

An International Initiative in Biomedical Research Training

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One stimulus for internationally coordinated educational programs is the need to preserve fundamental research technologies that might otherwise be lost. Such is the case for integrative and organ system pharmacology (IOSP). A sub-discipline of pharmacology, IOSP encompasses techniques critical for the identification and development of new drugs. Included are methods for defining the effects of chemical agents on isolated organs and organisms. Described in this article are the historical reasons for the decline in academic IOSP research and training, the implications for the loss of expertise in this area, and national and international efforts undertaken to preserve the skills necessary to conduct experiments in isolated tissues and intact animals.

Evolution of Drug Discovery

The identification of substances that relieve pain and suffering has been ongoing since at least the appearance of *Homo sapiens*. For most of the past 200,000 years, drug discovery was an empirical enterprise (Fig. 1). Thus, if an ancient obtained some symptomatic relief (efficacy) of an ailment while dining on a particular animal or plant, and survived (safety) the experience long enough to relate this finding to others, curative properties might be attributed to that particular meal. If, over time, his neighbors reported similar findings, the item would become a permanent part of the therapeutic armamentarium. Thus, paleo drug discovery was a linear process, with all experiments conducted in humans, and the only endpoints being efficacy and

safety. While random, slow and cumbersome, and fraught with many false positives, there are therapies still available today that originated from this approach. Included in this group are the salicylates, opioids, cardiac glycosides, gold salts, and ergot alkaloids.

Modern drug discovery began in the 19th century as a result of advances in chemistry and physiology (Fig. 2). The ability to purify plant and animal extracts, and to characterize chemical structures, made it possible to identify the active constituents of natural materials that display medicinal properties. Moreover, the synthesis and testing of chemical analogs of these substances made possible a systematic classification of drugs on the basis of their chemical properties and physiological effects. This in turn

allowed for the design and execution of the hypothesis-driven experiments needed to begin defining drug mechanisms of actions and the pathophysiology of disease. This approach to drug discovery lasted for approximately 100 years. It is termed the Physiological Period (Fig. 2) because the biological testing of old drugs and new chemical derivatives almost exclusively involved the use of isolated organs and intact animals. This work established the methodologies and principles of IOSP. By the mid-20th century it was clear that drugs exert their effects by interacting with biochemical pathways, and that the

from physiological to biochemical systems. Besides being less costly, biochemical assays make possible the screening of hundreds of chemicals to quickly identify those with the most promising mechanistic profiles before advancing them for analysis in the more time-consuming, and laborious, physiological and behavioral tests. This era, the Biochemical Period (Fig. 2), was the favored approach for a generation.

Towards the end of the 20th century, advances in molecular biology opened new avenues for drug discovery. As it was now established that most drugs act by attaching selectively to receptors or enzymes, artificial systems could be

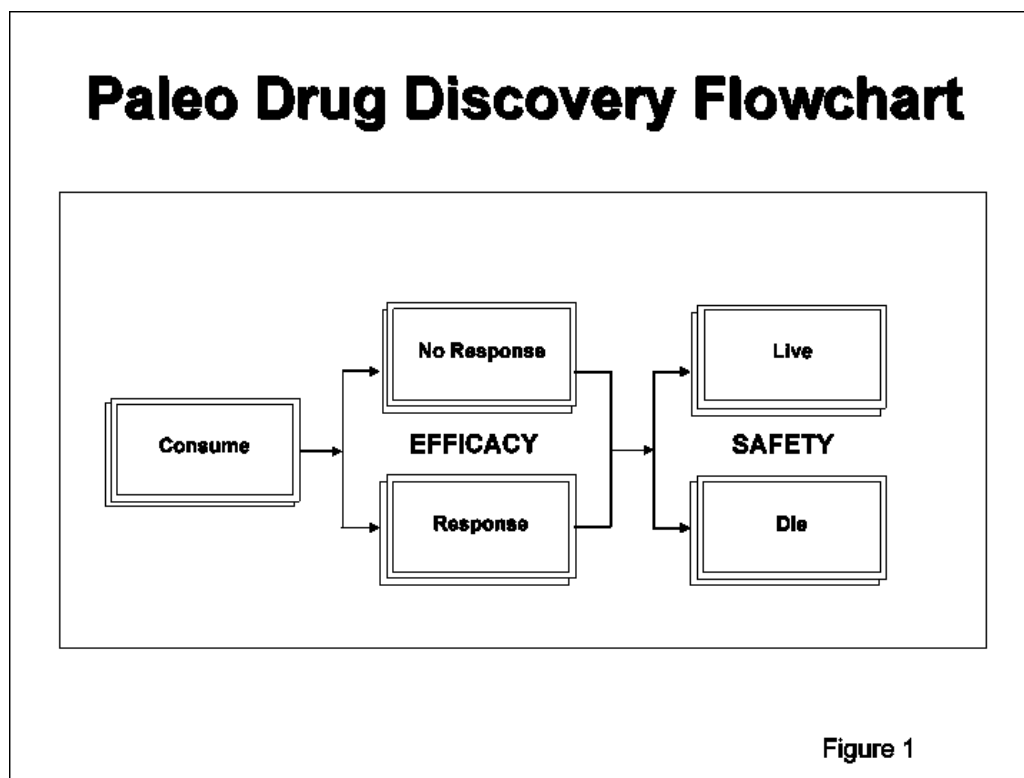


Figure 1. The drug discovery process in the prehistoric world.

physiological and clinical responses to these agents result from effects at the cellular level. This led to a shift in emphasis for drug candidate testing

constructed using cloned genes to express a desired target, and thousands of compounds assayed rapidly for their ability to interact with the site (high

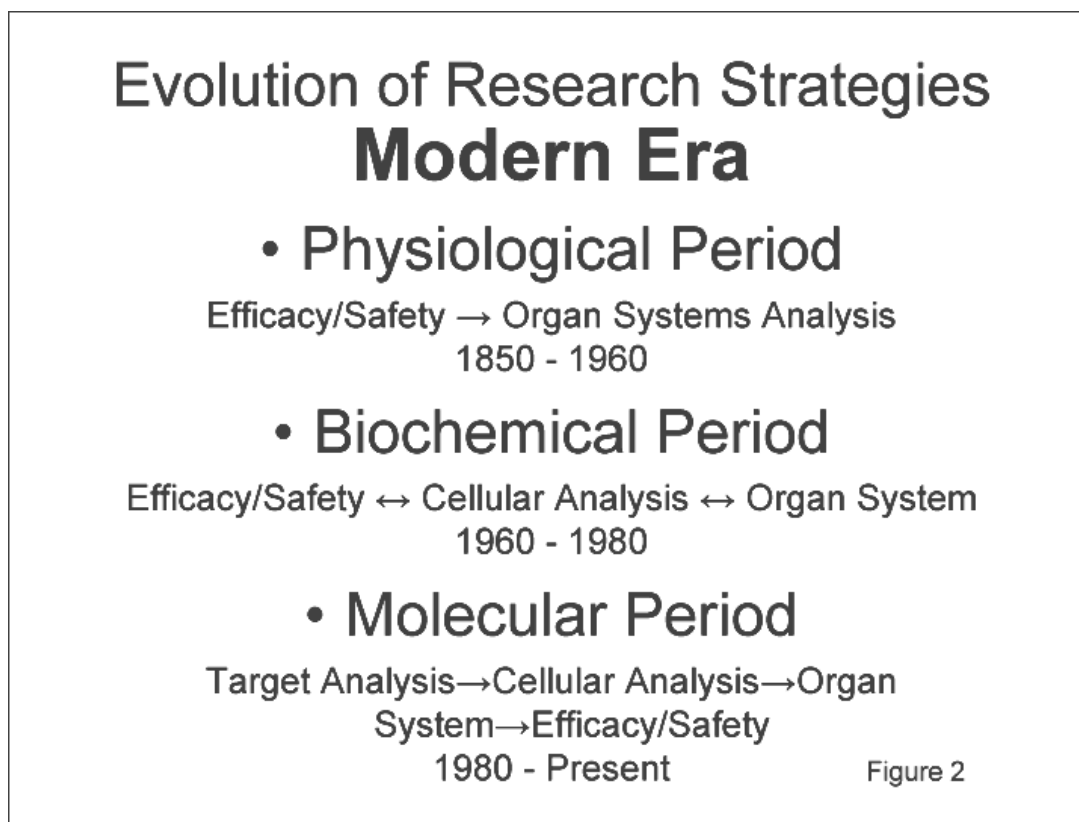


Figure 2. Categorization of predominant drug discovery techniques in the modern world.

throughput screening). Identified leads are then examined in biochemical assays to ensure they affect cellular function, after which they are tested in organ systems and intact animals to determine whether they are safe and display pharmacologically meaningful effects. Thus, the Molecular Period (Fig. 2), which began in the 1980's and extends to the present, is characterized by a shift in the initial objective of drug discovery from first identifying agents that display efficacy and safety, and therefore likely clinical activity, to first identifying agents on the basis of their target selectivity, which may or may not ultimately prove to be of any clinical benefit.

Decline in Organ System Training

Changes in the approach to drug discovery reflected shifts in research

emphasis and training in the academic community. Whereas in the 1950's and 1960's physiological, behavioral and biochemical studies were awarded the bulk of federal biomedical research funding, by the end of the 20th century research in the molecular sciences was favored. As federal support for physiological research waned in comparison to molecular studies, investigators and academic departments abandoned work in the former to concentrate on the latter. Besides slowing advances in the physiological sciences, over time this change of priorities reduced the number of faculty with interests and expertise in this area, thereby diminished training opportunities in the field (Fig. 3).

A decline in the use of laboratory techniques is not unusual given the dynamic nature of the scientific

the decline in IOSP training has led to manpower shortages in the field in the pharmaceutical industry and

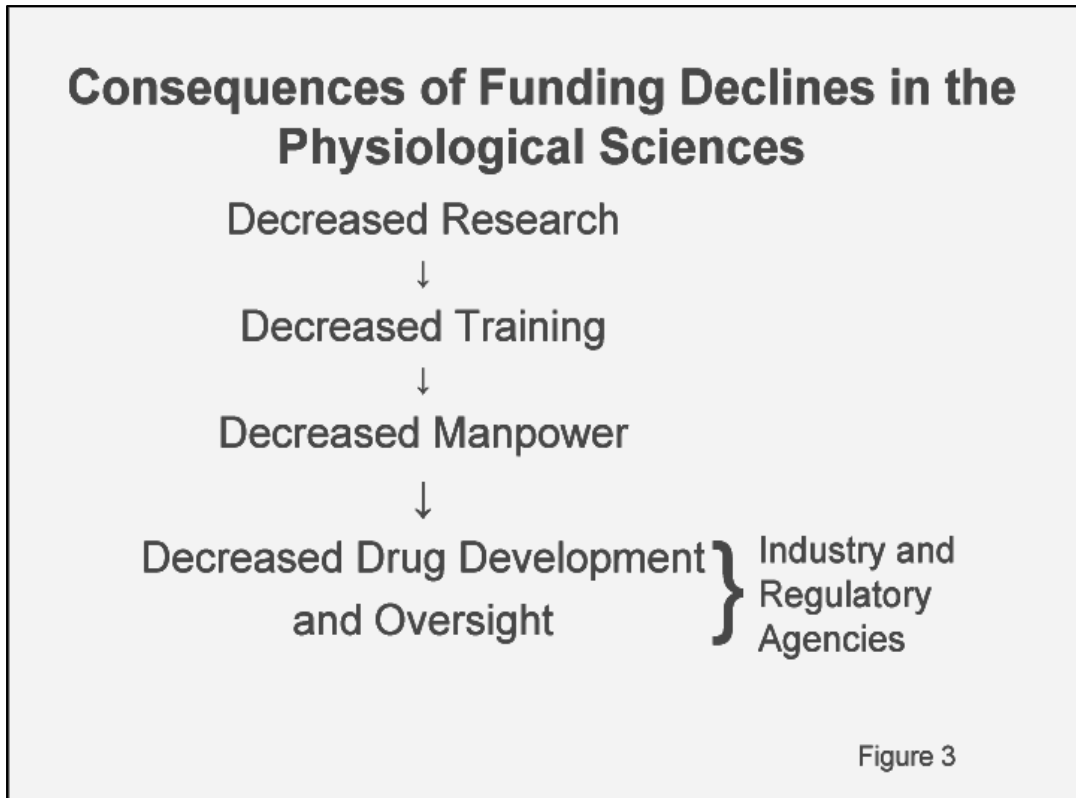


Figure 3. Sequential ramifications of reductions in IOSP-related research support.

enterprise. Indeed, obsolescence is to be expected as new technologies are developed that are more efficient and make possible a more in-depth and precise analysis of the subject than older methodologies. To the extent that molecular studies are yielding the most novel and exciting insights into the mechanisms of disease and drug action, it is not surprising such work is generously funded and that students are interested in pursuing careers in this area. However, while IOSP techniques are no longer widely employed in academic laboratories, they remain an essential part of the drug discovery and development process. Because of this,

government regulatory agencies (Fig. 3). While new recruits to pharmaceutical companies are adept at cloning, expressing and sequencing genes, many have no hands-on experience working with organs or intact mammals, a required skill for identifying drug candidates and for evaluating and monitoring new drug applications and clinical trials. It is speculated this lack of expertise and the steady erosion in the population of those capable of teaching IOSP are responsible, at least in part, for the decline in the number novel drugs reaching the market. Thus, the techniques utilized by physiologists and pharmacologists to study isolated

organs and intact organisms remain relevant and important for contemporary drug discovery programs, as do the scientific principles that underlie them.

Training Initiatives

For over a decade both academic and industrial scientists and administrators warned of the consequences of a decline in IOSP training. As the number of experts in the field dwindled, the pharmaceutical industry established in-house programs, or funded courses at local universities to provide instruction in the area. The growing shortage of physiological pharmacologists, and their important role in academic and industrial research,

professional organizations, such as the American Physiological Society and the American Society for Pharmacology and Experimental Therapeutics, in 2004 the United States National Institutes of Health (NIH) began funding short courses in integrative and organ system pharmacology. The NIH interest in IOSP is not only driven by the needs of industry and regulatory agencies, but also by the realization that such expertise is critical for transferring basic research discoveries to the clinic. For example, lack of IOSP training limits the ability to phenotype fully genetically modified animals, one of the major tools of the molecular biosciences.

Currently, the NIH supports

Table 1: Topics Covered in Typical IOSP Training Program

- **Intensive Exposure to Animal Experimentation**
- **Training in Organ System Techniques**
- **Behavioral/Physiological Phenotyping**
- **Pharmacokinetics/Pharmacodynamics**

was ultimately noted by government and private agencies. Following meetings with representatives of the pharmaceutical industry and of

summer IOSP short courses at four institutions: University of Nebraska, Michigan State University, University of North Carolina at Chapel Hill, and the

University of California, San Diego (<http://www.nigms.nih.gov/Training/IOSP.htm>). Enrollees include graduate students, university faculty, and industry scientists, both foreign and domestic. Topics covered during these two-week offerings include principles of pharmacokinetics, the effects of the body on drugs, and pharmacodynamics, the effects of drugs on the body (Table 1). Much of the instruction is laboratory-based, with extensive exposure to whole animal experimentation and organ system techniques. The students receive instruction on methods for characterizing the behavioral and physiological phenotype of genetically modified or drug-treated laboratory animals (Table 1).

While this brief exposure to IOSP does not produce experts in the field, it does increase student awareness about methodologies available for undertaking such studies, and about resources for obtaining additional information. The courses also provide instruction on the ethical treatment of animals, and the proper handling and maintenance of these subjects. In addition, students are made aware of the importance of such studies for determining the clinical relevance of their work.

As drug research is a worldwide enterprise, the lack of IOSP-trained scientists is an international concern. This is especially true in those countries with large pharmaceutical companies such as the United States, the United Kingdom, France, Switzerland, and Japan. In those with a growing presence in pharmaceutical research, including China, India, and Hungary, a lack of access to IOSP skills is hindering the

development of this industry and the discovery of new drugs. Even regions with little or no pharmaceutical research, such as most of the African continent and Southeast Asia, are also affected by the decline in IOSP training as it slows the development of new drugs elsewhere that are needed to treat medical conditions prevalent in these areas. While the countries with more developed research enterprises are now funding IOSP training programs, this is not the case in most of the world. To address this issue, the International Union of Basic and Clinical Pharmacology (IUPHAR) assembled a task force to assess the global need for IOSP training and to design programs to meet the demand for such instruction at strategic locations around the world. The task force is composed of representatives from Europe, Asia, Africa, North America, South America, India, and Australia. Because the type and method of IOSP training will differ among the countries in these regions, programs will be customized to meet local needs. Nonetheless, all will include instruction in specified learning objectives to establish an international standard for basic instruction on this topic.

Conclusion

As the IUPHAR program involves collaboration among academic institutions around the world, it is a prime example of a global research and training initiative. In this instance the impetus for the undertaking is provided by a practical need for specially trained scientists that requires maintaining the didactic and research programs necessary for this purpose. This

undertaking exemplifies how academia, industry, and federal governments can work together in pursuing a common goal. As an ancillary benefit, it is likely the relationships forged in establishing this program will lead to other types of international research collaborations among the participants. From these will grow a greater appreciation for the

infrastructural and instructional needs of other countries. This is especially important for rectifying such deficiencies in the developing world, as it faces the greatest challenges in providing medical services and educational opportunities for its inhabitants.