gy—that the present is the key to the past—can limit rather than enhance our understanding of the fossil record. Without an understanding of process and geologic context, simple extrapolation from the present to the past can be misleading. After all, we live today in an unusual world: sea level is low, the continents are dispersed, ice occupies the poles, and the shelly fauna of the oceans is composed largely of aragonite rather than calcite. The full range of possible environmental conditions on Earth has not been experienced in the short span of human history, or even the past few hundred thousand years. This lack of Recent analogs for many phenomena seen in the geologic record makes the present-day world an incomplete and biased sample of life on earth.

BOOKS: PHARMACOLOGY

How Cannabis Acts

Steven R. Childers

There are few topics more controversial than marijuana. It is an ancient drug, and the history of cultivation of the marijuana plant, *Cannabis sativa*, goes back at least 12,000 years. The modern debate on marijuana's medicinal potential, which dominates current public interest in the United States and Europe, is also not new. Numerous detailed inquiries have explored both the safety and the possible therapeutic value of marijuana; these include reports from the Hemp Drugs Commission of the government of British India (1894) and from Mayor La Guardia's committee on marijuana in New York City (1944). Remarkably, even such older reports provided balanced evaluations of the advantages and potential hazards of marijuana, but their conclusions have been overshadowed by the arguments that dominate both sides of the marijuana debate.

The Science of Marijuana
by Leslie L. Iversen
Oxford University Press, Oxford, 2000. 301 pp. 29.95, £18.99. ISBN 0-19-513123-1.

Until recently, scientific research on the cannabinoids contributed little to this debate. Delta-9 tetrahydrocannabinol (Δ^9-THC), the principal psychoactive ingredient of marijuana, is virtually insoluble in water and is difficult to study in vitro or in vivo. For years, researchers believed that THC acted in the brain via relatively nonspecific mechanisms such as altering the fluidity of nerve cell membranes. Cannabinoid research lagged behind other fields of psychopharmacology, and progress in understanding the mechanisms of THC was slow. But the field changed dramatically in the mid to late 1980s, when a specific receptor for THC, the CB_1 cannabinoid receptor, was found in high densities in various regions of the brain. We now recognize that the body contains its own endogenous cannabinoid systems, comprising cannabinoid receptors in neurons and immune cells, together with endogenous cannabinoid-like substances (which include anandamide and related arachidonic acid compounds). Cannabinoid research has provided important information on mechanisms of THC action. For example, high levels of CB_1 receptors in such areas as the cerebellum, substantia nigra, and globus pallidus contribute to the effects of marijuana on motor control and coordination, whereas CB_1 receptors in hippocampus mediate effects on short-term memory. This research has developed a scientific basis for understanding many of the actions of THC, along with some proposed therapeutic targets of the drug. Such information was crucial for the much-anticipated 1999 report from the Institute of Medicine of the U.S. National Academy of Sciences that reviewed the scientific basis for marijuana therapeutics and made specific recommendations for further study.

Pot heads. Engraving from R. Wisset's 1808 *Treatise on Hemp* showing flowering heads of female cannabis plants.

CREDIT: FROM R. WISSET, *A TREATISE ON HEMP* [J. HARDING, LONDON, 1808]/COURTESY L. IVERSEN

These results also provide the basis for Leslie Iversen's *The Science of Marijuana*. A well-known neuropharmacologist, Iversen was an important contributor to the House of Lords select committee report on cannabis. He is, therefore, in an excellent position to summarize historical and recent research on cannabinoid actions. He has written a remarkably well-balanced volume that provides the scientific background for the current debate on marijuana use. Readers who wish to know only one side of this question, or want only final answers to the complex issues of marijuana therapeutics, should look elsewhere. Iversen's book explores these issues from all sides, with reports from diverse scientific fields. It is a treasure trove of information about the history of marijuana use and legislation, and it effectively summarizes in lay terms the cannabinoid research that now offers a potential scientific foundation for medical, political, and legal decisions about marijuana.

The most important, and most extensive, part of the book deals with the potential therapeutic uses of marijuana, the cornerstone of the current public debate. Here, Iversen not only summarizes the potential advantages and side effects of marijuana for each of the proposed therapeutic uses of the drug, but also discusses therapeutic alternatives and whether marijuana offers any actual advantages over currently legal prescription drugs. He concludes that for some, but not all, of the proposed therapeutic targets, cannabinoids could offer potential advantages in terms of efficacy and safety, as long as negative side effects and issues of drug delivery are adequately addressed. Only well-controlled clinical trials will be able to provide clear answers to these questions, and Iversen has presented an effective blueprint for future studies.

One interesting puzzle of cannabinoid science remains unanswered: the mammalian brain contains extremely high levels of CB_1 cannabinoid receptors, among the highest amount of any class of neurotransmitter receptor in the brain. Why do we need so many receptors for THC-like substances? Perhaps the endogenous cannabinoid system mediates a number of important brain functions—but these are clearly not vital functions, because CB_1 knockout mice remain viable despite the loss of the CB_1 receptor gene. It is also likely that such high numbers of receptors are crucial for the observed actions of marijuana. THC itself is a weak partial agonist at these receptors; if these receptors were present at the levels typical for those of other neurotransmitters, marijuana might produce only slight effects. But with a high number of receptors, even partial agonists can have substantial effects. We can speculate that it is our brains' supply of cannabinoid receptors that determines the effects of marijuana, whether as a drug of abuse or as a therapeutic agent.

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