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REVIEW OF REVIEWS

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DRUGS AND PERFORMANCE IN SPORTS

The appearance of this book, edited by Strauss (1), truly fits the times. 1988 was the year of the Olympics, and at no time had drugs in sports received more public attention and media coverage. Indeed, as this review was being written, the news had just reported that Ben Johnson, the most celebrated track athlete of the Olympics, after winning a gold medal and setting the world record in the one hundred meters race, was disqualified for using anabolic steroids.

The world was shocked. Many are unable to understand why so many athletes are willing to risk disaster with drugs. The answer is simple. In order to achieve fame, fortune and adulation, some athletes feel the gamble worth taking, and seek advantages to achieve these goals. Hence, drug use in sports is a major problem—and not just in top athletes. It may be even more serious at the teenage level.

Proof of drug enhancement of sports performance is difficult to establish scientifically. As Strauss and Curry aptly point out in the opening chapter, races are often won by a fraction of one percent. To demonstrate this experimentally, however, a large number of trials in comparison with a placebo would have to be performed under conditions controlling nutrition, fatigue, and motivation. Although scientists may rightfully be skeptical of the value of drugs, many athletes are not. Some athletes may be naive, but many others may have good reasons for being satisfied customers. It is difficult to refute that a very good sprinter became the greatest ever after taking anabolic steroids. And there were other medal winners also who, if their performances were not abetted by anabolic steroids, were not hindered by them either. No wonder top athletes often become suspect of drug use after superior performances.

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The book, besides discussing the use of drugs in sports, covers a variety of topics relevant to sports medicine. Other maneuvers that might improve performance are examined, including nutrition, blood doping, oxygen breathing, and altitude training. Psychological aids to performance are discussed as well as a thoughtful analysis of why sports records are constantly improving. The drug classes considered are the anabolic steroids, stimulants, and depressants. The ethics of drug use in sports are examined and sometimes the line drawn may be thin. Why can painkillers be given to an injured athlete to enable performance and risk still further injury, but not anabolic steroids to speed up the healing process of a muscle tear? A highly informative chapter on the detection of drugs in urine and interpretation of the data is provided by Catlin, who was in charge of urine testing at the 1984 Olympic Games in Los Angeles. I don't see how any pharmacologist with an avid interest in sports would not want to have this book.

THE GREAT DRUG DEBATE

The Public Interest, a quarterly periodical hardly known to most pharmacologists, sponsors three highly informed and constructive articles about ways to regulate drug abuse. All three authors take cognizance that present drug policies have largely failed and that drug control efforts have been very ineffective and costly. Despite bipartisan support from the President and the First Lady to enact more repressive antidrug measures, the writers do not appear to be overly impressed by such an approach, and instead advance their own views that are likely to stir emotion.

Nadelmann (2) argues the case for legalizing drugs. He asserts that drug-control policies have failed because they are fundamentally flawed. The benefits of legalization would reduce government expenditures on enforcing drug laws and new tax revenues from legal drug production and sales would benefit the public treasury. Crime rates would be reduced and the quality of urban life would increase significantly. Although legalization of a drug might well increase its use, he has reasons to believe that the repeal of drug laws would not lead, as many people fear, to a dramatic rise in drug abuse. He concedes that the health costs for the use of legal drugs such as alcohol and tobacco have been extremely high, but notes that Americans are just beginning to recognize this and this has led to the decreased use or to milder forms of alcohol and tobacco usage.

He stresses that legalization is a means to put drug dealers out of business. It is not an endorsement of drug use but rather a recognition of the rights of adult Americans to make their own choices free of the fear of criminal sanctions. It is a proposal for the redirection of attention and effort by

government to provide assistance and positive inducements rather than criminal penalties and more repressive measures. There is a lot of common sense expressed in these views but current morality and politics lend little support, if not strong opposition, to the legalization of drugs.

Kaplan (3) acknowledges the failure of our drug policies but takes a more cautious and pragmatic route, arguing that legalization ignores basic pharmacology. Sanctions, if any, should be imposed on a drug-by-drug basis. The issue boils down to carefully weighing the costs of criminalization of each drug against the anticipated public health costs were that drug to become legally available. For example, advocates of cocaine legalization would need to make a serious estimate of how many more people would use the drug after it were legalized; how many would become dependent and how much harm would this cause them and society. He opines that if the number of those dependent upon cocaine merely doubled, considering the costs imposed by treating these users as criminals, legalization of cocaine should be worthwhile. But, if there is a fifty-fold increase in cocaine use, that is another matter. Since such a situation cannot be guaranteed not to come to pass, it would be irresponsible to legalize cocaine based on existing knowledge. He favors increasing law enforcement efforts to decrease drug availability at open air drug markets and to force dealing indoors where a large percentage of potential customers are afraid to go. Pressure on the buyer would also have an impact on drug demand. Seizing the car of the buyer should be a regular feature of drug enforcement as well as routine urine analysis for any of the typical crimes arising out of drug use. Not least, more money should be invested in drug treatment.

Reuter also analyzes the supply and demand facets of drug abuse, scoring the efforts and funds put into drug enforcement programs while deploring the lack of commitment to treatment programs (4). In the fiscal year 1988, he notes that 75% of the drug budget was devoted to enforcement, out of a total expenditure of nearly $4 billion, but success was not in evidence even though larger quantities of drugs might have been seized. For example, if interdiction is truly successful, one might expect the price of drugs to increase. In fact, the price of cocaine has remained fairly stable because smugglers have become more sophisticated in their evasion activities. Sometimes the maneuver is quite simple. In the case of marijuana, as the Coast Guard increased its efforts against the seaborne traffic, the smugglers merely shifted to shipping smaller loads. By halving the size of the average shipment, the task confronting enforcement agencies doubled. While Reuter does not advocate the abandonment of interdiction programs, he says that if some of their costs were allocated to treatment, not only would there be a decrease in economic benefits, but also in a reduction in a number of social costs (such as fear of crime) would make the shift worthwhile.

COCAINE ADDICTION

The pharmacology of a drug does not change but it is sometimes very difficult to convince people of this simple fact, especially when a substance of abuse is involved. In such instances, views concerning the potential harmfulness of the agent become colored largely by prevailing public opinion. This has certainly been the case with alcohol, heroin, and marijuana. With cocaine, there has even been a recycling of attitudes.

It was not many years after Freud popularized the euphoriant use of cocaine in the 1880s that its addictive liabilities became apparent. In this country, usage diminished following the 1914 Harrison Narcotic Act (cocaine was legally defined to be a narcotic), but revived again shortly after restrictive legislation against the amphetamines became effective in 1970. Sniffing of cocaine hydrochloride became popular, and although there were instances of severe complications, many could enjoy cocaine recreationally without becoming compulsive users. With the advent of crack cocaine, however, increasing numbers have become addicted and have died from cocaine overdosage. The toxic effects of cocaine noted are similar to those described in considerable detail in many papers in the older literature.

One of the most comprehensive discussions on cocaine was written in German by Hans Maier, a Swiss psychiatrist who died in 1945 at age 65. His book was published in 1926 after he had spent more than nine years making observations on the drug. Kalant (5) has provided a highly readable English translation that attempts to present Maier's views in the perspective of modern psychiatry.

Maier terms cocaine addiction as an illness and provides descriptions of the acute and chronic effects of cocaine in experimental animals and humans. The account in humans is quite exhaustive. The discourse on the clinical effects includes interesting case histories and descriptions of disturbances in central nervous effects related to perception, cognition, memory, personality, attention, volition, and intellectual function. Acute and chronic cocaine diagnosis and treatment as well as their medical and legal and social aspects are also discussed. Much of what he writes and warns about still applies. Why can't we learn more effectively from the past?

THE PSYCHOPHARMACOLOGY OF ADDICTION

This volume contains eleven papers presented at a meeting held in London in 1986. Edited by Lader (6), topics of varying degrees of interest to psychopharmacologists are discussed and are concerned with drugs, techniques, and approaches. The drugs included are the benzodiazepines, ethanol, opioids, caffeine, and nicotine. The methodology ranges from biochemical binding to psychological testing related to anticipation, reward, and conditioning. There are also essays on personal and social aspects of nicotine and

opiate use. Although some useful information can be found here, this book is not a must; indeed, I would be inclined to be parsimonious.

Opiopeptins—Brain Peptides with Opiate-like Activity

Several volumes on this topic have been published recently, including one for semi-popular reading. When opiate binding sites and native peptides with opiate-like activity were discovered in the 1970s, their innovators could hardly have imagined the wide range of biologic functions they might influence. It has now become abundantly clear that the role of opioid receptors and their ligands far transcends opiate pharmacology. In addition to the brain, opioid receptors are widely distributed in the periphery, including the gastrointestinal tract, adrenals, and hematopoietic systems. And it now appears that the endogenous ligands participate not only in pain mechanisms but also in other central actions regulating endocrine functions, eating, drinking, water balance, temperature regulation, and many behavioral functions. Morever, certain peripheral systems seem also so fall within their influence.

Confusion exists with respect to the nomenclature of the opiate-like peptides. The designated generic term "endorphin", a contraction of endogenous and morphine, although widely used, has been by no means universally accepted—for good reasons. Hughes & Kosterlitz, the discoverers of the enkephalins, the first opiate-like peptides were not enthused. They believed that the properties of their peptides differed considerably from others such as β-endorphin, which exhibited more potent opiate-like effects. Time has proven that the enkephalins should not be grouped with β-endorphin.

Three families of opiate-like peptides are now established to be derived from different precursor genes. The three types have distinct neuronal pathways that are known as enkephalinergic, endorphinergic, and dynorphinergic. As a generic appellation for all the peptides with opiate-like activity, "opiopeptins" is clear in its meaning, especially since morphine has recently been demonstrated to be a true endogenous substrate of the brain and adrenals.

MESSENGERS OF PARADISE

Levinthal (7) narrates a fascinating story on opiopeptins in the brain for the lay public, but even specialists in varying fields will find the book interesting and informative. The author attempts to ascribe roles for the opiopeptins in the behavior of the individual as well as society. He brings to bear evolutionary and developmental concepts to advance his ideas by attempting to link opiopeptin changes in the brain with the behavior of protoreptilians and the human fetus. A number of regulatory functions are ascribed to the opiopeptins, including those involved in analgesia, stress, autistic behavior, emotionality, addiction, alienation, doubt, creativity, laughter, play, and

social comfort. I like the breadth of this approach, but understandably the author had to be selective in his citations and often noncritical to make his case plausible. Specialists are bound to question some of the generalities and imprecise statements that detract from the scholarliness of the presentation.

The errors related to pharmacology are not that serious, but the infractions are annoying. For example, heroin is stated to be twenty to twenty-five times stronger than morphine but one magnitude less would be more accurate. Also, anglophiles will bristle to learn that credit for the discovery of etorphine is given to a pharmaceutical company in the United States rather than Great Britain. Furthermore, the drug is stated to be 5,000–10,000 times more potent than morphine, its dose given as one-ten thousandth of a gram. Using such figures, the analgetic dose of morphine would calculate to be 50–100 mgm, which could be lethal since the accepted therapeutic dose is 10–15 mgm. Finally, a major omission is the failure to describe the pivotal role of those who identified the sensitive sites in the brain concerned with opiate action, by microinjection techniques.

The chapter describing the isolation of the opiopeptins is of particular interest to pharmacologists. The author obviously consulted many investigators who played significant if not major roles in pioneering their discovery. In 1975, the first class of opiopeptin, the enkephalins, was announced. The identification of a second family, the endorphins, followed soon after, but not until several years later were the third family, the dynorphins, purified.

There are some who insist that the discovery of the opiopeptins resulted from the identification of opiate binding sites but in fact, isolation attempts were already under way when the opiate receptors were identified. This can be an important point in the distribution of honors such as the Nobel prize. Recognition is usually accorded to three persons, and some believe that at least one investigator among those involved in identifying recognition sites should be honored in conjunction with the discoverers of the native opioid ligands. However, the controversy over the identification of opiate receptors has clouded the issue and has interfered with proper recognition for Hughes & Kosterlitz. It is my strong conviction that by now the initial pioneers in the discovery of the enkephalins should have been honored by a trip to Stockholm. I wish I could afford to give away a million dollars!

THE OPIATE RECEPTORS

Pasternak (8) edits a monograph that provides a comprehensive and authoritative treatise on the state-of-the-art of opiate receptors. Most of the authors are and have been major contributors in opiate pharmacology. In general, they have accomplished their assigned task by making balanced presentations based on extensive citations from the literature. Topics include

the conceptual evolution of multiple opioid receptors, their characterization and localization by both in vitro and in vivo techniques. The endogenous opioid ligands are covered and include essays on their classification, pharmacologic effects, mechanism of action on ion channels and second messenger systems, and their possible role in tolerance and physical dependence development.

The opening chapter by Martin, who is generally recognized as the prime innovator in the field, provides a conceptual overview of the evolution of the opioid receptor. He gives much credit to his predecessors at the US Public Health Hospital in Lexington, who developed the methodology in the clinic and the experimental laboratory that enabled quantitative assessments of opiate action. Basic also to the evolution of the concept of receptors was the development of narcotic antagonists. Nalorphine was the antagonist that played an instrumental role during the early days, and Martin gives equal credit to investigators at the University of California at San Francisco and the Merck Laboratories for its discovery, but as has been pointed out (9), the studies really began in San Francisco and were initiated at Merck only after Chauncey Leake, the Chairman of the Department of Pharmacology at UCSF, provided the Merck group with the ideas and data of his graduate students, Elton McCawley & Ross Hart.

One of the major achievements in the 1970s was the demonstration of opiate binding sites. It is now well-known that three laboratories independently made this innovation in 1973. However, previously, many laboratories tried to detect opiate binding sites but failed. Success hinged upon notions of stereospecificity and the availability of a labeled opiate agonist or antagonist with high specific activity. Pasternak mentions a number of early investigators who applied concepts of stereospecificity in their approach but who failed to develop the proper tool for solving the problem. He indicates that the attempts began as early as 1965, but for the record, I should like to claim the dubious honor of having failed first. Sung and I (10) attempted in 1953 to demonstrate a difference in tissue affinity for d- and l- methadone, but our method for determining the two isomers did not allow us even to come close to a solution.

Some other chapters in Pasternak's book should be mentioned. Compelling arguments and data are marshalled by the Zukins for renaming the sigma receptor. The electrophysiology of the opiates is becoming increasingly complex, and is discussed by Chavkin more evenly and fairly than in most reviews of the area. Even though the authors (Smith, Law & Loh) start with poor and imprecise definitions of tolerance and physical dependence, they provide a highly provocative concept of tolerance and dependence based on some extensive in vitro data. On balance, this is an excellent monograph that can be recommended for specialists as well as nonexperts.

REGULATORY ROLE OF OPIOID PEPTIDES

Edited by Illes & Farsang (11), this volume consists of 37 papers presented at a meeting held in Budapest in 1987. The articles are grouped under one of five headings, but this classification is not always followed. There are topics on regulatory mechanisms related to neuronal excitability, neurohormonal release, central nervous system integrative mechanisms, and cardiovascular mechanisms, as well as a section on opiod peptides and their receptors. As is generally the case with published proceedings, the titles range widely and the presentations of the subject matter may be broad or narrow in focus. I found the papers of those who elected to review or overview the state-of-the-art in their respective areas of greater interest. Particularly impressive is the extensive discussion provided by Fuxe and his associates on the role of the opiopeptin system in neurotransmission and neuroendocrine regulation. It is revealing also to read of the reports from laboratories in Eastern countries, which do not always appear in the popular journals of the West.

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