Book Reviews

Issues of Drug Development

Orphan Drugs. Medical versus Market Value. CAROLYN H. ASBURY. Lexington (Heath), Lexington, Mass., 1985. xviii, 221 pp. $27.

The Orphan Drug Act was passed in the last days of the 97th Congress and became law in January 1983. The law is designed to provide incentives for the development and marketing of medically useful therapies that have become "orphans" in our market-oriented system. Though this system has produced major therapeutic advances in areas such as infectious diseases, contraception, and mental illness, relatively rare conditions like multiple sclerosis, Huntington's disease, or myoclonus have not fared as well. The problem is that to develop and obtain approval to market medicines for such conditions can be enormously expensive—costing tens of millions of dollars. High development costs coupled with small markets, lack of patent protection, and potentially high liability risks all contribute to the problem of orphanization. Though the pharmaceutical industry has made some drugs for rare diseases available as a form of corporate good will, many potentially useful therapies remain on the shelf as orphans.

Though this problem has long been recognized by many academic researchers and the relevant patient groups, orphan drugs were a relatively low-priority issue in Congress until an episode of the television program "Quincy" dramatized the problem in 1981. This was the catalyst for expanded media attention and public hearings. An alliance of patient groups, the National Organization for Rare Diseases, came together in this new environment to become an effective lobby for congressional action. After a series of political maneuvers and delicate compromises, the Orphan Drug Act was enacted and signed by President Reagan.

These events are vividly described in this book by Carolyn Asbury. She provides an expert, insider's view of the problem. In addition to her Ph.D. thesis work on orphan drugs, she collaborated with Congressman Waxman's House Subcommittee on Health and the Environment to prepare and analyze a survey of 196 orphan drug candidates as part of the hearings process. This provided valuable information on the scope and causes of the problem, which had previously been analyzed only piecemeal.

Asbury's book provides an extensive analysis of the orphan drug problem and its relations to other developments in pharmaceuticals. She has pulled together and synthesized a great deal of useful material that has previously been accessible only in academic conference volumes and journals. Though the book will sometimes be tedious reading for the general reader, it will reward those who are persistent. It is quite comprehensive and includes among other things a fascinating discussion of the organizational changes now occurring in molecular biology and what these portend for the orphan drug problem.

A key policy question, of course, is how effective the Orphan Drug Act will be in stimulating the development of drugs for rare illnesses. The last few chapters of Asbury's book analyze the legislation and discuss what has occurred since it was passed two years ago. Under the act, the Food and Drug Administration is empowered to assign orphan drug status to any drug for which there is no reasonable expectation that development and distribution costs would be covered by U.S. sales. FDA guidelines have designated as orphan diseases those with patient populations of less than 200,000. The act provides for a 50-percent tax credit on the costs of clinical development for a drug for an orphan disease and a seven-year marketing exclusivity period. It also requires the FDA to provide recommendations to sponsors who wish to know, in advance of testing, what will be required to obtain marketing approval. Some modest public funds for orphan drug R&D are also authorized by the legislation.

Though it is too soon to assess the effectiveness of the law, there have been both encouraging and discouraging developments. On the plus side, great strides have been made in expanding the sources of information on orphan drugs. As Asbury indicates, a strong network of cooperating institutions representing industry, government, universities, and voluntary health groups has evolved in the orphan drug area. As a result, many of the compounds that were identified as orphans now have corporate parents. Six orphan products were approved by the FDA in 1983 and five in 1984. In addition, 37 products under development were given orphan drug status by the FDA in 1984. This is a dramatic increase in orphan drug development.

Whether this momentum will carry beyond the exploration of known orphan drug compounds into new areas of R&D is much more conjectural. The key economic incentives provided by the act, tax credits, have been little utilized by the pharmaceutical industry. Pharmaceutical firms have argued that the economic stimulus for long-term R&D on orphan drugs provided in the act is too small and too limited in character. Many of the R&D expenditures that are necessary for regulatory approval (for example, those for preclinical testing and animal toxicology tests) do not carry tax credits. In addition, the act provides inadequate incentives for products for which liability risks are large, such as vaccines, in the case of which firms have continued to withdraw from the market and R&D activity.

The orphan drug problem is obviously a complex one that gives rise to difficult policy trade-offs and dilemmas. It will require continued societal attention in the years ahead. This book by Asbury is a valuable contribution to our understanding of the problem.

HENRY G. GRABOWSKI
Department of Economics,
Duke University,
Durham, North Carolina 27706

Pan paniscus

The Pygmy Chimpanzee. Evolutionary Biology and Behavior. RANDALL L. SUSMAN, Ed. Plenum, New York, 1984. xxviii, 435 pp., illus. $59.50. From a symposium, Atlanta, Ga., Aug. 1982.

Based on contributions to a widely attended symposium held in conjunction with the ninth congress of the International Primatological Society, this volume focuses on the systematics, molecular biology, morphology, behavior, and ecology of a single primate species: *Pan paniscus*, the pygmy chimpanzee, the least known of the great apes. A number of evolutionary questions arise with respect to the pygmy chimpanzee. First, what exactly are its phyletic affinities with the other African hominoids, in particular the common chimpanzee? Second, does it represent, as its common name implies, a phyletic dwarf—as the talapoin monkey does among Old World

monkeys and the pygmy marmoset, and possibly all callitrichids, do among New World monkeys—or is it merely a scaled-down version of the common chimpanzee? Third, how good a model does it make among extant primates as an ancestor to hominids, in particular *Australopithecus*? These and other questions are dealt with in this book.

As to the question of phyletic position, an array of data on various blood group systems and electrophoretic and immunological studies of serum proteins combined with analysis of mitochondrial DNA give overall similar results. It is clear from the molecular data that the pygmy chimpanzee and the common chimpanzee have a common lineage subsequent to the separation of the gorilla and hominid (*Australopithecus–Homo*) lineages. Sarich puts the time of divergence between the two chimpanzees at about 1.5 million years ago. In the light of this relatively recent date of divergence, it is interesting to note that on the basis of blood group serology pygmy chimpanzees not only constitute a species apart but are even so distant from the common chimpanzee as to be placed in a separate genus, as Socha suggests.

The uniqueness of the pygmy chimpanzee is underscored by a number of morphological and metrical studies of the dentition, cranium, post-cranium, and body composition. Kinzey shows that the pygmy chimpanzee is characterized by a mosaic of primitive and derived hominoid dental features having a distributional pattern somewhat different from that seen in the common chimpanzee. The most interesting finding seems to be that the pygmy chimpanzee shows a relatively high incidence of wear of incisors and a more efficient shearing mechanism of the molars. Using data on dietary composition offered by Badrian and Malenky in another chapter of this book, Kinzey interprets both these features in terms of adaptation to a diet relatively rich in pith and leaf petioles. From an allometric perspective, however, as is noted by Shea, differences in postcanine tooth size between the chimpanzees are largely accounted for by overall cranial size differences, suggesting similar diets in the two species. This demonstrates once more, it seems to me, that small dietary differences are reflected in crown design rather than tooth proportions.

I hoped that the findings on dental allometry would also have implications for the question whether the pygmy chimp is a phyletic dwarf. On the basis of his study on dental scaling in mammals, S. J. Gould suggested ten years ago that lineages characterized by dwarfing exhibited lower coefficients of interspecific allometry than standard interspecific series. In the meantime various authors have challenged Gould's prediction by showing, for example, that dental scaling does not depart significantly from isometry in dwarfing lineages. Thus, the finding that pygmy and common chimpanzee have a proportionately similar-sized postcanine tooth area neither supports nor rejects the hypothesis that pygmy chimps are dwarfs. An answer to this question depends on fossil evidence, which unfortunately is at present nonexistent.

A straightforward answer can also not be given to the question whether the pygmy chimpanzee is a scaled-down version of the common chimpanzee. As Shea neatly demonstrates, size and shape differences between the two chimpanzee species reveal a complex pattern of different allometric relationships. Though within major body regions most dimensions strongly scale along ontogenetic trajectories, comparisons among these regions reveal uncoupling of the ontogenetic patterns between the species. In other words, the various regions are characterized by a gradient in the degree of pedomorphosis in the pygmy chimpanzee. The most strongly pedomorphic region is the skull, including the teeth, the trunk and forelimb being moderately pedomorphic and the hindlimb being monomorphic, that is, actually relatively longer than in the common chimpanzee. Shea even suggests, with tongue in cheek I presume, that the pygmy chimpanzee may as well be referred to as the "long legged" chimpanzee. Using slightly different measurements and additional data on limb girdles and joint surfaces, Jungers and Susman confirm Shea's interpretations to a large extent.

By contrast, the views offered concerning the importance of the pygmy chimpanzee as a model for the ape-hominid transition differ widely. As expected, Zihlman reiterates the thinking expressed in her earlier papers. She argues that the strong similarities between the pygmy chimpanzee and Lucy, a specimen of *Australopithecus afarensis*, in body size, cranial capacity, hindlimb length, and inferred hindlimb mass make the pygmy chimpanzee a better morphological link between the early hominids and ape ancestor than is any other hominoid. McHenry acknowledges that in specific regions, such as shoulders and feet, the pygmy chimpanzee resembles early hominids more closely than do other extant hominoids. But for other parts, as McHenry stresses, early hominids are better matched by the common chimpanzee, gorilla, or orangutan, and best of all by modern humans. This leads him to conclude that the common ancestor of apes and humans does not have a living analogue, and its reconstruction should be based on all extant and extinct hominoids. For Sarich, a divergence date for pygmy and common chimpanzees some time during the early Pleistocene renders any special evolutionary relationship between pygmy chimpanzees and hominids impossible. Nonetheless, he does not reject the idea that the study of pygmy chimpanzees may provide special insights into the African hominoid radiation and hominid origins.

The majority of the contributions on the ecology and behavior of the pygmy chimpanzee are based on studies of natural populations that have been observed at two specific sites just south of the Zaire River: Lomako and Wamba. Pygmy chimpanzees in these two areas, in contrast to those in many other regions, are fortunately free from human predation. Two reports on feeding ecology show slight differences between the two populations in dietary composition and group size that are most closely associated with habitat differences. A most intriguing finding is that adult males and females share plant food, a behavior that often occurs in a sociosexual context. That such behavior may be of relevance for hypothesized food sharing and high interindividual tolerance among early hominids, as Kuroda suggests, is certainly an idea worth debating. From another perspective, similarities between pygmy chimpanzees and humans in certain aspects of sexual behavior, such as a high frequency of ventro-ventral copulations and continued sexual receptivity throughout the menstrual cycle, have been known from captive and field studies, and these observations are extended here by new data presented by Thompson-Handler *et al.* The final chapter provides a sobering outlook, all too familiar for primate species, for the pygmy chimpanzee: extinction in the near future. Mubalamata vehemently points out that it is only through quick and efficient intervention that the pygmy chimpanzee will be able to survive. Finally, this overall well-edited book is dedicated to Hal Coolidge in recognition of his pioneering research on this most fascinating of the African great apes.

WALTER LEUTENEGGER
Department of Anthropology,
University of Wisconsin,
Madison 53706