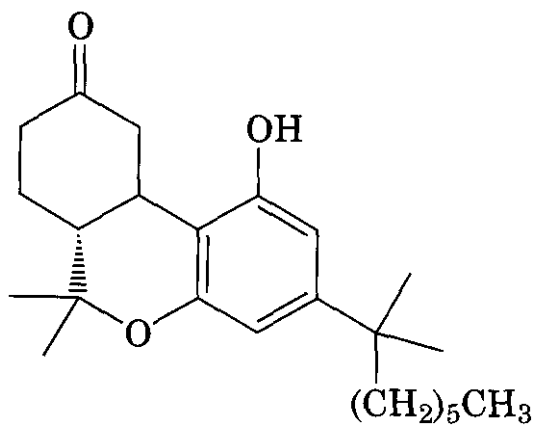
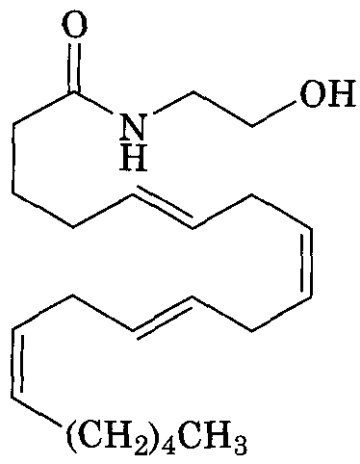
or two cancer patients receiving chemotherapy would dose themselves with their own sedative in the form of marijuana. An unexpected blessing from this uncontrolled combination was a reduction in the nausea experienced during chemotherapy. A variety of anticancer agents cause severe nausea and vomiting, including nitrogen mustard, adriamycin, 5-azacytidine, cyclophosphamide, and methotrexate: the unique situation arose in which the remedy was discovered by the patients themselves (21). Although smoking reefers gives rapid absorption and close control of the effects, smoking is itself carcinogenic and cannot be recommended to those who are unaccustomed to it; thus, when the physicians in charge were made aware of their patients' discovery, they devised a controlled clinical trial in which measured doses of THC were dissolved in sesame oil and administered in gelatin capsules. A placebo was similarly prepared for use in a randomized, double-blind, crossover experiment (21). The results left no doubt that a majority of patients benefited from THC pretreatment, even those who had previously been refractory to the effects of the standard antiemetics such as prochlorperazine. There remained the problem of tachycardia associated with THC treatment. The multiplicity of effects of THC have led to the synthesis of large numbers of analogs (22), particularly in the hope of finding non-morphine-like analgesics without addictiveness and without the other CNS effects of THC. The analog nabilone (16) had been shown to exert less effect than that of THC on the cardiovascular system, while retaining the mixture of CNS actions, including analgesic, antianxiety, and antipsychotic properties (23). When tested as an antiemetic, nabilone proved to be superior to THC (24) and has been used for this purpose for more than 30 years. The first 10 years of clinical experience was reviewed (25).

After the demonstration of THC binding sites in the CNS (26), a search for an endogenous ligand produced the long-chain ethanolamine derivative (17) of arachidonic acid, known as anandamide (27). Subsequently, the glycerol ester of arachidonic acid (18), known as 2-AG, was shown to be a more abundant endogenous ligand in the brain than anandamide (28). Further development has tended

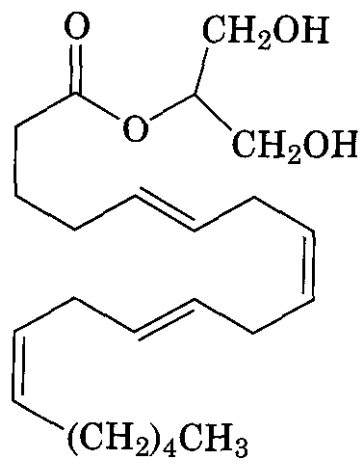


(16) nabilone

to concentrate on analogs of the natural ligands, notably the methyl derivative of anandamide (19), which is resistant to the amide hydrolase that terminates the action of anandamide itself and the dimethylheptyl analog (20) that is traceable to the earlier modifications to THC (29). Such analogs tend to have activity similar to that of THC.



(17) anandamide



(18) 2-AG

An interesting twist in the tail is provided by the observation that anandamide is also a ligand for the so-called enigmatic vanilloid re-