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THEORETICAL REVIEW

Marihuana and the Cardiovascular System

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CLARK, S. C. *Marihuana and the cardiovascular system.* PHARMAC. BIOCHEM. BEHAV. 3(2) 299–306, 1975. – The actions of marihuana on the cardiovascular system in man are the most consistent physiological effects produced by acute administration. Significant tachycardia and conjunctival injection are well established effects. When the subject is upright, marihuana produces a fall in blood pressure; however, either no significant effect or a slight increase in blood pressure occurs when the subject is supine. Marihuana has been reported to increase limb blood flow and produce no significant effect on electrocardiogram of normal subjects. It, however, interferes with the integrity of peripheral vascular reflex responses. Although the detailed mechanism of action has not been elucidated, there is evidence that marihuana produces both sympathetic nervous system stimulation and parasympathetic nervous system blockade. No data are available that indicate the acute administration of marihuana presents a significant hazard to the cardiovascular system of normal subjects.

Marihuana Cannabis Δ^9-Tetrahydrocannabinol Cardiovascular system

DESPITE the current interest and controversy regarding marihuana, it has been known to man for many centuries. Obtained from the herbaceous annual plant *Cannabis sativa L.* [56], it is in fact one of man's oldest cultivated non-food plants. The first detailed description of cannabis is often said to have appeared in a medical book prepared by the legendary Chinese Emperor, Shen Nung (circa 2700 B.C.). This pharmacy treatise was probably written by early Han dynasty scholars only a few centuries B.C. However, archaeological data suggest that knowledge of the use of cannabis for various purposes goes back at least 6,000 years [40,42].

The history of the medical uses of cannabis has been recently reviewed in *Marihuana and Health*, a Report to Congress from the Secretary, U.S. Department of Health, Education and Welfare [47]. This Report agrees with others [8,40] that in North America there is now no currently accepted medical use of cannabis outside of an experimental context. There was a time, however, when extracts of cannabis were as commonly used for medicinal purposes as aspirin is today [47]. In the 19th century the drug was widely prescribed in the Western world for various ailments and discomforts, such as coughing, fatigue, rheumatism, asthma, delirium tremens, migraine headaches, and painful menstruation [21, 40, 47]. Although its use was already declining somewhat because of the introduction of synthetic hypnotics and analgesics, it remained in the *U.S. Pharmacopoeia* until 1937.

Because of an increasing social concern regarding the use of marihuana a number of experimental studies were undertaken during the 1930's. The results of the 1933 Panama Canal Zone Study [58] and the 1944 Mayor's Report from New York City [1] will be discussed further below. It is interesting to note how extensive these studies were and that regardless of the many methodological limitations, much of the more recent work has confirmed findings that were at least suggested in these early studies.

Because of changes in the attitudes towards cannabis and the laws governing its use, following these studies there was a prolonged period in which research was almost totally discontinued. During the 1930's the U.S. Federal Bureau of Narcotics (since renamed the Bureau of Narcotics and Dangerous Drugs) initiated an educational campaign that resulted in considerable distortion and misinformation about the drug [21]. With the subsequent passage of the *Marihuana Tax Act* in the U.S. in 1937 and an amendment in 1938 to the *Opium and Narcotic Act* in Canada, medical and intoxicant uses of cannabis in these two countries were banned.

Although numerous studies of marihuana have been

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undertaken in the past several years, as pointed out in 1968 by Weil *et al.* [64], and emphasized in detail in a recent article by Klonoff [39], research on marihuana is still fraught with a large number of legal and attitudinal hurdles and obstacles. The Canadian Le Dain Commission [40] recognized these frustrations and further noted that since the widespread and middle-class use of cannabis in North America is a relatively recent phenomenon, it has not, in the past, been considered a particularly high priority research area from a public health standpoint.

During the 1950's, however, the United States Army found the synthetic derivatives of cannabis of sufficient interest to warrant considerable investigation. Recently declassified studies suggest that these drugs possess a variety of potentially valuable therapeutic properties [11, 24, 25, 40]. Published reports emphasize the drug's low toxicity and suggest that the use of marihuana be examined in the treatment of fever, pain, epilepsy, migraine headaches, high blood pressure and psychoses.

At this point in time, it seems essential to establish what the pharmacological effects of cannabis are, even though clinical usage will be dependent upon the development of analogues which dissociate the psychological effect from other pharmacological effects.

Bicher and Mechoulam [7] have shown that in mice and rabbits, intraperitoneal injection of 20 mg/kg of Δ^9-THC was equivalent in analgesic activity to that of 10 mg/kg of morphine sulphate injected subcutaneously. They suggest that Δ^9-THC or related compounds could find use as potential non-addictive analgesics. No clinical confirmation of these results have been published, although they have been confirmed by additional animal studies [20].

Other non-clinical studies have suggested that cannabis may have antibiotic properties [22, 51] or be effective in the treatment of hypertension [25]. Clinical observations, while incomplete, indicate potential value in the treatment of glaucoma [26], in the treatment of alcoholism [8, 21, 47] and as an appetite stimulant [21].

Hollister [27], although not particularly optimistic that marihuana will ultimately have any significant therapeutic value, notes that attempts reasonably could be made to exploit therapeutically the sedative-hypnotic action.

As tantalizing as such observations are, in general, one would have to agree with the Le Dain Commission [40] that "many of the alleged therapeutic properties of marihuana and its derivatives have not been thoroughly studied in a modern scientific and clinical context and their general medical potential still remains a matter of conjecture". Obviously much remains to be done.

CARDIOVASCULAR EFFECTS

It has been known for many years that the acute administration of cannabis is associated with cardiovascular effects. It seems pertinent to review what is known of these effects since the drug is widely used by individuals, at least some of whom have coexisting heart disease.

Animal data are difficult to interpret. One is interested in obtaining data which can be extrapolated to man. Yet, how does one establish with a psychotropic drug whether there are major species differences? How does one find, in an animal and in man, common endpoints for establishing comparative doses? How does one solve problems of solubilization of cannabis products or of routes of administration, so that the data are relevant to the inhalation of marihuana smoke by man?

Most animal studies are concerned with administration of very large doses of Δ^9-THC. Even though problems of solubilization and of routes of administration frequently make one suspect that the effective dose received was much less than the administered dose; nevertheless, many of the results may represent toxic rather than pharmacological responses.

Then too, the animal studies frequently use variable endpoints in establishing dosage: ataxia in dogs, mice and cats [51], abolition of the corneal reflex in rabbits [17,51], assumption of the thinker position, or taming in monkeys [23, 49]. Certainly it must be questioned whether most of these endpoints are relevant to intoxication in man. For example, ataxia is seen only with very high doses in man [51]. Considering these major methodological limitations of animal studies on cannabis, it is not surprising that variable effects in heart rate, blood pressure and other physiological parameters have been demonstrated [9]. Indeed, the Le Dain Commission correctly observes that "many investigators have questioned the wisdom of focusing limited time and financial resources at this time on cannabis studies involving animal species and tests of questionable applicability to man".

Reference has already been made to two early human studies, the Panama Canal Zone Study and the La Guardia Study. In considering these studies, one must remain cognisant of the many technological limitations present at the time the studies were done. An additional limitation of these early investigations was the paucity of knowledge on the active chemical constituents of cannabis. (Since chemical studies on cannabis in the 1940's, it has been thought that the tetrahydrocannabinols were responsible for most of the psychological and physiological effects of marihuana and hashish [43]. Following the structural elucidation of Δ^9-THC in 1964 by Ganoi and Mechoulam [16], progress in the chemistry of cannabis has been rapid. However, considerable work remains to be completed in the field of cannabis chemistry before discussion of current studies can include exact consideration of the varying dosages employed [28]. While many of the studies to be discussed specify the content of Δ^9-THC in the marihuana used, recent work would indicate these dosages are much less accurate than was presumed (Personal Observations). Although it is now generally accepted that Δ^9-THC is the major active constituent of *Cannabis sativa L.* in man [30, 31, 32, 52, 64] and in animals [23,49], Weil and associates [64], and Hollister [27] have emphasized that Δ^9-THC has not been established as the sole determinant of marihuana activity.) Accordingly, evaluation of these studies is complicated by uncertainties as to the dosage and composition of the material used.

In order to overcome such limitations, some early workers employed an available synthetic compound, synhexyl (pyrahexyl) [60, 61, 67]. Use of this synthetic compound further complicated analysis of the early literature; however, a recent study by Hollister, Richards, and Gillespie [30] indicates synhexyl does have comparable effects to Δ^9-THC.

In one of the first clinical reports, in 1933, 34 soldiers, all known or suspected of being marihuana smokers, were studied in the Panama Canal Zone Study [58]. A marked increase in pulse rate was reported, with no appreciable variation in blood pressure before and after smoking. No

reference was made to changes in the conjunctival vessels. Unfortunately, doses and type of marihuana employed were not specified.

A clinical study of 72 prisoners, 48 of whom were previous cannabis users, was part of the 1944 La Guardia Report from New York City [1]. Some subjects received an alcoholic extract of marihuana orally and others smoked marihuana cigarettes. With both methods of administration an increase in pulse rate was the most consistent effect although it was usually accompanied by a rise in blood pressure. Again no reference was made to reddening of the conjunctivae. In a few instances a temporary sinus tachycardia or sinus bradycardia was noted, but except for these there were no abnormalities in rhythm. Further the electrocardiogram showed no abnormalities which could be attributed to a direct action on the heart.

To consider the effects of long-term administration on psychological functioning, in 1946 Williams *et al.* [67] studied a small group of prisoners that had formerly used marihuana. Six subjects received pyrahexyl compound orally and six others smoked marihuana cigarettes. The drug was given in self-chosen doses at self-chosen intervals. An initial increase in pulse rate was noted in both groups, as was injection of the sclerae. In those subjects smoking marihuana, the pulse rate remained elevated on chronic administration for the first three weeks, after which it was not significantly different from the preliminary pre-smoking period even though the smoking of marihuana was continued. However, in the subjects receiving pyrahexyl, a tachycardia occurred only for several days then the pulse rate fell below control level until treatment was discontinued 28 days later. Systolic blood pressure was not altered during the period of pyrahexyl medication; however, in the marihuana group, it was slightly increased during the 39-day smoking period and remained elevated after discontinuation of treatment. Such differences may be due to pharmacological differences between crude marihuana and pyrahexyl or to differences in dosage.

Until Weil *et al.'s* [64] study in 1968, most studies of cannabis on man either employed marihuana extracts and/or had various methodological limitations. Weil's work was the first formal double-blind study in which both experienced and naive subjects smoked marihuana and which included many of the important controls omitted from previous studies. As in the early studies discussed above, Weil *et al.* observed an increased heart rate and dilatation of the conjunctival blood vessels. They did not measure blood pressure because they felt previous studies had failed to demonstrate any consistent effect on blood pressure in man. Subsequent discussion will include further details of their study.

Considering the paucity of reports of other consistent physiological effects of the acute administration of marihuana it is not surprising that the major focus of physiolocical studies has been the cardiovascular system. Since the three early clinical studies previously discussed [1, 58, 67], numerous reports on the cardiovascular effects of cannabis have appeared in the literature. To improve clarity, these studies will be discussed according to various cardiovascular parameters rather than considering them study by study. When doses are given, an attempt has been made to present them as mcg/kg. Occasionally when insufficient data were presented, mcg doses were divided by 70 (i.e. average 70 kg man) to give mcg/kg doses.

Heart Rate

The tachycardia produced in man by psychologically active doses of cannabis products is sufficiently reproducible that it has been increasingly employed as a biological assay of the material being studied. Thus an increase in heart rate has been used as an aid to monitor the cannabis effect of various compounds, dosages, dosage forms and modes of administration.

In their study, Hollister *et al.* [30] confirmed the earlier findings of Williams *et al.* [67] that orally administered synhexyl (pyrahexyl) in an average dose of 1370 mcg/kg caused significant increases (up to 46%) in heart rate. Under the same protocol, large doses ($\bar{X}$ = 581 mcg/kg) of synthetic Δ^9-THC when administered orally, produced a comparable tachycardia (up to 32% above control). Numerous other workers have confirmed the production of a significant tachycardia with varying doses (as low as 120 mcg/kg [31] but averaging around 300 mcg/kg [31, 63, 65], of both natural [31, 36] and synthetic [63, 65] Δ^9-THC administered orally. Regardless of the method of administration, in those studies in which a comparison was made, the tachycardia was greater in the erect (approximately 20% increase from control heart rate) as compared with the recumbent position (approximately 10%) [63,65]. Jones and Stone [36] gave four times the usual oral dose (1,285 mcg/kg) and produced an 18% increase in heart rate in the recumbent position. Taken together, such observations may suggest dilatation of capacitance vessels, with a component of reflex tachycardia in the erect position.

The effects of intravenous administration of synthetic Δ^9-THC have been studied in man. Perez-Reyes *et al.* [52] used a microsuspension of Δ^9-THC with 25% human serum albmin as the vehicle, and terminated the infusion when the subjects felt they had arrived at their desired level of high. In six graduate students with previous marihuana experience, an average dose of 40.69 mcg/kg produced an average tachycardia of 21.85 beats per minute. Of considerable interest are the results on injection of 11-OH- Δ^9-THC, a metabolite of Δ^9-THC. It was previously reported to be twice as potent as the parent compound in producing specific neurologic and behavioural responses when injected intravenously in mice [9]. Thus, it was implicated as the active form of Δ^9-THC. Perez-Reyes *et al.* [52], however, found the two compounds equipotent in their ability to induce tachycardia in man.

In a number of the recent studies of cannabis, plant material has been administered by a smoking procedure, This seems logical as most cannabis is used this way in North America [14, 21, 41, 59] and, as previously mentioned, Δ^9-THC has not been proven to be the only determinant of marihuana activity. However administration by smoking adds yet a further complication in determining the actual amount of active ingredient retained by the subject because of the added variable of the amount of Δ^9-THC in the exhaled air.

Using the tachycardia produced by Δ^9-THC extracted from cannabis as a biological assay, Isbell *et al.* [31] report that the smoked material was 2.6 times as potent as that administered orally. As this figure compares amounts of Δ^9-THC administered and since only approximately 50% of the Δ^9-THC contained in marihuana smoke is actually delivered, the relative potency may actually be more in the order of 5. It should be noted, however, that this apparent

difference in potency may reflect the rate of effective administration of THC since more Δ^9-THC will be absorbed per unit time after inhalation.

Galanter *et al.* [15] administered 10 mg of synthetic Δ^9-THC by intermittent smoking of cigarettes to 12 male users of marihuana. The magnitude of their pulse increment (51%) was highly correlated with their subjective experiences. When three of these subjects were subsequently given the same dose (estimated at 21–57 mcg/kg Δ^9-THC absorbed) of carbon-14-labelled Δ^9-THC by the same procedure, the time course of its concentration in plasma was highly correlated with the pulse increment, both peaking at 15 minutes after starting to smoke (i.e. 5 minutes after finishing smoking) and then rapidly declining. Subjective symptoms, however, appeared later and dissipated more slowly.

Numerous workers have also found a significant increase in heart rate following smoking of natural *Cannabis sativa L.* [6, 12, 34, 35, 36, 37, 38, 40, 45, 46, 50, 53, 64]. A wide range of doses was administered, as considerable variation occurred in the amount of Δ^9-THC in the material smoked and in the actual method of smoking. Although the various studies had many other differences in protocol, estimated doses as small as 6.25 mcg/kg delivered to the subject produced a significant increase in heart rate in both naive and experienced subjects [38]. Although Weil *et al.* [64] found no difference between a delivered dose of 2.25 mg and 9.0 mg in naive subjects, detailed dose-response studies have shown a greater tachycardia when a larger dose of Δ^9-THC is administered [12, 34, 38, 46, 53]. Most workers calculate the dose delivered to the subject as being approximately 50% of the amount of Δ^9-THC present in the cigarette smoked [38, 46, 62]. In addition, the Δ^9-THC content of expired air is usually ignored, although this loss could be significant. A recent preliminary study showed that, with a standardized smoking procedure, of the Δ^9-THC administered, 30–40% was retained by the subject [10]. However, inter-study comparisons of Δ^9-THC dosages are of limited value, because the considerable variations in the smoking procedures employed, can result in large differences in the amount of Δ^9-THC retained (Personal observations).

The Report to Congress from the Secretary, U.S. Department of Health, Education and Welfare summarizes the effects of cannabis on heart rate as follows: "Smoked doses of 4 and 15 mg Δ^9-THC have resulted in average pulse rate increases of 18 and 33 respectively. Correlation between dose and pulse increase is not especially high across investigators, but all report increases of 10–40 beats for doses ranging from 2–70 mg THC" [47].

Conjunctival Injection

Hollister *et al.* [30] found that both synhexyl and synthetic Δ^9-THC when administered orally resulted in injection of the conjunctivae. Other workers have confirmed this finding with oral administration of larger doses of Δ^9-THC [31]. Significant reddening of the conjunctivae due to dilatation of blood vessels have frequently been reported following smoking of marihuana [35, 36, 40, 64]. Further, Kiplinger *et al.* [38] have shown this effect to be dose related. They also observed that the reddening may be of two types: (1) injection of the vessels of the bulbar conjunctivae resulting in prominent vascular injection and (2) dilation of the vessels supplying the episclera resulting in a diffuse pink colour over the scleral portion of the eye. The former generally occurred after all doses of Δ^9-THC, while the latter occurred only after the highest dose of THC. As the conjunctival injection occurs with oral administration, it is not totally a result of local irritation by the smoke but could result from an inhibition of tear glands and subsequent drying of the eye [40]. The Le Dain Commission report on Cannabis [40] concludes that the clinical significance is probably minimal.

Blood Pressure

Reports in the literature, on a wide range of cannabis dosage and various methods of administration, have indicated inconsistent effects on blood pressure. Unless specified, in the following discussion of the various studies, the blood pressures were measured intermittently with a sphygmomanometer or the details of measurement were not described.

Hollister and co-workers [30] found that orally administered doses of both synhexyl (1370 mcg/kg) and synthetic Δ^9-THC (581 mcg/kg) reduced both systolic and diastolic blood pressure approximately seven percent. Without substantiating data, they state that the fall in blood pressure was less evident when the patient was sitting as compared with the effect of assuming an upright posture. In fact, they report that two patients had syncope, one mild and one fairly severe. With subjects erect Waskow *et al.* [63] found that oral doses of 286 mcg/kg synthetic Δ^9-THC also resulted in a significant fall in systolic blood pressure (7.9%). They found no significant change in the supine position. Likewise, Isbell *et al.* [31] found no significant changes in the supine systolic or diastolic blood pressures with oral administration of their high dose of Δ^9-THC (480 mcg/kg). Weiss *et al.* [65] measured arterial blood pressure with a non-invasive ultrasonic device attached to a pneumatic cuff and placed on the upper arm; systolic and diastolic pressures being registered automatically on mercury manometers. With oral administration of 300 mcg/kg synthetic Δ^9-THC, they observed a 2.0% fall in mean arterial pressure in the upright position, however a 3.6% increase in the recumbent position. Only the increase was statistically significant. (They also found with the same oral dose of Δ^9-THC that the increase in average mean arterial pressure with head-up tilt was less than that during control periods. In fact during the second to third hour post-drug, the average mean arterial pressure fell slightly on tilt. This effect was noted clinically in 7 of the 8 subjects, who had manifestations of orthostatic hypotension and presyncope during the first 2 to 3 minutes after head-up tilt. Only one subject had presyncope after placebo.)

During their study of the effects of intravenous administration of synthetic Δ^9-THC, Perez-Reyes *et al.* [52] determined the blood pressure at intervals throughout the experiments. Unfortunately, they do not report the results.

Generally, studies of the effect of smoked *Cannabis sativa L.* have shown either no effect or a slight increase in blood pressure [6, 31, 34, 40, 54]. The fact that all of these studies were done with the patient in the supine position probably accounts for the absence of any reports of a decrease in blood pressure. This would be consistent with the previously discussed reports on oral administration of cannabis, where decreases in blood pressure were reported when the patients were either sitting or standing.

Isbell *et al.* [31] found no significant change in the

supine systolic or diastolic blood pressures, when their high dose (100 mcg/kg Δ^9-THC delivered) was smoked. Likewise, Rodin *et al.* [54], found no significant change at the low dose employed ($\bar{X}$ = 32.5 mcg/kg Δ^9-THC delivered). At delivered doses above 71 mcg/kg Johnson *et al.* [34] found significant increases in both systolic ($\bar{X}$ = 17 mmHg) and diastolic ($\bar{X}$ = 10 mmHg) blood pressures. Beaconsfield *et al.* [6] also found systolic pressure increased slightly in some subjects, but overall there was no significant change. Likewise in preliminary studies the Le Dain Commission reported slight increases in systolic blood pressure at higher doses.

In summary, if the subject is upright, cannabis administration generally results in a fall in blood pressure. However, when the subject is supine, cannabis has either no significant effect on blood pressure or causes a slight increase. The general pattern seems to be the same regardless of dosage form, method of administration and perhaps even dosage. These results suggest the possibility of dilator effect on capacitance vessels and secondary effects on venous return, cardiac output and arterial blood pressure.

Other Cardiovascular Effects

An increase in limb flow following exposure to cannabis has recently been reported by two groups. Beaconsfield *et al.* [6] employed a smoking procedure, not described in detail, to administer a delivered dose of approximately 5 mg of Δ^9-THC to six marihuana naive subjects. They abandoned a planned double-blind study upon finding the subjects could distinguish dummy simulated marihuana cigarettes, the composition of which is not described, from the natural product. Instead, they assessed the effects of tobacco smoking in three subjects one week after investigation of their response to marihuana and completely omitted the use of placebo. Limb blood flow was measured by venous-occlusion plethysmography. Previous studies by these workers have confirmed the validity of the method of measuring limb blood flow under their experimental conditions [4,5]. They found that following the smoking of marihuana, blood flow increased concommitantly with the rise in pulse rate. There was a significant increase in both forearm and calf flow after the cigarette was finished but a slight rise only in hand flow. Thirty minutes later, forearm and calf flow were still elevated whereas mean hand flow had fallen to around control levels. Thus the peripheral vasodilation seems to be more marked in arterioles of skeletal muscle than in those of skin. The authors suggest the possibility that circulatory adjustments occur in other vascular beds because the increase in peripheral flow was unaccompanied by a fall in systemic pressure.

Using the venous occlusion technique with a Whitney mercury-in-rubber strain gauge [66], Weiss *et al.* [65] measured forearm blood flow. When 300 mcg/kg of synthetic Δ^9-THC was administered orally to 8 healthy male cannabis users under single-blind conditions, the forearm blood flow, measured in the recumbent position, was increased significantly compared to placebo. There was no significant alteration in mean upright forearm blood flow, however. The decrease in mean forearm blood flow with head-up tilt was significantly greater following Δ^9-THC administration than following administration of the placebo. The placebo consisted of 1 ml of 95% ethanol diluted in cherry syrup, which was the vehicle for administration of Δ^9-THC.

Thus, in the two studies reported to date cannabis produced an increase in limb blood flow. Weiss *et al.* [65] found this increase with the subjects in the recumbent but not the upright position. Beaconsfield *et al.* [6] do not specify the position of their subjects. However, it is reasonable to assume they were in the recumbent position.

From their studies, Beaconsfield and associates and Weiss and co-workers report various other cardiovascular effects of cannabis in man. Both groups report an interference with the integrity of peripheral vascular reflex responses. Beaconsfield *et al.* [6] found that mental arithmetic and cold caused no significant change in hand flow after smoking, whereas before cannabis these stimuli induced the expected reduction in flow. The fact that hand flow was unaffected by standard stimuli suggests that marihuana smoking obtunds the body's vasomotor reflex mechanism. Thus, the authors suggest, in an emergency, following the use of cannabis, the subject's reflex vascular responses might not be as rapid or as widespread as when he is not under the influence of the drug [6]. Weiss *et al.* [65], report an attenuation of reflex venoconstriction after Δ^9-THC. After pressure has stabilized in an isolated venous segment, the increase in venous pressure following a maximal deep breath was used as an index of venomotor reactivity. The usual reflex venoconstriction in response to a maximum deep breath was attenuated in all and transiently abolished in four subjects after Δ^9-THC administration. Various animal studies on cannabis and related compounds, reviewed by Hardman *et al.* [24] further suggest an interference with the integrity of peripheral vascular reflex responses. These studies show a reduction of the common carotid occlusion pressor reflex which is a sensitive and reproducible method for evaluating durgs which inhibit central sympathetic outflow.

A number of additional cardiovascular parameters were studied by Weiss and co-workers [65]. Open venous tone, the ratio of the increment in venous pressure to the increment in forearm volume (ΔP mmHg/ΔV ml^3) was measured by an equilibration method. Although open venous tone was increased more after Δ^9-THC than after placebo, no statistically significant changes were noted. The ventricular preejection period was measured with a simultaneous electrocardiogram, phonocardiogram and external carotid pressure transducer. Calculation was made by subtracting left ventricular ejection time from the Q-S_2 interval. Administration of Δ^9-THC significantly shortened the preejection period. Calculated forearm conductance, the reciprocal of forearm vascular resistance, was expressed in arbitrary units as the ratio of forearm blood flow to mean arterial blood pressure. Mean recumbent forearm conductance was significantly greater after Δ^9-THC; however, there was no significant change in mean upright forearm conductance. After head-up tilt a significantly greater decrease of mean forearm conductance occurred following administration of Δ^9-THC. The significance of these various cardiovascular effects of cannabis will be discussed in the following section dealing with the mechanisms of action of cannabis on the cardiovascular system on man.

Following cannabis administration, changes in the electrocardiogram (EKG) are reportedly minmal for normal subjects. Hollister *et al.* [30] found EKGs uniformly within normal limits following oral administration of Δ^9-THC or synhexyl. Smoking marihuana tended to flatten T-waves, in various leads, in many subjects studied by Johnson and Domino [34]. However, this finding was not constant and

less prominent than T-wave changes induced by exercise. Also, two of 15 subjects in their high-dose (delivered doses above 71 mcg/kg) study developed premature ventricular contractions occuring at a rate of less than 1 per 25 beats. The authors agree that EKG changes are minor after marihuana and suggest that the effects might be related to smoking rather than to a pharmacological effect of THC per se. However, they did not observe these changes in the two subjects that smoked placebo marihuana. Beaconsfield *et al.* [6] report that in five of six naive subjects, the main change observed in the EKG during and for 30 minutes after smoking was increased width and decreased amplitude of the P-wave in Lead 2 and inversion of the T-wave in Lead 3. Weiss and coworkers [65] recorded the EKG in their determination of ventricular pre-ejection period; no specific reference was made to any abnormalities.

The cardiovascular effects of marihuana in subjects with existing heart disease has been virtually ignored. However, recently Aronow and Cassidy [3] studied its effects in patients with angina pectoris due to coronary disease. They found that smoking one marihuana cigarette containing 19.8 mg Δ^9-THC decreased exercise performance significantly more than smoking one placebo marihuana cigarette. Whether this effect is greater than that of smoking high-nicotine cigarettes is not known. Nevertheless, if the widespread use of marihuana continues, its effects on subjects with cardiovascular pathology will warrant further study.

Mechanism of Action

Various hypotheses have been presented to explain the mechanism of action of cannabis on the cardiovascular system in man. There is evidence that marihuana acts to enhance sympathoadrenal activity and also that it exerts anticholinergic effects. Moreover, marihuana probably also interferes with peripheral vascular reflex responses.

The emphasis in recent clinical studies has been on the interaction of cannabis and the sympathetic nervous system. In particular, this interaction has been studied in an attempt to explain the consistent tachycardia produced by marihuana and to correlate this action with the other cardiovascular effects in man. In the absence of laboratory studies the tachycardia has hitherto variously been ascribed to release of adrenaline and altered autonomic activity [33], to central excitation [33] and depression [44] and to an atropine-like effect [19].

From their studies, Weiss *et al.* [65], conclude that several of the cardiovascular effects seen with Δ^9-THC administration appear to be consistent with increased sympathoadrenal activity. Intravenous adrenaline infusion produces shortened pre-ejection period [55], increased heart rate [55], and increased forearm blood flow and venous tone [57]. All of these cardiovascular effects are observed following ingestion of Δ^9-THC. Using a modification of Anton and Sayre's [2] method, Weiss *et al.* [65]. also found an increase in urinary free adrenaline following Δ^9-THC. These findings raise the possibility that the augmented rate of adrenaline secretion was responsible for the circulatory changes. Hollister *et al.* [29] also report a transient early rise in adrenaline excretion following ingestion of Δ^9-THC; however they attribute this to anxiety aroused by the test situation since they saw a similar rise in placebo-treated subjects in a previous study. Perfusion with Δ^9-THC of the coronary circulation of the isolated rat heart is reported not to alter heart rate [65], although systemic administration does. This would imply that the tachycardia is not a direct effect and may further reflect increased sympathoadrenal activity.

Various groups have blocked the cannabis-induced tachycardia with the beta-adenergic blocking agent propranolol [6, 13, 37, 48]. This work further implicates the sympathetic nervous system (although not necessarily adrenaline release) in the mechanism of action of marihuana on the cardiovascular system in man. Beaconsfield *et al.* [6] found that both the tachycardia and the increased muscle flow were blocked by 40 mg of propranolol given orally every six hours for 48 hours. Contrary to Weiss *et al.* [65], however, they suggest that adrenaline release during cannabis smoking is unlikely to be the exciting stimulus. They reason that, in the presence of a beta-adrenergic blocker, the constrictor effects of adrenaline would be unopposed; forearm flow should therefore fall and blood pressure rise. Since neither forearm flow nor blood pressure changed significantly they argue that adrenaline release cannot be important. Further support for this thesis comes from their findings that blood lactate, nonesterified fatty acids and glucose, which are normally increased by adrenaline, were unchanged after marihuana.

Thus, there appears to be little doubt that at least in part the mechanism of action of cannabis on the cardiovascular system in man is a result of its action on the sympathetic nervous system. The details, however, remain to be elucidated.

It has long been assumed that cannabis also has effects on the parasympathetic nervous system. Review articles on marihuana typically refer to its effect in producing dryness of the mouth and throat [21,40,47] and this action has been interpreted as an atropine-like effect [34]. In contradistinction to the general impression that marihuana has an anticholinergic action is an early report describing an occasional case in which a state approaching vaso-vagal syncope develops [18]. Current knowledge would suggest these cases were more likely a result of hypotension following an abrupt change from the supine or sitting to the erect position.

Renault *et al.* [53] report a suppression of the normal sinus arrhythmia by cannabis. Since this non-specific response is mediated by the vagus, they suggest marihuana may have its effects on heart rate by altering normal vagal tone. The maximal heart rates they obtained in response to their largest doses of smoked marihuana (3.25 mg delivered dose) were in the range of 140 to 160 beats per minute – rates similar to those seen in the absence of vagal tone. To study further the effects of marihuana on autonomic tone, they recorded heart rate while subjects performed the Valsalva manoeuver. Marihuana suppressed the cardiac slowing which occurred during the Valsalva manoeuver; however, the pulse slowing after exhalation persisted following marihuana administration. These results are difficult to interpret in the absence of direct blood pressure recording, especially since heart rate does not usually slow during the Valsalva manoeuver. Observed effect on the expiratory slowing (which is associated with increased vagal activity) does not support arguments for an atropine-like action. Since the slowing of heart rate following exhalation is usually associated with increased vagal activity, one would expect that if marihuana did have an atropine-like action, it should have some effect on this slowing. In subjects that were clinically atropinized (0.6 mg subcutaneously) by Beaconsfield and associates [6], cannabis

produced an additional elevation in heart rate. Therefore they conclude that it is unlikely that the marihuana induced tachycardia results from an atropine-like effect on efferent vagal activity. On the contrary, they suggest that vagal activity may normally limit the degree and duration of cannabis-induced tachycardia, as a greater and more sustaned increased in pulse rate and blood pressure occurred after smoking in subjects given atropine.

Thus, as in delineating the specific action of cannabis on the sympathetic nervous system, it is apparent considerable work is required to further delineate its action on the parasympathetic nervous system.

In spite of the previously discussed limitations of animal studies of marihuana it is still interesting to note that Gill *et al.* [20] have presented evidence from isolated tissue experiments for an atropinic and two muscarinic substances in the aqueous extract of cannabis. These substances have not been chemically identified; however the authors suggest that it is probable that the atropine-like material, rather than Δ^9-THC, chiefly causes the salivary and heart rate effects of marihuana. This conclusion is not consistent with experiments in man when Δ^9-THC produced tachycardia.

SUMMARY

It is now very clear that marihuana has considerable cardiovascular effects, although the varying experimental protocols make it difficult to assay the dimensions of these changes and to establish mechanisms. At this point in time, it is not clear how cardiac effects are mediated through the autonomic nervous system, nor whether observed peripheral vascular effects are primary or a function of changes in cardiac output or reflexly altered sympathetic tone.

REFERENCES

1. Allentuck, S. The clinical study, in the Mayor's Committee on Marihuana: The Marihuana Problem in the City of New York: Sociological, Medical, Psychological and Pharmacological Studies, Lancaster, Pa., J. Cattell Press, 1945, as cited in *The Marihuana Papers,* edited by Solomon, D., New York, New American Library, 1968, p. 308.
2. Anton, A. H. and D. F. Sayre. A study of the factors affecting the aluminum oxide-trihydroxyindole procedure for the analysis of catecholamines. *J. Pharmac. exp. Ther.* **138:** 360–365, 1962.
3. Aronow, W. S. and J. Cassidy. Effect of marihuana and placebo-marihuana smoking on angina pectoris. *New Engl. J. Med.* **291:** 65–67, 1974.
4. Beaconsfield, P. A. Effect of exercise on muscle blood flow in normal and sympathectomized limbs. B. Collateral circulation before and after sympathectomy. *Ann. Surg.* **140:** 786–795, 1954.
5. Beaconsfield, P. and G. Ginsburg. Effect of changes in limb posture on peripheral blood flow. *Circ. Res.* **3:** 478–482, 1955.
6. Beaconsfield, P., J. Ginsburg and R. Rainsbury. Marihuana smoking: cardiovascular effects in man and possible mechanisms. *New Engl. J. Med.* **287:** 209–212, 1972.
7. Bicher, H. F. and R. Mechoulam. Pharmacological effects of two active constituents of marihuana. *Archs. int. Pharmacodyn.* **172:** 24–31, 1968.
8. Bloomquist, E. R. *Marihuana the Second Trip.* Beverly Hills, Cal.: Glenco Press, 1971, p. 88.
9. Cavero, I., R. K. Kubena, J. Dziak, J. P. Buckley and B. S. Jandhyala. Certain observations on interrelationships between respiratory and cardiovascular effects of (-)-Δ^9-trans-tetrahydrocannabinol. *Res. Communs. chem. pathol. Pharmacol.* **3:** 483–492, 1972.
10. Clark, S. C., C. Greene, G. W. Karr, K. L. MacCannell and S. L. Milstein. Cardiovascular effects of marihuana in man. *Can. J. Physiol. Pharmac.* **52:** 706–719, 1974.
11. Domino, E. F., H. F. Hardman and M. H. Seevers. Structure activity relationships of Δ^3-tetrahydrocannabinols. *Proc. West. Pharmac. Soc.* **14:** 14, 1971.
12. Dornbush, R., L. M. Fink and A. M. Freedman. Marijuana, memory, and perception. *Am. J. Psychiat.* **128:** 194–197, 1971.
13. Drew, W. G., G. F. Kiplinger, L. L. Miller and M. Marx. Effects of propranolol on marihuana-induced cognitive dysfunctioning. *Clin. Pharmac. Ther.* **13:** 526–533, 1972.
14. Fort, J. A World view of marihuana. *J. Psychedelic Drugs* **2:** 2–12, 1968.
15. Galanter, M., R. J. Wyatt, L. Lemberger, H. Weingartner, T. B. Vaughan and W. T. Roth. Effects on humans of Δ^9-tetrahydrocannabinol administered by smoking. *Science* **176:** 934–936, 1972.
16. Ganoi, Y. and R. Mechoulam. Isolation, structure and partial synthesis of an active constituent of hashish. *J. Am. Chem. Soc.* **86:** 1646–1647, 1964.
17. Garattini, S. Effects of a cannabis extract on gross behavior, in *Hashish: Its Chemistry and Pharmacology,* edited by Wolstenholme, G. E. W. and J. Knight. London: J. and A. Churchill, 1965, pp. 70–82.
18. Gaskill, H. S. Marihuana, an intoxicant. *Am. J. Psychiat.* **102:** 202–204, 1945.
19. Gill, E. W. and W. D. M. Paton. Pharmacological experiments *in vitro* on the active principles of cannabis, In: *The Botany and Chemistry of Cannabis,* edited by Joyce, C. R. B. and S. H. Curry. London: J. and A. Churchill, 1970, pp. 165–173.
20. Gill, E. W., W. D. Paton and R. G. Pertwee. Preliminary experiments on the chemistry and pharmacology of cannabis. *Nature* **228:** 134–136, 1970.
21. Grinspoon, L. Marihuana. *Scient. Am.* **221:** 3–11, 1969.
22. Grlic, L. Recent advances in the chemical research of cannabis. *Bull. Narcot.* **16:** 29–38, 1964.
23. Grunfeld, Y. and H. Edery. Psychopharmacological activity of the active constituents of hashish and related cannabinoids. *Psychopharmacologia* **14:** 200–210, 1969.
24. Hardman, H. F., E. F. Domino and M. H. Seevers. General pharmacological actions of some synthetic tetrahydrocannabinol derivatives. *Pharmac. Rev.* **23:** 295–315, 1971.
25. Hardman, H. F., E. F. Domino and M. H. Seevers. Structure activity relationships of Δ^3-tetrahydrocannabinols. *Proc. West. Pharmac. Soc.* **14:** 14–20, 1971.
26. Helper, R. S. and I. R. Frank. Marihuana smoking and intraocular pressure. *J. Am. Med. Ass.* **217:** 1392, 1971.
27. Hollister, L. E. Marihuana in man: three years later. *Science* **172:** 21–29, 1971.
28. Hollister, L. E. Status report on clinical pharmacology of marihuana. *Ann. N.Y. Acad. Sci.* **191:** 132–141, 1971.
29. Hollister, L. E., F. Moore, S. Kanter and E. Noble. Δ^1-tetrahydrocannabinol, synhexyl and marihuana extract administered orally in man: catecholamine excretion, plasma cortisol levels and platelet serotonin content. *Psychopharmacologia* **17:** 354–360, 1970.
30. Hollister, L. E., R. K. Richards and H. K. Gillespie. Comparison of tetrahydrocannabinol and synhexyl in man. *Clin. Pharmac. Ther.* **9:** 783–791, 1968.

31. Isbell, H., C. W. Gorodetzsky, D. Jasinski, U. Claussen, F. U. Spulak and F. Karte. Effects of (-)-Δ^9-trans-tetrahydrocannabinol in man. *Psychopharmacologia* **11**: 184–188, 1967.
32. Jasinski, D. R., C. A. Haertzen and H. Isbell. Review of the effects in man of marijuana and tetrahydrocannabinols on subjective state and physiologic functioning. *Ann. N.Y. Acad. Sci.* **191**: 196–205, 1971.
33. Joachimoglu, G. Natural and smoked hashish. In: *Hashish: Its Chemistry and Pharmacology*, edited by Wolstenholme, G. E. W. and J. Knight. London: J. and A. Churchill, 1965, pp. 2–14.
34. Johnson, S. and E. F. Domino. Some cardiovascular effects of marihuana smoking in normal volunteers. *Clin. Pharmac. Ther.* **12**: 762–768, 1971.
35. Jones, R. J. Marihuana-induced "high"; influence of expectation, setting, and previous drug experience. *Pharmac. Rev.* **23**: 359–369, 1971.
36. Jones, R. J. and G. C. Stone. Psychological studies of marihuana and alcohol in man. *Psychopharmacologia* **18**: 108–117, 1970.
37. Kiplinger, G. F. and J. E. Manno. Dose-response relationships to cannabis in human subjects. *Pharmac. Rev.* **23**: 339–347, 1971.
38. Kiplinger, G. F., J. E. Manno, B. E. Rodda and R. B. Forney. Dose-response analysis of the effects of tetrahydrocannabinol in man. *Clin. Pharmac. Ther.* **12**: 650–657, 1971.
39. Klonoff, H. Strategy and tactics of marijuana research. *Can. Med. Ass. J.* **108**: 145–149, 1973.
40. LeDain Commission: *Cannabis: A Report of the Commission of Inquiry into the Non-Medical Use of Drugs.* Ottawa: Information Canada, 1972, pp. 11–165.
41. Le Dain Commission: *Cannabis: A Report of the Commission of Inquiry into the Non-Medical Use of Drugs.* Ottawa: Information Canada, 1972, p. 33.
42. Le Dain Commission: *Interim Report of the Commission of Inquiry into the Non-Medical Use of Drugs.* Ottawa: Information Canada, 1970, p. 71.
43. Loewe, S. Pharmacological study, in The Mayor's Committee on Marihuana: *The Marihuana Problem in the City of New York: Sociological, Medical, Psychological and Pharmacology Studies,* Lancaster, P.A., J. Cattell Press, 1945, as cited. In: *The Marihuana Papers,* edited by D. Solomon. New York: New American Library, 1968, p. 339.
44. Loewe, S. Pharmacological study, in The Mayor's Committee on Marihuana: *The Marihuana Problem in the City of New York: Sociological, Medical, Psychological and Pharmacological Studies,* Lancaster, P. A., J. Cattell Press, 1945, as cited in Beaconsfield, P., J. Ginsburg and R. Rainsbury. Marihuana smoking: cardiovascular effects in man and possible mechanisms. *New Engl. J. Med.* **287**: 209–212, 1972.
45. Low, M. D., H. Klonoff and A. Marcus. The neurophysiological basis of the marijuana experience. *Can. Med. Ass. J.* **108**: 157–165, 1973.
46. Manno, J. E., G. F. Kiplinger, S. Haine, I. F. Bennett and R. B. Forney. Comparative effects of smoking marihuana or placebo on human motor and mental performance. *Clin. Pharmac. Ther.* **11**: 808–815, 1970.
47. *Marihuana and Health: A Report to the Congress from the Secretary, Department of Health, Education and Welfare.* Washington, U. S. Government Printing Office, 1971, p. 53.
48. Martz, R., D. J. Brown, R. B. Forney, T. P. Bright, G. F. Kiplinger and B. E. Rodda. Propranolol antagonism of marihuana induced tachycardia. *Life Sci.* **11**: 999–1005, 1972.
49. Mechoulam, R., A. Shani, H. Edery and Y. Grunfeld. Chemical basis of hashish activity. *Science* **169**: 611–612, 1970.
50. Meyer, R. E., R. C. Pillard, L. M. Shapiro and S. M. Mirin. Administration of marijuana to heavy and casual marijuana users. *Am. J. Psychiat.* **128**: 198–204, 1971.
51. Miras, C. J. Some aspects of cannabis action. In: *Hashish: Its Chemistry and Pharmacology,* edited by Wolstenholme, G. E. W. and J. Knight. London: J. and A. Churchill, 1965, pp. 37–53.
52. Perez-Reyez, M., M. C. Timmons, M. A. Lipton, K. H. Davis and M. E. Wall. Intravenous injection in man of Δ^9-tetrahydrocannabinol and 11-OH-Δ^9-tetrahydrocannabinol. *Science* **177**: 633–635, 1972.
53. Renault, P. F., C. R. Schuster, R. Heinrich and D. X. Freeman. Marihuana: standardized smoke administration and dose effect curves on heart rate in humans. *Science* **174**: 589–591, 1971.
54. Rodin, E. A., E. F. Domino and J. P. Porzak. The marihuana-induced "social high": neurological and electroencephalographic concomitants. *J. Am. Med. Ass.* **213**: 1300–1302, 1970.
55. Salzman, S. H., S. Wolfson, B. Jackson and E. Schechter. Epinephrine infusion in man. Standardization, normal response, and abnormal response in idiopathic hypertrophic subaortic stenosis. *Circulation* **43**: 137–144, 1971.
56. Schultes, R. E. Random thoughts and queries on the botany of cannabis. In: *The Botany and Chemistry of Cannabis,* edited by C. R. B. Joyce and S. H. Curry, J. and A. Churchill, London: 1970, pp. 11–38.
57. Sharpey-Schafer, E. P. Venous tone. *Br. Med. J.* **2**: 1589–1595, 1961.
58. Siler, J. F., W. L. Sheep, L. B. Bates, G. F. Clark, G. W. Cook and W. A. Smith. Marihuana smoking in Panama. *Milit. Surg. Nov.:* 269–280, 1933.
59. Smith, D. E. Acute and chronic toxicity of marihuana. *J. Psychedelic Drugs* **2**: 37–42, 1968.
60. Stockings, G. T. A new euphoriant for depressive mental states. *Br. Med. J.* **1**: 918–922, 1947.
61. Thompson, L. J. and R. C. Proctor. Continued use of pyrahexyl in treatment of alcoholic and drug withdrawal conditions. *N. C. Med. J.* **14**: 520–523, 1953.
62. Truitt, E. B. Biological disposition of tetrahydrocannabinols. *Pharmac. Rev.* **23**: 273–278, 1971.
63. Waskow, I. E., J. E. Olsson, C. Salzman and M. M. Katz. Psychological effects of tetrahydrocannabinol. *Archs. Gen. Psychiat.* Chicago, **22**: 97–107, 1970.
64. Weil, A., N. Zinberg and J. Nelsen. Clinical and psychological effects of marihuana in man. *Science* **162**: 1234–1242, 1968.
65. Weiss, J. L., A. M. Watanabe, L. Lemberger, N. R. Tamarkin and P. V. Cardon. Cardiovascular effects of delta-^{9}-tetrahydrocannabinol in man. *Clin. Pharmac. Ther.* **13**: 671–684, 1972.
66. Whitney, R. J. The measurement of volume changes in human limbs. *J. Physiol., Lond.* **121**: 1–27, 1953.
67. Williams, E. G., C. K. Himmelsbach, A. Wikler, D. C. Ruble and B. J. Lloyd. Studies on marihuana and pyrahexyl compound. *Public Health Rep.* **61**: 1059–1083, 1946.