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 its parts are used for fibres, seed, oil, and 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.

3.3 THC and other cannabinoids dissolve readily in fat but not in water. This limits the possible forms of administration. Pain relief can be obtained by oral ingestion of cannabis, with a peak effect after about 1 hour. THC is present in the lungs after smoking, and is absorbed into the blood. The effects of smoking can be felt within seconds, but they last for a shorter time than those obtained by oral ingestion. In the digestive tract, THC is converted to C11 and C13 metabolites, which have weaker effects than THC itself. THC and its metabolites can be detected in urine for some time after use.

3.4 Smoking delivers 30 per cent or more of the total THC in a cannabis cigarette to the bloodstream. The biochemical pathways by which cannabinoids are absorbed and metabolised are not fully understood.

3.5 Once THC has entered the bloodstream, it is widely distributed in the body, especially in fatty tissues. The effects produced by a recent dose. (The implications of this for roadside testing of drivers are considered below, at paragraph 4.9.)

3.6 According to Professor Trevor Robbins of the Medical Research Council (MRC) and Professor Roger Pertwee of the University of Aberdeen, it is now recognised that THC interacts with a naturally occurring system in the body, known as the cannabinoid system (see Box 1). CB1 receptors are found mainly in the brain; 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 still being researched.
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 events within the cell. 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 best known. However, the term is now used more widely to include 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.
5 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. Back

6 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. Back


8 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. Back