increasing doses of marijuana or tobacco smoke for six months in which the lungs of the tobacco-exposed rats, but *not* those of the marijuana-exposed rats or the unexposed control animals, showed anatomic and physiologic evidence of emphysema (Huber and Mahajan 1988).

EFFECTS ON AIRWAY PATHOLOGY

It is possible that habitual cannabis smoking may cause airway injury and inflammation in the absence of either respiratory symptoms or any demonstra-

ble alteration in lung function. Therefore, to determine the effects of marijuana and tobacco smoking on the gross appearance of the visible portion of the lower respiratory tract of healthy individuals, Roth et al. (1998) performed videobronchoscopy on a small cohort of 40 relatively asymptomatic nonsmokers (NS; n = 10), smokers of marijuana only (MS; n = 10), smokers of tobacco only (TS; n = 10) and smokers of both marijuana and tobacco (MTS; n = 10), all of whom had no or few abnormalities in lung function. A visual bronchitis index score was used to evaluate the presence and extent of airway erythema (redness), edema (swelling) and hypersecretion. Biopsies of the bronchial mucosa were also performed to correlate the visual endoscopic observations with microscopic histopathologic evidence of airway injury and inflammation (vascular hyperplasia, submucosal edema, inflammatory cell infiltrates and hyperplasia of surface mucus-secreting [goblet] cells). In addition, bronchial lavage (saline rinse) was performed to evaluate the peripheral airways for evidence of inflammation (reflected by increased numbers of neutrophils) and/or elevations in interleukin-8 (IL-8), a potent neutrophil chemoattractant and activator. Bronchitis index scores were found to be significantly higher in MS, TS and MTS than in NS. Bronchial mucosal biopsies were positive for two of the histopathologic features of airway injury in 97% of all smokers and for three criteria in 72%, whereas none of the biopsies from NS showed greater than one positive finding. The percentage of neutrophils in bronchial lavage fluid correlated with IL-8 levels and exceeded 20% in 0 of 10 NS, 1 of 9 MS, 2 of 9 TS, and 5 of 10 MTS. These findings suggest that regular smoking of marijuana and/or tobacco by young adults is associated with a high frequency of endoscopically and microscopically apparent airway injury and inflammation even in the absence of any symptoms or physiologic evidence of injury.

The effect of habitual use of marijuana on the microscopic pathology of the lower airways was systematically evaluated by a single "blinded" pathologist from bronchial mucosal biopsies obtained at bronchoscopy from healthy volunteer subjects participating in the Los Angeles cohort study (Fligiel et al. 1997). These subjects included 40 MS, 31 TS, 44 MTS and 53 NS, most of who did not report significant respiratory symptoms or demonstrate significant abnormalities in lung function. The histopathologic features that were examined included basal cell hyperplasia; stratification; squamous metaplasia; goblet cell hyperplasia; cellular disorganization; nuclear variation; mitotic figures; increased nuclear-to-cytoplasmic ratio; inflammation; and basement membrane thickening. Regular smoking of marijuana alone (average of 3-4 joints per day) was associated with a greater frequency and severity of abnormalities for most of the features examined compared to the changes noted in the nonsmokers and at least as extensive abnormalities as those found in the smokers of tobacco alone (22 cigarettes per day). The similar frequency and extent of bronchial histopathology in the marijuana-only compared to the tobacco-only

smokers is noteworthy in view of the marked disparity between the daily number of marijuana vs. tobacco cigarettes consumed by these two groups of subjects. Interestingly, for nearly all histological features examined, abnormalities were noted more commonly in the combined smokers of marijuana plus tobacco than in smokers of either substance alone, implying additive effects of the two smoked substances on airway injury.

These findings have the following important implications:

- Habitual marijuana smoking can cause potentially serious airway pathology at a relatively early age even in the absence of any clinical or physiologic evidence of disease.
- Regular marijuana use produces at least as much damage to the mucosa of the larger airways as the regular smoking of tobacco, despite the considerably smaller daily number of marijuana joints smoked by the MS (average of 3-4 joints/d) than the daily number of tobacco cigarettes smoked by the TS (mean of 22 cigarettes/d), suggesting that marijuana has a more damaging effect than tobacco per cigarette smoked. The similarity in airway histopathology despite the disparity in the amount of plant substance smoked might be explained, at least partly, by the four-fold increase in deposition of tar from a single marijuana cigarette compared to a tobacco cigarette of the same weight (Wu et al. 1988). The latter increase in deposition could be due to differences in cigarette filtration and smoking technique for the two types of cigarettes: marijuana cigarettes do not have filter tips, are more loosely packed and are generally smoked with a four-fold longer breathholding time than tobacco cigarettes. The differences in filtration enhance delivery of tar to the smoker's mouth from marijuana compared to tobacco cigarettes, and the far longer breathholding time employed in smoking marijuana than tobacco provides more opportunity for respiratory deposition of ultra-fine smoke particulates and absorption of toxic gas-phase constituents in the smoke (Wu et al. 1988; Tashkin et al. 1991).
- The observation that marijuana and tobacco appear to have additive effects on bronchial epithelial histopathology in the combined smokers of both substances is of concern since the prevalence of tobacco smoking is substantially higher among marijuana smokers than nonsmokers of marijuana. For example, in the UCLA cohort, approximately 50% of the marijuana smokers also smoked tobacco, whereas the prevalence of tobacco smoking among adults in California in general is approximately 20%.
- Some of the histopathologic changes in the marijuana smokers, notably the frequent loss of ciliated bronchial epithelial cells and their replacement by non-ciliated cells, such as hyperplastic mucus-secreting (goblet)

cells or reserve (basal) cells, or by metaplastic squamous epithelium, could explain the high frequency of symptoms of chronic bronchitis (chronic cough and sputum production) in smokers of marijuana alone. The hair-like projections (cilia) of the normal ciliated bronchial epithelial cells play an important role in mucociliary clearance of secretions. Excessive mucus production by hyperplastic goblet cells (and by hypertrophied submucosal mucus glands) and diminished clearance of these secretions because of the loss of cilia can lead to an accumulation of excess mucus, leaving cough as the only mechanism for mucus clearance. Since the mucus lining the airways also traps inhaled bacteria, other microorganisms and other potentially harmful particles, an intact mucociliary clearance mechanism is the lung's first line of defense against infection and other noxious insults. Marijuana-related damage to this mechanism could therefore predispose to lower respiratory tract infection and other adverse consequences of inhaled particulates.

- A carcinogenic effect of marijuana is suggested by certain histopathologic alterations in the bronchial epithelium of smokers of marijuana with or without tobacco. These include squamous metaplasia, cellular disorganization, nuclear variation, mitotic figures and increased nuclear-to-cytoplasmic ratio, which have long been considered to represent potential precursors for the subsequent development of bronchogenic carcinoma (Auerbach et al. 1961).

BRONCHIAL EXPRESSION OF IMMUNOHISTOCHEMICAL MARKERS OF DYSREGULATED GROWTH AND PRE-TUMOR PROGRESSION

A number of genetic alterations are responsible for the transformation of lung cells from normal to cancerous. Bronchial biopsies obtained in 12 MS, 14 TS, 9 MTS and 28 MTS from the UCLA cohort were therefore examined for alterations in some of the genes involved in the pathogenesis of lung cancer, as reflected by surrogate end-point markers that have been linked to an increased risk of lung cancer. Immunohistological studies of these biopsies showed marked overexpression in the bronchial epithelium of MS of Ki-67 (a marker of cell proliferation) and epidermal growth factor receptor (EGFR) (Barsky et al. 1998). Moreover, p53, one of the most common tumor suppressor genes altered in human cancers, was expressed in 11% of subjects who smoked marijuana together with tobacco. These findings suggest that smoking marijuana, like tobacco smoking, causes dysregulated growth of bronchial epithelial cells, possibly reflecting an increased risk of marijuana smokers for the subsequent development of lung cancer.

EFFECTS ON ALVEOLAR MACROPHAGES

Effects on Alveolar Macrophage Structure

Alveolar macrophages (AMs) are the major cells that reside in the peripheral air spaces of the lung and normally constitute over 90% of the cells recovered by bronchoalveolar lavage (BAL). These important immune effector cells play a crucial role in the lung's immune defense system. MS, TS and MTS all show an increase in the number of AMs recovered from the distal air spaces by BAL, compared to NS in the order of MTS > TS > MS > NS, and the effects of marijuana and tobacco smoking on the accumulation of AMs in the lung appear additive (Barbers et al. 1987). Examination of the ultrastructure of AMs recovered by BAL from smokers of marijuana and/or tobacco and nonsmokers by transmission electron microscopy has revealed marked abnormalities in the AMs of the smokers of either or both substances, consisting mainly of larger and more complex cytoplasmic inclusions than observed in the AMs of nonsmokers (Beals et al. 1989). Furthermore, ultrastructural differences were noted between the AMs of MS and TS, suggesting that exposure to marijuana or tobacco could lead to differences in the functional activity of these cells.

Effects on Alveolar Macrophage Function

The functional activity of human alveolar macrophages has been assessed by examination of their microbicidal activity and their production of reactive oxygen species, reactive nitrogen intermediates and inflammatory cytokines.

MICROBICIDAL ACTIVITY

AMs from both MS and TS have been shown to be impaired in their ability to kill *Candida albicans* (Sherman et al. 1991a) and *Candida pseudotropicalis* (Baldwin et al. 1997) compared to AMs from NS, although no defect in phagocytosis for fungi was noted (Sherman et al. 1991a). AMs from MS, but not those from TS, have also been shown to be deficient in their ability both to phagocytose and to kill the pathogenic bacterium, *Staphylococcus aureus*. The cause of these marijuana-related deficits in AM fungicidal activity and bacterial phagocytosis and killing is unclear but could be due, at least partly, to marijuana-induced deficiencies in the production of toxic oxygen species or reactive nitrogen intermediates, such as nitric oxide.

PRODUCTION OF REACTIVE OXYGEN SPECIES ("RESPIRATORY BURST")

Earlier studies demonstrated a reduced ability of AMs from MS to generate superoxide anion (O_2) both under basal conditions (compared to AMs from either NS or TS) and when stimulated (compared to AMs from TS), in contrast to an enhanced generation of O_2^- by AMs from TS under both basal and respiratory-burst stimulated conditions (Sherman et al. 1991a,b). Since reactive oxygen species serve as important effector molecules for microbial killing, the different respiratory burst characteristics of AMs from MS compared to those of AMs obtained from TS imply that different mechanisms may contribute to impairment of fungicidal activity of alveolar macrophages derived from smokers of these two different substances. It is tempting to speculate, however, that, since oxidants, including O_2^-, released from AMs, can also cause lung tissue injury, the marijuana-related impairment in the respiratory burst activity of AMs may provide protection against smoke-related damage to the peripheral airways and alveoli. Thus, it is possible that the dampening effect of marijuana smoking on the production of toxic oxygen radicals by immune effector cells in the lung could account for the absence of abnormalities in small airways function and alveolar diffusing capacity (physiologic markers of tobacco-related small airways disease and/or emphysema) in smokers of marijuana alone, in contrast to the presence of such physiologic abnormalities in smokers of tobacco, with or without marijuana (Sherman et al. 1991a,b).

PRODUCTION OF REACTIVE NITROGEN INTERMEDIATES AND PRO-INFLAMMATORY CYTOKINES

Preliminary data suggest that the impairment in the bactericidal activity of AMs from MS may be due to a marijuana-related impairment in production of reactive nitrogen intermediates (e.g., nitric oxide), which also serve as important effector molecules in bacterial killing. This impairment, in turn, could be secondary to a marijuana-related inhibition of AM production of inducible nitric oxide synthase (iNOS) in the course of infection (Baldwin et al. 2000). *In vitro* studies using AMs from MS in killing assays for *S. aureus* in the presence or absence of an inhibitor of iNOS with and without the addition of specific pro-inflammatory cytokines (interferon- [INF] and granulocyte-macrophage colony stimulating factor [GM-CSF]) suggest that the inhibition in bactericidal activity may be due to a marijuana-related impairment in production of key cytokines (e.g., INF and GM-CSF) that mediate the induction of iNOS. Other data indicating an inhibition of lipopolysaccharide-stimulated production of TNF- , IL-6 and GM-CSF by AMs from MS but not from TS provide further support for this hypothesis (Baldwin et al. 1997).

EFFECTS ON OTHER IMMUNE CELLS

Several *in vitro* and animal studies suggest that ^{9}-tetrahydrocannabinol (THC) is a powerful immune modulator and that it has a predominantly immunosuppressive effect on a variety of immune cells, including macrophages, natural killer cells and T lymphocytes (Klein, Friedman and Specter 1998). These observations are consistent with the finding of cannabinoid (CB) receptors on immune cells (Bouaboula et al. 1993). The immunosuppressive effect of THC appears to be due to its inhibition of lymphocyte production of immunostimulatory helper T cell type-1 cytokines (e.g., interleukin-2 [IL-2] and interferon gamma [IFN-]) and its parallel promotion of the production of immunoinhibitory helper T cell type-2 cytokines, such as interleukin-10 [IL-10] and interleukin-4 [IL-4] (Newton, 1994). It is possible that this immunosuppressive effect of THC could impair the host's ability to develop an antibacterial immune response and thereby facilitate bacterial infection. This possibility was studied in a mouse model of *Legionella pneumophila,* a cause of community-acquired and opportunistic pneumonia (Newton, Klein and Friedman 1994). Mice pre-treated with ^{9}-THC prior to infection with a sublethal dose of *L. pneumophila* failed to develop cell-mediated protective immunity and died when re-challenged with the organism, while control mice not pre-treated with ^{9}-THC became immune to repeated infection and survived. It is possible that a similar mechanism could be responsible for an increased predisposition of human users of marijuana to pulmonary infection.

CLINICAL IMPLICATIONS

The clinical implications of the above findings concerning the impact of regular marijuana smoking on the microbicidal activity of human AMs, as well as the inhibitory effect of THC on the ability of experimental animals to develop a protective anti-bacterial immune response, are that marijuana smoking may impair the lung's defense against infection, in part due to impairment in the critical antimicrobial function of alveolar macrophages, thus predisposing to pneumonia. The associated impairment in tracheobronchial mucociliary function (implied by the histopathologic evidence of marijuana-associated damage to the normal ciliated epithelial lining of the lower respiratory tract) further undermines the ability of the lung to defend itself against infections. In marijuana smokers with HIV infection, the combined effects of these two factors could add to the already increased risk of immunosuppressed patients with AIDS for pulmonary infection. The reported frequent contamination of marijuana with the fungus, *Aspergillus fumigatus*, (Kagen et al. 1983) and with potentially pathogenic gram-negative bacteria (Ungerleider et al. 1982) could

further heighten the risk of opportunistic fungal and bacterial pneumonia in the immunocompromised patient. A few clinical case reports and limited epidemiological studies (*vide infra*) provide some clues, but as yet no definitive evidence, as to the real risks of immunocompromised patients for the development or respiratory infection as a complication of marijuana smoking.

CLINICAL CASE REPORTS

Several clinical cases have been reported of invasive *Aspergillus* pneumonia in immunocompromised patients, including patients with AIDS (Denning et al. 1991), chronic granulomatous disease (Chusid et al. 1975), bone marrow transplantation (Hamadeh et al. 1988), renal transplantation (Marks et al. 1996) or small cell lung cancer treated with chemotherapy (Sutton, Lum, and Torti 1986), all of whom smoked marijuana. The precise role of marijuana in these cases of invasive pulmonary aspergillosis is unclear. While it is possible that the opportunistic fungal pulmonary infection in these patients may have been due primarily to their underlying immune compromise in the face of possible contamination of marijuana with *Aspergillus* (Kagen et al. 1983), the further possibility that an independent superimposed effect of marijuana smoking on pulmonary host defenses was a critical factor cannot be excluded. It is also possible that habitual marijuana smokers without any identifiable underlying immune deficiency could be predisposed to pulmonary infection as a consequence of the deficits in the lung's host defense caused by regular cannabis use. Recently, a 23-yr-old heavy smoker of both marijuana and tobacco with a history of intravenous opioid use but no clinical evidence of an underlying immune deficiency was reported to have developed miliary necrotizing granulomata, associated with progressive exertional dyspnea, bilateral nodular pulmonary infiltrates and a blackened alveolar exudate of carbon-laded macrophages (Cunningham et al. 2000). Although actual fungal infection was not documented, the authors suspected either infection with an unidentified fungus inhaled with the marijuana smoke or hypersensitivity to inhaled fungi as the most likely cause of the necrotizing granulomata.

EPIDEMIOLOGICAL STUDIES

Outpatient Visits for Respiratory Illness

In an epidemiological cohort study of the impact of marijuana smoking on the health care utilization of Kaiser Permanente health plan members, marijuana smoking history was ascertained from a comprehensive, multi-phasic health screening questionnaire and the medical experience of daily or near-

daily users of marijuana who never smoked tobacco (n = 452), as ascertained from medical records reviews, was compared with that of a demographically similar group of nonsmokers of either substance (n = 450) (Polen et al. 1993). Frequent marijuana smokers had small but significantly increased risks of outpatient visits for respiratory illness (relative risk [RR] = 1.19; 95% C.I. = 1.02, 1.16), as well as for other types of illness, compared with nonsmokers, in addition to a small increased risk of hospitalization. Neither independent nor additive or interactive effects of tobacco combined with marijuana were examined in this study.

Studies in Subjects with AIDS or HIV-Seropositivity

In an early, small-scale case-control study of 31 patients with severe manifestations of AIDS (13 with confirmed Kaposi's sarcoma and 18 with an opportunistic infection) compared with 29 symptom-free patients referred with possible AIDS, marijuana use was associated with a significantly increased risk for progression to Kaposi's sarcoma or opportunistic infection (OR = 3.7 [95% C.I. 1.10-12.30]; $p < 0.05$) (Newell et al. 1985). In another early prospective study in which logistic regression was used to assess lifestyle factors associated with progression or non-progression of 386 HIV seropositive individuals to end-stage AIDS within 2-3 years of enrollment, marijuana use in the preceding 3 months was identified as one of only two lifestyle factors or the only factor associated with progression to AIDS (n = 32) in univariate or multivariate analyses, respectively (Tindall et al. 1988). A more recent cohort study of risk factors for the first episode of bacterial pneumonia in 629 HIV-seropositive injection drug users (IDUs), of whom 40 subsequently developed pneumonia, revealed that smoking illicit substances (marijuana or crack cocaine) was significantly associated with the development of bacterial pneumonia in multivariate analysis (OR = 2.24; 95% C.I. 1.03-4.89) (Caiaffa et al. 1994). It is particularly noteworthy that among HIV-seropositive IDUs with a previous history of *Pneumocystis carinii* pneumonia, smoking illicit drugs had the strongest effect on risk of bacterial pneumonia (OR = 22.94; 95% C.I. 2.18-241.10). These few epidemiological studies suggest that HIV-seropositive patients who smoke marijuana regularly may be particularly vulnerable to opportunistic pulmonary infection. However, the possible incrimination of marijuana smoking for predisposing HIV-seropositive patients to pneumonia requires further investigation by more rigorous epidemiological studies, particularly in view of the growing interest in medicinal marijuana for patients with AIDS.

Mortality

The relationship of marijuana use to mortality was examined in a cohort of 65,171 Kaiser Permanente health care members, 15-49 yrs of age, who com-

pleted health-screening questionnaires that included questions on marijuana use (Sidney et al. 1997). Follow-up for assessing mortality was conducted for 6-12 yrs following questionnaire completion. Current marijuana use was not associated with a significantly higher risk of mortality in either men or women, compared with nonuse, except for an increased risk of death due to AIDS in men. However, the latter association was felt to be due to confounding by male homosexual behavior among the current marijuana smokers, rather than an effect of marijuana itself on mortality due to AIDS.

OTHER CLINICAL CONSEQUENCES

Barotrauma and Lung Bullae

Isolated cases of spontaneous pneumothorax and/or pneumomediastinum have been temporally associated with marijuana use (Feldman et al. 1993; Mattox 1976; Miller. Spiekerman and Hepper 1972). These complications are believed to involve barotrauma to the lung from the increased intrathoracic pressure that develops when a marijuana smoker performs a Valsalva maneuver against a closed glottis after deep inhalation of the smoke in an effort to "pressurize" the smoke within the lung to enhance absorption of THC. Several cases of large upper zone lung bullae have recently been reported in otherwise healthy young male marijuana smokers with relatively little exposure to tobacco (Johnson et al. 2000) The mechanism for bulla formation in these cases could be due to a direct toxic effect of components in marijuana smoke on the lungs of susceptible smokers and/or airway barotrauma related to the high intrathoracic pressures generated during marijuana smoking. The clinical significance of pneumothorax and/or pneumomediastinum could be exaggerated in patients with AIDS who already have pulmonary deficits due to effects of current or previous pulmonary infectious or noninfectious pulmonary complications of AIDS.

CONCLUSION

Frequent marijuana use can cause airway injury, lung inflammation and impaired pulmonary defense against infection. The major potential pulmonary consequence of habitual marijuana use of particular relevance to patients with AIDS is superimposed pulmonary infection, which could be life threatening in the seriously immunocompromised patient. In view of the immunosuppressive effect of THC, the possibility that regular marijuana use could enhance progression of HIV infection itself needs to be considered, although this possibility remains unexplored to date. A few mainly older epidemiological studies in

HIV-positive individuals have identified marijuana use as a significant risk factor for acquisition of opportunistic infections and/or Kaposi's sarcoma. Further investigation of the real risks of pulmonary complications from regular marijuana use by HIV-positive patients is required using rigorous epidemiological methodology.

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