Time in Review

"There is a time for all things . . . but what time is it?"

Dr. Joyce Mordenti, organizer of the Symposium which was presented at the APhA Annual Meeting in March 1986 in San Francisco, asked me whether this *Journal* would consider publishing the symposium articles. I gave her a "qualified" yes and indicated to her that each article would necessarily have to withstand the same rigors of peer review as all articles we publish. Why?

Journal editors and publishers alike are often accused by the scientific community of succumbing to "pressures" and publishing proceedings of symposia in which the papers are not routinely subject to the same rigors of peer review as research articles and are therefore often "uneven" and perhaps "unmitigated disasters".

The first five articles in this issue were presented at the aforementioned symposium, entitled "Interspecies Scaling and Principles of Animal Extrapolation". All have undergone rigorous peer review and the presentations as they appear in the issue reflect the authors' addressing the concerns of the reviewers. Dr. Mordenti's introductory remarks described the rationale for holding such a symposium. "The drug industry depends heavily on research conducted in laboratory animals; yet most pharmacists are not familiar with the principles of interspecies scaling, and few pharmacy schools, if any, have this subject in the curriculum. We decided that the annual meeting of the Americal Pharmaceutical Association would be an ideal time to show pharmacists how to incorporate the principles of interspecies scaling into their teaching, their research—even their interpretation of package inserts.

"Although we don't realize it, we are continuously confronted with the problem of interspecies scaling. As pharmacists, we must interpret animal data in package inserts. What does it mean if a rat received seven times the human dose . . . is that a high dose, an equivalent dose, or a low dose? As laypersons about to drink a glass of soda with artificial sweetners, we must decide what really killed the test rat, and was it a high dose or a low dose? As parents, we must be able to explain to a sobbing child that their dead pet hamster actually lived a full lifetime, albeit short in human years.

"Recently, I read the transcript of a speech entitled, 'Of mice, microsomes, and men.'[1] It was delivered in San Francisco by Dr. Bernard Brodie on the occasion of his selection as recipient of the 1963 Torald Sollmann Award from the American Society for Pharmacology and Experimental Therapeutics. Although the speech was delivered 23 years ago, I thought that today's symposium in San Francisco would be an excellent time to discuss some of the salient points in Dr. Brodie's speech.

"On the topic of species variability to drug response Dr. Brodie wrote:

> The concept that man is a unique mammal pervades pharmacology and medicine. . . . Perhaps it is high time to ask what we really mean when we say that man differs from animals in response to drugs. Drugs that are excreted unchanged . . . (show) . . . a good correlation between the effects in animals and in man, but with drugs that have some degree of lipid solubility and hence undergo biotransformation, the variation between species strains, and even individual men is fantastic. Such differences in activity and toxicity have been generally attributed to differences in tissue "sensitivity" though, in fact, they are often a reflection of differences in metabolic handling of the drug. When the effects of drugs are related to their plasma or tissue levels, much of the apparent variation disappears. Consequently it might be much more profitable in the future to relate effects to drug levels than to look for the mythical animal with man-like enzymes.

"On species and strain differences Dr. Brodie wrote:

> Nature has raised an enormous barrier to drug development by assigning the drug-metabolizing enzymes to various species in astonishingly diverse amount. So great are these differences that it is often a matter of pure luck that animal experiments lead to clinically useful drugs. If our investigator is still searching for the animal species with man-like enzymes, he surely would be discouraged upon discovering that he must look not only for the species but the inbred strain of that species. Thus, there may be a 500% range in the duration of action of hexobarbital among a number of inbred strains of mice compared to the remarkably uniform response by individual mice of a given strain. In contrast, members of a non-inbred strain vary considerably in their reaction to the drug. These findings suggest that heredity rather than environment is the important factor in determining the rate of drug metabolism.

"On projection of animal data to man Dr. Brodie wrote:

> Ordinarily a drug is screened in man only after it is found to be active in animals in reasonable doses for a reasonable period of time. This has seemed a practical way to screen drugs since substances active in animals generally prove to be active in man. In fact, they are often more active in man since foreign organic compounds are usually metabolized more slowly in man than in animals. However, compounds with low activity in animals are rarely selected for clinical trials . . . (so) our present methods of screening might well be overlooking a large portion of the drugs which would be of therapeutic value in man. The problem of projecting results to man highlights the importance of testing a drug in man as soon as possible to see whether its rate of metabolism would make it clinically practical. The practice of studying the physiological disposition of a drug in man only after it is clearly the drug of choice in animals may not only prove shortsighted and time-consuming but also may result in relegating the best drug for man to the shelf. . . . Preliminary screening in man should be designed to eliminate the ineffective drugs—not to eliminate the effective ones.

"Dr. Brodie's presentation demonstrated his great insight into interspecies differences in drug action and elimination. But we have not come very far in the past 23 years. The ability to interpret the results of an experiment on a laboratory-sized animal in such a way that it has meaning when applied to humans has obvious value in the medical sciences. I hope that today's symposium will be the start of a new trend, the beginning of an interspecies scaling movement. As a daily component of pharmaceutical research, interspecies scaling is expected to (1) produce more clinically meaningful data from animal experiments, (2) predict the activity, efficacy, and toxicity of a pharmaceutical compound in humans with a minimum number of animal trials, (3) reduce the number of animals required for experimentation, (4) hasten the drug testing and approval process, and (5) allow us to interpolate drug doses between species."

I hope the five symposium articles act to stimulate your thoughts regarding time concepts and interspecies scaling. There is one time concept that does not appear to me to be touched upon and that is the concept of "not enough" time. I hope you, as readers, take the time to read these interesting articles, which discuss similarity principles, intrinsic geometries, problems of neoteny, psychological relativity, syndesichrons, and apolysichrons.

—Sharon G. Boots, Ph.D.

1. Brodie, Bernard. *Pharmacologist*, **1964**, *6*, 12–26.

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