over 20 years have elapsed since Hardman *et al*[4] first described this effect of drugs related to THC, the most studied active principle of cannabis.

In anaesthetised animals, THC and cannabis extracts consistently produce bradycardia and hypotension.[5] In man, on the other hand, a single dose of cannabis (smoked or ingested) or intravenous THC produces a tachycardia (up to 160/min) with either no change or a slight increase in systolic and diastolic blood pressures[3 6–9] and an increase in limb blood flow.[3] The tachycardia is dose related[10] and is detectable[8] at 50 μg of THC per kg body weight. It reaches a maximum within 30 minutes and persists for longer than 90 minutes.[6 11] After a single oral dose of THC (300 μg/kg) the tachycardia may persist for as long as 12 hours[12]; electrocardiographic changes may also occur.[6 13] Occasionally, large single doses of cannabis taken by mouth[14 15] or smoked[16] produce orthostatic hypotension in man.

The tachycardia induced by taking cannabis for short periods appears to be due to increased sympathetic tone, because it is abolished by β-adrenoceptor blockade.[3 15 17] If, in the short term, cannabis acts through a β-adrenergic mechanism, then it should increase the strength as well as the rate of contraction; and, indeed, in tests on healthy volunteers cannabis caused shortening of the pre-ejection period, lengthening of the left ventricular ejection time, and an increase in stroke volume, suggesting an enhancement of left ventricular performance.[17] In another investigation,[18] however, the only changes found in left ventricular function were secondary to tachycardia. These discrepancies may have been due to differences in dose and tolerance.

When cannabis is taken for long periods the effects are different. Both bradycardia and hypotension develop, probably as a result of decreased sympathetic tone in the peripheral blood vessels[19] with resulting parasympathetic dominance.[20 21] The bradycardia is reversed by vagotomy, ganglion block, and anticholinergic drugs.[20] THC also reduces venous tone,[20] so explaining the orthostatic hypotension. Men given 210 mg of THC daily for 18-20 days showed a decrease in heart rate and a fall in systolic and diastolic blood pressure[22] accompanied by impaired cardiovascular responses to standing, exercise, Valsalva's manoeuvre, and cold pressor tests—all suggesting sympathetic insufficiency. Other effects included fluid retention and gain in weight; tolerance developed to the orthostatic but not the supine hypotension. During ingestion of THC[22] responses to both an alpha-agonist (phenylephrine) and a beta-agonist (isoprenaline) were unchanged, while parasympathetic block with atropine alone or with the beta-adrenoceptor blocker propranolol caused the heart rate to increase, suggesting that cannabis acts centrally to produce both sympathetic insufficiency and enhanced parasympathetic activity. More recent evidence[23] suggests that cannabis modulates sympathetic outflow by a dual mechanism: it reduces spontaneous sympathetic efferent activity and (like barbiturates) it suppresses inhibitory mechanisms. This accounts for the apparent increase or decrease in sympathetic outflow in different species or within the same species under different experimental conditions—such as with and without anaesthesia.

Has cannabis any clinical potential? Dimethylheptyltetrahydrocannabinol produces in man a long lasting tachycardia and supine and orthostatic hypotension, with a virtual absence of psychological effects[24]; in contrast, the synthetic cannabis derivative nabilone (Lilly 109514) produces a dose-related euphoria and postural hypotension without tachycardia, but with rapidly developing tolerance.[25] The pharmacological properties of the cannabinoids can thus be separated —though the prospect of new hypotensive drugs that produce postural hypotension, with or without tachycardia, and the possibility of tolerance is not encouraging. With better hypotensive agents already available the time has perhaps come to take a broader look at the whole group of lipophilic drugs[9] rather than concentrating on the cannabinoids.

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Algodystrophy

Sudeck's atrophy and the shoulder-hand syndrome are rare conditions, but most clinicians will remember seeing a case. Not many will have made the diagnosis themselves. In fact, these conditions are usually not diagnosed in their early stages, and since treatment becomes more difficult and less effective in the later stages this group of disorders remains a cause of serious chronic and permanent disability.

A workshop held recently at the Royal College of Physicians under the auspices of the British Association for Rheumatology and Rehabilitation decided that there were three essential diagnostic features of algodystrophy—the name by which the condition is known in France, and the one recommended for general use, being non-committal about aetiology and yet emphasising the clinical combination of pain and dystrophic changes. Characteristically there is, firstly, intense, ill-defined pain and hyperaesthesia; secondly, vasomotor changes and disturbance of sweating; and, thirdly, osteoporosis.

Algodystrophy may occur in virtually any part of the locomotor system,[1] though the hand and foot are the parts most commonly affected. Pain, always prominent, is particularly distressing and constant, with associated hyperaesthesia and tenderness. Vasomotor changes[2] are usually, but not always, a

notable feature, with vasodilation, oedema, and slightly raised temperature and sweating in the early stages. After a few weeks cold cyanosis develops. The skin is smooth and shiny, and in longstanding, severe cases the soft tissues and sweat glands atrophy.

Sudeck[3] described the osteoporosis that occurs in all but the mildest cases and may become obvious within a few days. Generalised loss of bone density may be seen in the affected region, but the more distinctive radiological appearance of small, usually rounded, areas of increased translucency, measuring up to 10 mm in diameter, may be superimposed.

The cause of algodystrophy remains an enigma. Most cases occur after trauma, and an attempt to secure compensation is often thought relevant. The same syndrome may, however, develop after myocardial infarction, herpes zoster, hemiplegia, or barbiturate treatment. The condition has been linked with causalgia and attributed to an excessive outflow of sympathetic nervous discharges from the dorsal horn of the spinal cord. Normal inhibition is lost by interference with the inflow of afferent stimuli along the thickly medullated nerve fibres from peripheral mechanoreceptors. This theory provides an explanation for the efficacy of repeated intensive exercise and the use of vibrators and cooling sprays—and it also explains why sympathetic ganglion blocks,[4] sympathectomy, and guanethidine infusions[5] have all been successful in treatment. Beta-blocking agents by mouth give poorer results.

Corticosteroids have been used empirically, both systemically[6] and locally,[7] with some success, and recently calcitonin[8] has been used enthusiastically in France, where controlled trials are now in progress. We need further scientific studies and controlled trials of treatments, but the first step if we are to make progress is to recognise the disorder earlier and more widely.

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Drug treatment of chronic stable angina pectoris

Beta-adrenoceptor-blocking drugs now occupy the prime place in the management of patients with chronic stable angina pectoris. They reduce the frequency and severity of anginal attacks, lessen consumption of glyceryl trinitrate, ameliorate electrocardiographic ST segment depression, and improve exercise tolerance.[1]

The beta-blocking drugs in current use are relatively free from major side effects—provided the contraindications are observed; they should be used with caution in patients with heart failure, heart block, severe mitral and aortic valvular disease, peripheral vascular disease, or obstructive airways disease. Furthermore, these drugs should not be withdrawn rapidly from patients with angina, since in some cases this provokes a rebound increase in the frequency and severity of the pain.[2] Obstructive airways disease and heart failure are not absolute contraindications. Cardioselective beta-blockers (such as metoprolol and atenolol) may be tried under close supervision in patients with obstructive airways disease, and digitalis has been used to advantage with beta-blockers in patients with angina and abnormal left ventricular function.[3] Some patients, however, with severe stable angina pectoris cannot be prescribed beta-blockers because these are either ineffective or ruled out by coexistent disease. What alternatives are there?

A short-acting nitrite such as glyceryl trinitrate will usually have been the first drug used, and indeed is still one of the most effective drugs for symptomatic relief of angina. Taken sublingually its onset of action is rapid, but the effect lasts only 20-30 minutes. Glyceryl trinitrate does not appreciably dilate diseased coronary vessels[4]; it reduces venous return and therefore ventricular stroke output, so that the systolic pressure falls and left ventricular work decreases. Unfortunately in the frequent doses needed for severe angina glyceryl trinitrate causes flushing, headache, and postural hypotension—side effects that set the limit to the tolerable dose.

The value of long-acting nitrites such as pentaerythritol tetranitrate and isosorbide dinitrate in the treatment of angina is still strongly debated.[5–8] Taken by mouth in the doses currently used these drugs show no consistent beneficial effects[9]—and perhaps this is not surprising, since nitrites are metabolised rapidly in the liver, so that little active drug reaches the systemic circulation.[10] Higher doses might prove more effective[11]; 2% nitroglycerin ointment, however, has been shown[12 13] to increase exercise capacity for as long as five hours after a single application to the skin of the chest or forearm (as a ribbon of ointment covered with an occlusive dressing).

Prenylamine, dipyridamole, and vitamin E have been advocated as antianginal agents, but studies have generally shown them to be no more effective than placebo.[8 14–16] New drug preparations for the treatment of angina invariably have a strong placebo effect, and double-blind trials are essential for their evaluation.

Such trials have shown that perhexilene maleate reduces the frequency and severity of anginal attacks, and it does not appear to precipitate heart failure or airways obstruction.[18] It reduces exercise-induced tachycardia in man, but, unlike beta-blockers, it has no effect on the resting heart rate.[19] Perhexilene has been shown to produce coronary and systemic vasodilatation in animals and to reduce left ventricular work and to decrease myocardial oxygen consumption.[20] Minor side effects such as dizziness, nausea, headaches, and impotence seem to be common during the first month of treatment,[18] and prolonged treatment can cause dose-related abnormalities in liver function tests, though these are usually reversible on stopping treatment.[21] Overt hepatotoxicity is fortunately rare. Polyneuropathy[22] and raised intracranial pressure[23] have also occurred in several patients on long-term treatment but again have proved reversible. A proximal myopathy[24] has been reported in one patient. Clearly the ratio of benefit to risk has to be calculated carefully before this effective antianginal drug is prescribed for long-term use.

Verapamil interferes with the inwards displacement of calcium ions across cardiac cell membranes, decreases cardiac contractility, decreases the oxygen requirements of the heart, and does not block beta-adrenoceptors.[25] Its effectiveness in the treatment of angina is still a matter of debate.[26–31] It may precipitate heart failure and cause hypotension at high doses and should not therefore be used in conjunction with beta-blockers.[32]

Within the last few months another calcium antagonist,