Ann. Rev. Pharmacol. Toxicol. 1987. 27:429–37

REVIEW OF REVIEWS

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ANIMAL WELFARE AND RESEARCH

The right of scientists to conduct research on animals for the benefit of mankind is threatened today by animal activists. The need to justify the use of experimental animals for seeking the cause and treatment for diseases has become more than a nuisance; indeed, it has become an increasingly dangerous barrier to progress. These problems have necessitated that bioscientists leave their ivory towers to espouse their cause and to solicit allies in support of it. To this end, the Office of Public Affairs of the Federation of American Societies for Experimental Biology sponsored a special symposium "Government, Media, and the Animal Issue" at the 1986 Annual Meeting. This session drew a standing-room-only audience. The proceedings have appeared in the organization's official publication. They feature the comments of a panel of speakers including not only experts in federal and state relations, university public affairs, and city government but also representatives of the print and TV media (1).

The more militant animal activists create a climate of fear in the halls of scientific research and attract media attention by breaking into laboratories to steal valuable research animals. However, the major damage is done by more shrewd activists who have taken over the directorships of wealthy animal welfare organizations. Such activists have hampered research by lobbying for more and more legislation under the guise of promoting animal rights. Horton points out that in 1980 there were only six bills on animal research in state legislatures throughout the country, but by 1983 there were fifty bills. In 1985 eighty bills were pending in twenty-one states. Many of these bills are still active today. Although the biomedical community has been successful in staving off most of the bills, this merely preserves the status quo, whereas each victory for the animal activists represents a cumulative gain.

0362-1642/87/0415-0429$02.00

Illegal break-ins also serve the cause of animal activists because of the media exposure they receive. Morse details the happenings at his institution when animal activists vandalized a laboratory and stole videotapes documenting experiments on baboons. Officials at the University of Pennsylvania failed to react immediately and effectively because they thought that the animal-rights activists had no political base and would not challenge the validity of the research project. Moreover, the university officials believed that the National Institutes of Health would resist political pressure and support the beleaguered research project. They also felt that law enforcement would be galvanized into action by the illegal break-ins and destruction of property. However, the scientists and university administrators soon found that they had grossly underestimated the strength of the animal-rights activists and overestimated the amount of support they would receive from NIH and law-enforcement officials.

Some very sage advice, flavored strongly with good common sense, on confronting animal-rights activists is provided by a politician and two media representatives. Mayor Moran of Alexandria points out that to protect one's profession, one must become known and involved in community affairs. Effective lobbying requires build-up of credibility before an issue is joined. If the issue is already joined do not give up but establish an agenda to continue the fight for another round. Nissenson, a news reporter, emphasizes the necessity of responding to a reporter. When you do not respond, the reporter assumes you have something to hide. It may not be possible to convert an antivivisectionist, but a responsible reporter can be persuaded by facts and logic. It is important, therefore, to find a way to communicate to the public that experimentation on cats, dogs, and other animals will benefit many people. The media are not the enemy, but ultimately are the most powerful ally for the truth. These views were echoed, but qualified, by Rensberger, a science writer. He notes that most people who write about science and medicine are extremely pro science and medicine. However, these writers also see themselves having watch-dog roles in journalism rather than as promoters of science.

DRUG DISCOVERIES

Sneader chronicles the background leading to the discovery of new drugs (2). This book is likely the most comprehensive book on the subject, although it makes some important omissions. Nearly all the drug groups that act on various organs and systems for the prevention, diagnosis, alleviation, and curing of diseases generally listed in older and current pharmacology textbooks are discussed. Although both primary and secondary sources have been consulted, the citations could have been more precise. The primary

references are more likely to refer to chemical aspects and the secondary ones to pharmacological and clinical facets. As a result, some interesting insights are given on the physical and chemical considerations in drug development and on the struggle between individuals and companies for patent rights. However, the discussion of pharmacological concepts leading to drug discoveries is unbalanced, and some misstatements are made with reference to pharmacologic or clinical matters.

Oxophenarsine (Mapharsen), naloxone (Narcan), and *p*-aminosalicylic acid are examples of notable omissions. Sneader devotes ten pages to arsenicals. In this section he emphasizes the efforts of Ehrlich and his colleagues that led to the discovery of compound 606, or arsphenamine, and later, to that of neoarsphenamine. He also relates the problems associated with the therapeutic application of these two agents because of solubility, stability, and irritant properties, but does not describe how these problems were finally solved. Tatum proposed the use of oxophenarsine, which circumvents these obstacles, and it became the drug of choice for treating syphilis for more than a decade, until it was supplanted by penicillin. Naloxone, because of its more selective effect as a pure opiate narcotic antagonist, has replaced nalorphine as the antidote of choice for opiate overdose. Moreover, naloxone has become the indispensable pharmacological tool for characterizing and identifying opiatelike action; Fishman & Blumgart deserve much credit for their innovation. *p*-Aminosalicylic acid was an important adjunct for the treatment of tuberculosis and was used in conjunction with streptomycin or isoniazid for at least two decades.

Examples of the lack of pharmacological balance are primarily the author's disregard for some highly important contributions by US investigators. The pioneering concepts of Ahlquist in proposing α- and β-adrenergic receptors, and those of Martin for μ, κ, and σ opiate receptors, opened new vistas and resulted in many new drugs. Yet, Sneader hardly discusses these works. Instead he devotes considerable space to the conceptualization of the H_2-histamine receptor, which was a subsequent event. No credit is given to Axelrod and Brodie, who provided the definitive information that the common active metabolite of acetanilid and acetophenetidin (phenacetin) is acetaminophen. This finding provided the pharmacologic rationale for the introduction of acetaminophen as a drug.

Sneader's book also contains some errors or misconceptions about drug action. The Straub tail effect of opiates is ascribed to the cat instead of the mouse. Diphenoxylate is stated to be nonaddicting because of its rapid metabolism by the liver. However, the chief reason diphenoxylate is nonaddicting is its poor solubility, which limits it absorption and intravenous usage. Buprenorphine is termed a κ agonist, but it is well-established to be a partial μ agonist. The main drawback to divinylether as an anesthetic is

attributed to the inability of anesthetists to control its rapid action instead of to its proclivity to cause liver damage. In comparing the toxicity of aspirin and acetaminophen, Sneader appears to be unaware that prior to the introduction of safety caps, aspirin was a major cause of drug deaths among infants and children, and management of aspirin toxicity was complicated and difficult.

Some interesting and amusing anecdotes are provided with respect to the politics and human aspects of selecting generic names for drugs. Differences between the British and Americans in assigning generic names include such well-known examples as adrenaline/epinephrine, noradrenaline/norepinephrine, pethidine/meperidine, paracetamol/acetaminophen, mepacrine/quinacrine, ergometrine/ergonovine, etc. Sneader relates an amusing story about the latter drug that is likely true although he does not bother to substantiate it. The noted British pharmacologist, Sir Henry Dale, and collaborators had isolated an alkaloid from ergot, which they deemed new and named "ergometrine." However, three other laboratories reported the isolation of a substance from ergot with similar properties at about the same time. Because each of the four teams gave a different name to the new alkaloid, the American Medical Association found it necessary to adopt yet another name, ergonovine. This action so piqued Dale that he resigned as British correspondent of the AMA.

The value of the book lies in its more comprehensive treatment of drug discoveries than is generally covered in most pharmacology and medicinal chemistry textbooks or drug monographs. If there were an elementary course on drug discovery, the book would meet the need. However, historians would find it short of being a scholarly treatise. The errors within, although usually minor, are too much in evidence, and the impact of some major drug discoveries on the social and economic well-being of mankind, although mentioned in passing, could have been presented with better perspective. Despite these criticisms, I found the book useful and readable. There is much valuable information, coupled with interesting tidbits, for pharmacologsts, chemists, and medical historians.

RISK ASSESSMENT

In the introductory article of a new journal, intended as a vehicle for the presentation and critical analysis of recent developments in toxicology, Wilkinson discusses risk assessment and regulatory policy (3). He points out that although the development of many chemicals for the benefit of mankind ("and for profit") has immeasurably improved the quality of life, mistakes and miscalculations have been made due to insufficient consideration of the long-term consequences of releasing newly developed chemicals into the

environment. As a result, the public, led by environmental activists, has demanded both more restrictive legislation and an assurance of the safety of chemicals. Balancing the demands of consumer advocates and industrial groups has become increasingly difficult for the federal government. Wilkinson addresses some problems inherent in regulating the potential human health risks of chemicals, in the current regulatory procedures, in attitudes for resolving these problems, and he describes some future approaches that might be considered.

The fundamental problem facing toxicologists and regulators is that chronic health effects of chemicals cannot be assessed by direct experimentation. Consequently, the investigator assessing risk must extrapolate data under laboratory conditions unlike those to be encountered in the field. Thus, as cited in a National Academy of Science report, regulatory processes need to be separated into two processes, risk assessment and risk management. Risk assessment is a scientific study. Alternatively, risk management is not; it involves a series of value judgments including benefits, costs, and political considerations (4). Thus, according to Wilkinson, the key elements to effective regulation are compromise and common sense. Compromise entails recognizing that every chemical cannot be tested for everything. Regulators should not demand from scientists more than they can provide. The public must be made fully aware of the fact that at the low levels of exposure usually encountered, the risks associated with the vast majority of chemicals are infinitesimal compared with the many other risks that are accepted as a part of everyday life.

NITROPLASTERS AND BIOAVAILABILITY

Woodcock and associates use a sexy introduction to introduce a pharmacokinetic analysis of the capacity of nitroplasters to deliver glyceryltrinitrate through the skin (5). The application of nitroplasters on the chest for prophylaxis of angina pectoris has gained considerable popularity, but so has its misuse for inducing erection by application on or near the penis. Nitroplasters incorporate a controlled drug-release system in which absorption of glyceryltrinitrate is a zero-order process and the amount of drug released per unit time is held below the transport capacity of the skin. The authors cite recent studies indicating that different nitroplasters, even when stated to have the same release rate, provide different plasma drug levels. Such findings suggest that the data were derived under different conditions or that the manufacturers' specifications are unreliable. For more definitive data, knowledge of the rate of release of nitrate from different plasters is essential. Also, bioavailability studies need to be held to a set of standard conditions in which the plaster application site and blood collection site are specified.

MAKING A SCIENTIFIC DYNASTY

Kanigel authors a fascinating account of the master-apprentice system underlying great discoveries in science (6). The lure to entice the reader is the description of the trials, tribulations, and triumphs of four generations of scientists. Each started as a student apprentice and then assumed the role of mentor. The scene is the house that James Shannon built, the National Institutes of Health, and the plot involves the love-hate relationships that develop between teachers and pupils working together. Worship and adulation turn into rage and resentment when recognition in terms of prizes and awards are doled to some, but not to the others, by third parties. The stories are true, and the characters are real. What makes the book particularly intriguing is that its leading characters are pharmacologists.

As a worker ploughing the same fields with a long-time, if not intimate, acquaintanceship with my four contemporaries, my interest could hardly not be titillated when the book became available. I was prepared at first to dislike the account because I was conditioned in part by a review that was not quite to my taste (7). As a friend of the family, I resented the intrusion into some private matters and the stirring-up of old controversies that might better have been brought up later. However, since the book has been published, there's no sense in trying to ignore its contents.

Upon reading the book, I had to concede that Kanigel, although he may have opened some old wounds and created a few new ones, had done a masterful job of reporting and writing. He has provided an absorbing and entertaining narration of the apprentiship system, which, clearly, he began only after digging deeply. His copious notes were gained not only by personal interviews with each of the four principals but with a strong supporting cast as well, including their superiors, pupils, colleagues, administrative underlings, and relatives. Thus, the views Kanigel presents are often a consensus rather than his own, and they reflect an attempt to be fair to the parties concerned. Particularly impressive is that the author also took the pains to understand the science. He succeeds admirably in translating the conceptualizations and experimental approaches of the pharmacologists into simple language for the lay public.

The head of the lineage is Bernard B. Brodie, or "Steve," who is described as brilliant, imaginative, demanding, and dictatorial. He brought American pharmacology to the forefront in the 1950s and 1960s with his innovations in drug metabolism and neuropharmacology. He was considered to be a maverick by some scientists because he appeared to be undisciplined in his approach and because he sometimes blatantly ignored some of the published literature and made conclusions not justified by the data. However, wins are based on hits and home runs, not strike-outs, and it is difficult to belittle Brodie's

prodigious feats. In determining the physiological disposition of a drug, he was not content to determine just its biotransformation profile, as was the tendency of many chemists of his time, but he sought always to relate the therapeutic and toxic effects of a drug to its biotransformation products. In addition to biotransformation, rapid relocalization can be important in terminating drug action, and depletion of endogenous substrates can result in prolonged effects long after a drug has been metabolized. Altered disposition of bioamines can have genetic, evolutionary, or pathological bases, as well as be affected by drugs, and such changes might cause mental aberrations. These are the legacies of a highly fertile and inquiring mind.

His pupil, Julius Axelrod, is characterized as the ultimate efficient experimentalist. Axelrod's cohorts did not consider him demanding, but he was indirectly so by the excitement he showed for, and the close attention he paid to, their experiments. His intuitive insight permitted him to devise simple techniques to provide logical answers to complicated perplexing problems. Axelrod's first studies with Brodie on the biotransformation of acetanilid are classic. Acetaminophen was found to be the active metabolite of both acetanilid and acetophenetidin (or phenacetin), and when the latter compound was found to cause renal damage the sales of acetaminophen (Tylenol, Datril, etc) for headaches and menstrual pains were exceeded only by those of aspirin. Neither investigator benefitted financially from this basic discovery. Axelrod was not considered to be a conceptual theorist, but the conclusions he derived from his data are meaningful, logical, and difficult to refute. His experiments demonstrating termination of catecholamine action by neuronal reuptake processes and by catecholamine-O-methyl transferase biotransformation are the major reasons he shared the Nobel Prize, but he personally considers the discovery of the microsomal drug-metabolizing enzymes to be his best work. Conflict with respect to priority rights in this area caused the rift between him and his mentor.

Axelrod's student, Solomon Snyder, has no conflicts with his mentor. Snyder's respect and affection for his teacher have only grown with the years. As a scientist, Synder is a hybrid of his academic grandfather and father. Like Brodie, he concocts ideas at his desk, but although not a bench scientist, like Axelrod he uses intuitive insight and the tools at hand to solve complicated problems. He appears to be as demanding as his forebearers for data, but Snyder prefers psychological approaches, using the carrot more often than the stick to spur his students. His underlings usually meet his demands but do not feel threatened. They find him easy and exciting to work with. His laboratory was and is a production factory for the ideas he spews, generally along the lines of using biochemical, neuroanatomical, and neurophysiological data for correlating drug action on various types of receptors. Linking ornithine decarboxylase activity to tissue regeneration, correlation of antipsychotic

activity to dopamine binding, catecholamine and histamine disposition mechanisms were some innovative contributions from his laboratory. However, the biggest splash he made (and the biggest headache he caused) resulted from the discovery of "the" opiate receptor with Candace Pert.

Candace Pert is hardly ever described as a mere scientist. The adjectives others used include smart, quick, imaginative, undisciplined, obsessed, and sloppy. The discovery of the opiate receptor gave her fame, but it also made her infamous because she sought greater recognition for her role on the project. The study also embroiled her and Snyder in a conflict with other laboratories that had initiated analogous experiments years earlier. Without minimizing the important contribution of these workers in facilitating the characterization of the opiate receptor, I accord major credit to Snyder and Pert for solving the problem in less than a year. Pert was a graduate student when these pioneering studies were performed, but any doubts of her independent capabilities can be met by subsequent work from her laboratory, which is concerned with the characterization of the bombesin receptor and the correlative studies on receptor sites and neuronal pathways using autographic imaging techniques.

Some interesting glimpses of the private lives and personalities of the characters are also provided. Although all four scientists evince sparks of genius, they did not always excel in the classroom. Snyder graduated *cum laude* but Brodie was a high-school dropout. Axelrod never received *A*'s in science courses, and all his applications to medical schools were rejected. There was discussion by Pert's teachers on whether to drum her out of graduate school because some thought her thinking and laboratory techniques sloppy. Brodie in his prime was a lady charmer, a skillful poker player, a writer of humorous articles on pseudoscientific topics, a practical joker, and an administrator torturer. One point not brought out by Kanigel is the affection and loyalty Brodie won from many of his former pupils, even though they were intimidated by him. Axelrod, although warm, kind, and affable in the laboratory, neatly comparmentalized his professional and private lives, and kept social interaction with his pupils to a minimum. He claims some of his best ideas came, not while in the laboratory, but when trying to go to sleep, listening to boring lectures, or shaving. Snyder, a gifted guitarist, has wide-ranging interests and is enjoyable company. However, he creates the most heat among his contemporaries. Most readily concede his creativeness, intellect, and instinct for important problems. However, debates about his ambitions, motivation, and means to achieve an end are often the topic of conversation in hallways, bars, and informal social gatherings. One famous pharamacologist told me flatly, "I will never cite Snyder." The adjectives used to portray Pert's personality are even more extreme than those used to describe her as a scientist, including impetuous, tempestuous, aggressive,

earthy, candid, theatrical, intense, intimidating, and draining. She confides about her problems being a graduate student while also a wife and mother, and describes being mugged three times.

In sum, the genealogy of four academic generations points to an elite group that contributed major breakthroughs to biomedical science. Each member of the family in succession became renowned and, with the exception of Pert, has been the recipient of numerous major awards. Their common link appears to be an unbounded enthusiasm for science and an ability to impose unusual demands on their students, whether dictatorially, benevolently, psychologically, or exuberantly. All worshipped their mentors in the beginning and acknowledge deep debts to their predecessor. The masters, in turn, lavished much praise on their apprentices. However, being humans as well as scientists, they reflect strengths and weaknesses of a very peculiar animal species and became embroiled in priority conflicts. All are excited by good data, but the enthusiasm of each was tempered by his or her individual personality traits. All had the intuitive insight to solve major problems with the experimental tools at hand and asked the right question at the right time. Nonetheless, their approaches to projects were not always as systematic or rationalized in the manner demanded by peer-review committees for research grants. Indeed, Axelrod once told me, tongue in cheek, that one reason he never thought too seriously about any of the numerous academic offers he received was because he was afraid he would not be able to write grant proposals that would gain approval in time and amount. In truth, he had his cake and could eat it all at NIH.

The book makes great reading for the lay public as well as scientists. It is highly recommended for all and should be a must for graduate students and postdoctoral fellows embarking on a career in pharmacology.

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