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CHAPTER TWENTY-TWO

Division of Clinical Pharmacology

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"The Lord hath created medicines out of the earth; and he that is wise will not abhor them."

—ECCLESIASTICUS 38:4

CLINICAL pharmacology is the study of drugs in man. Its two principal components are drug disposition (the effect of the body on the drug) and pharmacodynamics (the effect of the drug on the body). These broad categories have been expanded and combined over the years so that investigations reported under this label have ranged from receptor studies to controlled clinical trials.

The discipline of clinical pharmacology emerged in this country in the 1950s, led by studies of cardiovascular drugs by Harry Gold at Cornell and of human drug metabolism at the Goldwater Memorial Hospital in New York City, and by cardiovascular pharmacology programs at the National Institutes of Health. Academic clinical pharmacology units appeared at Johns Hopkins, Emory, Kansas, Yale, Vanderbilt, and many other universities. The study of drugs in man is, of course, of prime interest to the pharmaceutical industry. Industry-sponsored clinical pharmacology programs thus came on the scene at the same time, modeled after the Lilly unit in Indianapolis, which had been in operation since 1927. Other successful early units were sponsored by Hoffmann-La Roche, Upjohn, and Parke-Davis.

Clinical Pharmacology at Jefferson

Clinical pharmacology, as a special field, was introduced to Jefferson in 1966. In that year, the Smith, Kline & French Foundation provided funds to develop a joint Division of Clinical

Pharmacology in the Departments of Medicine and Pharmacology. Dr. John Capelli (Jefferson, 1962) was appointed Director in 1968.

Dr. Capelli pursued his fellowship training at the Michael Reese Hospital and Jefferson. Following his year as Chief Medical Resident, he was appointed Director of the Division of Clinical Pharmacology and a member of the Division of Nephrology. Dr. Lawrence Wesson was made a member of the Division of Clinical Pharmacology at that time.

Unfortunately, 1968 and 1969 were difficult years in the development of the medical practice plan for members of the full-time Faculty of the Clinical Departments at Jefferson. Dr. Capelli decided to resign his full-time position as Director of the Division of Clinical Pharmacology and enter private medical practice. Dr. Wesson was then appointed Director. Other members of the Division at that time were Drs. Peter Amadio of Wallace Laboratories, Elmer Funk, Jr., and Thomas N. Gates of Merck Sharp & Dohme, and Charles K. Gorby of Lankenau Hospital. This original Division of Clinical Pharmacology continued through June 30, 1973, when it was discontinued because of lack of financial support.

The Present Clinical Pharmacology Division

The present Clinical Pharmacology Program began in 1975 when senior officers of the Merck Sharp & Dohme Research Laboratories (MSDRL) approached their counterparts as Thomas Jefferson University with a proposal for a collaborative clinical pharmacology venture. The proposed arrangement had a number of unique characteristics. Unlike units funded by other pharmaceutical companies elsewhere, the administration and staffing of the Jefferson Unit would be entirely under the control of the University even though the major portion of the financial support would come from MSDRL. An advisory committee with representatives from both institutions initially oversaw the function and direction of the Unit. Although the major Unit effort would be committed to MSDRL studies, other projects from a variety of funding sources could be undertaken. The Unit would be a Division of the Department of Medicine and be located on the fifth floor of the 1907 Main Hospital Building. A letter of understanding that included these provisions was signed by officers from both institutions in December of 1976. Jefferson officials prominent in these early negotiations were Dr. Francis J. Sweeney, Jr., Vice-President, Medical Affairs; Dr. William Kellow, Dean of Jefferson Medical College; Mr. Byron Irwin, Associate Administrator, Thomas Jefferson University Hospital; Dr. Frank D. Gray, Chairman and Professor of Medicine; and Dr. C. Paul Bianchi, Chairman and Professor of Pharmacology. MSDRL was represented by Dr. William B. Abrams (Jefferson, 1947), Executive Director of Clinical Research; Dr. Richard O. Davies, Director, Clinical Pharmacology; Dr. Hubert C. Peltier, Vice-President for Medical Affairs; and Mr. Donald S. Brooks of MSDRL Legal. A letter of understanding was signed by Mr. George M. Norwood, Jr., interim President of Thomas Jefferson University, for Jefferson, and by Dr. P. Roy Vagelos, President of MSDRL, for Merck.

■ Research

A search committee was formed by the University, and in May 1977 Dr. Roger Ferguson was recruited to be the first Director. He received his medical degree at the University of Utah, then served his residency and was an M.S. in Pharmacology at the University of Iowa. Dr. Ferguson was active in antihypertensive drug research at Michigan State University. He had recently spent a sabbatical leave with Dr. Hans Brunner in Lausanne, Switzerland, where Dr. Ferguson undertook the first human investigation of a new class of agents, the angiotensin converting enzyme inhibitors (ACE inhibitors). Dr. Ferguson recruited the initial staff, and the first clinical study was undertaken in the fall of 1977. Peter H. Vlasses, Pharm.D., was appointed in 1978 as Assistant Director. Dr. Vlasses received his Doctor of Pharmacy degree from the Philadelphia College of Pharmacy and Science (PCPS); his special interest was in cardiovascular drug research.

Administratively, liaison with the Unit was the responsibility of Dr. William B. Abrams, Executive

Director of Clinical Research at Merck. Collaboration was initially implemented by Drs. David Cooper and John Schrogie through Dr. Davies. In 1980, Dr. Abrams assumed the liaison function directly. Dr. Abrams graduated from Jefferson in 1947, interned in Atlantic City, and received postgraduate training at the Children's Hospital of Philadelphia, Philadelphia General Hospital, and St. Louis University. He is a past President of the American Society for Clinical Pharmacology and Therapeutics. Dr. Abrams joined Merck in 1975, having previously been employed by Ayerst Laboratories and Hoffmann-La Roche, Inc. In order to facilitate the arrangements between the institutions, Thomas Jefferson University offered adjunct faculty positions to the Merck liaison officers. Thus, Dr. Abrams has been Adjunct Professor of Medicine since 1977. He received strong support relative to this liaison from Marvin E. Jaffe, M.D., Vice-President of Clinical Research, who was also a Jefferson Medical College graduate and a member of the adjunct faculty in neurology.

The initial direction involved active pursuit of ACE inhibitors and expansion of the Division's human research capabilities. Over the next several years, key personnel additions included Brian N. Swanson, Ph.D., Heschi H. Rotmensch, M.D., and, in a collaborative arrangement with PCPS, Mario L. Rocci, Jr., Ph.D. Dr. Swanson had expertise in assay development, especially high-performance liquid chromatography. Dr. Rotmensch brought expertise in pharmacodynamics, whereas Dr. Rocci was skilled in pharmacokinetic laboratory and data analysis. In this same period, the Unit underwent physical expansion, funded by MSDRL, to accomodate new laboratory and computer data processing facilities. With the assembling of this critical mass, the Division became very productive in its clinical research efforts.

The evaluation of ACE inhibitors in hypertension at Jefferson included dose-response, mechanism of action, comparative efficacy, and drug interaction studies with captopril, enalapril, and lisinopril. The ACE inhibitors subsequently have received extensive use in hypertension and congestive heart failure. The important Jefferson contributions to this field are summarized in a text edited by Drs. Ferguson and Vlasses, published in 1987.

Over its ten-year existence, 131 studies of new compounds were conducted by the Division of Clinical Pharmacology. Important contributors over this time also included Louis J. Reilly, Jr., M.D., and Michael D. Cressman, D.O. A wide range of therapeutic categories was represented, including diuretics, nonsteroidal anti-inflammatory drugs, antibiotics, ophthalmologic agents, and psychotherapeutic drugs. In general, this was an unprecedented period of research productivity in this field.

Many studies at Jefferson characterized the pharmacokinetics of the different investigational compounds in man. The special emphasis on pharmacodynamic assessments in these trials led to the development or application of many clinical and laboratory drug evaluation techniques. Important contributions in healthy volunteer experiments included the unraveling of the differential clinical pharmacology of the enantiomers of indacrinone, a uricosuric diuretic, and the assessment of systemic beta-blockade after dermal and ophthalmic application of timolol and other compounds. Parviz Mojaverian, Ph.D., undertook studies with the Heidelberg capsule, a pH-sensitive, radiotelemetric device. These studies led to important contributions to the understanding of the physiology of the interdigestive migrating myoelectric complex and pharmaceutical considerations dealing with gastric indigestible dosage forms (for example, enteric coated and sustained-release tablets). The nature and mechanism of many drug–drug interactions have also been evaluated. Close collaboration between Jefferson and Merck clinical and basic scientists evolved over this time. Extremely efficient processing of studies has resulted, facilitated by industrywide innovations in research data telecommunications. To date, well over 125 research and scholarly publications bearing the Jefferson affiliation have resulted from these evaluations. Recent research efforts have emphasized drugs affecting the prostaglandins and leukotrienes and their involvement in inflammation, pain, and local vascular regulation.

Education, and Service

In addition to research efforts, the Division of Clinical Pharmacology has participated actively in Jefferson Medical College's education and service

programs. Since 1977 the Division has offered a well-received fourth-year medical student elective course in clinical pharmacology employing a case-simulation format. Twelve postdoctoral (M.D., Ph.D., or Pharm.D.) Fellows as well as graduate and undergraduate medical and pharmacy students received training in the Division. Many faculty held cross-appointments in pharmacology, and a close working relationship evolved with many physician collaborators and the Hospital's Department of Pharmacy, directed by Joe E. Smith, Pharm.D. Unit faculty have served as teacher for the medical students, provided consultation for hospitalized and ambulatory patients on drug-related problems, served on pertinent comittees (for example, Pharmacy and Therapeutics, the Institutional Review Board) and have contributed to a variety of community services and professional organizations, both locally and nationally. In this regard, Dr. Vlasses was a founding member of the American College of Clinical Pharmacy in 1979, subsequently served as national President in 1983, and was honored as a Fellow in 1985.

Dr. Ferguson left Jefferson in 1985 to assume the Chair in Medicine at the University of Nevada at Reno. Discussions between Jefferson and MSDRL officers at that time led to a reaffirmation of the commitment of each party. The desire of both institutions was to maintain the activities in clinical research and to add investigations of a basic and mechanistic nature to this collaborative research effort. A revised letter of understanding, with funding commitment for a five-year renewal period, was executed in 1986. Key figures in the discussions leading to the continuation agreement in addition to Dr. Abrams were Willis C. Maddrey, M.D., Chairman of the Department of Medicine; Lewis W. Bluemle, M.D., President of Thomas Jefferson University; Marvin Jaffe, M.D., Vice-President of Clinical Research; and Edward Scolnick, M.D., President of MSDRL.

At this time, the role of the MSDRL Liaison was assumed by Dr. Keith H. Jones, Executive Director for Clinical Pharmacology. Dr. Jones received his medical degree at the University of Wales in 1966 and a Diploma in Pharmaceutical Medicine from the Royal College of Physicians in London in 1976. Prior to coming to MSDRL in 1979, he was employed by Beecham Pharmaceuticals, Surrey, England for ten years. Dr. Jones was appointed Adjunct Professor of Medicine at Jefferson in 1986.

A national search by Dr. Maddrey led to the recruitment of Thorir D. Bjornsson, M.D. as Director of the Division of Clinical Pharmacology in 1986. Dr. Bjornsson received his medical degree at the University of Iceland. He trained in clinical pharmacology at Stanford University and held previous faculty positions in clinical pharmacology at Duke University. He serves on the pharmacology study section of the National Institutes of Health.

As an expression of the commitment to clinical pharmacology and the desire to expand the scope of Divisional research, Dr. Maddrey provided funds for construction of a new Divisional facility encompassing 11,000 square feet of laboratory, clinical, and office space in the new Medical Office Building. The new Divisional facilities opened in April, 1987.

Dr. Bjornsson established three Sections within the Division: the Laboratory for Thrombosis and Atherosclerosis Research, which he heads; the Clinical Research Unit, headed by Dr. Vlasses; and the Laboratory for Investigative Medicine, headed by Dr. Rocci. Each Section has specific interests and functions as well as collaborative activities. Merck-funded projects as well as research programs funded through other sources (federal, foundation, and other pharmaceutical companies) are now commonly undertaken by the Divisional faculty. Divisional faculty are committed to developing a stronger program in drug development through clinical and basic research and training of future clinical pharmacologists. Dr. Bjornsson received a prestigious Pharmaceutical Manufacturers' Association Development Grant for Clinical Pharmacology in 1987 for expansion of the Division mission.

Thus, the decade spanning 1977–1987 has seen the evolution of a nationally recognized program in clinical pharmacology at Jefferson that would not have been possible without the strong collaborative venture with MSDRL. As the second decade begins, enthusiasm runs high for continued growth and recognition in an even broader realm of research as advances in biotechnology provide novel agents for the treatment of human disease.