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Marijuana Exposure and Pulmonary Alterations in Primates

SUZANNE E. G. FLIGIEL,*[1] TED F. BEALS,† DONALD P. TASHKIN,‡ MERLE G. PAULE,§ ANDREW C. SCALLET,§ SYED F. ALI,§ JOHN R. BAILEY§ AND WILLIAM SLIKKER, JR.§

**Department of Pathology, Wayne State University and VA Medical Center, Allen Park, MI 48101*
†Department of Pathology, University of Michigan and VA Medical Center, Ann Arbor, MI 48105
‡Department of Medicine, UCLA School of Medicine, Los Angeles, CA 90024
§National Center for Toxicological Research, Jefferson, AR 72079

FLIGIEL, S. E. G., T. F. BEALS, D. P. TASHKIN, M. G. PAULE, A. C. SCALLET, S. F. ALI, J. R. BAILEY AND W. SLIKKER, JR. *Marijuana exposure and pulmonary alterations in primates*. PHARMACOL BIOCHEM BEHAV **40**(3) 637–642, 1991.—As part of a large multidisciplinary study, we examined lungs from 24 periadolescent male rhesus monkeys that were sacrificed seven months after daily marijuana smoke inhalation of 12 months duration. Animals were divided into four exposure groups: A) high-dose (one marijuana cigarette 7 days/week), B) low-dose (one marijuana cigarette 2 days/week and sham smoke 5 days/week), C) placebo (one extracted marijuana cigarette 7 days/week), and D) sham (sham smoke 7 days/week). Lungs, removed intact, were formalin inflated, sectioned and examined. Several pathological alterations, including alveolitis, alveolar cell hyperplasia and granulomatous inflammation, were found with higher frequency in all cigarette-smoking groups. Other alterations, such as bronchiolitis, bronchiolar squamous metaplasia and interstitial fibrosis, were found most frequently in the marijuana-smoking groups. Alveolar cell hyperplasia with focal atypia was seen only in the marijuana-smoking animals. These changes represent mostly early alterations of small airways. Additional follow-up studies are needed to determine their long-term prognostic significance.

Primates Inhalation Smoking Marijuana Cannabinoids Lung Morphology Pathology

MARIJUANA smoking in the United States has increased dramatically in the past two decades. A recent nationwide study indicates that there are approximately 18 million young adults who admit to smoking marijuana (15). A significant percentage of these smokers are fairly heavy daily users of marijuana. Marijuana smoking exposes the lung to numerous irritants and carcinogenic aromatic hydrocarbons (14), so that the potential for chronic airway irritation is great. However, evidence regarding the actual effects of long-term marijuana smoking is inconclusive. While multiple studies suggest a harmful effect of marijuana on the lung (9, 10, 13, 19, 22), other investigators have failed to find deleterious effects (2,6). In order to clarify this issue, we examined bronchial tissue from human smokers of marijuana (7, 8, 11): we characterized bronchial wall alterations from young, heavy habitual smokers of marijuana, some of whom were also concomitant smokers of tobacco. We found that marijuana smokers frequently exhibited bronchial epithelial alterations of basal cell and goblet cell hyperplasia accompanied by basal lamina thickening. Additionally, we found changes of bronchial squamous metaplasia, as well as a focal increase of nuclear/cytoplasmic ratio. These findings of significant morphologic alterations in bronchial tissues of young asymptomatic human marijuana smokers are likely the result of the irritant and damaging qualities of the inhaled marijuana smoke. Therefore, it became of great importance to evaluate the effect of marijuana smoke on the remainder of the respiratory tree, including the smaller airways and the lung parenchyma. In order to accomplish this, we examined lung tissues from 24 primates that were exposed to marijuana smoke under carefully controlled conditions (20). The availability of tissues from the entire respiratory tree and the detailed knowledge of the quantity and frequency of the marijuana smoke administered allowed us to systematically evaluate the dose-related bronchopulmonary pathologic alterations induced by exposure to marijuana smoke.

METHOD

Animals

The present investigation was a part of a multidisciplinary study at the National Center for Toxicological Research, Jefferson, AR. The study involved 62 periadolescent male rhesus monkeys exposed daily for 12 months to marijuana smoke inhalation, using a smoke generator (ADL/ll smoking machines, A. D. Little Inc., Cambridge, MA) and a tight-fitting face mask which covered the subject's nose and mouth. Direction of air flow was controlled by one-way valves, assuring inhalation of

[1]Requests for reprints should be addressed to Suzanne E. G. Fligiel, M.D., Department of Pathology (113), VA Medical Center, Southfield and Outer Drive, Allen Park, MI 48101.

all generated smoke. The marijuana smoke was generated from marijuana cigarettes which were provided and characterized by the National Institute on Drug Abuse. The cigarettes were standardized to contain approximately 2.5% delta-9-THC. A smoke exposure consisted of one cigarette burned down to a 10-mm butt length (generally attained after 19–21 puffs which were generated over a period of 6–8 minutes).

Slikker and his colleagues (20) have demonstrated that maximal THC plasma concentrations occurring in the monkeys immediately after exposure to the smoke generated from one standardized marijuana cigarette were approximately 800–1000 ng/ml and decreased rapidly to about 60–80 ng/ml by 45 minutes after dosing. These peak THC plasma concentrations are considerably higher than those observed in humans (150–200 ng/ml) after smoking one relatively low potency marijuana cigarette and thus would correspond to the human inhalation of smoke from about four to five medium-potency marijuana cigarettes (20).

The animals were divided into four exposure groups (n = 15–16/group). In the high-dose group, animals were exposed to the smoke of one standard marijuana cigarette 7 days per week. In the low-dose group, animals were exposed to the smoke of a standard marijuana cigarette 2 days per week and to sham smoke conditions for the remaining 5 days. Placebo group animals were exposed to the smoke of one ethanol-extracted cigarette for 7 days a week. The sham group animals were exposed to sham smoke conditions for 7 days a week. The total duration of exposure for each group was 12 months. After a subsequent lag period of seven months, during which animals were not exposed to any smoke conditions, a total of 48 animals were sacrificed. This was accomplished following deep anesthesia with intravenous sodium pentobarbital (50 mg/kg), using the saphenous vein of the leg, with an injected minimum dose of 2 ml (100 mg). Absence of response to tactile stimulation, indicating complete unconsciousness, was a prerequisite for any surgical procedure on the animals.

Specimen Preparation

Lung tissues (an intact trachea with both lungs) from 24 animals—6 per each of the four exposure groups—were received fresh. All lungs were lavaged with 30 cc of sterile saline, and the lavaged material was processed for macrophage evaluation (3). Both lungs were then carefully inflated (intrabronchially) with a mixture of 10% buffered formaldehyde and 1% glutaraldehyde to attain their original inflated form. They were then submerged into the same mixture for several weeks. Following adequate fixation, the specimens were systematically sectioned into 1-cm parasagittal slices and carefully examined for the presence of gross abnormalities. A complete representation of all regions of the respiratory tree was sectioned and examined, using the following criteria of at least one section per designated area: 1. Tracheobronchial bifurcation; 2. and 3. Major bronchial bifurcation, upper lobe, right and left lungs; 4. and 5. Secondary bronchial bifurcation, right and left lungs; 6. and 7. Midbronchial bifurcation, lower lobe, right and left lungs; 8. and 9. Bronchiolar areas, upper and lower lobes, right and left lungs; 10. and 11. Peripheral lung parenchyma, upper and lower lobes, right and left lungs; 12. and 13. Central lung parenchyma, upper and lower lobes, right and left lungs. The sectioned tissue specimens were routinely processed, embedded in paraffin, sectioned at 5 microns each, and stained with hematoxylin and eosin (H + E). Selected sections were stained additionally with periodic acid-Schiff (PAS) stain or with Masson's trichrome stain. Thirteen glass slides with H + E-stained sections were prepared from each lung specimen; each slide contained between one to four sections of various lung regions. The sections were examined by light microscopy by a pathologist who was unaware of the smoking histories of the animal subjects.

Specimen Evaluation

For bronchial pathology assessment, we used the same histopathologic criteria that were established in our study of bronchial biopsies of our human marijuana-smoking subjects (8,11). In summary, we examined tissues for alterations of chronic bronchitis and any evidence of epithelial dysplasia or squamous metaplasia. These same criteria have been utilized in the present study for the entire tracheobronchial tree up to the level of bronchioles.

Bronchiolar alterations were assessed for the presence of peribronchiolar and intrabronchiolar inflammation, pigment deposition, macrophage accumulation, smooth muscle hypertrophy and fibrosis, in addition to the epithelial changes of epithelial and goblet cell hyperplasia and squamous metaplasia. We also searched for the presence of bronchiolitis and peribronchiolitis.

Lung parenchyma was evaluated in terms of interstitial or intraalveolar inflammation, fibrosis, macrophage infiltration, or early emphysematous change. Alveolar epithelial alterations of hyperplasia, atypia or squamous metaplasia were also assessed, as were other interstitial or vascular abnormalities.

RESULTS

Microscopic examination of sections obtained from large and midsized bronchi revealed focal basal and goblet cell hyperplasia, as well as focal basement membrane thickening. These alterations were found in several animals in all smoking categories including the sham group. Therefore, no significant differences in bronchial alterations were apparent between the different smoking groups in this study, and no unique bronchial findings could be attributed to any of these groups.

FACING PAGE

FIG. 1. (A) This alveolitis with accompanying interstitial pneumonia from the lung of a low-dose marijuana-smoking animal was found adjacent to an area of bronchiolitis. The cellular infiltrate, which can be seen within the alveolar spaces as well as within the expanded interstitium, consists of numerous lightly pigmented macrophages, lymphoid and plasma cells, and occasional polymorphonuclear leukocytes (H + E, ×700). (B) Photomicrograph of alveolar cell hyperplasia from a low-dose marijuana-smoking animal. The usual thin, flat, inconspicuous alveolar epithelium is replaced by large, columnar hyperplastic cells, some of which show early nuclear hyperchromasia and an increase of nuclear/cytoplasmic ratio (H + E, ×1400). (C) This lung tissue, obtained from an animal from the high-dose marijuana-smoking group, demonstrates focal alveolar cell hyperplasia with severe cytological atypia. The enlarged, atypical alveolar lining cells contain very large, abnormal nuclei which show a markedly increased nuclear/cytoplasmic ratio. The alveolar walls are considerably thickened due to interstitial collagen deposition (H + E, ×1400). (D) This animal from the high-dose marijuana-smoking group demonstrates the presence of granulomatous bronchiolitis. In addition to the mixed inflammatory and histiocytic infiltrate, this photomicrograph demonstrates the presence of multinucleated giant cells, some of which contain foreign intracytoplasmic material. A fairly sharp demarcation between the diseased bronchioloalveolar unit and the adjacent normal alveoli is evident (H+E, ×700)

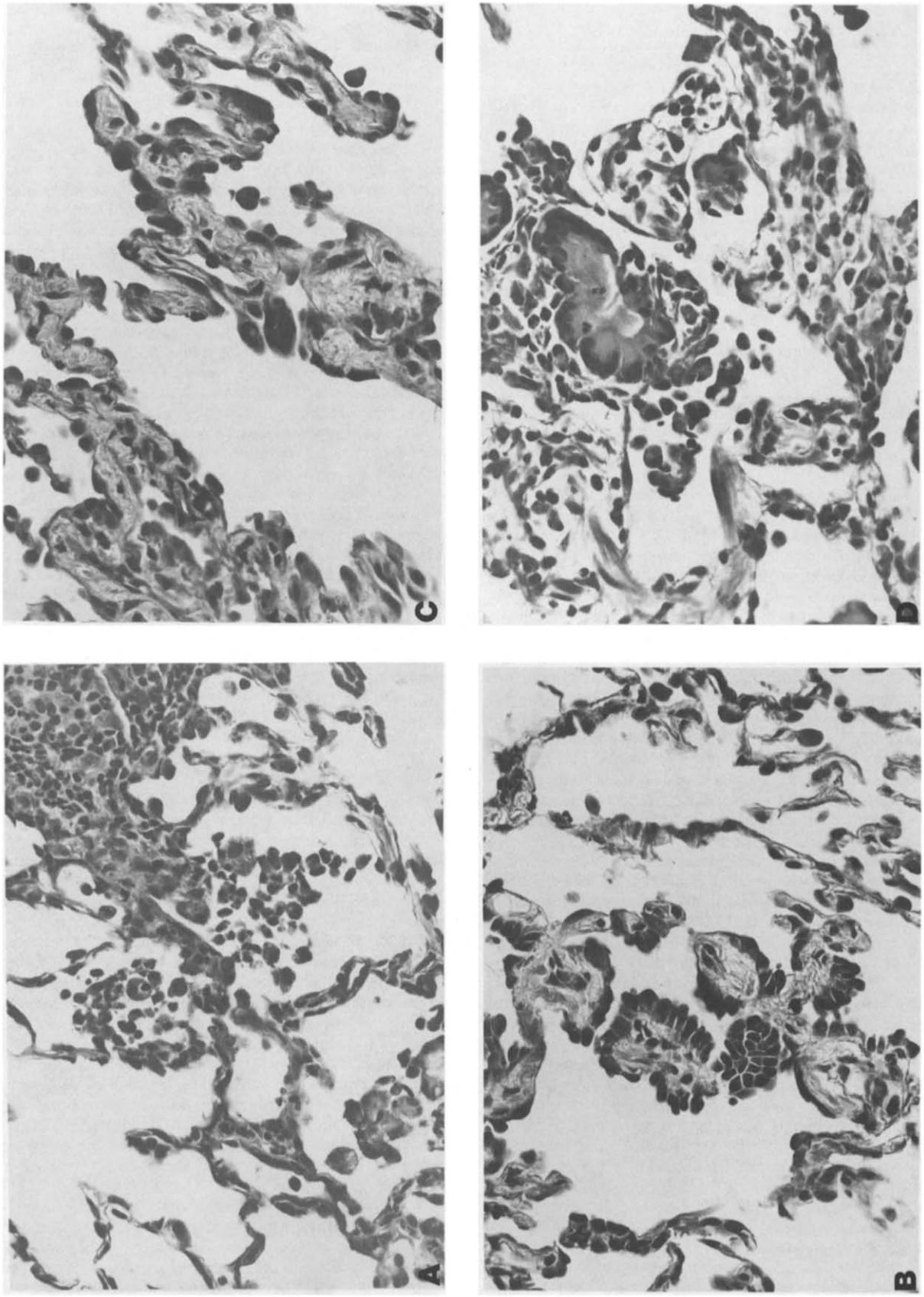
C
D
A
B

TABLE 1

SUMMARY OF HISTOPATHOLOGIC ALTERATIONS SEEN IN BRONCHIOLES AND ALVEOLI

Bronchiolar smooth muscle hyperplasia	seen in all groups
Bronchiolar goblet cell hyperplasia	seen in all groups
Bronchiolar epithelial hyperplasia	seen in all groups
Bronchiolar squamous metaplasia	highest in MS*
Bronchiolitis/peribronchiolitis	seen in all groups greatest frequency in MS greatest severity in MS
Alveolar cell hyperplasia	higher in all smokers
Alveolar cell hyperplasia with atypia	seen only in MS
Alveolitis	seen in all groups more severe in smokers
Granulomatous inflammation	seen in all groups more severe in smokers
Fibrosis (interstitial, peribronchiolar)	seen in all groups greatest frequency in MS greatest severity in MS

*MS = marijuana smokers.

Several interesting alterations were noted in the peripheral respiratory tree, within the bronchioles and alveoli (Table 1). Bronchiolar smooth muscle hyperplasia, goblet cell hyperplasia and epithelial cell hyperplasia were present in some animals in all four groups: therefore, no significant differences in the frequency of distribution of these pathological alterations were observed. Additionally, small foci of bronchiolar squamous metaplasia were found in some animals within all groups. However, only one out of 6 animals in the sham group was found to have this change, while 6 out of 12 marijuana-smoking animals had this finding.

Alveolitis with intraalveolar and interstitial accumulations of macrophages and a mixed, mostly mononuclear inflammatory infiltrate (Fig. 1A) was present with equal frequency in all animal groups. The intensity and the extent of these lesions, however, were greater in the three smoking groups than in the sham group. Similarly, changes of alveolar epithelial hyperplasia (Fig. 1B) could be found within some animals in all groups. Only two out of 6 sham smokers, in contrast to 4 out of 6 animals from the placebo group and 7 out of 12 animals from the marijuana-smoking groups, demonstrated this alteration. A further step in this morphological progression, alveolar epithelial hyperplasia with atypia (Fig. 1C), was found only in those animals who smoked marijuana (one third in each group).

The presence of bronchiolitis/peribronchiolitis characterized by mostly chronic inflammatory cells admixed with clusters of pigmented macrophages (Fig. 1A) was most frequently found in the marijuana-smoking animals, and its extent was correlated with the amount of marijuana smoked. High-dose smokers showed a more frequent and more extensive involvement than any other groups. Similarly, increased collagen deposition in the peribronchial or interstitial (Fig. 1C) location was noted more frequently and with greater severity in the marijuana-smoking animals as compared to the other groups. Of interest was the presence of granulomatous inflammation surrounding and within the bronchioles and the alveoli (Fig. 1D). This change was seen within some animals in all groups. Again, the intensity of this process was greater within the smoking groups. The varied morphologic appearance of these granulomatous changes suggests that several different etiologic agents may be contributing to this process. For example, while some animals had refractile polarizable material within their granulomas, others showed small pale nonpolarizable particles or large fragments of foreign material surrounded by giant cells. One animal from the high-dose smoking group demonstrated large areas of granulomatous lipid pneumonia.

DISCUSSION

Examination of the central and peripheral airways and pulmonary parenchyma from control groups of primates and from primates exposed to low and high doses of marijuana smoke revealed a variety of morphological alterations (Table 1). Although we sampled the entire respiratory tree, most of the abnormalities noted were at or below the level of respiratory bronchioles. The particular types of pathologic alterations and their distribution pattern bring out several interesting points, which are discussed below.

Some of the changes we found have also been described by other investigators. Long-term studies with marijuana smoke-inhaling rats (9, 10, 18) documented the presence of a dose-related alveolitis and pneumonitis localized in the proximity of respiratory bronchioles or alveolar ducts. These pulmonary lesions contained an admixture of granulomatous, chronic and acute inflammation and macrophages. Some areas also showed early fibrosis and alveolar cell hyperplasia. The studies with marijuana smoke-inhaling dogs (19) demonstrated evidence of bronchiolitis and focal squamous metaplasia of the trachea. What is important in both of these animal models is the fact that the same abnormal morphologic alterations were found in the experimental groups as well as in the control groups. The differences were those of severity of the process and the frequency with which these alterations were found. The marijuana-exposed animals were significantly more affected, and a relationship was noted to the length of exposure to marijuana and the amount of inhaled marijuana smoke. Another important issue was the fact that, with the exception of tracheal squamous metaplasia (19), the pathologic alterations affected mostly the small-airway region of the lung.

Previous studies of marijuana-induced damage to the respiratory system of humans (7, 8, 11, 13, 22) yielded somewhat different results than the animal studies. The most important difference was the fact that only the major upper airways (trachea, major bronchi) were available for examination in the human studies. Thus the entire lower respiratory tree, including the lung parenchyma, was not evaluated. The second critical issue in these human studies is the fact that there were few pure-marijuana smokers among these subjects. Many of these participants had a history of previous or concomitant smoking of tobacco, and some also smoked cocaine. It is therefore not surprising that the findings in the human volunteers were somewhat different from the above-described animal models. The humans showed mostly evidence of upper respiratory system irritation ranging from changes of chronic bronchitis with a thickened basement membrane and goblet cell hyperplasia (7, 8, 11) to loss of cilia, epithelial hyperplasia with atypia (13,22) as well as reserve cell hyperplasia and increased intraepithelial inflammation (7, 8, 11). The normal control participants did not show these alterations. The changes within the small airways of the human subjects, if any, could not be evaluated since these tissues were not readily accessible.

When comparing pulmonary morphologic alterations of human and animal subjects, one must consider several factors, especially the differences in smoking habits. This issue has been researched by Slikker and his colleagues (20), who reported that the peak plasma THC concentration levels attained in the rhesus monkeys in our study were equivalent to those THC levels that were predicted for human subjects after smoking four to five

medium-potency marijuana cigarettes. Considering that animals in our high-dose marijuana-smoking group received this level of marijuana dose 7 days per week for an entire year, we believe that this represents the equivalent of average to heavy chronic use of marijuana in the human.

The adverse effects of marijuana on human health have been well described (14,15). Pulmonary studies of marijuana smokers demonstrate abnormalities suggestive of large-airway changes (13,21). Although no physiologic evidence is available suggesting that small-airway abnormalities are present in these marijuana smokers, some studies of tobacco smokers (5) suggest that, with early small-airway abnormalities, no appreciable decrease in ventilatory function may be detectable. On the other hand, other studies of cigarette smokers indicate that the disease in small airways might be among the earliest changes in chronic bronchitis (4), and that some of the early changes seen in young tobacco smokers can be characterized as respiratory bronchiolitis (17) similar to that found in our primate lungs. Furthermore, Anderson's (1) studies of human lungs with emphysema suggest that the earliest precursor to that condition appears to be interstitial alveolitis, a lesion also observed in the lungs of our monkeys.

Thus we have evidence from the marijuana animal studies that small-airway alterations are known to occur. Additionally, the human tobacco-smoker studies demonstrate that early changes do occur in small airways and that these changes may be difficult to detect clinically. Therefore, our systematic examination of the entire respiratory tree of primates exposed to marijuana smoke represents an important study of lung alterations under these conditions. Interestingly, we found that, in some animals, there were large-airway alterations of chronic bronchitis, similar to those described in human subjects. However, these changes were less extensive than those found in humans (7, 8, 11). Furthermore, some animals from the two control groups demonstrated similar findings.

Changes that we found in the lower respiratory tree were more significant. Similar to other animal studies (10, 18, 19), we found that the types of pathological alterations were not unique since all groups of animals showed similar types of changes. The important finding in our study was that the intensity (severity) of many of the changes, as well as the frequency with which they were observed, were clearly related to the amount of marijuana the animals inhaled. This is especially true for the morphologic changes of respiratory bronchiolitis, bronchiolar squamous metaplasia and peribronchiolar/interstitial fibrosis. One alteration, alveolar cell hyperplasia with atypia (Fig. 2), was found only in the marijuana-smoking animals. These are important findings, since many of these have been described in the lungs of tobacco smokers and may be precursors of chronic bronchitis (4) or centrilobular emphysema (1). Atypical alveolar cell hyperplasia has been found in cigarette-smoking dogs (12) and in human subjects with adenocarcinoma (16), and its relationship to invasive malignant neoplasm remains the subject of further studies.

In summary, the findings from the present study indicate that exposure of primates to marijuana smoke leads to distinctive pathologic changes which may represent precursor lesions to more severe alterations such as chronic bronchitis or emphysema. Long-term studies with a prolonged follow-up are indicated in order to better define these potentially deleterious morphologic alterations.

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