BOOKS: PHARMACOLOGY

Drug Stories—of Origins and Uses

S. J. Enna

Every drug has a story. For example, the German scientists who developed methadone as a substitute for morphine originally named it Dolophine in honor of Adolf Hitler. Medical terms also have interesting ancestry. To illustrate, the term "addiction" is derived from Addictus, a Roman debtor whose capacity for spending borrowed money far exceeded his ability to repay. More fascinating are the roles empiricism, serendipity, and astute clinical observation play in identifying new drug therapies. Even in this era of genomics, computational chemistry, molecular modeling, drug targeting, and high throughput screening, clinical uses are still discovered by accident. Although, for instance, sildenafil (Viagra) was originally designed as a therapy for angina, its utility for treating erectile dysfunction was noted during clinical trials. In *Pills, Potions and Poisons*, Trevor Stone and Gail Darlington weave together historical facts, fables, and foibles to humanize the science of pharmacology and sustain the interest of a lay audience. The authors (a professor of pharmacology at the University of Glasgow and a practicing physician) hope that the volume will be used as a reference source on drugs and the conditions that they are used to treat.

Pills, Potions and Poisons
How Drugs Work
by Trevor Stone and Gail Darlington

Oxford University Press, New York, 2000. 492 pp. $27.50, £18.99. ISBN 0-19-850403-9.

Our earliest ancestors ingested a variety of plant and animal products to alleviate pain, fever, fear, and other maladies. Through trial and error, a number of these natural products were found to provide relief for particular conditions. Indeed, we are indebted to those individuals who, over the ages, lost their lives in demonstrations that some natural products are lethal. A major problem with crude plant and animal extracts, however, is that the amounts of active ingredients, and of any toxic substances also present, vary with each preparation, which makes the responses of patients unpredictable. But we still enjoy the benefits of the observations of these early experimentalists, with drugs such as atropine, aspirin, digitalis, and opiates. Their efforts also yielded many recreational drugs including cocaine (which also has medicinal uses), mescaline, and bufotenine. Natural product research continues to provide important leads, with recent examples ranging from antibiotics to the discovery of the remarkable analgesic properties of epibatidine, a substance derived from Ecuadorian tree frogs.

As chemistry matured in the 19th century, the active constituents of long-known natural products were purified and their chemical structures defined. This made possible chemical modification to improve their efficacy, their safety, and the properties affecting their absorption, distribution, metabolism, and elimination. With the introduction of pure substances, the concept of dose-response evolved, which enabled the systematic and quantitative comparison of drug risks and benefits.

The modern pharmaceutical industry traces its origin to the flourishing dye industry of the 19th century and to the pioneering work of Paul Ehrlich, a German chemist. Ehrlich proposed that chemicals could be targeted to individual cell types in the body, just as dyes had been found to be selective in staining certain types of bacteria. This concept of selectivity drives drug discovery to this day.

Many of Stone and Darlington's accounts illustrate how luck, clinical data, or combinations of both led to the discovery of important drug classes. For example, the antipsychotic properties of the phenothiazines (compounds that originated in the dye industry) were first noted by the French anesthetist Henri Laborit, who was treating patients with them because of their antihistaminic properties. Subsequent clinical studies evaluating other tricyclic compounds as potential antipsychotics yielded, instead, the first antidepressants.

Although chapters in the book are organized by therapeutic classes, the presentation makes it possible to appreciate that drug discovery continues to yield even more selective agents. This progress is due, in part, to advances in defining, at the molecular and cellular levels, the underlying mechanisms of pathology; these advances make progress much less dependent on serendipity than in earlier times. The result is a host of new chemical classes that have greatly improved the physician's ability to treat both common ailments and rare disorders. Selective inhibitors of angiotensin converting enzyme, serotonin re-uptake, phosphodiesterase, protease, and proton pumps are just a sampling of new drug classes developed in recent years. In addition to listing and describing these and the other pharmaceutical agents, Stone and Darlington speculate about the future of drug discovery for each of the conditions they consider.

The authors have taken on what many would consider the daunting task of explaining for the lay public the intricacies, and uncertainties, associated with drug discovery. They aim to increase the appreciation for pharmacology while educating readers about the risks and benefits of drug therapy. *Pills, Potions and Poisons* is a lucid and concise description of drugs and their uses. The text is not flawless—there are an inordinate number of typographical errors, including missing sentences, inconsistencies with regard to drug mechanisms, and some dated information on certain drugs of choice—but

Demons of tension. Hogarth's etching *Le Mal de Tête* suggests the distress that severe headaches can cause.

The author is in the Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical School, 39th and Rainbow Boulevard, Kansas City, KS 66160–7417, USA. E-mail: senna@kumc.edu

the science is sound and the information is topical and relevant to the interests of a general audience. The authors display a knack for making the arcane and esoteric interesting. Nonetheless, the ultimate success of a reference work depends more on its accuracy and utility than on its entertainment value; lay readers, as well as workers in the field, will learn much from perusing this volume. Stone and Darlington make it clear that the story of drug discovery is still in its early chapters and that, even with increasing costs and government regulations, we can anticipate more chemical marvels in the future.

BOOKS: PALEONTOLOGY

Ancient Reasons for Monsters

Mott T. Greene

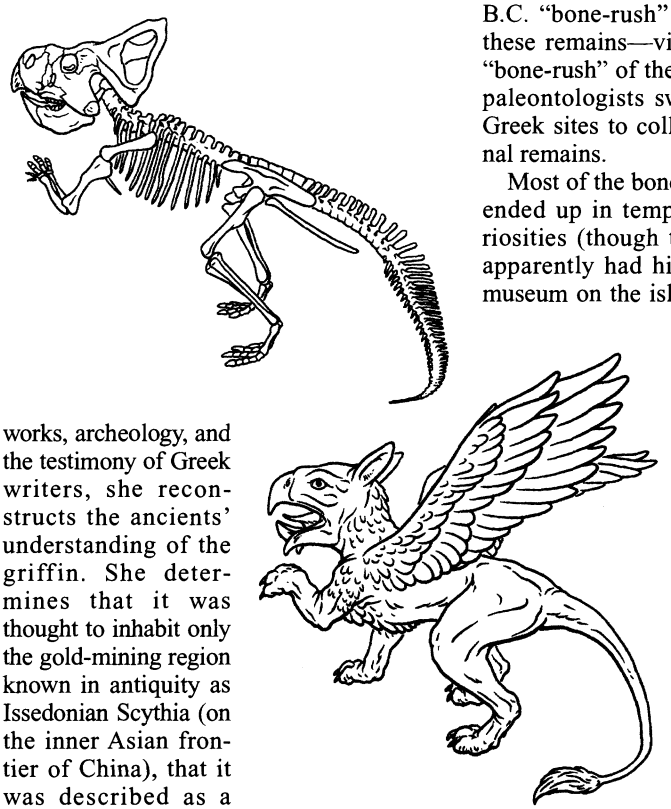
We are aware that the past has a past of its own. We know that the civilizations of antiquity had their own versions of history and prehistory. We also know of the Greek and Roman fascination with giants and monsters, and we are familiar with their versions of a "deep time" filled with battles between such creatures. What we have not heard before is that this mythology had an empirical foundation. The Greeks and Romans believed in giants and monsters not least because they had found their bones.

It is Adrienne Mayor's well-documented contention that the ancients constructed their deep time as we have constructed ours, through the discovery and analysis of the fossil bones of extinct creatures. If they told stories about these fossils that differ from our own, they examined the fossils with the same techniques we employ today: comparative anatomy, skeletal reconstruction, paleogeography, and museum display.

The First Fossil Hunters Paleontology in Greek and Roman Times
by Adrienne Mayor
Princeton University Press, Princeton, NJ, 2000. 381 pp. $35, £21.95. ISBN 0-691-05863-6.

The First Fossil Hunters is a historical and scientific detective story of the first rank. Mayor, a classical folklorist, brings together two lines of investigation that rarely meet: modern vertebrate paleontology and the study of classical Greek and Roman texts. Her results are as striking as they are entertaining. Aimed at a broad nonspecialist audience, the book will engage specialists with its serious purpose and extensive documentation and will please all readers with its profusion of maps, photographs, and drawings.

The first chapter, "The Gold-Guarding Griffin," is a showcase for Mayor's methodical ingenuity. Using inscriptions and art works, archeology, and the testimony of Greek writers, she reconstructs the ancients' understanding of the griffin. She determines that it was thought to inhabit only the gold-mining region known in antiquity as Issedonian Scythia (on the inner Asian frontier of China), that it was described as a quadrupedal and perhaps wingless bird with a fierce beak and armored head, that it nested on the ground and guarded its eggs and young, and that, though the creature was greatly feared, no informant ever claimed to have seen a living one. Then, using the tools and concepts of vertebrate paleontology, Mayor makes the case that this griffin is none other than *Protoceratops*, the dinosaur made famous by Roy Chapman Andrews in the 1920s. (His expeditions to the Gobi Desert and its environs collected abundant and widely distributed remains of *Protoceratops* along with eggs and nests attributed to the species.) How the author works her way to this conclusion makes a wonderful story, and I have no intention of spoiling it here.



Prototypical griffin. An artist's conception of the Scythian's nomads' reconstruction of the Cretaceous fossil *Protoceratops* skeleton (**top**) as a griffin (**bottom**).

Mayor then moves on to her major task, a discussion of Greek and Roman fascination with the remains of extinct mammals. Among the examples she considers are several proboscideans (mastodons, mammoths, dwarf elephants, and *Deinotherium*), woolly rhinoceroses, and giant species of cattle, giraffes, and bears. She shows us how Greek and Roman myths may be sifted for paleontological clues. Surveying the ancient geography of battlefields where "gods and giants" were supposed to have struggled, she maps these to known locations where giant mammalian fossils have been collected in abundance. She documents a 5th-century B.C. "bone-rush" to collect and display these remains—virtually identical to the "bone-rush" of the 1830s when European paleontologists swarmed over the same Greek sites to collect the same megafaunal remains.

Most of the bones collected in antiquity ended up in temples or cabinets of curiosities (though the Emperor Augustus apparently had his own paleontological museum on the isle of Capri). This is not much different than the fate of such bones before the end of the 18th century of the modern era. Indeed, the ancient mythic interpretation of the bones—bridging the gap between deep time and the historical past with stories of ancient catastrophes—differs little in spirit from the attempt to understand the surficial geology of Europe and the bones of the extinct creatures discovered there with reference to the great flood of Genesis, as was common until the 1830s.

I salute the author's refusal either to condescend to the ancients' study of fossils or to rationalize away their subsequent fabulations. The comparative anatomy of giant vertebrates was then and is now a difficult scientific study. The important point is not whether the Greeks and Romans were "correct" in their interpretations of fossils, but that the productive and serious study of fossil remains was extensively carried on in antiquity. Demonstrating this is what Adrienne Mayor has accomplished in her rich, spirited, and eminently readable book.

The author is in the Honors Program, University of Puget Sound, Tacoma, WA 98416 USA. E-mail: greene@ups.edu

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