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When you were given the National Medal of Science, you had made Nixon's White House 'Enemies' list. What did you do to get onto this list?

That was discovered in 1973 about two weeks after I got the National Medal of Science, which was hilarious. The newspapers, particularly the big newspaper in San Francisco, *The San Francisco Chronicle*, had this wonderful headline: 'Nixon gives medal to enemy'. Somehow, I'd gotten on the list of people who were opposed to Nixon and opposed to the Vietnam War. Nixon and I are shown in a photograph, where we shook hands and beamed at each other. When I hung it up in my office, my students prepared a lovely counterpart in calligraphy saying: 'Support your local enemy'. Those two were always hanging side by side in my office.

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Carl Djerassi's latest play *Phallacy* is running from 5 April–14 May 2005 at the New End Theatre in Hampstead, London, UK. For more information, go to: http://www.djerassi.com.

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Cannabinoid therapeutics: high hopes for the future

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The psychoactive properties of *Cannabis sativa* (cannabis) were first recognized 4000 years ago by the Chinese. However, it is the illicit properties of cannabis that are rendering it increasingly popular worldwide, with the number of recreational cannabis users rising considerably [according to a United Nations (UN) report] compared with other abused narcotics. At low doses, the effects are euphoria, feelings of relaxation, altered sensations, reduced pain and increased laughter, talkativeness and hunger. In addition, users experience decreased problem-solving ability, short-term memory and psychomotor performance. At higher doses, effects include personality changes and hallucinations. In addition to its recreational use, cannabis has been used in medicine for thousands of years for the treatment of diseases, such as malaria, constipation and rheumatism, in countries including China and India, as well as the Middle East. However, in the Western World, the medicinal benefits of cannabis were not appreciated until the middle of the 19th century.

Research into cannabinoids and their receptors

The active compounds of cannabis are cannabinoids. Interest in the potential medicinal value of these compounds led to the identification of over 60 separate cannabinoids and, of these, δ-9-tetrahydrocannabinol (THC) and cannabidiol have been extensively characterized. The resultant understanding of their interactions at the molecular level has enabled major advances over the past two decades in realizing the therapeutic potential of cannabinoids. THC is largely responsible for the psychoactive properties of cannabis and has demonstrated analgesic, antispasmodic, antitremor, anti-inflammatory, appetite stimulant and antiemetic properties. Cannabidiol has had anti-inflammatory, anticonvulsant, antipsychotic, antioxidant, neuroprotective and immunomodulatory effects.

The endogenous cannabinoid system was identified in the late 1980s, and, in 1992, anandamide, the first endogenous cannabinoid, was discovered. Anandamide, the name of which comes from the Sanskrit word for bliss, can be found in numerous areas of the brain, including the hippocampus, striatum, thalamus and cerebellum. Other endogenous cannabinoids, such as arachidonyl glycerol, have also been identified.

These compounds act via two distinct G-protein-coupled receptors – the cannabinoid (CB) receptors CB_1 and CB_2. Recreationally and medically, the biological effects of cannabis and other exogenous cannabinoids on CB_1 and CB_2 receptors have been extensively investigated. CB_1 is abundantly expressed in the brain, particularly in regions where anandamide is found, and those areas concerned with movement, postural control, pain and sensory perception, memory, cognition, emotion and autonomic and

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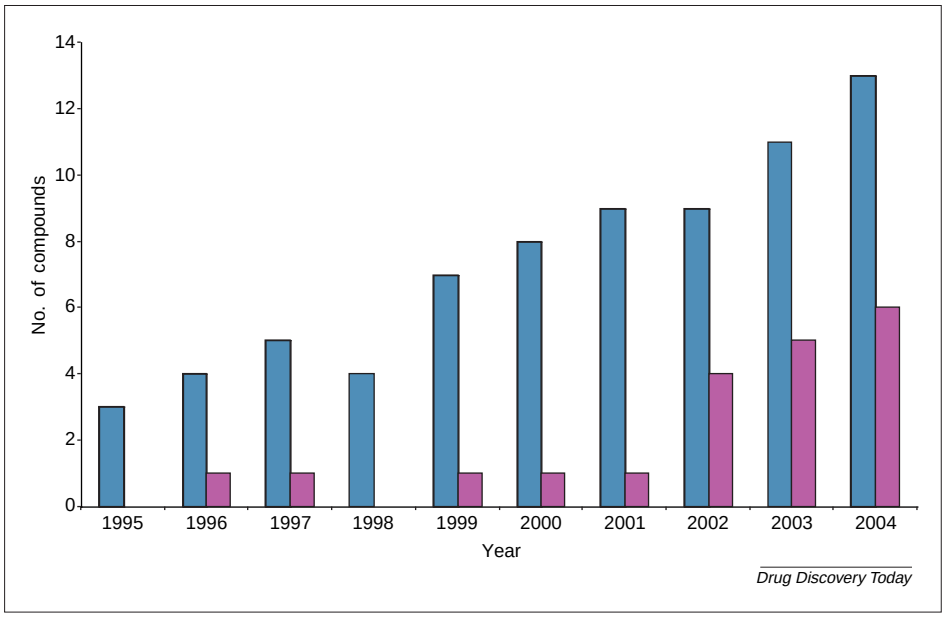

FIGURE 1

Number of cannabinoid 1 receptor agonists and antagonists under development 1995–2004. Blue bars represent number of CB_1 agonists in development, where purple bars represent CB_1 receptor antagonists.

endocrine functions. Interest in the medical potential of modulators of CB_1 is reflected in the substantial increase in the development of CB_1 modulators since 1998 (Figure 1). CB_1 antagonists have applications in the treatment of obesity and addiction to alcohol and nicotine; Sanofi-Aventis is developing its CB_1 antagonist, rimonabant, for all these indications. In Phase III trials in Europe and the USA, one year of treatment with rimonabant resulted in an average weight loss of 4.5–8.6 kg. In Phase II trials, this compound demonstrated positive results in smoking abstention, and clinical trials of rimonabant are ongoing in Australia, Canada and the USA for alcohol withdrawal. Regulatory filings in the European Union and the USA for obesity and smoking cessation are expected in 2005.

CB_2 receptors are expressed in the periphery, where they are most abundant on cells of the immune system. The role of CB_2 receptors is still under investigation, although they are believed to mediate immunological responses attributable to cannabis. The ambiguity surrounding the CB_2 receptor is reflected in the lack of drugs currently under development that target this receptor; however, as the role of CB_2 in the periphery is slowly elucidated, interest in its medical potential has amplified.

The homology between the CB_1 and CB_2 receptors is 44%, suggesting that the development of therapies that target a distinct receptor subtype with high affinity is feasible. Anandamide shows moderate affinity for CB_1 receptors when compared with THC and is more rapidly metabolized, yet they display similar pharmacologies. Although the precise functions of these receptors and the endogenous ligands are unknown, and the physiological effects of these cannabinoids remain unclear, various animal models of pain have indicated a role in analgesia.

A history of cannabinoids in medicine

In the UK, doctors were able to prescribe cannabis until 1971, when the UN passed the Convention on Psychotropic Substances, in response to growing concern regarding the abuse of psychotropic substances. However, in intervening years, it appears that attitudes have changed; a 1994 survey in the UK indicated that 74% of doctors wanted cannabis to be available for medicinal purposes. Many anticipate that exogenous cannabinoids will be effective in pain syndromes that are poorly understood, for example, treatment-refractive neuropathic pain and the spasms of multiple sclerosis (MS), and thus these compounds are attractive as therapeutics. It is hoped that exogenous cannabinoids could be effective treatments for an extremely disparate range of disorders, including nausea, rheumatoid arthritis, glaucoma, Crohn's disease, cancer and migraine. Cannabinoid agonists are also under investigation as appetite stimulators and as therapies for drug withdrawal. The growing interest in cannabinoids as therapeutic agents is reflected in the dramatic increase in the number of

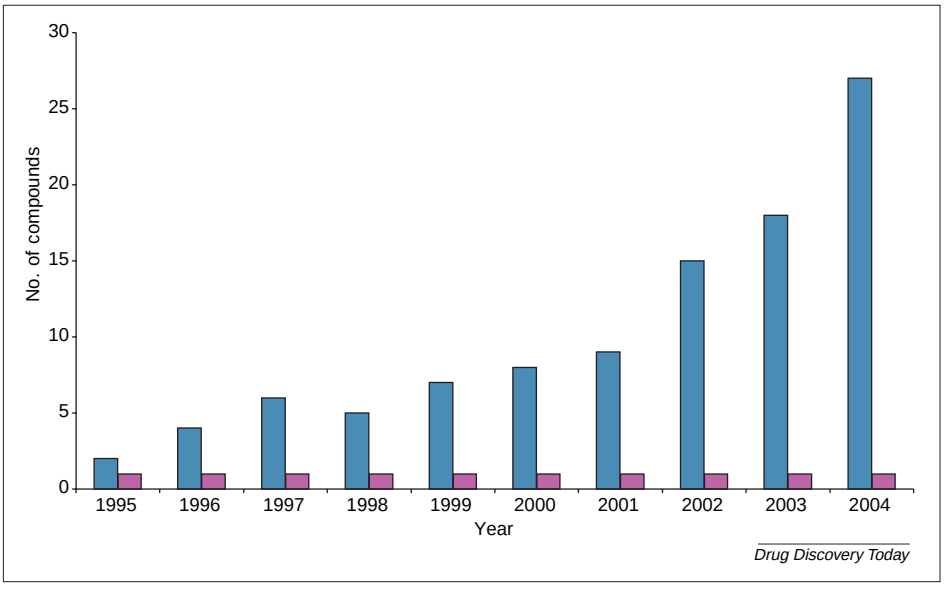

FIGURE 2

Cannabinoid drugs in development 1995–2004. Blue bars represent active compounds, where the purple bars represent fully launched drugs.

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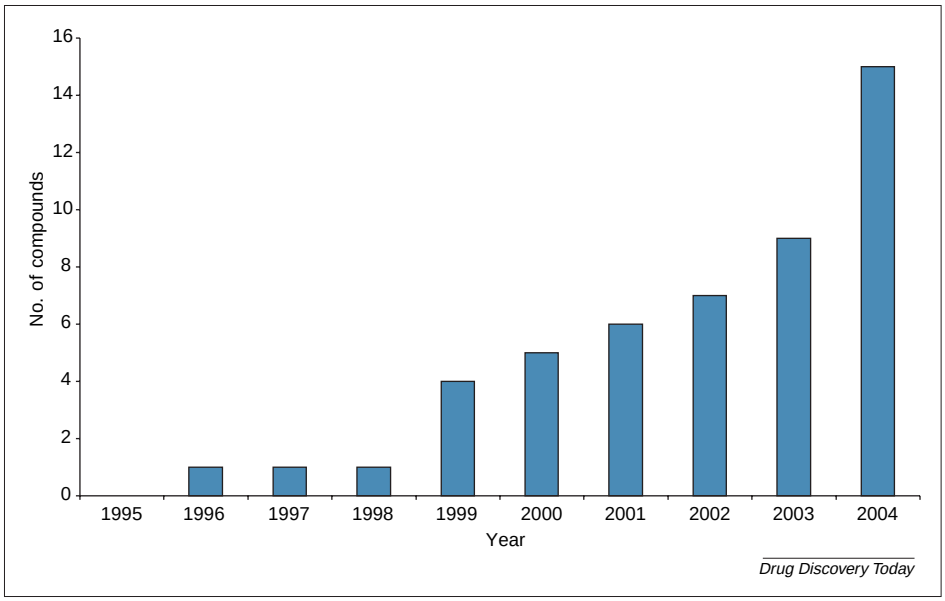

FIGURE 3

Number of cannabinoids under development for pain 1995–2004.

cannabinoids in active development (Figure 2).

The antiemetic effect of cannabinoids has been studied more extensively in humans than any other indication, and is the best supported therapeutic use of these compounds. Of the four cannabinoid drugs available on the market, two are intended for use as antiemetics. Marinol, which was launched in the USA by Solvay in 1986, is a CB_1 receptor agonist that acts via receptors located in the brain and is effective in chemotherapy-induced nausea and vomiting. Nabilone (Cesamet), which is classed as a narcotic, is a CB_1 agonist developed by Eli Lilly for nausea and vomiting that was originally launched in Canada in 1982 by Valeant. Finally, H G Pars is developing a formulation of dronabinol as an antiemetic to be used in conjunction with chemotherapy: it is awaiting registration in the USA.

Cannabinoids in pain, multiple sclerosis and AIDS

Although less widely studied in humans, the analgesic properties of cannabinoids have been appreciated since the time of the ancient Assyrians. Modern-day scientific research is also aware of the ability of cannabis and THC to reduce hyperalgesia and allodynia, validated by trials in animal models of pain and emphasized by the increase in cannabinoids under development for pain between 1995 and 2004 (Figure 3): similarly, the majority of cannabinoids currently in clinical development are indicated for alleviating pain (Figure 4). Nearly 40% of cannabinoids are under development for non-specific pain indications; however, more specific maladies, including cancer, neuropathic and post-herpetic pain, are also being targeted. Two similar compounds, SIMM18 and Bedrocan, were launched last year in The Netherlands, where recreational use of cannabis is decriminalized (under certain circumstances). Produced by specialist government-sanctioned companies, they are primarily for use in the treatment of MS, but are also indicated as analgesics. GW Pharmaceuticals, a global leader in developing cannabinoids for medicinal use, is investigating a sublingual formulation of THC derivatives for the treatment of cancer pain in Phase III trials. KDS2000, currently in Phase II clinical trials, is topically applied, and is being developed by Kadmus Pharmaceuticals for the treatment of post-herpetic pain.

MS is another disorder that is potentially treatable by cannabinoids, with 17.3% of active compounds being developed for this indication (Figure 4). In addition to SIMM18 and Bedrocan, three other products are currently in development. The most promising is Sativex (GW Pharmaceuticals), which is a whole plant extract containing THC and cannabidiol that acts as a CB_1 antagonist. Phase III results released earlier this year indicate that Sativex had an effect 'over and above' currently available treatments in 189 MS patients. Its ability to treat spasticity was considered statistically significant by GW Pharmaceuticals, with the company expressing no doubt over the therapeutic benefits of cannabis derivatives following numerous positive clinical trials. Earlier late-stage clinical trials indicated that the drug caused reductions in pain and sleep disturbances and an increase in quality of life: UK approval of Sativex is expected in mid-2005.

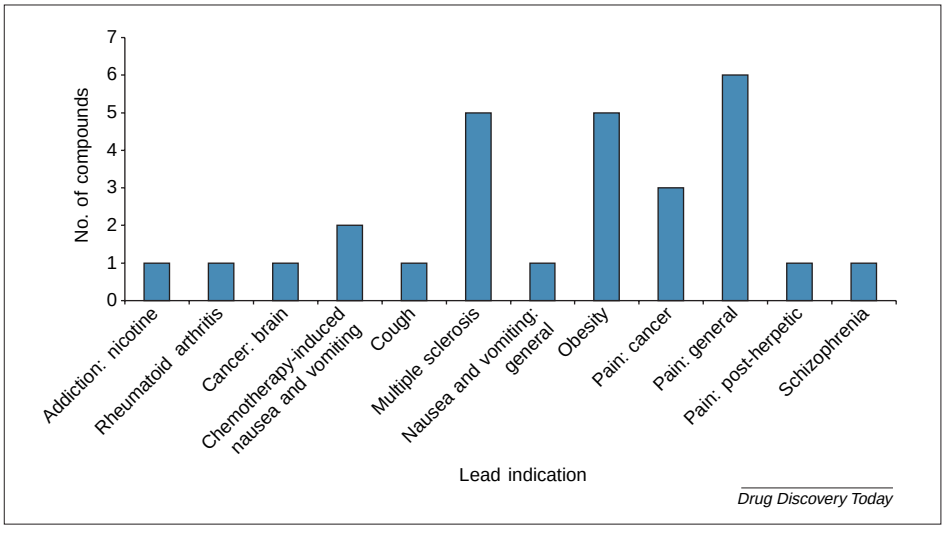

FIGURE 4

Lead indications of cannabinoid therapeutics.

conference report

Other cannabinoids in development for MS include Pharmos' early-stage CB_2 receptor agonist, HU308, and Pharmaxis' PXS2000, which is intended to retain the beneficial properties of cannabis without its psychotropic effects.

Cannabis has a profound effect on appetite stimulation – 'the munchies' as it is termed by recreational users. Studies as early as 1933 performed by a military committee illustrated increased food intake in subjects taking marijuana. In the USA, cannabis has been used in patients with AIDS to ameliorate the cachexic symptoms of the disease. Solvay and Nektar are currently collaborating to develop an inhaled formulation of dronabinol (currently undergoing Phase I development) for the treatment of wasting and weight loss in HIV patients.

The future of cannabinoids

The benefits of cannabinoids are extensive, with compounds under development for numerous indications other than those mentioned, including cough, bulimia, inflammation, Parkinson's disease, Tourette's syndrome and schizophrenia (Figure 4). It is therefore unsurprising that entire pharmaceutical companies, such as GW Pharmaceuticals, are focusing their R&D efforts on developing therapeutic cannabinoids. Enthusiasm about the therapeutic use of cannabinoids is curtailed only by consideration of the side effects of the drugs, which include psychomotor and cognitive impairment, postural hypotension, anxiety and panic attacks, acute psychosis and paranoia, palpitations and tachycardia. With the majority of cannabinoids in preclinical stages, it seems that the future of cannabis as a therapeutic agent remains uncertain, even amid its increasing popularity as a recreational drug.

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conference report

In vitro assays: crystal balls or random guesses?

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In Vitro *Screens in Drug Metabolism*
Orlando, FL, USA
13–14 December 2004

Organizers:
Cambridge Healthtech Institute

One of the central challenges in drug metabolism and pharmacokinetics is that of prediction, extrapolating data generated from *in vitro* models to the human response as early as possible. This is a problem that has been addressed by many review articles and conference sessions. The Cambridge Healthtech Institute presented its first meeting tackling this subject, In Vitro *Screens in Drug Metabolism*, on 13–14 December 2004 in Orlando, FL, USA. Would this conference produce any additional information to what is an information rich, but solution poor, subject? The combination of an interesting programme, the hot Florida sunshine and a hotel in the middle of Disney World ensured that the meeting was a success, both scientifically and socially!

Assay development with novel approaches to drug metabolism

Underscoring any predictive *in vitro* system must be the development of novel assays that correctly model the *in vivo* system and, preferably, increase knowledge of *in vivo* biology. The first session of the conference attempted to bring together emerging and validated technologies for *in vitro* screens, ranging from cytochrome P450 (CYP) turnover to novel cell lines. The regulation of CYP turnover was described by Amit Banerjee (Wayne State University, MI, USA). CYP expression is central to the metabolic processing of many chemicals, and thus CYP turnover could be an important predictor of metabolic capacity. Banerjee presented data showing the identification of specific components of the ubiquitination cycle that regulate CYP turnover, and hence ultimately control the level of CYP-mediated metabolism. *In silico* modelling was used to produce small molecule inhibitors of this process, resulting in a new set of chemicals that represent a promising novel method for regulating CYP-mediated metabolism.

Continuing the theme of small molecule inhibitors, Pierre-Yves Abecassis (Sanofi Aventis) described HTS for mechanism-based enzyme

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