NICHD ANNUAL REPORT OF INTRAMURAL RESEARCH, OCTOBER 1, 1983-SEPTEMBER 1984

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October 1, 1983 through September 30, 1984

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NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
INTRAMURAL RESEARCH PROGRAM

ANNUAL REPORT OF THE SCIENTIFIC DIRECTOR
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The Intramural Research Program is broadly concerned with the biological and neurobiological, medical and behavioral aspects of normal and abnormal human development. In addition to four major clinical research and training programs in the areas of genetics and endocrinology, a diversity of developmental models are under study in eleven fundamental research Laboratories, drawing upon observations in bacteria, Drosophila, yeasts, viruses, molluscs, frogs, rodents, and subhuman primates. Disciplines employed in these studies include biochemistry, virology, molecular biology, immunology, pharmacology, genetics, cell and neuronal biology, biophysics, mathematical and theoretical biology, reproductive physiology, and developmental psychology.

During the past year, the Program has seen several further major organizational changes. On June 30th, the Pregnancy Research Branch was disestablished consequent to the departure of its Chief, Dr. Gary Hodgen, and several of his colleagues for new positions at the Eastern Virginia Medical Center. The resources of the Pregnancy Research Branch have been employed to establish a new intramural Laboratory, the Cell Biology and Metabolism Branch, and Dr. Richard Klausner of the Laboratory of Biochemistry and Metabolism, National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases, has been recruited to lead the new Branch. Building 18 is presently being renovated to accommodate these new research interests. The Cell Biology and Metabolism Branch will focus on the developmental aspects of receptor regulation, metal metabolism, organelle structure and function, and the cell biology of gametes. The Branch's laboratory activities will take advantage of the extraordinary opportunities in cell biology occasioned by the recent advent of recombinant DNA, monoclonal antibody, and other new techniques. The Branch's clinical research activities will reflect the Institute's interest in the developmental aspects of metabolism. The human transferrin receptor will provide the major experimental model, and studies will be undertaken to determine how the cell regulates the biosynthesis of this receptor as a function of cellular iron economy and stimuli to cellular proliferation. The gene for this receptor, as well as the genetic regulatory elements, is being cloned in order to examine the molecular basis for transcriptional regulation. This receptor will also serve as a model for elucidating the pathway, mechanisms, and regulation of receptor degradation, inactivation, and sequestration. The Branch will explore the specific biochemical signals which determine the physical routing of the transferrin receptor within the cell.

The clinical studies to be undertaken by the Cell Biology and Metabolism Branch will employ a population of patients with hemochromatosis and other genetic diseases of metal metabolism. Patients (and normal volunteers) will be studied to determine the mechanisms by which cells regulate the distribution of iron throughout the cell, and the molecules responsible for the controlled intracellular traffic of iron. Therapeutic attempts at the level of "gene therapy" are contemplated for this patient population.

In another area of interest, the new Branch will explore the mechanisms by which the normal intracellular architecture is maintained, providing the basis for the function and dynamics of cellular organelles. Focus will be on the microtubule system and the Golgi apparatus, in order to learn how these structures are determined, how molecules restricted to different domains of these organelles are sorted, and whether there are signals that govern the localization and routing of different components of these organelles.

The Laboratory of Comparative Ethology, established in 1983, underwent a major building program during this year, and its extensive outdoor facility for free-ranging primates was opened in June.

A number of new sections were developed in the established Laboratories during this year, in recognition of new and independent research efforts that have emerged in the past several years. These sections and their Heads are:

Section on Comparative Behavioral Genetics, LCE (Dr. Stephen Suomi)
Section on Molecular Biology, HGB (Dr. Michael Zasloff)
Section on Molecular Structure and Protein Chemistry, ERRB (Dr. Hao Chia Chen)
Section on Adrenal Cell Biology, ERRB (Dr. Charles A. Strott)
Section on Metabolic Regulation, ERRB (Dr. K. P. Huang)
Section on the Regulation of Gene Expression, LDP (Dr. Howard J. Eisen)
Section on Drug Biotransformation, LDP (Dr. Ida S. Owens)
Section on Cellular Neurobiology, LNN (Dr. Yoke Peng Loh)
Section on Macromolecular Analysis, LTPB (Dr. Andreas C. Chrambach)
Section on Immunoregulation and Cellular Control, LDMI (Dr. Edgar E. Hanna)
Section on Steroid Hormones, DEB (Dr. D. Lynn Loriaux)
Section on Medical Endocrinology, DEB (Dr. Bruce C. Nisula)
Section on Reproductive Endocrinology, DEB (Dr. Richard J. Sherins)
Section on Developmental Endocrinology, DEB (Dr. Gordon Cutler, Jr.)
Section on Gamete Physiology, CBMB (Dr. Bela J. Gulyas)

Our clinical fellowships in adult, pediatric and gynecologic endocrinology, as well as the fellowship in human genetics, continue to thrive, and in the past year, we have also placed emphasis on recruiting physicians for full-time basic research training without clinical responsibility.

Peer review of intramural research has been strengthened significantly, with rigorous site visits to each Lab at 3-1/2 year intervals. During the past year, visits were made to the Endocrinology and Reproduction Research Branch, the Laboratory of Molecular Genetics, and the Developmental Endocrinology Branch, with detailed critiques prepared as a consequence of these visits. The membership of the Board of Scientific Counselors has been expanded from six to nine, reflecting the increasing diversity of research interests within the Intramural Program. The current Board membership includes:

James W. Lash, Ph.D., Professor of Anatomy, University of Pennsylvania
Aron Moscona, Ph.D., Louis Block Professor of Biological Sciences, University of Chicago
Roger Guillemin, M.D., Chairman, Laboratory for Neuroendocrinology, Salk Institute
John C. Marshall, M.D., Professor of Medicine, University of Michigan
Lewis P. Lipsitt, Ph.D., Professor of Psychology, Brown University

Allen H. Neims, M.D., Ph.D., Professor and Chairman, Department of Pharmacology and Therapeutics, University of Florida

The nominees for the remaining three Board vacancies are:

Story C. Landis, Ph.D., Associate Professor of Neurobiology, Harvard Medical School
Harold Amos, Ph.D., Professor of Bacteriology and Immunology, Harvard Medical School
John Phillips, Jr., M.D., Professor of Human Genetics, Vanderbilt University School of Medicine.

Other developments in the past year include the recruitment of a full-time veterinarian, Dr. John Donovan, who is supervising all aspects of the management of animals in our research. We have continued to see growth in outside sources of support of post-doctoral fellows. This year, the NIH has developed a new Intramural NRSA (National Research Scholarship Award) Program which enables American physicians to obtain research training in the Intramural Program without the need for a formal civil service position. Within the next three years, we shall recruit twelve NRSA trainees. We have also identified a number of bilateral agreements with foreign countries in which the foreign government supports the training of their post-doctoral fellows in our labs, and we are taking full advantage of such bilateral agreements. Good relationships have also been developed with a number of biotechnology companies, and they are endowing fellowships in our research training program as well. Our summer student program was very successful this year, with more than sixty undergraduate and medical students working in our Laboratories. Of this group, more than 50% were women and a third were minority students. The academic credentials of the group as a whole were singularly impressive, and our experience suggests that the decline in the number of talented young people considering careers in biomedical research may be reversing itself.

We have continued to develop new computer-based administrative procedures in the Office of the Scientific Director so as to maximize the efficiency with which our resources are shepherded. These new administrative approaches are ensuring the maximum yield with respect to scientific productivity while the current climate of constrained resources persists. With regard to laboratory space, we are now in the midst of an extensive renovation and building program. In addition to the new primate facilities for the Laboratory of Comparative Ethology at the NIH animal farm in Poolesville, Maryland, as well as the renovation and expansion of Building 18 for our new Cell Biology and Metabolism Branch, we are in the midst of renovating the tenth floor of the Clinical Center which will house the laboratories and offices of four of our Labs and Branches. The Developmental Endocrinology Branch has recently moved into its new corridor within this complex, and two more Labs will have moved by December, 1984. We are also on schedule with respect to the construction of two new floors of laboratory space and additional animal quarters in Building 6. Within established ceilings, our budget base and number of positions were increased significantly during the past year, as was the number of positions allocated for Visiting Fellows from abroad.

Seminars and workshops sponsored by this Program were numerous and popular throughout the year, such that this Institute organized a relatively large

fraction of the NIH's overall intramural seminar and workshop program. During the past year, seven major conferences with participants from throughout the world were hosted by the Intramural Research Program, including:

Mechanisms of Genetic Recombination (Airlie, Va.)
Molecular Biology of Xenopus Development (Airlie, Va.)
Ontogeny of Antibacterial Immunity and Bacterial Vaccines (NIH)
Pertussis Toxin (NIH)
Research on Mastery Motivation in Infancy and Early Childhood (NIH)
Mechanisms and Clinical Aspects of Steroid Hormone Resistance (New York)
Advances in Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (Toronto)

With regard to the major research interests and scientific results during the past year, particularly notable are the following:

Laboratory of Molecular Genetics--
Igor Dawid, Ph.D.

Investigators in this Laboratory use the tools of molecular and cellular biology to answer questions about gene transmission and recombination, and the regulation of genetic functions during development. The range of model systems under investigation includes bacterial and animal viruses, transformed animal cells, yeast, mouse and Xenopus embryos, and the fruit fly Drosophila melanogaster. Recombinant DNA technology and gene transfer methods are emphasized. The development of novel vectors is being pursued for the introduction and expression of isolated genes in animal cells.

Dawid's section has studied early development of the frog Xenopus laevis by the analysis of a group of gene sequences which are expressed for the first time in the late blastula and gastrula stages of embryogenesis. These sequences were isolated by cDNA cloning and yielded RNA molecules which are absent from the egg but present in the gastrula embryo. DG (differentiating gastrula) RNAs arise first within an hour after the midblastula transition, and show strong developmental regulation. A 17-amino acid peptide has been deduced from the cDNA sequence of one such DG RNA and synthesized chemically; DNA sequencing is being used to locate the 5' end of this DG gene, which will permit study of the gene's control region and the developmental regulation of its expression. In other Xenopus experiments, monoclonal antibodies have been raised against cell surface antigens in embryos in order to study the developmental regulation of their expression. The rationale for these studies lies in the fact that gastrula and neurula development involve cell migration, recognition, and adhesion, and distinct surface molecules undoubtedly play a role in these processes.

Studies by Dawid's group using the fruit fly Drosophila have focused on maternal-effect homeotic genes. Such genes specify the body plan, e.g., the three-dimensional formation of the bithorax complex. To study the fs(1)h homeotic gene, the region of the chromosome carrying it has been cloned by "chromosomal walking." An analysis of RNA transcripts from this region is underway, as is the cloning of cDNAs copied from the RNAs. Studies such as