Chapter 8

THE BRONCHODILATOR ACTION OF CANNABINOIDS

James D. P. Graham

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I. INTRODUCTION

Delta-nine-*trans*-tetrahydrocannabinol (Δ^9- or Δ^1-THC according to the numeration preferred) is an active bronchodilator. Its mode of action, though not fully elucidated, differs from that of the commonly used sympathomimetic medicaments such as salbutamol and terbutaline. It is, at the least, an adjuvant to customary therapy, which deserves more interest and usage than has so far been accorded to it.[1] THC being a principle active ingredient of the unique plant *Cannabis sativa* L., it is not surprising that this activity has been noted after ingestion of the raw material or inhalation of smoke from it. Cannabis, as a bronchodilator, is at present undergoing reevaluation and development.

II. ROUTES OF ADMINISTRATION

A. Ingestion

As a route for therapeutic administration ingestion may be ruled out at present as a consequence of variation in the rates and extent of absorption.[2] This difficulty probably accounts for reported failures to achieve worthwhile relief of reversible airway obstruction after oral administration.[3] In a carefully conducted trial on 16 patients in a stable condition,[4] comparison was made between placebo, 4 mg of salbutamol, and 2.5 and 10 mg of Δ^9-tetrahydrocannabinol (Δ^9-THC) administered in a Latin square design, the drugs being dissolved in ethanol and added to licorice extract immediately before swallowing. The results indicated that THC was not an effective oral bronchodilator. THC, however, is usually given orally as a capsule containing the drug dissolved in olive or sesame oil. In effective doses it is apt to cause psychic disturbance.

B. Intravenous Route

THC has been administered intravenously (i.v.) dissolved in ethanol and diluted to 10% with sterile human plasma,[5,6] but there is no need in the treatment of bronchoconstriction for such a technique, and psychic disturbance is likely to occur. The sophisticated study by Smith and Kulp[7] in which the patients breathed gas-oxygen-carbon dioxide mixtures from a recycling spirometer enabled the experimenters to keep the pressure of end tidal CO_2 in the lungs constant, while they recorded the effect of i.v. drugs on several measures of lung function. A plot relating bronchodilator response to log· dose increments of Δ^9-THC, cumulative and ranging from 27 to 201 μg/kg weight was recorded. THC given in this manner depressed respiration without altering the breathing pattern, and increased heart rate, cardiac output, and arterial pressure, but decreased venous pressure.

C. Inhalation

Equally as speedy as i.v. administration in onset and as effective is absorption from the pulmonary surfaces, which may be attained by the inhalation of smoked marijuana or Cannabis resin (hashish), mixed with tobacco, or THC dissolved in alcohol or other solvent and applied to tobacco, or pure Δ^9-THC in a solvent in aerosol form.[8,9] Smoke, even if it provides relief, is not a preferred vehicle for asthmatics, who have usually abandoned tobacco if they ever acquired the habit. It contains noxious gases and irritant particles and is liable to arouse initial coughing or constriction,[10] which may distress the patient, but not sensitize the bronchus to inhaled histamine.[11]

III. DEFINITIONS

The terms most frequently used in this section to describe measures of respiratory

function are as follows: *tidal volume* (TV), the volume of air moving in and out per respiration, as measured by a spirometer. *Functional residual capacity* (FRC), the combined volume of expiratory reserve and residual air. *Forced vital capacity* (FVC), the volume of maximal expiration after peak inspiration. *Flow rate*, the forced expiratory volume in 1 second of time (FEV 1.0) usually recorded in mid flow. The *peak expiratory flow rate* (PEFR) is measured with a device such as Wright's Peak Flow Meter, but maximum expiratory flow rate at 50% of *vital capacity* (VC) (MEF_{50} or MMFR) or other selected level (25 to 75% VC) may be more informative. These measures are for the most part relatively simple to make, but to measure *airways resistance* (R_{aw}) or its reciprocal (G_{aw}), or better still, the latter corrected for *thoracic gas volume* (V_{tg}), is more complex; it requires a measurement of alveolar pressure, flow rates, and the use of a whole-body plethysmograph. Nevertheless there are a considerable number of records of this nature and they increase. Gaseous interchange is measured by administering carbon monoxide (CO) and calculating its transfer, (T_{co}) from alveolar pressure, and CO concentration over time.

IV. ACTIONS

A. Herbal Cannabis, Marijuana

Inhalation of smoke from a cigarette made from marijuana (M) decreases airways resistance (increases conductance) in normal male volunteers[12,13] or in subjects in whom constriction was induced by exercise or by inhalation of an aerosol of methachol.[14] In the U.S. a standard product of predetermined weight and strength and a cannabinoid-free preparation for control purposes are supplied to bona fide research workers by NIDA. There are two principal drawbacks to this method as a route for therapy. In the long term it may aggravate any underlying lung pathology. Tashkin et al.[14] found the measures of lung function, FEV1, PEFR50, etc., conductance and diffusing capacity, reduced in 28 apparently healthy experienced males who were tested before and after *ad lib* smoking of M cigarettes at 2.2% THC strength for 47 to 59 days. In normally healthy subjects smoking M has no deleterious effect on oxygen uptake during exercise,[15] but habitual smoking of cannabis has been known to adversely affect lung physiology to a small but appreciable degree,[16-19] and to induce catarrh.[20]

To quote from the opinion of an experienced lung physician,[21] "There are considerable difficulties in assessing the potential hazards and benefits of cannabis. These include (in human studies), failure to control the pattern of breathing,[22] and frequently absence of measurement of carboxy haemoglobin." This criticism does not apply to the study made by Vachon et al.,[23] which is important in that it clearly established a dose-response relation between broncho-dilatation at low vital capacity (V_{max} 25), which is believed to detect and display any effects on bronchi of small caliber, which are early affected on the onset of bronchitis and asthma, and the THC content of the M preparation. The difference between the effects of the two dose levels could be seen in the maximum expiratory flow rates at 25% of lung volume. The reported studies confirm the principal finding of dilation.[24] Comparison of the effect of M smoke with oral THC in groups, each of seven subjects, revealed no differences between the sexes in this respect.[25] Marijuana of 2% THC smoked, and Δ^9-THC 15 mg orally, both increased conductance for a period of more than 2 hr; the dilator effect of M lasted longer than that of isoprenaline. An attempt (made elsewhere) with five stable patients assessed oral THC as less reliable than oral salbutamol,[26] but failed to demonstrate significant bronchodilation with an aqueous aerosol of Δ^9-THC, which was probably inactive for reasons of poor miscibility and solubility in the preparation used at that time.

B. Δ^9-Tetrahydrocannabinol

By the middle of the 1970s it had become obvious that Δ^9-THC was not merely the psychoactive principle in cannabis but that it was the most likely bronchodilator component. Since the pure material was now available, albeit in small quantities, as a consequence of the work of Mechoulam and colleagues, it was increasingly put to the test by inhalation of an aerosol. Vachon et al.[27,28] used propylene glycol vehicle delivered through a nebulizer in a dose of 0.5 mg THC at a concentration of 1.25%. They found the bronchodilator effect slower in onset than that of isoprenaline but longer lasting, and made no mention in this report of troublesome coughing or constriction. Tachycardia, euphoria, and increased airways conductance noted after relatively high doses were held by the authors to manifest in parallel, a concept which is the subject of some controversy, but supported by Tashkin and colleagues[29] again after administering high doses (5 to 20 mg) of THC. The second study of this series was carried out on seven volunteers in a complex cross-over design, testing every 2nd day. The full range of parameters (FVC, FEV1, MMFR, R_{aw}, conductance and DL_{co}) was recorded, but side effects were encountered which complicated the efficacy. They reported a prolonged tachycardia which they attributed to swallowing of the aerosol solution. The smallest dose (5 mg) brought about increased airways conductance for 5 hr. The work was repeated on 11 healthy males and 5 asthmatic patients.[30] The expected increase in conductance duly occurred, peaking after 1 to 2 hr and persisting for a further 3 hr, but again the dosage was high, all doses of Δ^9-THC producing a comparable maximal dilatation. This time the THC was dissolved in freon as a solvent and pressurizing agent. Three of the normal subjects and two of the asthmatics experienced irritation of the trachea and coughed initially. The considerable efficacy of Δ^9-THC, delivered as a metered dose-volume from a standard "Medihaler", with which patients are all too familiar, was perhaps first recognized during 1976,[9] when the effect of placebo solvent, 200 μg of Δ^9-THC and 100 μg of salbutamol, delivered in a fixed volume of 63 $\mu\ell$ freon per inhalation, was tested in a double-blind trial on ten patients in a stable condition. The standard clinical measures of FEV1, FVC, PFR, HR, and BP were recorded, and additionally plasma level of cross-reacting cannabinoid were determined by radioimmunoassay.[31] At these doses, salbutamol was quicker in onset, the drugs were equiactive after 1 hr, (see Figure 1) and the effect of THC persisted longer. There were no alterations in the pulse or psyche, but occasional irritation on first inhaling was noted. A repeat test on five male patients,[32] using a graded dose of 50 to 200 μg suggested that the lesser dose of 100 μg given as two successive inhalations each of 50 μg might be optimal with minimal irritation. There the matter rests until widespread application determines the best conditions of use of this neglected drug.

Gong et al. [32a] have evaluated the oral activity of several cannabinoids, viz., Δ^9-THC, Δ^8-THC, cannabinol (CBN), and cannabidiol (CBD), in healthy experienced male volunteers who smoked marijuana; diazepam was included in the study as a control psychoactive drug. They confirmed the bronchodilator activity of Δ^9-THC 20 mg orally, accompanied by tachycardia and some psychic disturbance, and a comparable dose-related bronchodilator action of Δ^8-THC in doses of 50 mg and 75 mg with much less cardiovascular or psychic effect. CBN and CBD in doses of 1200 mg were inactive. A study with combinations of low dose Δ^9-THC (5 mg) and CBN or CBD (400 mg) confirmed a previous report [32b] that CBD reduces the vascular and psychic effects of THC; but no interaction on bronchodilation was observed. Twenty-day administration of 20 mg Δ^9-THC orally (20 mg), CBN (600 mg), or CBD (1200 mg) produced no evidence of clinical tolerance to any of the actions of THC.

C. Synthetic Cannabinoids

Little has been done to investigate possible bronchodilator activity in the other prin-

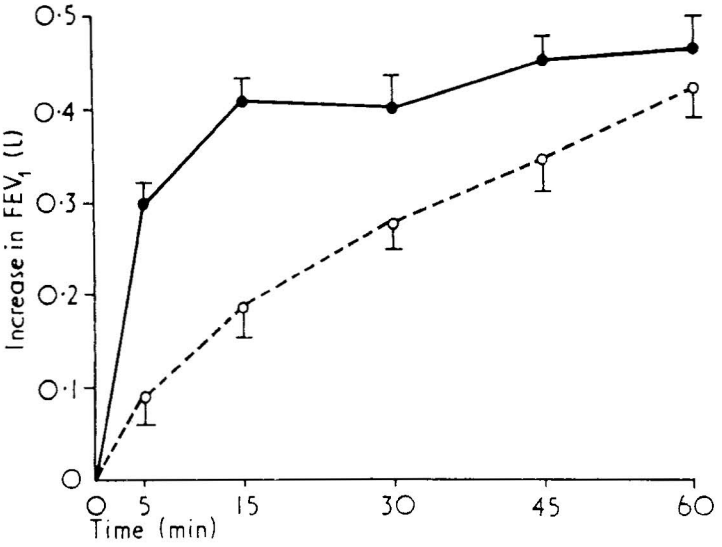

FIGURE 1. Comparison of the bronchodilator effect (increased FEV1) with time of 100 μg salbutamol (●) and 200 μg of Δ^1-THC (O) inhaled as a metered dose of aerosol in ten asthmatic subjects, double-blind with placebo control. (From Williams, S. J., Hartley, J. P. R., and Graham, J. D. P., *Thorax*, 31, 720, 1976. With permission.)

cipal cannabinoids. If parallelism with psychoactivity is essential, they would be expected to be of less interest. An early outcome of the pioneering efforts of the Adams-Todd schools on cannabis chemistry was the production of $\Delta^{6a\cdot10a}$-THC. The *n*-hexyl analog of this synthetic cannabinoid (Synhexyl, U.S., Pyrahexyl, U.K.) and the dimethylheptyl analog (DMHP) were compared with Δ^9-THC, orally in man, in 1968,[33] but only behavioral and cardiovascular effects were noted. Intravenous administration of 2.86 μg of DMHP per kilogram weight to three healthy subjects was reported as causing tachycardia and postural hypotension,[34] but again there is no mention of lung function studies. Not until the recent development of synthetic cannabinoids has interest in the matter been tentatively resumed. Nabilone,[35] a keto derivative of the cannabinoid skeleton, is a weak depressant of central nervous activity, which gives rise to postural hypotension and tachycardia. Preliminary tests with 2 mg orally produced a modest degree of bronchodilatation in healthy subjects but no similar effect in asthmatic patients. In the control subjects, conductance was increased to half the extent given by 4 mg of terbutaline orally. No attempt to explore this activity by inhalation of aerosol has been reported.

V. MECHANISM OF ACTION

There is no agreement as to the mode of action of bronchodilator cannabinoids, nor need there be but one. Many highly specific directly acting drugs are held to exert their effects by occupancy of a "receptor" (i.e., a binding site) which, when so engaged, activates a train of reactions which culminate in a detectible response. The proof of existence of such a mechanism demands a high degree of activity or even uniqueness of action in the agonist, and knowledge of an antagonist or "blocking" drug equally precise. Other active drug substances, such as steroids and prostaglandins, exert a multiplicity of effects but have no clearly understood single mode of action. Tetrahydrocannabinol and its congeners are of this sort. They exert many actions but there are

few convincing explanations; for example, an examination of the effects of THC, morphine, and the synthetic cannabinoids nabilone and nantradol demonstrated certain common responses in tests of the reflexes of the chronic spinal dog,[36] but the highly specific and potent morphine antagonist naloxone abolished the effects of the opioid but not of the cannabinoid. Since it is believed that morphine occupies specific receptors in the nervous system and in smooth muscle, the conclusion is made that THC does not act by occupying these same receptors, and that it must have a different site and mode of action despite the commonalty of effect. It has been maintained that both herbal cannabis (marijuana) and Δ^9-THC act chiefly on the larger airways.[37] This attempt to localize the site of action may be more directly related to the techniques of measurement of lung parameters (e.g., whole-body plethysmography) as compared with spirometer studies than to any fundamental truth. The bronchus of greater than 2-mm cross-section has an innervation from the autonomic pulmonary distribution, cholinergic bronchoconstrictor, and adrenergic bronchodilator. If the section of the bronchial tree which is primarily acted upon by cannabis is that innervated by the autonomic nervous system, M smoke, or THC aerosol could exert its effect peripherally by stimulating or depressing one or another branch, vagal or sympathetic; by modulating release of the neurotransmitter; by receptor blockade; or by initiation of reflexes or other mechanisms, including central action. These possibilities have been more or less explored and several have aroused interest and controversy. Tests have been carried out on isolated tracheal or bronchial fragments and on intact models of animal and man. The smoke of marijuana differs in many ways from Δ^9-THC delivered in a solvent aerosol.[10] Herbal cannabis contains compounds which exert an atropine-like effect, but they are few and weak and it is not likely that they play a significant part in the bronchodilator action. Atropine, in a dose which prevents the bronchoconstrictor action of inhaled methachol, brings no relief in postexercise asthma,[38] whereas THC and M smoke do. It is clear that Δ^9-THC is not an antagonist of acetylcholine (ACh) on smooth muscle receptors,[39,40] but it may be of significance that it reduces the output of transmitter ACh from cholinergic autonomic fibers in the intestinal smooth muscle of the guinea pig.[41-43] If this mechanism applies to bronchial muscle, THC could be expected to reduce constriction in normal animals and humans, as has been shown to occur. Not all physiologists believe that cholinergic activity is a prime determinant of bronchial tone, but most are agreed that sympathetic activity and sympathomimetic medication can affect bronchial caliber. There is evidence that Δ^9-THC depletes peripheral adrenergic nerve[44] or lung tissue[45] of its transmitter. If rat vas deferens, a smooth muscle, is equilibrated with tritiated norepinephrine (NA) there is a steady "overflow" into the biophase in which the muscle is suspended; electrical field stimulation causes mechanical contraction and a surge in the "overflow". Pretreatment with Δ^9-THC at 2.8 μM decreases this "release". In clinical practice this blocking action, which would favor constriction of the bronchus cannot be of importance because Δ^9-THC is an effective bronchodilator; either the effect on cholinergic nerve is dominant or there is a different explanation. Bronchial muscle relaxation brought about by administration of isoprenaline or other sympathomimetic agent is antagonized by a beta adrenoceptor blocker but not by THC,[4] which therefore does not occupy this receptor system (see Figure 2). By way of contrast, other workers,[46-48] one of whom used isolated rings of human bronchus, report considerable activity of propranolol against THC-induced bronhial relaxation. Shapiro et al.[1,49] found in volunteer male subjects that smoking a 1-g marijuana cigarette of 1 or 2% THC strength caused after 15 min an increase in airways conductance of 55 ± 6% which persisted for 1 hr; heart rate increased in parallel. Intravenous propranolol, unfortunately not shown directly to be sufficient to antagonize the effects of inhaled sympathomimetic but at a dose of 0.25 mg/kg wt considered to be adequate, did not reduce the bronchodilator

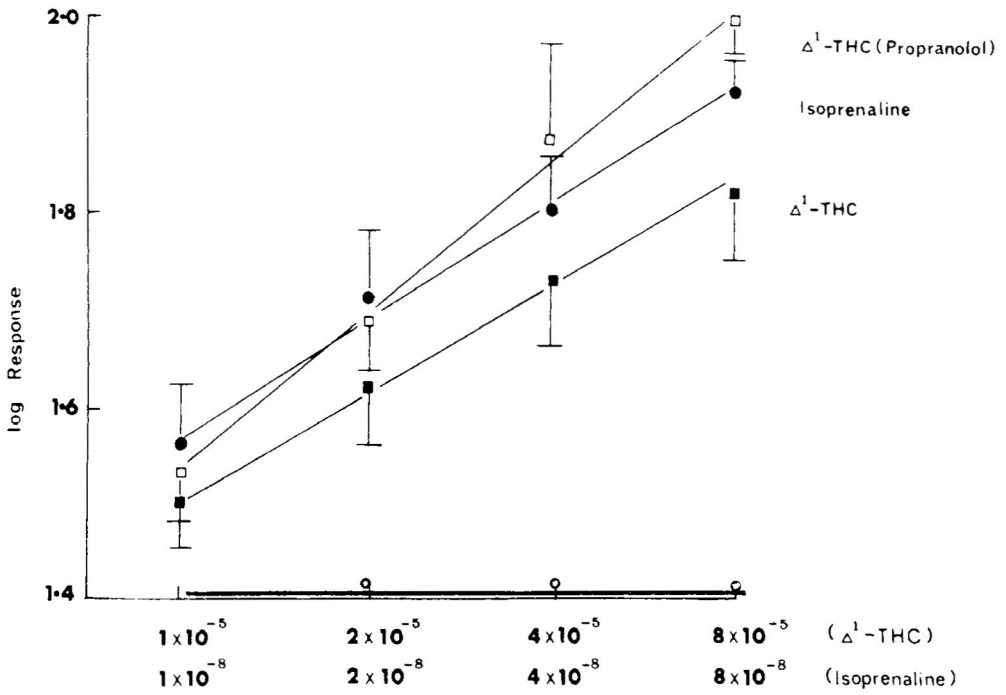

FIGURE 2. Isolated tracheal smooth muscle of guinea pig. Dose-response to isoprenaline before (●) and after (○), and to Δ¹-THC before (■) and after (□) propranolol (2 μg per mℓ). The spasmolytic effect of isoprenaline is abolished by the beta blocker, while that of THC is unaffected. Horizontal axis, drug concentrations; vertical axis, inhibition of relaxation as percent of maximum on log scale. (From Davies, B. H., et al., *Thorax*, 30, 83, 1975. With permission.)

action of a repeat inhalation of M smoke which now caused an increase of 67 ± 17%. This test was repeated on 11 volunteers using smoked placebo or marijuana which contained 10 mg of THC and propranolol i.v. in a dose of 0.2 mg/kg. The same persisting dilatation was recorded.

The observation that cannabinoid may in some circumstances act as an inhibitor of monoamine oxidase is not relevant. This enzyme system plays a minimal part in the inactivation of transmitter norepinephrine. There are conflicting reports as to whether or not THC is a significant central stimulant of the sympathetic outflow. Such a mechanism has been suggested on the basis of animal experimentation, but since a vigorous bronchodilatation can be demonstrated in healthy subjects who inhale 200 μg of Δ⁹-THC in aerosol with no consequent tachycardia or detectable plasma cannabinoid level,[9] this can play only a small part if any.

Despite discrepancies in the in vitro work and the reports that propranolol prevents the tachycardia and intoxication which follows the smoking of cannabis,[50-55] it seems clear that the prime site of action of THC as a bronchodilator is not on the sympathetic autonomic nerve. The most common variety of clinical bronchospasm, extrinsic asthma, is caused by inhalation of allergen. These substances provoke the release of antibody (IGE) which binds to cell membrane. In the lung there are great numbers of mast cells. When an excess of IGE on the surface is bridged by antigen the mast cell is disrupted and releases histamine (H), arachidonic acid, high-molecular-weight neutrophil chemostatic factor (HMWNCF), slow reacting substance of anaphylaxis (SRS-A), etc.[56]

It has long been known that a variety of electrolytes, H, PG, SRS-A, bradykinin,

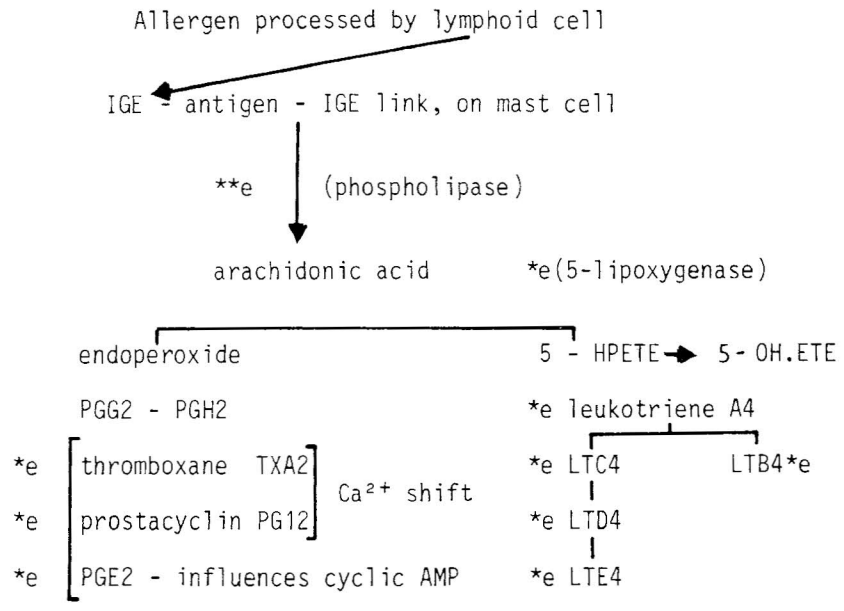

FIGURE 3. Cannabinoid releases arachidonic acid from tissue cells and inhibits the synthesis of generic prostaglandin. It may affect one or all of the enzymatically determined steps (e*) thus reducing the production or release of leukotrienes.

etc., are spasmogenic when tested on smooth muscle from intestine or bronchus; THC or nabilone fail to abolish spasm caused by some or many of these spasmogens. Burstein reported[57-59] an inhibitory action of THC on the conversion of precursor arachidonic acid to generic PG, and suggested that this was a mechanism fundamental to the action of THC (see Figure 3). A marked release of PG-like material has been reported on addition of Δ^9-THC to a guinea pig lung model.[60] This effect is suppressed by substances which inhibit the enzyme lipooxygenase, which is involved in the metabolism of arachidonic acid.[61] THC is not an aspirin[62] and work is now appearing on the interactions of indomethacin or aspirin which inhibit PG synthesis, or tranylcypromine which inhibits the production of thromboxane. If Δ^9-THC affects one or more of the enzyme-driven stages in the endoperoxide chain of metabolism of arachidonic acid it could alter the balance of thromboxane and prostacyclin, which (as is known only for their effect on platelet aggregation and vascular tone) exert opposing effects. Cannabinoids, including the precursor olivetol, modify the production of PG which in turn modulates cyclic AMP, the core biochemical mechanism which regulates the response to sympathetic nervous activity. There are barriers to the acceptance of this speculation in that olivetol, the relatively psychoinactive cannabinoid precursor, is in this respect more active than Δ^9-THC. Probably more directly involved in bronchospasm are the recently discovered hydroperoxide metabolites.[63-67] Arachidonic acid is converted by 5-lipoxygenase to 5-hydroperoxyeicosatetetraenoic acid (5-HPTE), which spontaneously converts to 5-OH ETE or enzymatically to leukotriene LTA4. Further degradation leads to the powerfully bronchoconstrictor substance LTB4 or by conjugation with glutathione to LTC4 which can degrade further to LTD4 and LTE4. These substances form a part of SRS-A and probably largely account for its constrictor activity. Nothing is known as yet on their precise mode of action in initiating contraction of bronchial muscle. THC may prevent their synthesis or release rather than antagonize their action.

A substance which has a steroidal quality to its structure, high lipid solubility which ensures ready penetration of barrier membranes, and marked lability in the channels

of its metabolism is likely to exert a nonspecific and ubiquitous spectrum of actions — a secondary rather than a prime mover in this respect.

VI. FUTURE PROSPECTS

A great deal of time and effort has been devoted to researching minor toxicological problems, many of them of doubtful significance to the therapeutic or social uses of this drug, but little exploration has been carried out in relation to respiratory function. Before the small advances made so far can be consolidated it is desirable to confirm and explain the empirical clinical findings with more and controlled experiments. There is particular need to make use of a nonpsychoactive cannabinoid as control. This necessary work has been truncated by recent financial stringency in the area of medical science and constrained by the necessity for research workers to conform with tight security requirements. The greater part of exploratory work therefore remains to be done; hence the following brief outline of what seems most urgent and needed.

A. Pharmacological

It is necessary to explore and establish improved animal models of bronchial reactivity, initially based on the classical techniques but modified by improved technology. Having selected a technique which gives meaningful and reproducible measurements with minimal internal variation it should be possible to demonstrate and compare quantitatively the effects of a selection of natural and synthetic cannabinoids on inherent tone in normal and sensitized bronchus.

Having demonstrated the bronchodilator activity of the cannabinoids and the parameters for optimal activity, which may explain the discrepancies noted above, it should be possible to distinguish the relative importance of the spasmogens believed to be released from mast cells (H, SRS-A, LTA4, etc.) and the autonomic factors in bronchospasm, and to explore possible inhibition of production and release or antagonism to a wide range of these spasmogens, and for several important or relevant spasmogens to quantitate the relation of sympathomimetics (e.g., isoprenaline, terbutaline, and salbutamol) in antagonizing these spasms and the relation of beta blocking drugs and other antagonists to that activity.

These trials should be repeated with a range of concentrations of a variety of the cannabinoids to determine whether they prevent spasm due to one or the other of the agonists, or if they relax established spasm, modify the action of the preferred sympathomimetics, or are affected in any way by specific receptor blockers.

B. Biochemical

It should be of importance to repeat the classical work on the inhibition of PG synthesis with indomethacin and tranylcypramine controls, and to test the effect of at least one active cannabinoid on the metabolism of arachidonic acid to leukotrienes.

C. Clinical

It is necessary first to establish the techniques best suited to the capability of the particular clinical laboratory. Effects which can be clearly established by the methods most commonly used by respiratory physicians are more likely to affect therapeutic practice than more sophisticated tests which can only be carried out at a few centers.

The effects of inhaled terbutaline or salbutamol should be compared with a range of doses of selected cannabinoids, natural and synthetic, in normal volunteers of both sexes and several age groups.

Inhalation of 50 to 200 μg Δ^9-THC is effective. The preparation of a suitable metered dose freon aerosol has been reported[9] with a drug-free sample serving as control. These

tests should be repeated on a small group of volunteer patients who suffer from chronic bronchial constriction and who are in a stable state on minimal medication which should be maintained. If the in vitro tests prove encouraging THC-leukotriene antagonism could be explored.

VII. CONCLUSION

It may be that the search for a highly active cannabinoid-related compound not subject to control by law will be a prolonged one. There is no reason to delay further exploration of the established efficacy of Δ^9-THC despite a few drawbacks. Statutory authorities should be requested to lift restrictions from aerosol preparations of not greater strength than 100 μg per metered dose. Such a preparation is not likely to be attractive to drug misusers, whereas it would benefit sufferers from asthma as a standby drug. The fact that the mechanism of action differs from that of the established therapies greatly enhances its attraction and justifies its promotion.[1]

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