CHAPTER 3 PHARMACOLOGY OF CANNABIS AND THE CANNABINOIDS

3.1 The plant *Cannabis sativa* is also known as hemp; it is related to the nettle and the hop. It grows readily in a warm climate, and the long, woody stems of the plant contain a resin (hashish), the resin secreted by the leaves and flower heads, which may be compressed into blocks.

3.2 The family of chemically related 21-carbon alkaloids found uniquely in the cannabis plant are known as cannabinoids. There are more than 60 different cannabinoids; one of these, D9-tetrahydrocannabinol (THC), is the most abundant and accounts for the intoxicating properties of cannabis. The Chairman of the House of Lords Select Committee on Science and Technology on its establishment in 1979.

3.3 THC and other cannabinoids dissolve readily in fat but not in water. This limits the possible forms of administration of the drug. For example, it is possible to be drunk for a considerable time and still be able to detect alcohol in the blood, but it is impossible to detect THC. The psychological effects persist for some time after the level of THC in the blood has begun to decline.

3.4 Smoking delivers 30 per cent or more of the total THC in a cannabis cigarette to the bloodstream. The route by which THC enters the body is an important factor in determining the duration of the effects. Smoking delivers THC into the lungs, and the blood capillaries in the lungs are in close contact with the bloodstream, allowing THC to enter the blood stream very quickly. In contrast, THC is delivered more slowly when ingested by mouth, as the drug has to pass through the liver and be metabolized before it can enter the bloodstream.

3.5 Once THC has entered the bloodstream, it is widely distributed in the body, especially in fatty tissues. This is because THC is fat-soluble, and fatty tissues have a high percentage of fat. THC is also excreted slowly from the body, which is why its effects may last for several hours.

3.6 According to Professor Trevor Robbins of the Medical Research Council (MRC), THC and other cannabinoids interact with a naturally occurring system in the body, known as the endocannabinoid system. This system is responsible for regulating a wide range of processes, including mood, appetite, and pain. CB1 receptors are found in the brain and throughout the body, while CB2 receptors are found mainly on cells of the immune system and are not present in the brain.

3.7 The roles played by CB1 and CB2 receptors in determining the various effects of cannabis in the body are not yet fully understood. However, it is known that THC interacts with CB1 receptors in the brain to cause euphoria and hallucinations, while CB2 receptors in the immune system may be involved in the modulation of inflammation and pain.

BOX 1: CANNABIS PHARMACOLOGY—TERMINOLOGY
In common with many other drugs, the effects of THC result from its ability to activate special proteins known as receptors found on the surface of certain cells. The drug binds specifically to these proteins and activates a series of chemical changes within the cell, such as alterations in the cell's activity. Drugs, such as THC, that are able to "switch on" a receptor are known as agonists at that receptor. Other substances, however, bind to the receptor and, rather than activating it, prevent its activation by agonists; such substances are known as receptor antagonists.

The term cannabinoid was originally used to describe the family of naturally occurring chemicals found in cannabis, of which THC is the most well-known. These include other cannabinoids, certain synthetic substances (e.g. nabilone—see Box 4 below), and the recently discovered endogenous cannabinoids (see paragraph 3.8 below).

3.8 Another important recent discovery has been that the body contains naturally occurring ("endogenous") compounds that can activate cannabinoid receptors. The most important of these "endogenous cannabinoids" are the fat-like materials arachidonylthanolamide ("anandamide") and 2-arachidonyl-glycerol (2-AG).

3.9 These discoveries have transformed the character of scientific research on cannabis, from an attempt to understand the mode of action of a psychoactive drug to the investigation of a hitherto unrecognised physiological control system in the brain and other organs. Although the physiological significance of this system is still largely unknown, one of the principal actions of THC and the endogenous cannabinoids seems to be to regulate the amounts of chemical messenger substances released from nerves in the brain, thus modulating neural activity.

3.10 The discovery of the endogenous cannabinoid system has significant implications for future pharmaceutical research in this area. Drugs that selectively activate CB1 or CB2 receptors (agonists), or selectively block one or other of these receptor types (antagonists), have already been developed by some pharmaceutical companies (Lambert p 109 and Q 438; Pertwee Q 285). Agonists to the CB2 receptor may have beneficial effects in modulating immune responses, and would not be expected to possess any psychoactive properties as the CB2 receptor is not found in the brain. Antagonists to the CB1 receptor are also being investigated, as novel therapeutic agents with the potential of reducing memory deficits associated with ageing or neurological disease, as novel treatments for schizophrenia or other psychoses, and as appetite suppressants.

3.11 It seems likely that most of the putative medical indications proposed for cannabis involve actions of the drug on CB1 receptors in the central nervous system. Extensive attempts were made by academic and pharmaceutical industry researchers during the 1970s to develop new chemically modified cannabinoid molecules that separated the desired therapeutic effects from the psychoactive properties of these substances; but so far no such compound has been discovered.
3.12 Research continues apace. Professor Patrick Wall of St Thomas' Hospital reports "intense activity in universities and pharmaceutical companies" in this field; "Large numbers of cannabinoids are being synthesised and investigated particularly by US companies" (p 31); "It is an exciting period" (Q 101, cp Q 125, Pertwee QQ 281-298 and Notcutt Q 411). According to Dr Lambert, "The pharmaceutical industry has now provided the researcher with a wide range of tools to probe the cannabinoid system".

3.13 Recent data from animal studies reveal that, in common with various drugs of addiction (heroin, cocaine, nicotine and amphetamines), THC activates the release of the chemical messenger dopamine in some regions of the brain of rats (Pertwee Q 311, Wall Q 126). This is considered important as this pattern of dopamine release is thought to be associated with the rewarding properties of these drugs and hence may be related to their ability to cause dependence.

3.14 Other recent scientific findings indicate a relationship between the cannabinoid system in the brain and the naturally occurring opioid system. The ability of THC to trigger dopamine release in the rat brain is blocked by prior administration of naloxone, a drug that selectively blocks the actions of opiates in the brain. This suggests that some of the psychoactive effects of THC and other cannabinoids may be mediated indirectly through an ability to activate the opioid system (Pertwee Q 311). Recent studies have also shown that the administration of THC to animals enhances the pain-relieving effects of morphine and related opiates. Furthermore, administration of naloxone (the opiate-blocker) to animals previously treated repeatedly with a cannabinoid produced some physical withdrawal signs; conversely, administration of a cannabinoid antagonist to animals previously dependent on heroin elicited some (but not all) of the signs of opiate withdrawal (see Appendix 4, paragraph 8). On the other hand, although some of the actions of THC may involve activation of the opioid system, THC does not mimic morphine or heroin either in its effects on animals or in the subjective experience of human users.

3.15 This new information may or may not be relevant to the debate as to whether cannabis induces physical dependence. We discuss the degree to which cannabis may induce dependence in man below, in Chapter 4.
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Dr Pertwee is a world expert on the cannabinoids, and current President of the International Cannabinoid Research Society. At the University of Aberdeen, he heads a research team of eight scientists engaged in research in this area. He was a contributing author to the BMA report.

Professor Wall is editor-in-chief of the medical journal *Pain*; he was a contributing author to the BMA report, and appeared before us on behalf of the ACT.


The opioid system consists of receptors normally activated by the enkephalins and endorphins, normally released in response to pain and stress. They are also activated by morphine, heroin and other opiates.