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CHAPTER TWENTY-ONE

Division of Environmental Medicine and Toxicology

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"It is evident that efforts to preserve health will be most intelligently and effectually applied when they are based upon an accurate and full knowledge of the agencies which cause disease."

—WILLIAM H. WELCH (1850–1934)

Research, Diagnosis, and Treatment

In the fall of 1984, the Department of Medicine embarked on a new venture, the Division of Environmental Medicine and Toxicology. The Division was planned to comprise three separate but interacting components, as follows: (1) a basic science research component with scientists whose goal would be to determine the mechanism of action of toxins; (2) a clinical services component with physicians board certified in Occupational Medicine and in Medical Toxicology; and (3) a clinical toxicology unit with physicians and scientists who work collaboratively to improve and refine methods for the diagnosis and treatment of poisoned patients.

There are several reasons why the creation of this Division should be seen as a bold venture. Neither Occupational Medicine nor Medical Toxicology has typically been granted more than "backroom" status in Departments of Medicine. Also, relatively few schools of medicine have had full-fledged programs in toxicology at all, the subject usually having been treated as an appendage to the Department of Pharmacology. Flourishing groups in the basic science specialty of toxicology have generally been limited to schools of public health or pharmacy. The initiative of the Department of Medicine in developing a Division of Environmental Medicine and Toxicology equal

in status to the other 12 Departmental Divisions represented a break with tradition. It was also a wise anticipation of future needs and opportunities.

Strides toward the reduction of morbidity and mortality have been made in many areas of medicine. Antibiotics and vaccines against infectious diseases, antiarrhythmic and vasoactive drugs against heart disease, anti-inflammatory drugs, and dialysis may be cited as accomplishments. Such advances have caused a refocusing of attention. With the elimination or control of some illnesses, the remaining problems, often of obscure cause, command greater attention. There is clear evidence that many forms of illness are toxin-mediated, with some of the toxins being of natural origin and some man-made. The majority of such toxin-mediated diseases have not been brought under control. It was in the hope of contributing new initiatives in this area that Jefferson embarked on this course.

The past decade has been dominated by what has been called "descriptive and regulatory toxicology." Descriptive toxicology involves the administration of potentially toxic substances to subjects and thereafter attempting to identify and quantify adverse effects. Regulatory toxicology involves the effort to translate laboratory data into risk assessment and then using this to establish guidelines for human exposure to toxic agents.

There are serious drawbacks to the overemphasis of descriptive and regulatory toxicology. Not the least of these is the fact that they involve serious decision making, such as setting limits for human exposure, without knowing the underlying mechanism of toxin action. The Division of Environmental Medicine and Toxicology has been built in a way that is calculated to avoid these difficulties. All of the newly appointed staff members are devoted to research aimed at clarifying the mechanisms by which toxins act, thus providing a more substantive basis for such measures as risk assessment. In addition, it provides the scientific basis for advances in diagnosis and treatment.

The first full-time appointment to the Division was that of Lance L. Simpson, Ph.D., (University of California, Berkeley), who is currently Professor of Medicine and Pharmacology and Chief of Environmental Medicine and Toxicology. Dr. Simpson took his undergraduate degree at Vanderbilt University in Nashville, Tennessee, and did his doctoral work at the University of California in Berkeley. He next did a postdoctoral Fellowship at the College of Physicians and Surgeons of Columbia University. His graduate work was done in the Laboratory of Chemical Biodynamics, under the supervision of Professor Melvin Calvin, a Nobel Laureate. His postgraduate work was done under the joint supervision of Dr. Maurice Rapport, Professor of Psychiatry and Biochemistry, and Dr. S. C. Wang, Professor of Pharmacology, both at the College of Physicians and Surgeons. After completing his studies in 1971, Dr. Simpson joined the staff at the Columbia-Presbyterian Medical Center. He remained there until moving to Jefferson's Medical Department in the fall of 1984.

Dr. Simpson has been working on toxins since his undergraduate days at Vanderbilt University. Most of his effort has been directed toward the study of protein toxins that act on the nervous system. These substances include poisons of microbial origin, such as botulinum toxin and tetanus toxin, as well as poisons of snake venom origin, such as alpha and beta bungarotoxin. This work has several motives, including determining the mechanism of toxin action, determining the structure of toxin molecules and then correlating structure with function, developing drugs for the treatment of poisoned patients, and constructing synthetic vaccines that can be used to immunize patients. More recently, another aspect of toxin-related research has been added. There are certain toxins, or pieces of toxins, that appear to have value as potential therapeutic agents. For example, tissue-targeted toxins that can locate and kill neoplastic cells may have clinical utility in the treatment of cancer. This area of research has now been added to the overall scope of activities.

Although work on protein toxins has been the main theme of Dr. Simpson's research, there was one stretch of time when another aspect of toxicology was undertaken. From the late 1970s until the early 1980s Dr. Simpson was involved in a collaborative research project with the New York City Police Department. The purpose of the work was to assess the effects of illicit drug use on criminal behavior, and thus the project was one in behavioral toxicology. The method used by the

investigators was to observe crime while it was occurring. These observations were then compared with data on drug use by the offenders. The crimes of interest were larceny, assault, robbery, and gun-related incidents; the drugs of interest were opioids and central nervous system stimulants. A wealth of data was collected and the findings are to be published in a book that will appear in 1988.

During Dr. Simpson's relatively short tenure as Chief of the Division, he has added four members to the staff. Three of these were principally oriented toward research, and one mainly clinical. The first addition to the research staff was Kevin Chinn, Ph.D., Assistant Professor of Medicine. Dr. Chinn did his graduate work in the Department of Physiology at the University of Hawaii, where he worked under the guidance of Dr. Howard Gillary. While there he took an interest in the use of highly sophisticated electrophysiological techniques as a means for studying the effects of drugs on the nervous system.

In 1981 Dr. Chinn moved on to a postdoctoral Fellowship in the laboratory of Dr. John Lisman at Brandeis University, and two years later he joined the laboratory of Dr. Toshio Narahashi at Northwestern University. During the both of these fellowships Dr. Chinn was able to enhance his electrophysiological skills. In the fall of 1986, he moved to his present position at Jefferson.

Dr. Chinn is one of the few toxicologists in the nation who is capable of using the patch clamp technique for the study of excitable tissues. This technique in microelectrophysiology allows him to study the actions of toxins on individual ion channels in nerves and heart. He is employing the method to analyze the effects of agents such as insecticides on sodium channel behavior. Chinn is responsible for the finding that one insecticide in particular, Deltamethrin, is capable of blocking the transition of sodium channels between the open and closed states. These and other of Dr. Chinn's findings help to explain the cellular and molecular basis for the toxicity of certain poisons.

In addition to this major thrust of his work, Dr. Chinn has developed methods that permit the injection of real or suspected toxins into individual cells that are grown in tissue culture. This is an especially powerful technique, and it promises to help resolve the mechanism of action of many toxic agents. It is potentially a method for examining the effects of therapeutic agents as well.

The next member to join the Division was Dr. Charles Mactutus, Ph.D., Assistant Professor of Medicine, an investigator trained both in toxicology and in the experimental analysis of behavior. Dr. Mactutus did his graduate work with Dr. David Riccion in the Department of Psychology at Kent State University, where he did research in the area of learning and memory. In 1979 he accepted a postdoctoral Fellowship at the Johns Hopkins University, where he was able to apply his background in experimental psychology to the study of central nervous system toxicology. While at Johns Hopkins, he performed a series of experiments to examine the influence of prenatal carbon monoxide exposure on learning and memory of the offspring. This work, which was designed to provide a model of cigarette smoking during pregnancy, demonstrated persistent alterations in memory. The research was widely cited, both in the scientific press and in the lay press.

Dr. Mactutus moved from Johns Hopkins to accept a position at the National Institute for Environmental Health Sciences. He was instrumental in forming and leading a group of investigators who studied the effects of toxins on central nervous system development. The group examined a number of environmental substances, including tetraethyl and triethyl lead. In early 1987 Mactutus joined Jefferson's faculty. He is establishing a new program in central nervous system toxicology that emphasizes a multidisciplinary focus; using a lifespan approach, he will perform psychological and toxicological studies aimed at assessing the impact of prenatal or early neonatal exposure to toxins on subsequent neurological and psychological development.

The most recent recruit to the Division is Dr. Masaru Tanaka, Ph.D., who is a Research Associate. Dr. Tanaka did his entire training at the University of Tokyo, and later for many years was a member of the Faculty at the University of Hawaii. Dr. Tanaka is an expert in the field of protein chemistry. He has developed exquisite methods for the isolation, purification, and characterization of proteins from both procaryotic and eucaryotic sources. His past work has focused

on substances isolated from bacteria as well as substances derived from the mammalian cardiovascular system. Dr. Tanaka has joined the Division to work with Dr. Simpson and will oversee research on the isolation and characterization of protein toxins.

Clinical Services

In the spring of 1987 the Division formally initiated its clinical activities by inaugurating an Occupational and Environmental Medicine Clinic. The physician who currently holds principal responsibility in the Clinic is Dr. Jack Snyder. Dr. Snyder (M.D., Northwestern) is an unusually well-trained individual. His medical degree was followed by a law degree at Georgetown University. He completed his Master's Degree in Forensic Science at George Washington University and his Master's in Public Health at Johns Hopkins University. Finally, Dr. Snyder took a Ph.D. degree in the Department of Pharmacology and Toxicology at the Medical College of Virginia. He is licensed to practice both law and medicine.

Dr. Snyder has done postgraduate work in occupational medicine, internal medicine, and pathology. He is board certified by the American Board of Pathology in Anatomic and Clinical Pathology and by the American Board of Medical Toxicology.

Dr. Snyder's main interest in the area of clinical medicine is the acutely and seriously poisoned patient. This interest finds its expression in three different settings: (1) he is responsible for seeing patients who come to the Occupational and Environmental Medicine Clinic; (2) he has a close association with the Emergency Room; poisoned patients who are treated initially in the Emergency Room and who are subsequently candidates for inpatient care are admitted to Dr. Snyder's service; and (3) he is a member of the Advisory Board of the Delaware Valley Regional Poison Control Center. In collaboration with other medical and related professionals, Snyder oversees the activities of the poison information service for Philadelphia and the surrounding areas.

In addition to clinical responsibilities, Dr. Snyder is building a research program. Following up on his Ph.D. thesis work, he is establishing a laboratory that focuses on liver pathology. He is interested in the adverse effects of alcohol on the function of liver membranes, and especially those untoward effects that might be mediated by enzymes such as phospholipase. Beyond this, he is attempting to learn whether there are adverse interactions between alcohol and environmental toxins. Snyder is pursuing the hypothesis that some aspects of what has traditionally been called alcohol-induced liver pathology is in reality the outcome of an interaction between alcohol and environmental substances.

A Future Clinical Research Unit

The Clinic will not function separately from teaching and research. It will provide both medical students and house staff with practical opportunities in the diagnosis and treatment of occupational and environmental health problems. The possibility that man-made substances can cause disease has given rise to two rather robust areas of research. Basic scientists have contributed a great deal to our understanding of mechanisms of toxin action. Clinical scientists and investigators trained in public health have provided a wealth of epidemiological data. Both of these have added to our growing knowledge of the link between man-made substances and human illness. However, each has its acknowledged shortcomings. Basic science focuses on the study of animals or tissues obtained from animals, and therefore the data have to be extrapolated to humans. This is sometimes appropriate, sometimes not. Epidemiology, too, has its weakness. The use of statistical techniques and large populations does help to identify broad trends and associations, but it cannot establish whether the illness of a particular individual is due to the specific hazards that surround that individual.

A consensus among investigators in occupational and environmental medicine is that there must be more physicians involved in research. The nature of the research needed is that in which the physician-scientist studies individual patients or specimens obtained from patients. There is a tendency to view patients as though they belong to one or the other of two discrete states, healthy or ill, but this clearly is an

oversimplification. When one is dealing with patients exposed to hazardous substances, there is a gradation. There may well be a time when the patient is healthy and a later time when he is ill, but between these two extremes is a period of mounting vulnerability and susceptibility.

It would be a magnificent accomplishment in occupational and environmental medicine if physician-scientists, who are regularly seeing patients from the workplace, could develop chemical markers or related techniques for detecting those individuals who are in transition from a healthy to an ill state. In essence, this would be a meshing of environment medicine with preventive medicine. Not only would this safeguard the welfare of the individual worker, but it would spare what would otherwise have been lost productivity, and it would forestall the entire compensation issue and possible litigation.

The development of markers for incipient disease is a great challenge. Nevertheless, it is a legitimate undertaking for a physician-scientist, and therefore it is a part of the scope of activities of the Division of Environmental Medicine and Toxicology.