

ACUTE PULMONARY PHYSIOLOGIC EFFECTS OF SMOKED MARIJUANA AND ORAL Δ^9 -TETRAHYDROCANNABINOL IN HEALTHY YOUNG MEN

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Abstract Acute pulmonary physiologic effects of smoked marijuana and oral Δ^9 -tetrahydrocannabinol were investigated in 32 healthy, experienced male marijuana smokers. After smoking of marijuana assayed at either 1 or 2 per cent Δ^9 -tetrahydrocannabinol, specific airway conductance increased immediately, reached peak levels at 15 minutes and was still significantly elevated at 60 minutes. In contrast, specific airway conductance decreased after both tobacco smoking and deep-breathing maneuvers that simulated marijuana smoking. Inhalation of 1250 μ g of isoproterenol caused

specific conductance to rise to less than 60 per cent of the average peak increase observed after 2 per cent marijuana. After ingestion of 10, 15 and 20 mg of Δ^9 -tetrahydrocannabinol in 12 subjects, specific airway conductance rose significantly as compared with placebo, attained peak levels three hours after ingestion and remained elevated for four to six hours. These findings indicate that both smoked marijuana and oral Δ^9 -tetrahydrocannabinol cause definite dilatation of the airways lasting as long as 60 minutes and six hours, respectively. (N Engl J Med 289:336-341, 1973)

IT has been estimated that there are well over 200,000,000 regular marijuana users throughout the world.¹ Although the usual route of administration of this widely used agent is by inhalation of the smoked material, there are few detailed data regarding pulmonary physiologic effects of marijuana or its major active ingredient, Δ^9 -tetrahydrocannabinol (THC). Published studies in animals indicate merely that very large doses of Δ^9 -THC cause apnea or a reduction in respiratory rate as part of a general depression of central-nervous-system responses.² Previous studies of pulmonary function after acute marijuana inhalation in man revealed only that marijuana had no significant effect on respiratory rate³ or on tidal volume.⁴ Since submission of our report, Vachon and his associates have reported that inhalation of marijuana smoke in 17 subjects caused significant airway dilatation and no change in the ventilatory response to carbon dioxide.⁵

The present study was undertaken to determine the acute effects of both smoked natural marijuana and oral synthetic Δ^9 -THC on plethysmographically determined specific airway conductance in a group of experienced marijuana smokers. Effects on airway dynamics after tobacco smoking and inhaled isoproterenol were studied in the same group of subjects for comparison with the changes after marijuana. Specific airway conductance, a measure of airway caliber, was selected as the major experimental feature since it was reasoned a priori that marijuana smoke might have an irritant effect on the airways, resulting in airway narrowing by analogy with the acute bronchoconstrictor effect of tobacco cigarette smoke.⁶

METHODS

Subjects

Subjects were experienced male marijuana smokers (21 through 30 years of age) who had smoked at least 3 marijuana joints a week and no tobacco cigarettes for at least the preceding 6 months. In ad-

dition, they had no history of the regular use of other drugs, no serious medical or psychiatric illness and normal base-line complete blood counts, routine urinalyses, blood chemical studies, chest x-ray films, electrocardiograms and pulmonary-function studies. The latter included spirometry using a 13.5-liter spirometer (Warren E. Collins, Inc.), single-breath oxygen test for distribution of ventilation,⁷ single-breath diffusing capacity for carbon monoxide⁸ and airway resistance and thoracic gas volume determined in a 900-liter variable-pressure body plethysmograph with use of the panting technic of Dubois et al.^{9,10}

Pulmonary effects of smoked natural marijuana and oral synthetic Δ^9 -THC were studied separately in 2 series of experiments.

Smoked Marijuana Experiments

Thirty-two male volunteers who fulfilled the criteria listed above were studied. Subjects consented to be sequestered for 36 days on a special ward of the Neuropsychiatric Institute of the University of California at Los Angeles for extensive psychologic, electroencephalographic, ophthalmologic and physiologic studies. They had agreed to refrain from cannabis use for 2 weeks before study. After hospitalization, they were randomized in double-blind fashion into 3 groups, each subjected to inhalation of a different amount of Δ^9 -THC. Each afternoon of the 4th through the 31st day of hospitalization, subjects in each group smoked a joint containing 7 mg per kilogram of body weight of a blended natural marijuana preparation containing 0 or approximately 1 or 2 per cent Δ^9 -THC as assayed by gas-liquid chromatography. All marijuana and placebo material was supplied by the National Institute of Mental Health, under whose auspices all THC extraction, assay and blending procedures had previously been performed. The 0 per cent preparation that served as a placebo control had been obtained by exhaustive extraction of the active cannabinoids with 95 per cent ethanol until assays for Δ^9 -THC, Δ^8 -THC, cannabidiol and cannabidiol were all 0.0 per cent. The 1 per cent and 2 per cent preparations were each supplied by the National Institute of Mental Health in 2 batches. The 2 lots of the 1 per cent preparation had been assayed at 1.0 and 1.1 per cent Δ^9 -THC, and those of the 2 per cent material at 2.0 and 2.1 per cent Δ^9 -THC.

A uniform smoking technic was employed in an attempt to standardize delivery of volatilized THC into the lungs. Each subject inhaled the cigarette smoke deeply over 2 to 4 seconds and held his breath for approximately 15 seconds, with resumption of normal breathing for several seconds before repeating the procedure. Each joint was consumed in this manner over a period of approximately 10 minutes. A forceps was used to hold the butt, or "roach," to permit complete consumption of the butt, where a large fraction of the smoked THC is concentrated.

Screening pulmonary-function studies were performed on the 1st hospital day. In addition, to determine the responsiveness of the airways to inhalation of a standard therapeutic dose of a sympathomimetic bronchodilator, subjects underwent measurements of airway resistance and thoracic gas volume before and 5, 10, 15, 30 and 60 minutes after inhalation of a total of 0.25 ml of isoproterenol hy-

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drochloride 1:200 (1250 µg) via a De Vilbiss nebulizer connected to a positive-pressure breathing device powered by compressed air.

On the 6th day of hospitalization, subjects underwent serial measurements of airway resistance and thoracic gas volume before and after smoking their usual daily joint of marijuana or placebo ("early" marijuana intoxication). Other measurements included heart rate, determined from the electrocardiogram, respiratory rate and systolic and diastolic blood pressure. Two sets of initial control measurements were made over 15 minutes before smoking, and measurements were repeated immediately and 5, 10, 15, 30 and 60 minutes after the completion of smoking. To ascertain whether acute effects of marijuana inhalation were altered by chronic daily marijuana use, the same protocol was repeated on the 30th hospital day ("late" marijuana intoxication). In a few subjects studied in the initial stages of these experiments, the "early" intoxication session was omitted.

On the last hospital day, additional studies were performed to determine the effect of the deep-breathing technic used in smoking marijuana on airway dynamics and to compare the effect of tobacco-cigarette smoking on bronchomotor tone with that of marijuana smoking. First of all, plethysmographic measurements were made before and after a 10-minute period in which subjects merely went through the same deep-breathing maneuvers used when smoking marijuana without actually smoking. After measurements had returned to initial values, plethysmographic measurements were repeated both before and after a 10-minute period during which the subjects smoked a standard-length, unfiltered tobacco cigarette using an ad lib smoking technic. Measurements were performed in the same time sequence as that employed in the marijuana experiments.

Oral Δ^9 -Tetrahydrocannabinol Experiments

After completion of the in-hospital smoked marijuana study, 12 subjects were recruited from the latter study to participate in another series of experiments designed to determine the effects of different doses of synthetic oral Δ^9 -THC on airway tone. At approximately 10 a.m. on 4 separate days, after an overnight fast, subjects ingested placebo and 10, 15 and 20 mg of Δ^9 -THC according to a random double-blind crossover design. Placebo and the different doses of THC were suspended in sesame oil and made up into identical-appearing gelatin capsules. Measurements of the same indexes as those determined in the smoked study were carried out over a 30-minute initial control period, at the end of which subjects ingested the test medication. Measurements were repeated at 30, 60, 90 and 120 minutes and at hourly intervals thereafter up to 6 hours after ingestion. Lunch was permitted between 2 and 4 hours after oral administration of THC.

RESULTS

Smoked Marijuana

From each set of measurements of airway resistance and thoracic gas volume, specific airway conductance was calculated to correct for changes in airway resistance due to changes in gas volume.¹¹ For each subject, per cent changes in specific airway conductance, airway resistance, thoracic gas volume, respiratory rate, heart rate and systolic and diastolic blood pressure were calculated from the average of the initial control values determined over the 15-minute period before smoking. Average initial control values for these measurements, as well as average results of screening pulmonary-function studies and physical data, are indicated in Table 1 for each group of subjects (placebo and 1 per cent marijuana and 2 per cent marijuana). At each interval after the completion of smoking, per cent changes for individuals within each group (placebo and 1 per cent marijuana and 2 per cent marijuana)

were averaged. Since no differences were noted between the results of "early" and "late" marijuana intoxication, these results were lumped together for each group.

Similar calculations were performed for experiments involving simulated marijuana smoking, cigarette smoking and isoproterenol inhalation.

Figure 1 shows the average per cent changes in specific airway conductance after the smoking of placebo and 1 per cent and 2 per cent marijuana. After 1 per cent and 2 per cent marijuana smoking, specific airway conductance increased immediately, rose to maximal levels over the next 15 to 30 minutes and then gradually declined to levels that were still slightly higher at 60 minutes than those noted immediately after smoking. At all times, these increases were statistically significant as compared both with initial control values (Student's *t*-test, $p < 0.01$) and with the placebo group (*t*-test for comparison of two means, $p < 0.05$). Although the average increases after 2 per cent marijuana were greater than those after the 1 per cent preparation, these differences were not statistically significant.

Per cent changes in airway resistance paralleled those in specific airway conductance, whereas thoracic gas volume, respiratory rate and systolic and diastolic blood pressure did not change significantly.

In Figure 2 the average per cent changes in heart rate after placebo and marijuana smoking are shown. After 1 per cent and 2 per cent marijuana, heart rate increased significantly ($p < 0.01$) to maximum levels immediately after smoking and then declined over the ensuing hour in contrast to specific conductance, which rose to peak levels more slowly and then declined more gradually (Fig. 1). A greater tachycardia followed 2 per cent marijuana as compared with 1 per cent marijuana, but the differences were not statistically significant. After placebo, no tachycardia occurred; in fact, heart rate decreased slightly but significantly at 30 and 60 minutes.

Figure 3 shows the average per cent changes in specific airway conductance after simulated marijuana smoking, tobacco smoking and isoproterenol inhalation. Per cent changes after 2 per cent marijuana are indicated for comparison. Immediately after both simulated marijuana and tobacco smoking, specific conductance fell slightly but significantly and then returned to control levels, in contrast to the significant, sustained increases that followed 2 per cent marijuana. Isoproterenol caused conductance to increase significantly, but the maximum average increase after 1250 µg of isoproterenol was less than 60 per cent of that after 2 per cent marijuana.

Oral Δ^9 -Tetrahydrocannabinol

For each subject, per cent changes in specific airway conductance, airway resistance, thoracic gas volume, respiratory rate, heart rate and systolic and diastolic blood pressure at each interval after placebo and each dose level of THC were calculated from the average of initial control values. For all subjects, per cent changes

Table 1. Physical Characteristics and Base-Line Physiologic Data of Participants in the Smoked-Marijuana Study.*

MEASUREMENT	AGE	HEIGHT	WEIGHT	VC	FEV ₁	SBO ₂	D _L CO	R _A	V _{TG}	SG _A	RESPIRATORY RATE	BLOOD PRESSURE		HEART RATE
	yr	cm	kg	% predicted*	%	Δ N ₂ %	% predicted*	cm H ₂ O/liter/sec	liters	ml/min/cm H ₂ O/liter	min ⁻¹	SYS-TOL-IC	DIAS-TOL-IC	min ⁻¹
Placebo (10)	23.9	180.3	71.0	110.2	79.8	0.8	98.2	1.53	3.49	0.216	15	115	75	77
	± 0.6	± 2.3	± 2.3	± 4.5	± 1.6	± 0.2	± 7.0	± 0.13	± 0.15	± 0.014	± 2	± 2	± 1	± 3
1% marijuana (12)	24.5	177.9	71.1	106.0	84.5	0.7	92.2	1.43	3.43	0.228	16	115	76	74
	± 0.8	± 1.5	± 1.3	± 5.3	± 1.6	± 0.2	± 6.8	± 0.09	± 0.11	± 0.012	± 1	± 2	± 1	± 3
2% marijuana (10)	24.0	178.6	77.2	103.7	84.0	0.7	86.6	1.46	3.11	0.235	15	121	79	80
	± 0.8	± 1.3	± 3.2	± 3.4	± 1.5	± 0.2	± 5.6	± 0.07	± 0.15	± 0.016	± 2	± 3	± 2	± 4

*All values are means ± SE. VC indicates vital capacity, FEV₁ forced expiratory volume in 1 sec, FVC forced vital capacity, SBO₂ Fowler's single-breath oxygen test, D_LCO diffusing capacity for carbon monoxide, R_A airway resistance, V_{TG} thoracic gas volume, SG_A specific airway conductance, & BP blood pressure. Figures in parentheses represent no. of subjects.

*% of predicted values for VC & D_LCO are based on the regression equations of Kory et al.¹² & of Hamer & Meade as reported by Cotes.¹³ respectively.

in each measurement were then averaged at each interval for placebo and for each dose level of THC. Because of the crossover design of the oral study, the significance of changes after each dose level of Δ^9 -THC from those that followed both placebo and each of the other dose levels of THC was analyzed with use of the t-test for paired observations.

Per cent changes in specific airway conductance after placebo and 10, 15 and 20 mg of THC are shown in Figure 4. Significant increases as compared with placebo occurred one hour after ingestion of all doses of THC and persisted for four to six hours. A dose-response relation was demonstrated in that increases after 20 mg were significantly greater than those after 15 and 10 mg at 120 minutes and 120 to 360 minutes, respectively, and increases after 15 mg were significantly greater than those after 10 mg at 120 to 240 minutes. After 20 mg of THC specific conductance increased to a maximal level at 180 minutes. The bron-

chodilator responses after 15 and 10 mg of THC reached initial peak levels at 90 minutes, then declined and peaked again at 180 and 240 minutes, respectively, which was usually within an hour after the subjects had finished lunch. As observed with smoked marijuana, changes in airway resistance after oral THC generally paralleled the changes in specific airway conductance. No changes in respiratory rate or systolic or diastolic blood pressure were noted. Thoracic gas volume decreased slightly (less than 11 per cent) after oral THC; these decreases were significant as compared with placebo ($p < 0.05$) at 30 to 240 minutes after 15 mg of THC and at 180 to 240 minutes after 20 mg of THC.

Per cent changes in heart rate after oral Δ^9 -THC are shown in Figure 5. After 10 and 15 mg, the heart rate rose significantly ($p < 0.05$) compared with placebo at 90 minutes, reached peak levels at 180 to 240 minutes, and declined to control levels by six hours.

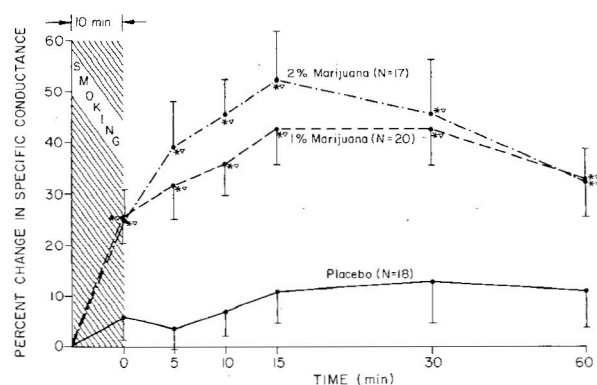


Figure 1. Specific Airway Conductance as a Function of Time after the Smoking of Placebo or Natural Marijuana Assayed at 1 per Cent or 2 per Cent Δ^9 -Tetrahydrocannabinol.

For this and subsequent figures, points and vertical bars represent the means of individual per cent changes from initial control values ± S.E. (see text).

*Statistically significant as compared with zero ($p < 0.01$).

▽ Statistically significant as compared with placebo ($p < 0.05$), with use of t-test for comparison of two means.

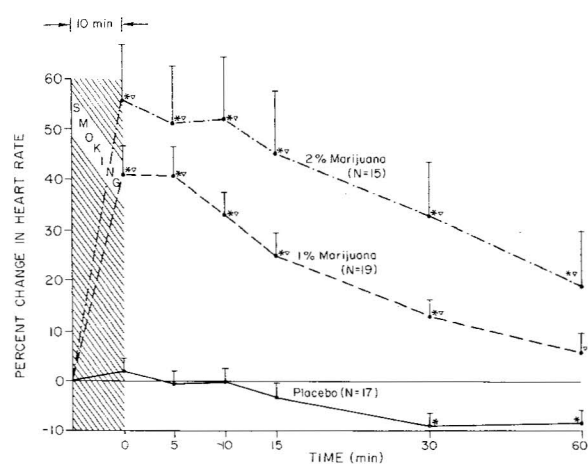


Figure 2. Heart Rate as a Function of Time after Smoking of Placebo or Natural Marijuana Containing 1 per Cent or 2 per Cent Δ^9 -Tetrahydrocannabinol.

*Statistically significant as compared with zero ($p < 0.01$).

▽ Statistically significant as compared with placebo ($p < 0.05$), with use of t-test for comparison of two means.

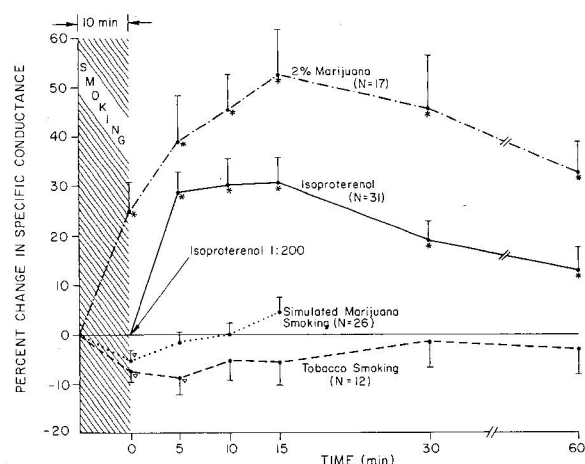


Figure 3. Specific Airway Conductance as a Function of Time after Simulated Marijuana Smoking, Tobacco Smoking and the Inhalation of 0.25 MI of Isoproterenol 1:200 (Values after Smoking of 2 per Cent Marijuana Are Shown for Comparison).

*Statistically significant as compared with zero ($p < 0.01$).

▽ Statistically significant as compared with zero ($p < 0.05$).

After 20 mg of THC, average heart rate increased more markedly at 60 to 90 minutes, showed a later and more pronounced secondary rise at five hours and was still elevated at six hours. These changes were quite variable, however, and were not significantly different from placebo with use of paired-data analysis. In contrast to the lack of temporal relation between the cardiac and bronchomotor effects of smoked marijuana, the changes in heart rate and specific conductance after

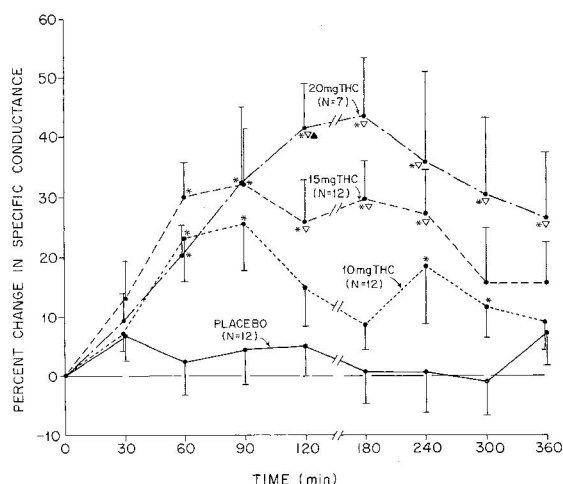


Figure 4. Specific Airway Conductance as a Function of Time after Ingestion of Placebo and of 10 Mg, 15 Mg and 20 Mg of Δ^9 -Tetrahydrocannabinol (THC) (See Text).

*Significantly different from placebo ($p < 0.05$), with use of t-test for paired observations.

▽ Significantly different from 10 mg of THC ($p < 0.05$), with use of t-test for paired observations.

▲ Significantly different from 15 mg of THC ($p < 0.05$), with use of t-test for paired observations.

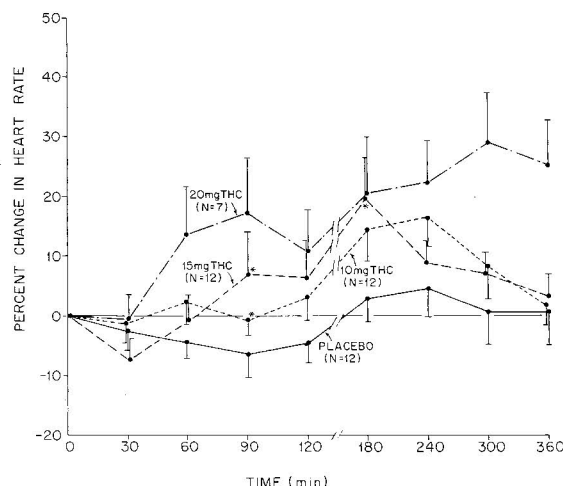


Figure 5. Heart Rate as a Function of Time after Ingestion of Placebo and of 10 Mg, 15 Mg and 20 Mg of Δ^9 -Tetrahydrocannabinol.

*Significantly different from placebo ($p < 0.05$), with use of t-test for paired observations.

oral THC were roughly parallel, except for the delayed peak increases in pulse rate after 20 mg of THC.

DISCUSSION

Our finding of a significant increase in specific airway conductance after smoked marijuana substantiates the observations of Vachon et al.³ and suggests that one or more of the volatilized cannabinoids of smoked marijuana result in dilatation of the airways. Since thoracic gas volume remained unchanged, the dilatation was due not to an increase in lung volume but rather, most probably, to relaxation of the smooth muscle of the tracheobronchial tree, although the possibility of laryngeal relaxation cannot be excluded.

The time course of changes in specific conductance was similar to that reported for the psychologic effects of smoked cannabis,³ suggesting a possible cause-and-effect relation between the effects of marijuana on the central nervous system, including psychologic effects, and the effects on bronchomotor tone. Such a relation is consistent with the presumed influence of psychologic factors on bronchomotor responses in asthma¹⁴ and the apparent efficacy of hypnosis in the treatment of bronchial asthma,¹⁵ although we are not aware of any evidence that resting bronchomotor tone in normal man may be substantially altered by changes in emotional status. Conversely, central-nervous-system and bronchial effects of marijuana may be related to entirely independent pharmacologic effects on brain tissue and bronchial smooth muscle. No data are available on possible effects of marijuana or Δ^9 -THC on isolated bronchial smooth muscle to help answer the question whether the bronchial effects observed in our study are independent of those on the central nervous system.

The temporal dissociation that we observed between the increases in specific conductance and those in heart rate after smoked marijuana is consistent with

that previously found between the marijuana-induced "high" and pulse increment.¹⁶ These temporal differences might reflect differences in concentrations of Δ^9 -THC (or its metabolites) in different tissues (brain, heart, bronchi) or differences in tissue responsiveness.

The deep-breathing maneuvers used in smoking cannabis did not contribute to the marijuana-induced bronchodilation since specific conductance did not increase during simulated marijuana smoking. In fact, these maneuvers may have partially diminished the dilator effect of cannabis since they decreased specific conductance slightly. The constrictor effect of tobacco cigarette smoking observed in our subjects has been noted previously and has been attributed to a cholinergic reflex initiated by stimulation of irritant receptors on the mucosal surface of the airways by deposited particulate material.¹⁷ It is reasonable to assume that a similar phenomenon occurs during marijuana smoking that would further blunt the dilator effect of inhaled cannabis.

The average increases in specific conductance after placebo marijuana smoking, although not statistically significant, contrast with the significant decreases in specific conductance observed after simulated marijuana and tobacco smoking. These observations suggest either that ingredients in the marijuana plant other than the cannabinoids that were extracted (Δ^9 -THC, Δ^8 -THC, cannabinal and cannabidiol) have bronchodilator properties or that a psychogenic mechanism was responsible for the airway dilatation similar to that noted in asthma.¹⁴ It is of interest that heart rate, unlike specific conductance, showed no tendency to rise after inhalation of placebo marijuana, possibly indicating the role of suggestion.

The increases in specific conductance after synthetic oral Δ^9 -THC indicate that this cannabinoid is a potent systemically active bronchodilator with a long duration of action (at least six hours for the 20-mg dose). The dilatation was not due to an increase in lung volume since it was accompanied by an actual reduction in thoracic gas volume. The mechanism for the slight but significant decrease in lung volume after oral THC is not clear. The time course of the bronchodilator effect was roughly similar to that reported for both the psychologic effects and plasma levels of Δ^9 -THC after oral administration of the drug.¹⁸ The delay in onset of bronchodilator effect (one hour) paralleled that of the tachycardia and is consistent with a delay in absorption of the drug from the gastrointestinal tract. The occurrence of a second peak increase in specific conductance at 180 and 240 minutes after 15 and 10 mg of THC, respectively, may have been due to enhanced intestinal absorption of the drug after lunch.

The significantly greater bronchodilator effect with increasing oral doses of Δ^9 -THC indicates that the drug has an easily titratable pharmacologic action, and is more consistent with a direct effect on bronchial smooth muscle than with one mediated indirectly via the emotional "high."

In summary, our results suggest that, in healthy

young men, both smoked marijuana and oral Δ^9 -THC cause significant dilatation of the airways lasting as long as 60 minutes and six hours, respectively. The dilatation after smoked marijuana is not due to the deep-inhalation smoking technic, contrasts sharply with the constriction that follows cigarette smoking, and is greater in magnitude than that after inhalation of therapeutic doses of isoproterenol. A dose-response relation was suggested for smoked marijuana and demonstrated for oral THC.

Further investigation is required to determine the site and mechanism of cannabis-induced airway dilatation, possible differences in the response of the airways of inexperienced and experienced marijuana smokers and the effects of marijuana smoking and oral Δ^9 -THC on the airways of asthmatic subjects. In addition, possible bronchodilator effectiveness of cannabinoids other than Δ^9 -THC should be investigated.

In our study, we investigated the acute physiologic effects of smoked unadulterated marijuana containing two standardized doses of Δ^9 -THC on the airways of healthy young men with normal pulmonary function. Our results do not preclude the development of bronchitis or aggravation of existing bronchitis from possible irritating effects on the airways of chronic marijuana smoking, acute marijuana smoking in patients with established airways disease or the smoking of adulterated preparations.

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INDICATIONS OF THE THYMUS-DERIVED NATURE OF THE PROLIFERATING CELLS IN SIX PATIENTS WITH SÉZARY'S SYNDROME

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Abstract The Sézary syndrome consists of erythroderma, lymphadenopathy and abnormal mononuclear leukocytes. In four of six patients with this syndrome, the abnormal cells were smaller than the classic large Sézary cell. The membrane properties of circulating abnormal cells, studied by conventional stains, electron microscopy, cytogenetic analysis, immunofluorescence, and rosette formation, manifested similar ultrastructural and chromosomal characteristics whether the cells

were large or small. The abnormal cells were devoid of membrane-bound immunoglobulin detectable by immunofluorescence, did not bind aggregated human IgG, were able to form spontaneous rosettes with sheep erythrocytes and, in the three patients studied, were killed by a specific rabbit antihuman T-cell antiserum. These findings indicate that these cells are related to thymus-derived lymphocytes. (*N Engl J Med* 289:341-344, 1973)

THE Sézary syndrome is characterized by generalized pruritic and pigmented erythroderma, lymphadenopathy and the presence of abnormal leukocytes in the skin infiltrates and in the peripheral blood.^{1,2} Ultrastructural studies of the classic large Sézary cells showed that their main feature was the cerebriform and serpentine aspect of the nucleus.³ Abnormal karyotypes with polyploidy and heteroploidy and with marker chromosomes were documented by cytogenetic studies of these cells.^{4,5} A "small cell variant" of the Sézary syndrome was recently described, these abnormal cells being featured by indented nuclei, hyperdiploidy or pseudodiploidy with marker chromosomes.⁵ Whether Sézary cells belong to the lymphocytic or to the monocytic series has been much disputed in the past. The results of recent studies are strongly in favor of their lymphoid nature.^{4,5}

It is generally agreed that human and animal lymphoid cells belong to two major populations: the bursa-derived or bone-marrow-derived (B) lymphocytes and the thymus-dependent (T) lymphocytes. These B and T populations can be distinguished by cytoplasmic membrane markers. Membrane-associated immunoglobulins detectable by rather insensitive methods such as direct immunofluorescence,^{6,7} the receptor for antigen-antibody complement complexes⁸ and the ability to bind heat-aggregated human IgG^{9,10} have been shown to be B-cell markers in man. On the other hand the spontaneous formation of rosettes with sheep erythrocytes under specific conditions¹¹ appears to be a characteristic (though unexplained) property of

human T lymphocytes.¹²⁻¹⁴ T-cell-specific heteroantisera recently became available in some laboratories.¹⁵⁻¹⁷ These markers have been used to classify lymphoproliferative diseases on the basis of the type of cells involved. This classification may be of considerable clinical and etiologic interest. Reports from several laboratories have indicated that chronic lymphocytic leukemia is usually identifiable as a B-cell neoplasia.^{7,18-24} Moreover, the study of surface Ig has led most^{18,20,22,23} but not all^{19,24} investigators to the notion that this B-cell proliferation is presumably of a monoclonal nature.

In a previous study from our laboratory the Sézary cells from three patients were shown to be devoid of membrane-bound Ig, suggesting their possible thymic-derived origin.²⁵ The results of our further cellular studies performed on six other patients confirm this hypothesis.

PATIENTS

The 6 patients were 50 to 80 years old. All had a history of generalized erythroderma with pruritus and lymphadenopathy for 2 to 4 years. Skin biopsies showed the classic features of the Sézary syndrome. Two patients had never been treated. The 4 other patients had been given various therapeutic regimens but had had no treatment for more than 3 months at the time of the study. Hematologic data are summarized in Table 1.

METHODS

Peripheral blood and bone-marrow smears were stained with Wright-Giemsa and periodic acid-Schiff reagents and for peroxidase monocytic specific esterases and β glucuronidase.

For electron microscopy buffy-coat pellets were fixed in glutaraldehyde, post fixed in 1.25 per cent osmium tetroxide for ½ hour, embedded in Epon No. 812 and stained with uranyl acetate.

Cytogenetic analyses (kindly performed by Dr. I. Emerit) were obtained on phytohemagglutinin-stimulated peripheral cells after 3 to 4 days' culture.

Membrane-bound Ig samples were studied by direct immunofluorescence, with alternative examination under phase contrast. Rabbit

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