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COVER

The image shows astrocytes from rat cerebral cortex in culture, stained with antibodies against glial fibrillary acidic protein (GFAP; green) and nestin (red). Some cells only express GFAP, whereas others express both nestin and GFAP (co-expression shows up as orange-yellow fluorescence). A significant number of astrocytes only express nestin, indicative of dedifferentiation. The image, made by Vittorio Gallo of the LCMN, was obtained by a double exposure of the same microscopic field on a Zeiss Axiophot fluorescence microscope (40× oil immersion lens).

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AND

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DIVISION OF INTRAMURAL RESEARCH

ANNUAL REPORT

1997

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SCIENTIFIC DIRECTOR'S PREFACE

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 five major clinical research and training programs in the areas of genetics, endocrinology, and maternal-fetal medicine, a diversity of developmental models are under study in eighteen fundamental research Laboratories and Branches, drawing upon observations in bacteria, *Drosophila*, plants (*Arabidopsis*), yeasts, viruses, mollusks, zebrafish, frogs, rodents (including transgenic and "knock-out" mice), and subhuman primates. Disciplines employed in these studies include molecular biology, biochemistry, virology, immunology, pharmacology, genetics, cell and neuronal biology, biophysics, mathematical and theoretical biology, electrophysiology, reproductive physiology, structural biology, and developmental psychology. During the past year, we have emphasized a number of research projects that we believe have a particular promise and timeliness. In these areas, new resources have been added so that the investigators will be optimally poised to exploit their recent findings. These projects address aspects of the cellular and molecular biology of development (growth and differentiation) wherein we anticipate significant results with broad implications for biomedical research. Indeed, it is our notion that the central, and arguably the most exciting, questions in contemporary biology focus on the cellular and molecular mechanisms and interactions that guide a single fertilized egg cell through its development into a multicellular, highly organized and specialized adult organism.

The past year was an extremely productive one for this Intramural Research Program, and the year's scientific advances in each Laboratory and Branch are fully detailed on the following pages. Two new Laboratories were established in 1997—the Laboratory of Integrative and Medical Biophysics (LIMB) and the Laboratory of Structural and Physical Biology (LSPB). The investigators in these Laboratories, and their research resources, were transferred from the NIH's Division of Computer Resources and Training and the National Center for Research Resources after NIH leadership concluded that the research goals of the LIMB and LSPB scientists were more consistent with those of an intramural research program than a service organization. Dr. V. Adrian Parsegian is the Chief and two tenure-track scientists, Drs. S. Bezrukov and S. Leikin, complete the LSPB. The interests of this Laboratory are focused on the intracellular forces responsible for molecular conformation and assembly (including hydration forces responsible for channel dynamics), DNA-protein interactions, and the alteration of molecular conformation by electrical stimuli. Dr. Ralph Nossal is Chief of the LIMB, and the interests of this Laboratory are primarily in light scattering at a basic level, as well as the theoretical and applied basis of imaging of cells, tissues and organs (including MRI and other non-invasive techniques that rely on lasers). The LIMB includes two additional tenured scientists, Drs. R. Bonner and P. Basser. An important recent achievement in this Laboratory is the development of Laser Capture Microdissection, which permits the isolation of individual cells or groups of cells from complex tissues, to the end that the individual cell can be assayed for mRNA and protein expression, etc.

Late in the year, Dr. Richard Klausner asked to be relieved of his responsibilities as Chief, Cell Biology and Metabolism Branch (CBMB), given the transcendent challenges of his newer position as Director, NCI. Happily, Dr. Klausner's own immediate laboratory group will continue to function within the CBMB. Dr. Juan Bonifacino was appointed as the new Chief of this Branch. Bonifacino is an internationally recognized cell biologist, with a particular interest in the molecular signals that determine the assembly, routing, compartmentalization, and internalization of cellular proteins and multi-protein complexes. The appointment of Dr. Bonifacino to this important position reflects the institutional value that we have placed on cell biology, and the recognition that this very demanding, but rewarding, area of contemporary biomedical research profits greatly from the long-term support characteristics of the NIH's Intramural Program.

Also in 1997, we completed the construction of our new zebrafish facilities, and were fortunate to recruit two tenure-track scientists who are focused on this model for the study of vertebrate development. Drs. Brant Weinstein and Ajay Chitnis joined us after completing their post-doctoral fellowships at the Harvard Medical School; Dr. Weinstein's major interest is in the development of the cardiovascular system as well as hematopoietic differentiation, and Dr. Chitnis' major interest is in the development of the nervous system. We now have approximately 10,000 fish tanks, with an elegant facility proximate to the Laboratory of Molecular Genetics (LMG), and a satellite facility elsewhere on the campus. The zebrafish has the mutability of *Drosophila*, but demonstrates the classical stages of vertebrate embryogenesis; genetic screens should allow the

identification of hundreds, if not thousands, of hitherto unappreciated vertebrate gene functions. Moreover, a particular advantage of zebrafish is the optical clarity of the embryo.

During the past year, we completed the renovation of an additional corridor of space in Building 10, which has allowed expansion of the Laboratory of Cellular and Molecular Biophysics (Joshua Zimmerberg, M.D., Ph.D., Chief). In particular, this corridor provides new space in which to house this Laboratory's cooperative research program with NASA. This maneuver has also allowed the Institute to centralize all of its space in Building 10 on the 8th, 9th, and 10th Floors; heretofore, the labs in this Building have been quite dispersed. Locating the laboratory space on these floors also allows much closer proximity to our clinical research wards. The new space has also allowed the addition of a new independent research group led by Forbes D. Porter, M.D., Ph.D. in the Heritable Disorders Branch. During 1997, we also began construction of another building for the Laboratory of Molecular Embryology (LME)/CBMB complex, which will allow still further expansion of the research of both Laboratories, providing a significant core for Institute research in these rapidly growing and critical fields. The Laboratory of Eukaryotic Gene Regulation moved to vacated LME space, and in turn, vacated space in Building 6B, which permitted the addition of the two new zebrafish research groups in the LMG. The NICHD Intramural Research Program now comprises more than 150,000 sq. ft. of laboratory, office, and animal space.

In November, ground was broken for the NIH's Clinical Research Center, a 250-bed state-of-the-art hospital, which reflects rapidly evolving concepts of inpatient as well as outpatient care. The Building should be completed by 2002, at which time all of the Institute's patients, except those of the Perinatology Research Branch (PRB), will be housed in the new facility.

The PRB conducts clinical and laboratory research on factors responsible for perinatal morbidity and mortality, with a particular focus on those factors in high-risk urban populations. The Branch is emphasizing a multidisciplinary approach and utilizing the expertise from a number of clinical specialties (including obstetrics, perinatal pathology, neonatology, and diagnostic imaging), as well as from basic sciences and epidemiology/demography, to improve our etiologic understanding, diagnosis, treatment, and prevention of low birth weight and perinatal morbidity and mortality. The three elements of this intramural research Branch are located off-campus so that the Branch investigators have immediate access to a large population at risk for perinatal disorders. The primary Branch research site is therefore located in a regional academic medical center, and the Institute is currently negotiating a new infrastructure support contract designed to bring the Branch closer to the main NIH campus.

The Institute's vaccine development program continues to be exceptionally successful. Drs. John Robbins and Rachel Schneerson, who lead this program, were honored with the 1996 Albert and Mary Lasker Foundation Award for Clinical Research for their development of the *Haemophilus influenzae* conjugate vaccine. This vaccine, now used world-wide, has eliminated the most common cause of acquired mental retardation (a consequence of the meningitis commonly caused by this organism), saving at least one-half billion dollars yearly in U.S. health care costs. Indeed, this is one of the most important achievements, with respect to the public health, of any intramural scientific group at the NIH in modern times.

Notable also during 1997 were the appointments of two NICHD tenure-track investigators, Drs. Yoshihiro Nakatani and Leonid Chernomordik, to tenured positions. Dr. Nakatani's group is located within the Laboratory of Molecular Growth Regulation. His focus is on the molecular mechanisms of gene expression in the context of chromatin. Dr. Chernomordik's group is located within the Laboratory of Cellular and Molecular Biophysics, and his interests are in the mechanisms that underlie membrane fusion. Two scientists were appointed to the tenure track following international searches in 1997. Dr. Mary Lilly was recruited from the Carnegie Institution and will join the Cell Biology and Metabolism Branch. Her interest is in mechanisms that link developmental signals with cell cycle control, with a focus on the endocycle in *Drosophila*. Dr. Tamas Balla's laboratory is within the Endocrinology and Reproduction Research Branch and he is primarily interested in signal transduction in endocrine cells, with a particular interest in the roles of calcium, phosphoinositols, and kinases in various signaling cascades.

A major issue confronting the NIH and the Nation as a whole is the recent and dramatic decline in patient-oriented research, i.e., research that requires interaction between a physician-investigator and a patient (in contrast to disease-oriented research in which, for example, a Ph.D. investigator might study oncogenes in the laboratory but not in patients *per se*). The number of physicians participating in patient-oriented research has fallen over the past decade for a number of reasons, while disease-oriented research, as informed by cell and