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Journey to Africa With the HHS Secretary

PREPARED TO MAKE A DIFFERENCE

by Yvonne Maddox
Acting Deputy Director, NIH

As I climbed the steep steps of the KC 135 military aircraft—a refueling plane—I knew that my trip to sub-Saharan Africa would be the experience of a lifetime. The mission for our 27-person delegation was "to develop an understanding of the countries' health care delivery systems and to see how the United States might . . . partner with colleagues in Africa." Our six-day itinerary would take us to Mozambique, South Africa, Botswana, and Côte d'Ivoire.

The mission was headed by DHHS Secretary Tommy Thompson; the

Yvonne Maddox (right), met by U.S. ambassador to Ghana Nancy Powell upon arrival at Kotoka International Airport, Accra

troops were leaders from NIH, CDC, FDA, HRSA, Congress, the White House, the National Security Council, the Department of State, USAID, private nongovernmental organizations, academia, and the pharmaceutical industry. As we left from Andrews Air Force Base Easter evening, March 31, Thompson advised us that our job was "to look and see, listen and hear, and return to this place prepared to make a difference." En route to Mozambique, NIAID Director Tony Fauci briefed

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INCOMING NIH DIRECTOR VOWS DEDICATION TO 'FACTS, NOT FACTIONS'

by Celia Hooper and Fran Pollner

From the moment in late March that he was nominated by George Bush to become the next NIH director, Johns Hopkins radiology chief Elias Zerhouni has been on a fast track from Baltimore to Bethesda.

Elias Zerhouni

Senate hearings on his nomination were held April 30; his confirmation by the full Senate by voice vote came two days later. Zerhouni was expected to be sworn in at NIH in an informal ceremony on May 20, replacing acting director Ruth Kirschstein and ending the more than two-year hiatus between NIH directors since Harold Varmus departed on the eve of 2000.

NIH officials who attended the confirmation hearings before the Senate Health, Education, Labor, and Pensions Committee said they were impressed with Zerhouni's candid and skilled responses to politically sensitive questions and the way he focused on the scientific bottom line.

When it comes to political hot-button issues, Zerhouni told the senators, his role as NIH director would be to inform the debate by developing and communicating the most objective scientific data—to present scientific facts, not to support political factions.

Fielding questions on human embryonic stem cells, Zerhouni indicated that he believed that the cell lines that have been approved for NIH-supported research (see "Human Embryonic Stem Cells: Opportunity Delayed but Not Denied," *The NIH Catalyst*, November–December 2001, page 1) would be sufficient for researchers to begin to probe for answers to the fundamental questions on which the cells may shed light.

Zerhouni's interest in stem cell research is more than academic. As executive vice dean of The Johns Hopkins University School of Medicine—a position he has held since 1997—he launched and organized the Institute for Cell Engineering, described on the Hopkins website as "dedicated to exploiting the practical and ethical uses of progenitor cells."

Throughout his career at Hopkins, Zerhouni has been tapped to handle complex tasks combining consensus-building and managerial skills with a broad and deep knowledge of basic research, clinical medicine, and biomedical engineering. He is profiled on the Hopkins website as an acknowledged and "gifted clinician, scientist, and inventor," as well as "a leader with the administrative ability to juggle multiple tasks effectively and the leadership skills to energize people around strategic goals."

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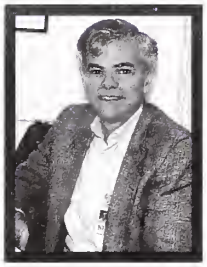
Sharing Scientific Riches



Michael Gottesman

This issue of *The Catalyst* includes a review of some of the research achievements of the NIH intramural programs in the past year.

Even a casual glance reveals a rich trove of basic science discoveries, technological advances, and new strategies to prevent, diagnose, and treat human ailments. True to the NIH mission to "do research to improve the public health," there are numerous examples of disease-oriented and patient-oriented research that may soon become the standard of care. We should be proud of these achievements, make the public aware of them, and be generous in our efforts to help all of our scientific colleagues benefit from our research tools and our knowledge.

Thus, it is the policy of the NIH to share research resources and, wherever possible, research databases with the rest of the scientific community (see policy documents **<http://ott.od.nih.gov/NewPages/RTguide_final.html>** and **<http://www.nih.gov/news/researchtools/index.htm>**). In keeping with this policy, the scientific directors and their Committee on Large Database Sharing recently issued a statement supporting an NIH Draft Statement on Sharing Research Data (**<http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-02-035.html>**). The SDs concluded that the "general principles outlined in the statement are applicable to scientists in the NIH intramural research program involved in the collection and analysis of large-scale databases."

A few examples serve to illustrate the important effects of providing research tools and data to our scientific colleagues. Research tools such as transgenic animals have become an integral part of research advances in many fields of biomedicine; it is inefficient and unjustifiable to use public monies to recreate transgenic mice, for example, that have already been characterized and described in the public literature. We expect our scientists, and our colleagues in the extramural community to provide such animals to other legitimate laboratories within a reasonable time frame after publication (see **<http://www1.od.nih.gov/oir/sourcebook/ethic-conduct/resources.htm>**). Similarly, the NCBI's GenBank provides genome data and analytic software at no charge to the public; the entire human genome sequence, arguably one of the great scientific advances of recent years, is freely available. Such should be the case, too, with published structural data, such as X-ray coordinates. The reward for such openness is the enormous acceleration of progress in biomedical research.

What are the responsiblities of investigators who oversee large databases that have not yet been fully mined for publication? Microarray analyses and clinical and epidemiologic databases come to mind. In these cases, the duration of data collection, the human subjects research (privacy) concerns, and the investment of the individual investigator are all factors that influence the degree and pace of public release. In the statement by the SDs, it is suggested that the Boards of Scientific Counselors should weigh in on how public release of such large databases should be handled; with long-term clinical studies, specific committees are often involved in assuring release of accurate data that do not violate individual privacy.

NIH-supported investigators have an obligation to publish their findings and make their data available so that our achievements can advance science and improve public health. That's the NIH mandate. I welcome the comments of the intramural community on how best to share data and research tools. ■

Selected NIH Intramural Research Accomplishments 2001–2002

Organized According to Government Performance and Results Act Goals

Goal A: Add to the body of knowledge about normal and abnormal biological functions and behavior

Identification of disease genes

- *GNAS1* mutations that underlie McCune-Albright syndrome (MAS) found to underlie non-MAS fibrous dysplasia (NIDCR, NIDDK)
- Protocadherin defect found to underlie Usher 1F syndrome (NIDCD)
- TMC1, a novel transmembrane protein, found to underlie DFNA36, DFNB7, and DFNB11 (NIDCD)
- More prostate cancer susceptibility genes identified using DNA chip technology (NHGRI)
- Germline mutations in the Fas immune cell receptor associated with autoimmune lymphoproliferative syndrome also found to increase lifetime lymphoma risk (NIAID, NCI, NHGRI, CC)
- Altered *COMT* gene found to disrupt dopamine function in prefrontal cortex and increase risk of schizophrenia (NIMH, NIAAA)
- *ST7*, new tumor suppressor gene found on chromosome 7, is involved in tumors arising from epithelial cells, such as breast, prostate, colon, and ovary (NHGRI)
- Novel cytokine receptor-binding protein that regulates receptor shedding and innate immune responses provides new insights into the regulation of airway inflammation (NHLBI)
- A macromolecular complex involved in the initiation and regulation of membrane trafficking provides new insight into mechanisms of vesicle formation (NHLBI)
- Complete genomic sequence and regulatory elements modulating gene expression have been determined for the ABCA1 transporter, the protein whose gene is defective in Tangier disease (NHLBI)
- Analysis of *FOXL2*, a gene that determines the age of menopause by controlling the number of ovarian follicles formed, is an entry point to understanding the regulation of reproductive lifespan (NIA)
- Mutation in a gene normally associated with spinocerebellar ataxia (*SCA3*) can produce a clinical picture more similar to Parkinson's disease in different racial groups, showing how ethnic background can affect expression of genetically determined disease (NIA)

Important new animal models

- Transgenic mouse model to study relationship between carcinogens and skin cancer using transformation-associated recombination cloning (NIEHS)
- Mouse model to assess the toxicity of combination anti-AIDS regimens (NIEHS)
- Knockout mouse model of amelogenesis imperfecta sheds light on hereditary dental

enamel defect (NIDCR)
- Mouse model of β-thalassemia suggests gene therapy is successful if at least 10 percent and ideally 20 percent of stem cells are corrected (NHGRI)
- Mouse models to explore diversity of brain signals regulating appetite and body size; mice lacking the M3 muscarinic acetylcholine receptor are hypophagic and lean (NIDDK, NIAAA, NIMH)
- *PDS* knockout mouse model to study inner-ear defects and deafness in Pendred syndrome (NIDCD)
- Mouse model for human nonsyndromic hearing impairment (DFNA36/B7/B11)
- Mouse model for Usher syndrome type 1D (NIDCD)
- Transgenic mouse model of a targeted disruption of a cyclic nucleotide phosphodiesterase gene provides new insights into the regulation of insulin homeostasis (NHLBI)
- Animal model of immune-mediated aplastic anemia shows pivotal role of type 1 cytokines in causing severe marrow cell destruction (NHLBI)
- Animal model demonstrates that cocaine craving increases progressively over weeks or months of forced cocaine abstinence, in parallel with increases in brain-derived neurotrophic factor in reward-associated brain circuitry (NIDA)
- Knockout mouse model demonstrates that animals with a D2 dopamine receptor deletion do not self-administer morphine (NIDA)

Basic discoveries in cell, molecular, and structural biology with implications for the treatment of human disease

- A peptide fragment of myelin basic protein was found to have encephalogenetic potential in humans, providing direct evidence of an autoimmune etiology for multiple sclerosis (NINDS)
- New insights into how p53 protects health: the relation of the structural biology of p53 to its tumor suppressor effects elucidated by identification of specific phosphorylation sites (NIEHS, NCI)
- Elucidation of the mechanisms of mitochondrial DNA disruptions by the various AIDS drugs to inform the development of safer, more effective antiviral medications (NIEHS)
- Elucidation of role of p38 kinase signaling in cellular response to cytoxic agents suggests new molecular target for cancer (NCI, NIA)
- Many genes differentially expressed in ovarian cancer are coordinately expressed, suggesting the presence of a small number of key pathways in ovarian tumorigenesis (NIA)
- Mitochondria from human breast cancer cell lines found to be defective in the repair of one form of oxidative DNA damage, suggesting another factor in breast tumorigenesis (NIA)
- Changes in X-chromosome structure, as well as interruption of specific genes, may lead to early menopause (NIA)
- High levels of homocysteine, resulting from folic acid deficiency, found to promote dysfunction and degeneration of nerve cells in well-established mouse models of Alzheimer's and Parkinson's diseases (NIA)
- Discovery that auditory pitch recognition differences are mostly genetic presages identifying the involved genes and how they function (NIDCD)
- Wnt-7A signaling protein excess leads to disoriented bundling in embryonic ear and hearing loss (NIDCD)
- Identification of induced cell surface channel on red blood cells infected with malaria parasites presents potential target for vaccine or drug (NICHD, NIAID)
- βeta-Amyloid found to bind to mouse immune cell receptor and to induce free radicals, findings that may suggest new therapies to slow Alzheimer's progress (NIAID, NCI)
- β-Amyloid binding to a rat brain receptor blocks signals thought to be involved in learning and memory before the formation of β-amyloid plaques in Alzheimer's (NIEHS)
- CD21 identified on B-cell surface serves as a vehicle for HIV spread throughout body and to CD4 T cells (NIAID)
- Removal of cholesterol from cells decreases HIV's ability to produce new virus particles and infect additional cells, suggesting a novel anti-HIV therapy (NIAID)
- A single gene change allowed *Yersinia pestis*, the plague bacterium, to survive in the flea midgut and evolve from transmissibility via contaminated food or water to a flea-borne agent (NIAID)
- Antibodies against the cellular receptor for IL-10 completely eliminated leishmania parasites in mice, suggesting a new way to prevent recurring infections in people (NIAID)
- Mutations in genes encoding antibodies that enhance response to antigens found to be similar in young and old humans, suggesting that effective response to antigenic challenge persists well into old age (NIA, NCI)
- Effect of normal and mutant MARCKS protein on cell adhesion suggests a role for MARCKS in the migration of brain neurons during development (NIEHS)
- Discovery of new cytochrome p450 arachidonic acid hydroxylase (CYP2J9) in mouse brain sheds light on brain responses to environmental neurotoxins (NIEHS)
- The human Cockayne syndrome protein found to be involved in DNA repair of oxidative damage (NIA)
- Neuronal responses to visual stimuli in monkeys suggest process for memory formation (NIMH)
- Prefrontal cortex activities in monkeys related to perception, integration of information, and translation into action shed light on brain processes underlying disturbed behavior in schizophrenia and mood disorders (NIMH)
- fMRI reveals connectivity among different areas of the brain involved in different aspects of language processing (NIMH, NIDCD)
- Learning a motor task requires consolidation of the learning in the motor cortex before subsequent distribution and storage in other cortical areas (NINDS)
- Brain imaging identifies human brain region activated by anticipation of reward (NIAAA)
- Discovery that marijuana activates the same reward pathways as cocaine and heroin and idenitification of the site of rewarding action of endomorphin-1, an endogenous μ-opioid agonist, have implications for treatment of addiction (NIDA)
- Blocking natural killer T lymphocytes and interleukin-13 turned off the suppression of immune system tumor surveillance in mice, presenting a promising approach to cancer immunotherapy and vaccine development (NCI)
- Altered protein (histone H2AX) found to indicate double-stranded DNA breaks may be useful clinically in establishing optimal ionizing radiation dose and identifying patients with increased sensitivity to radiation and other chemically induced DNA disruptions (NCI, NIDDK)
- New understanding regarding the way steroid receptors turn on genes that respond to hormones such as androgen and estrogen may help in developing receptor-targeting drugs (NCI)
- Oxyradical-induced mutations in the *p53* gene pinpointed early in the development of liver and colon cancer may enable prediction of a person's risk for these cancers and early interventions to interrupt the cancer-forming process (NCI)
- Two bone-related proteins expressed by many primary tumors found to enable tumor cell evasion of complement-mediated attack (NIDCR)
- Dynamin-related protein 1, a mediator of mitochondrial fission, found to be required for apoptosis (NINDS)
- Insight into the interdependent association of three oral bacteria that play a role in dental plaque formation may lead to preventive interventions (NIDCR)
- Receptor differences in the white blood cells of Caucasians, African-Americans, and Asians may help explain differences in response to certain infections among people

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of different racial backgrounds (CC, NCI)
- Different *Helicobacter pylori* strains, with strain-specific differences in genetic content shown by microarray, were found to induce varying degrees of inflammation, ulceration, and cancer susceptibility in a gerbil model (NIAID)
- Restoration of vascular blood flow with inhaled nitric oxide has implications for the treatment of atherosclerosis and coronary artery disease (NHLBI, CC)
- Aberrant transcriptional control in alveolar macrophages may be a contributing factor in the pathogenesis of pulmonary fibrosis (NHLBI)
- Anti-TNF therapy in asthma alters the airway inflammatory response (NHLBI)
- Data from an ongoing study of the natural history of lymphangioleiomyomatosis have established clinical, pathological, physiological, and genetic criteria that define disease severity and progression (NHLBI)
- New pathway for the transport and removal of intracellular cholesterol by HDL and the specific plasma apolipoproteins in HDL that act as cholesterol acceptors have been identified in *ABCA1* transgenic mouse studies (NHLBI)
- Despite lower initial HIV viral loads among infected women, women and men were found to progress to AIDS at similar rates, suggesting that initial viral load is not predictive in women as it is in men and that treatment decisions need to be adjusted accordingly (NIAID)
- X-ray crystallography determines structure of γδ T-cell receptors, which may bind phosphoantigens released from pathogens causing tuberculosis, malaria, and other diseases—findings with implications for vaccine design (NIAID)
- Variant of *CX3CR1* gene found to protect against atherosclerosis and myocardial infarction (NHLBI, NIAID)
- MRI shows structural changes in brains of psychotic, nonschizophrenic children that resemble those in schizophrenic children and differ from findings in normal children (NIMH)
- Insight into the synchronous firing of brain cells in response to an object of attention (while ignoring less relevant features of a given visual scene) has implications for managing ADHD (NIMH)
- Maintaining levels of the enzyme CYP2J2 and its products protects against the cell injury in the heart and blood vessels that occurs during angioplasty and other hypoxia-reoxygenation scenarios (NIEHS)
- Molecular insights into inflammatory disorders: The roles of TNF receptor subtypes in the pathogenesis of tristetraprolin-induced TNF excess suggest that inhibiting the type I receptor or stimulating the type 2 receptor might be therapeutically useful in such conditions as rheumatoid arthritis and Crohn's disease (NIEHS)
- DNA replication errors generated by newly discovered DNA polymerase η found to resemble the hypermutation process in genes that code for immunoglobulin proteins and may shed light on how to enhance immune function (NIEHS, NLM)
- Elucidation of how the alloimmune environment reshapes the immune response of the donor after stem cell transplantation and identification of innate T-cell responses to known and putative tumor-specific antigens informs immunotherapeutic strategies (NHLBI)
- Elucidation of the metabolic underpinnings of insulin receptor impairment in type 2 diabetes should inform the development of new therapies (NIA)
- Development of a theoretical analysis of how water is transported through membranous channels (NIDDK)
- K-Opioid actions found to modulate internalization of the dopamine transporter, as well as cocaine effectiveness and cocaine sensitization (NIDA)
- Self-administered heroin and amphetamine found to produce brain hyperthermia (NIDA)
- Methamphetamine shown to have the potential to lower anti-apoptotic pathways in brain as well as increase pro-apoptotic pathways (NIDA)
- Corticotrophin-releasing factor found to be involved in processes underlying stress-induced relapse to heroin and cocaine seeking (NIDA)
- Leptin found to be involved in relapse to heroin seeking induced by acute food deprivation (NIDA)

Goal B: Develop new or improved instruments and technologies for use in research and medicine

Advances in imaging
- Improved MRI with magnetization transfer contrast for managing cataracts and other lens changes (NINDS, NEI, NHLBI)
- New imaging technique—diffusion tensor MRI—to follow stroke in progress (NICHD, CIT)
- Transcranial magnetic stimulation to enhance understanding of fMRI of the brain (NINDS)
- Development of manganese as a tracer in imaging neuronal activity and connectivity (NINDS)
- "Virtual colonoscopy"—automated polyp detection using a computer algorithm to analyze CT scans of the abdomen and pelvis—shown to be feasible for real patients with real polyps (CC, CIT)
- Development of a small animal PET scanner to visualize biochemical processes and track biochemical pathways in vivo (CC, CIT, SEIB)
- Development of a PET ligand for central nervous system nicotinic cholinergic receptors (NIDA)

Advances in bioinformatics
- New software to analyze tumor DNA changes (NCBI)
- Improving the accuracy of PSI-BLAST protein database searches for sequence similarities (NLM)
- Addition of new genomes and new functionalities to the COGs (Clusters of Orthologous Groups of proteins) database to enhance the classification of proteins from complete genomes (NLM)
- New technique to gain insight into three-dimensional protein structure and to correlate structure and sequence information involves the new Conserved Domain Database in conjunction with several other web-based tools (NLM)
- MAPS (MicroArray Project System) database to manage and interpret microarray gene expression data (NIEHS)
- Developing tools for toxicogenomics: a DNA database for *Xenopus laevis* expressed sequence tags, a model to evaluate effects of environmental toxins on development (NIEHS)
- Internet connectivity and communications network established throughout African sites of the Multilateral Initiative on Malaria (NLM)
- Functional atlas of *Caenorhabditis elegans*, the first comprehensive catalog of protein interactions in a eukaryotic organism (NLM)
- Computational research supports a role for "junk DNA" in genomic organization, cellular activities, and gene expression (NCBI)
- Genomic analysis of radiation-resistant bacterium to elucidate DNA damage and repair mechanisms; sequence placed in GenBank (NLM)
- Evolutionary analyses of two bacterial genomes deposited into GenBank—*H. pylori* and *Chlamydia pneumoniae*—provide insight into mechanisms of bacterial pathogenesis (NLM)
- A collection of 15,000 sequence-verified and annotated mouse cDNAs, primarily derived from early mouse embryos, has been freely distributed to the research community (NIA)
- Completion of the draft genome sequence of the mouse (within the Mouse Sequencing Consortium) and initiation of the collaborative program to sequence the genome of the laboratory rat lays the groundwork for cross-species comparisons of mice, rats, and humans (NHGRI)

Advances in biotechnology
- Manipulations of cell-culture conditions induced the formation of pancreas-like cells from mouse embryonic stem cells that survived unchanged when injected into diabetic mice, a promising first step toward developing a treatment (NINDS, NIDDK, NIMH)
- Adult mouse bone marrow cells injected into newborn mice migrate to the brain and form cells resembling nerve cells (NINDS)

- New evidence of the existence of circulating skeletal stem cells (in adult mice, rabbits, guinea pigs, and humans) and their ability to form bone (NIDCR)
- Stem cells isolated from pulp of adult human teeth and grown in lab generate a dentin structure in mice and may be basis for clinical tissue engineering to repair or replace teeth (NIDCR)
- New system (MALDI/mass spectroscopy) to rapidly identify and characterize markers of genetic variations (single nucleotide polymorphisms) may hasten discovery of cancer genes (NCI)
- Development of new technologies for prevention of nosocomial pneumonia and ventilator-induced injury may reduce patient morbidity and mortality in the intensive care unit (NHLBI)
- New cell-culture process to generate large numbers of dendritic cells from cells circulating in the blood for use in cancer immunotherapy (NCI)
- Rationale for waiting 28 days between donations established in studies pinpointing the effects on white blood cell donors of the cell collection process and agents used to augment the yield (CC)
- Tool to measure a patient's capacity to repair treatment-induced DNA double-strand breaks may aid in the selection of more successful treatment regimens (CC)
- New technique of in vivo site-directed mutagenesis using oligonucleotides to assess large volume of genes rapidly (NIEHS)
- Rapid functional analysis of mutations in *p53* tumor suppressor gene using yeast as an in vivo test tube (NIEHS)
- Use of a biologically active triple helix–forming oligonucleotide to generate gene knockout mice by a novel mechanism (NIA)

Goal C: Develop new or improved approaches for preventing or delaying the onset or progression of disease and disability

- Elucidation of the molecular basis of alphavirus assembly to guide the design of agents to prevent viral entry and infection in such conditions as encephalitis and arthritis (NIAID)
- Children with hereditary retinoblastoma found at risk for early-onset lung cancer and are candidates for aggressive antismoking efforts (NCI)
- Estrogen replacement therapy found to attenuate systolic blood pressure rise in postmenopausal women (NIA, NHLBI)
- First evidence found in rats and mice that dietary restriction increases levels of growth factors in brain and stimulates new nerve cell production, with implications for strategies to combat age-related neurodegenerative disorders (NIA)
- An observational study of hormone use in postmenopausal women in the Baltimore Longitudinal Study of Aging revealed better memory performance in women receiving hormone therapy than in those who had never been treated (NIA)
- Angiotensin converting enzyme inhibitor treatment was associated with a lower decline in muscle strength and walking speed in older hypertensive women (NIA)
- Blockade of CB1 receptors found to block acute effects of marijuana in humans (NIDA)
- Strategies to prevent kidney cancer suggested in finding that obesity and hypertension are related to increased renal cancer risk in men (NCI)
- Newly discovered atherosclerosis-associated protein markers for glaucoma present intervention points to prevent disease progression (NEI)
- Tests devised to identify genetic polymorphisms that affect Taxol metabolism and its toxicity in breast cancer patients set the stage to tailor taxol dose to each patient and avert its toxic effects (NIEHS)
- In utero exposure to diabetes found to increase offspring's risk of diabetes and obesity (NIDDK)
- The association of visceral adiposity in healthy older adults with aortic stiffness suggests that keeping weight within normal limits and visceral fat low may slow vascular aging and reduce heart disease and stroke risk (NIA)
- Silicone breast implants were not linked to increased risk for most cancers nor to increased mortality in a large and continuing epidemiologic study undertaken to address this public health concern (NCI)
- Cell phone use was not found to increase the risk of brain tumors in an ongoing case-control study (NCI)
- First national prevalence data on bullying among middle school and high school students identifies potential risk and protective factors (NICHD)
- First national data on where children drown in the U.S. (by age, race, and sex) establish targets for prevention (NICHD)
- Participation in the African-American Hereditary Prostate Cancer Study and the African-American Diabetes Mellitus Study should lead to discovery of genes involved in prostate cancer and susceptibility genes to type 2 diabetes (NHGRI)

Vaccine Development

- Candidate vaccines against pediatric otitis media caused by two different pathogens found safe and immunogenic in early trials (NIDCD)
- Clinical trial begins of AIDS vaccine encoding core HIV proteins (VRC)
- Clinical trial begins of papilloma virus vaccine to prevent cervical cancer (NCI)
- Conjugate vaccines against *Salmonella typhi* and *Staphylococcus aureus* performing well in early clinical trials (NICHD, NIDDK)
- New DNA-based vaccine prevented Ebola virus infection in monkeys (VRC)
- A hybrid vaccine formed by removing key genes from dengue virus and replacing them with WNV genes protected mice from West Nile virus infection (NIAID)
- Live, attenuated dengue virus vaccine found to be safe and highly immunogenic in early clinical trials (NIAID)
- A multiprotein DNA/MVA vaccine protected macaques from illness following mucosal challenge with an extremely pathogenic HIV/SIV virus (NIAID)
- A DNA vaccine augmented with IL-2 prevented AIDS in monkeys (VRC)
- A vaccine directed against a component of sand fly saliva prevented leishmaniasis in mice (NIAID)
- Nasal administration of a respiratory syncytial virus (RSV)/human parainfluenza (HPIV) virus construct stimulated strong RSV- and HPIV-specific immune responses in rhesus monkeys (NIAID)
- Transgenic animals can be engineered to secrete malaria proteins in their milk, offering a practical option for large-scale vaccine production in developing countries (NIAID)
- Identification of group A Streptococcus (GAS) molecules produced by all human isolates of GAS examined from worldwide sources that may be suitable for human vaccine components (NIAID)
- CMV pp65 protein canarypox construct prevents cytomegalovirus reactivation after stem cell transplantation (NHLBI)
- Seroconversion studies of B19 parvovirus in sickle cell anemia patients presage a recombinant vaccine trial of baculovirus-engineered empty capsids (NHLBI)

Goal D: Develop new or improved methods for diagnosing disease and disability

- Men with the lowest levels of prostate-specific antigen found to be unlikely to benefit from frequent PSA surveillance to detect early prostate cancer; for those whose PSA levels are between 2.0 and 4.0 ng/mL, a PSA velocity greater than 0.1 ng/mL/year was found to be associated with a 6.5-fold increased risk for developing prostate cancer (NIA)
- Clinical proteomics initiative combining laser capture microdissection, protein microarrays, and proteomic signatures enhances the diagnosis (and treatment) of an array of cancers (NCI)
- Diagnostic approaches based on immunological detection of the *Pseudomonas aeruginosa* type III secretory apparatus and its associated cytotoxins provide evidence for early colonization and/or infection in children with cystic fibrosis (NHLBI)
- Combining three measures (diffusion-weighted MRI of brain, NIH Stroke Scale

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score, and time from symptom onset to brain scan) enables early prediction (and tailored management) of stroke recovery (NINDS)

- Only one of the brain differences found in boys with ADHD, compared with unaffected boys, has also been found in girls with ADHD (NIMH)
- New triple-lipid screening test measures total and HDL cholesterol and triglycerides all at once (CC)
- A multicopy gene-based nucleic acid detection system in oral gargles to obviate need for bronchoscopy to diagnose *Pneumocystis carinii* pneumonia (NIAID, CC)

Gene expression patterns

- Identification of genes expressed differently in normal ovary and ovarian cancer cells promises far earlier detection of ovarian cancer than currently possible (NIA)
- DNA microarrays combined with artificial neural network analysis yield highly accurate differential diagnoses of four complex childhood cancers—neuroblastomas, rhabdomyosarcoma, non-Hodgkin's lymphoma, and Ewing tumors (NHGRI)
- DNA microarrays yield gene expression profiles that distinguish hereditary (*BRCA1* and *2*) from sporadic breast cancers, with implications for treatment (NHGRI)
- Two distinct subtypes of diffuse large B-cell lymphomas (with different prognoses) identified by gene expression profiling (NCI)

(Note: Diagnostic advances are also inherent in the isolation of the disease genes listed in "Goal A.")

Goal E: Develop new or improved approaches for treating disease and disability

- Recombinant immunotoxin BL22 induced complete remissions in majority of chemotherapy-resistant hairy cell leukemia patients and shows promise in the treatment of more common leukemias as well in a Phase I study not anticipated to demonstrate efficacy (NCI)
- Successful transplantation of pancreatic islet cells to treat type 1 diabetes (NIDDK)
- Phosphocysteamine shows promise in treating an otherwise fatal genetic disorder (infantile neuronal ceroid lipofuscinosis) and, because it can cross the placenta and enter the brain, has potential also as a prenatal treatment (NICHD)
- New, less-toxic stem-cell transplantation regimen eliminates the need for radiation in patients with chronic granulomatous disease (NIAID, CC)
- New protein, thymosin β4, found to promote corneal wound healing in experimental model (NIDCR)
- Minimally invasive, image-guided tumor ablation with radiofrequency current established as a less damaging alternative to open surgery in patients with kidney tumors (NCI, NINDS, CC)
- St. John's wort does not interfere with antiepileptic drug pharmacokinetics in healthy volunteers and should not compromise treatment in patients with seizure disorder (NINDS, CC)
- Rhodopsin effect of isotretinoin in causing night blindness in rats suggests treatment strategy against retinal and macular degeneration (NEI)
- Continuing identification of genes encoding cancer antigens in melanoma, breast, ovarian, prostate, and lung cancers contribute to expanding immunotherapeutic anticancer strategies (NCI)
- Primate findings that testosterone protects against the proliferative effects of estrogen on breast tissue were put to the test in the first controlled study combining testosterone with estrogen replacement in young women with ovarian failure (NICHD)
- High rate of complete remission and voice and speech preservation in patients with head and neck cancer achieved in a Phase I study of Taxol and radiation (NCI, NIDCD)
- Clinical trial launched of PS-341, an agent that blocks activation of a pathway needed by head and neck cancer cells to grow and form blood vessels (NIDCD, NCI)
- Anthrax toxin modified to selectively kill tumor cells that express plasminogen activator, an enzyme overproduced in a wide array of human tumors, may be effective in preventing cancer invasion and metastasis (NIDCR)
- Gene therapy to produce heme oxygenase-1 protects against vascular constriction and excessive growth following injury and may be useful in treating vascular diseases, preventing restenosis postangioplasty, and reducing vasoconstriction during stroke (NHLBI, VRC)
- Genotype and phenotype resistance testing may help select the most appropriate highly active antiretroviral therapy drug combination in drug-experienced patients (NIAID, CC)
- Enzyme replacement therapy shown to be effective for patients with the hereditary metabolic disorder Fabry's disease (NINDS)
- High-dose intravenous immunoglobulin shown to ameliorate Stiff-Person Syndrome (NINDS)
- Endogenous marijuana-like substances shown to mediate the vasodilated state that complicates advanced liver cirrhosis, and a cannabinoid receptor antagonist looks promising in reversing this condition (NIAAA)
- Improved safety and efficacy of allogeneic stem cell transplantation achieved in the treatment of hematological and nonhematological malignant disease (NHLBI)
- Clinical trial of immunosuppression in severe aplastic anemia demonstrates that early robust improvement in blood counts predicts long-term survival without malignant evolution (NHLBI)
- Overexpression of the ABCA1 transporter in mice found to markedly decrease diet-induced atherosclerosis, indicating that drugs that upregulate the expression of the ABCA1 transporter may be a unique new approach to treating cardiovascular disease in humans (NHLBI)
- Classes of drugs (tropanes, GBR12909) found to bind to the "cocaine site" on the dopamine transporter without interfering with dopamine uptake—and having no abuse potential themselves—offer leads to treatment of cocaine addiction (NIDA)

Three NIHers Elected to NAS

At NIH, April showers often bring not just May flowers, but the equally pleasing election of intramural scientists to the ranks of the prestigious National Academy of Sciences. Among the 72 new members and 15 foreign associates elected to the Academy this year were:

- **Harvey Alter**, chief, Infectious Diseases Section, and associate director of research, Department of Transfusion Medicine, Clinical Center
- **Adriaan Bax**, chief, NMR Biophysical Spectroscopy, NIDDK
- **Joseph Fraumeni**, director, Division of Cancer Epidemiology and Genetics, NCI

All three scientists are NIH legends. Alter has made profound contributions to the study of hepatitis viruses and won the Clinical Lasker award in 2000 (see **<http://www.nih.gov/catalyst/2000/00.11.01/page7.html>**).

Bax has been one of NIH's most-cited chemists—biophysicists, actually—for his pioneering methods in structural biology.

Fraumeni is one of the fathers of epidemiological research at NIH, one of the most-cited scientists in his field, and the co-discoverer of Li-Fraumeni syndrome (cancers associated with germline *p53* mutations). ■

From the Meeting Field

Memories Are Made Of This—and That

text and photos by Masashi Rotte, VRC

From time to time, the Catalyst *reports on talks given by NIH intramural scientists at meetings held outside NIH. Masashi Rotte, a pre-IRTA at the VRC, attended the 11th annual Federation of American Societies for Experimental Biology meeting and wrote up a few of the presentations he heard. The theme of the meeting, which was held in New Orleans from April 20–24 and sponsored by seven U.S. and 24 international scientific societies, was "Translating the Genome." Nearly 15,000 biomedical researchers attended.*

Robert Seder, chief of the VRC Cellular Immunology Section, chaired a symposium on "Generation and Maintenance of Memory Cells," at which NHLBI's **John Kelly** and the VRC's **Chang-You-Wu** reported their findings. Kelly, of the Laboratory of Molecular Immunology, examined memory CD8 T-cell maintenance in a group of Stat5a knockout mice and in another group of *Stat5a* knockout mice that were transgenic for *Stat5b*.

The Stat family of proteins are involved in cytokine signaling through the intracellular Jak-Stat pathway. Kelly found that *Stat5a* knockout mice had decreased numbers of CD8+ memory cells compared with the control wild-type mice, but the *Stat5a* knockouts that were *Stat5b* transgenic had increased numbers of CD8+ memory cells. In addition, the CD8+ T cells of the transgenic group showed increased proliferation in response to IL-15, a cytokine that signals through Stat5a and Stat5b. Kelly noted that he did not expect the *Stat5a* knockout to have such a profound effect on CD8 cells.

John Kelly

Chang-You-Wu

Wu, a staff scientist, reported that IL-12 is not essential to sustain memory Th1 cells in vivo. The cytokine IL-12, which is crucial in the induction of naive CD4 cells to Th1 cells, was knocked out of mice on a Balb/c background. Antigen-specific Th1 cells were generated in vitro and adoptively transferred to wild-type and knockout mice. Wu found that the adoptively transferred cells persisted as memory cells in vivo in equivalent frequencies in both wild-type and IL-12-/- animals at various time points over four months.

However, the IL-12-/- Th1 memory cells generated less vigorous Th1 responses upon antigenic restimulation. Wu's results indicate that IL-12, while not necessary to maintain Th1 memory cells in vivo, may be required for the preservation of Th1 responses.

Pernille Hansen, a visiting Fellow from Denmark in the NIDDK Metabolic Diseases Branch, presented a poster on "Plasma Renin Activity in Adenosine 1 Receptor Deficient Mice: Effect of Salt Intake and Genetic Background." Renin, a plasma enzyme, is secreted in response to low plasma sodium content and/or low blood volume. As a result, renin can affect blood pressure and sodium excretion. Hansen, with colleagues Josephine Briggs and Jurgen Schnermann, examined the potential role of adenosine 1 receptor (A1AR) in the control of plasma renin. The investigators regulated salt content in the diet of wild-type and *A1AR* knockout mice and then measured plasma renin activity.

Pernille Hansen

Booki Min

To their surprise, there were no significant differences in activity between the wild-type and knockout mice fed a normal salt diet and no regulation of plasma renin activity in response to a change in the salt content of the diet in the *A1AR* knockout. They concluded that A1AR does not have a significant effect on plasma renin activity and its regulation by salt intake. Hansen said she plans to investigate the dependence of A1AR expression levels on dietary salt content and the effects of angiotensin receptor on plasma renin.

Booki Min, of the NIAID Laboratory of Immunology, summarized his work on memory CD4+ T cells in his poster on "Neonates Support 'Homeostatic' T Cell Proliferation." Using neonatal mice as a host and model for lymphopenia, Min adoptively transferred CD4 single positive thymocytes and purified naïve CD4+ T cells into the host and tracked the proliferation of the transferred cells.

Even in the absence of antigen, nearly one-fifth of the transferred cells divided seven or more times over a two-week period. The progeny cells had high levels of CD44 expression and produced IFN-γ, indicating a memory phenotype. It was determined that the frequency of progeny cells could be diminished by increasing the number of CD4+ cells in the initial adoptive transfer; the frequency was increased by thymectomy. In this neonatal model, Min said, CD4 T cells "undergo a proliferative process that generates a population of memory CD4 T cells."

He plans to further explore what is driving the CD4+ cell division in the absence of antigen, the role of cytokines in the division, and whether divided and nondivided cell populations respond equally to antigenic stimulation.

Francisco Borrego

Francisco Borrego, of the NIAID Laboratory of Allergic Diseases, presented a poster explaining how "CD94/NKG2A Recycling and Transmission of the Inhibitory Signal are Independent Processes." Borrego analyzed the trafficking of CD94/NKG2A, a receptor expressed by NK cells that binds the nonclassical MHC I molecule HLA-E. Using a labeled antibody and a confocal microscope to track the receptor, he found that the receptor was continuously cycling between the cell surface and an as-yet-to-be-identified intracellular compartment.

Using various biochemical inhibitors, he also demonstrated that CD94/NKG2A traffics differently from other NKG2 receptors and likely uses the cytoskeleton to move around the cell. Because CD94/NKG2A has an inhibitory effect on NK cells, this receptor may be important in the study of NK cell responses in tumor rejection and viral infection, he said. He will pursue this research to determine the compartment that CD94/NKG2A cycles to and whether this cycling is necessary for the receptor's function. ■

Journey to Africa

continued from page 1

us on scientific and biomedical issues facing Mozambique and other African nations.

Maputo, Mozambique

Despite the bleak economic picture (see box, page 9) and devastating floods in the past year, Mozambique draws strength from new leadership and continuing health projects with the United States and others.

HHS is currently working with the Ministry of Health to enhance HIV surveillance, prevention, and treatment in partnership with the National AIDS Council and nongovernmental organizations. HHS has also helped Mozambique prepare a proposal to the Global Fund, which could provide significant support.

A key part of our visit was making a commitment for future collaborations. Secretary Thompson and Mozambique's minister of health, Francisco Songane, signed a Memorandum of Understanding outlining HHS and USAID cooperation with Mozambique's Ministry of Health in an integrated and comprehensive approach to the AIDS pandemic.

A highlight of the Maputo visit was a tour of the Primeiro de Maio Health Center, where Thompson saw an HHS-supported initiative, to be launched this summer, to integrate networks of care for people with AIDS. Visits to the Sisters of Charity Orphanage and cholera tents at Mavalane Hospital made an indelible impression on all of us.

Tommy Thompson (seated, left) and Mozambique Minister of Health Francisco Songane sign a Memorandum of Understanding, as (left) Dr. Alfredo Vergara, epidemiologist for the Mozambique Unit of the DHHS Global AIDS Program, and U.S. ambassador to Mozambique Sharon Wilkinson look on

Children at the Sisters of Charity orphanage in Mozambique; (foreground) Scott Evertz, director of the White House Office of National AIDS Policy

Pretoria, South Africa

An hour by jet from Maputo found us at our next stop—Waterkloof military base, South Africa. The health needs of the country are staggering, as every day brings 1,800 new HIV cases. The AIDS death rate is projected to double in the next five years. Thompson had requested a formal meeting with the health minister, Dr. Manto Tshabalala-Msimang, to discuss health-sector cooperation and priorities. One of the Health Ministry's most urgent requests was for help in establishing medical infrastructure, including Global Fund money for HIV/AIDS. We had fruitful discussions on the long-term effects of nevirapine and other AIDS therapies in this country with limited resources.

HHS' research at several South African field sites on prevention of mother-to-child transmission of HIV has strong support, but Tshabalala-Msimang wanted to discuss other health concerns—food safety, TB and other infectious diseases, teen pregnancy, nutrition, and biotechnology. She promised to visit NIH in the upcoming months to pursue these issues.

A one-hour bus trip through the hills of South Africa took us to the St. Francis Care Center, a hospice and nursery for AIDS orphans in Boksburg. We gave hugs, smiles, and encouragement to the children and their caretakers, but what was most needed were drugs that could improve and prolong lives. Our aid to South Africa must focus on this.

The Ford Corporation of South Africa provided a bright spot. Their assembly plant in Mamalodi has a workplace program for HIV prevention, education, and HIV/AIDS care for workers, their families, and the community. CDC now has cooperative agreements with the American Center for International Labor Solidarity (ACILS) to help South African trade unions establish similar programs. Thompson signed a new agreement with ACILS, continuing DHHS support.

The next day we viewed how the South African military is coping with HIV/AIDS in its "Masibambisane 'Beyond Awareness' Program." To determine the effect of HIV and to combat the spread of AIDS in the military, the South African National Defense Forces teamed up with the U.S. Department of Defense to support an educational campaign. If successful, this pilot program may be extended to other countries with U.S. military connections.

Gabarone, Botswana

Travel to Gabarone was a return trip for me. A little over a year ago, I opened an NICHD conference there on treatment of women and children with AIDS. That conference, like the current visit, highlighted the progress Botswana has made in combating HIV/AIDS. The president of Botswana, Festus Mogae, calls AIDS the "challenge of the millennium."

Youth dancers of Gabarone performing at a groundbreaking ceremony for a new Tebelopele Voluntary Testing and Counseling site

Indeed, Botswana now ranks as one of the four countries hardest hit by the AIDS pandemic. According to the latest UNAIDS report, AIDS will account for a fourfold increase in the death rate in this country by 2005. There is a bright side, however, in that the new minister of health, Joy Phumaphi, has made a commitment to drug therapy for AIDS and to adopting the global standard for TB control. These are major steps in a country that still relies heavily on traditional healing. Phumaphi took the extraordinary step of publicly taking a HIV test two years ago and is a strong voice for Mogae's anti-AIDS campaign.

The delegation was greeted and guided throughout the Botswana leg of our trip by Phumaphi and U.S. Ambassador John Lange. We began with a luncheon to celebrate public-private part-

Outside the vaccination clinic at Port Bouet Hospital

Photos by Corina Gardner
Office of the HHS Secretary

nerships with U.S. institutions that are helping Botswana fight HIV/AIDS and TB. This included researchers and staff from the NIH-Harvard-Botswana Partnership for HIV research and education, the HHS BOTUSA (Botswana/USA) Project, Bristol-Myers Squibb, and the Gates/Merck Initiative.

We then got a closer look at the BOTUSA Project—a collaborative effort with the CDC that started in 1995 as an innovative AIDS project for "Prevention of Mother-to-Child-Transmission" (PMTCT). The project provides more than 200 cross-country traveling antenatal counseling and educational clinics. It also offers HIV outreach activities for youth, such as radio drama, theater, and music. Key to the BOTUSA Project are the Tebelopele ("make a new start today") Centers. These free, voluntary counseling and testing centers operate under the premise that the gateway to HIV prevention and care is knowing one's HIV status. Thompson, Phumaphi, and Lange pitched the first spades of earth in a groundbreaking ceremony at the site of a new Tebelopele center, where we were entertained by local youth in their dance of the spirit.

Abidjan, Côte d'Ivoire

A four-hour flight put us in the country once called the Ivory Coast. The HIV/AIDS pandemic is ravaging this country, and the number of children who have been orphaned is horrific. Malaria and TB are serious health problems as well. U.S. Ambassador Arlene Render met us for what would be a whirlwind eight-hour visit.

At Port Bouet General Hospital, we had the opportunity to interact with HIV-positive clients who had come for group counseling, which appears to save money, build acceptance, and reduce the stigma of AIDS. Secretary Thompson unveiled a plaque commemorating the donation of a group counseling room on behalf of the American people. He also officially launched the DHHS Global AIDS Program's PMTCT activities in that country.

Tommy Thompson at the ribbon-cutting ceremony at Port Bouet General Hospital, Abidjan; seated at right is Minister of Health Abouo N'Dory Raymond

Dating to 1988, one of the longest-running HHS projects in Africa is the Project Retro-CI, a HIV/AIDS epidemiological and laboratory research project in Abidjan. Partners in the collaboration are the CDC, the Côte d'Ivoire Ministry of Public Health, and the Institute of Tropical Medicine, Antwerp, Belgium. In 2000, HHS added primary prevention, surveillance, and treatment components. Our delegation toured the virology and clinical labs, which are focusing on vaccine research, antiretroviral treatment, and HIV diagnostics.

HHS-supported virology lab at Port Bouet, Abidjan

The Last Leg and the Next Steps

From Abidjan, we headed back to Germany and the military plane that would get us back home slightly before noon, Saturday, April 6. Secretary Thompson will soon be meeting again with the delegation to determine our next steps.

I learned a lot from this trip across sub-Saharan Africa—not only that these four countries have quite different cultures, beliefs, and public health needs but also that their peoples share both the pain and the courage that are the concomitants of poverty and pandemic.

I saw the scourges of AIDS and other infections—and the courage of young volunteers in the AIDS counseling and testing centers as they told us about their strategies for counseling the partners of HIV-positive people. I will not forget the orphaned toddlers who danced with us or the wailing patients in the cholera tents or the strong voices of African leaders who believe their countries will survive. And I believe that my country will help to make that so. ■

Out of NIH . . .

The countries visited by the DHHS delegation and NIH's current activities there are listed below.

Mozambique:
Area: 300,000 sq. mi.
Population: 19 million
Infant mortality: 139/1,000 live births
Life expectancy: 36 years
Notes: 70 percent of the population is below the poverty line; average per capita income is $230 per year.
NIH grants: Three extramural awards as components of domestic awards, $107,000 total (FIC, NIGMS)

South Africa:
Area: 475,000 sq. mi.
Population: 44 million
Infant mortality: 60/1,000 live births
Life expectancy: 48 years
Notes: 4 million South Africans are now infected with HIV—the largest number of any country in the world.
NIH grants: Bilateral agreements on Science and Technology and public health, including HIV/AIDS; six extramural research grants; 25 awards as components of domestic awards; 5 visiting scholars; 3 international research fellowships; $10,089,000 total (NCI, NHLBI, NIAAA, NICHD, NIAAA, NIDA, NIDCR, NIGMS, NIMH, NINDS, NIAID, FIC)

Botswana:
Area: 225,000 sq. mi.
Population: 1.5 million
Infant mortality: 63 deaths/1,000 live births
Life expectancy: 37 years
Notes: 36 percent of adults are HIV positive; approximately one baby in Botswana is infected with HIV every hour.
NIH grants: Nine extramural awards as components of domestic awards or Extramural Training Grants; $2.3 million total (NIAID, NIMH, NICHD, FIC)

Côte D'Ivoire:
Area: 125,000 sq. mi.
Population: 17 million
Infant mortality: 94 deaths/1,000 live births
Life expectancy: 45 years
Notes: 48 percent literacy rate.
NIH grants: Two extramural awards, $341, 707 total (FIC, NICHD)

Research Ethics in Developing Countries: NIH Course Opens a Two-Way Street

by Fran Pollner

In a clinical resesarch study in Malawi involving children who had succumbed to severe malaria, investigators paid for the casket and the post-autopsy transport of bodies back to the village in order to be able to perform autopsies to learn more about the pathogenesis of cerebral malaria. "In this country [the United States]," Zeke Emanuel observes, "some people might call that undue inducement" to secure consent for autopsy.

"But," he says, "this is not something to pontificate over. This is an example of an ethical dilemma for which there is no obvious judgment. This is a case of our needing to learn about the cultural practices [that inform] death and burial in Malawi, the realities of moving bodies around in that country." For every country, he says, there is a context that defines the ethical boundaries of clinical research.

Fran Pollner

Ezekiel Emanuel

Emanuel is the director of the Department of Clinical Bioethics at the Clinical Center and has been conducting ethics grand rounds at NIH and—with Christine Grady, head of the department's section on human subjects research—leading a course in clinical research ethics since his arrival here in 1998. Last year, the department started taking the show on the road—to developing countries in Africa with substantial numbers of NIH-supported research protocols in malaria, AIDS, and other infectious diseases.

In March 2001, Blantyre, Malawi, became the site of the first course on "Ethical and Regulatory Aspects of Clinical Research in Developing Countries."

The idea to create such a course emerged from conversations begun in the summer of 2000 between Emanuel, Grady, and Libby Higgs, program officer for NIAID's International Tropical Medicine Research Program.

These conversations expanded to overseas contacts, course content was taking shape, and Emanuel had already planned travel to Malawi and Mali to get "on the ground" exposure to clinical research realities there when *The Washington Post* published a six-part exposé of clinical research abuses in developing countries. Called "The Body Hunters," the series ran in late December 2000 and detailed the harm done to indigenous research subjects enrolled in trials sponsored largely by outside drug companies. It had no effect on course development, per se, but the six articles were included in the voluminous notebook of background reading handed out to every participant.

The Malawi course was attended by 47 people from 11 countries; it generated collaborations that are producing cross-cultural dialogue, empirical research on ethical aspects of clinical research, and position papers on such increasingly relevant and pressing issues as "reasonable availability," or the extent to which researchers are obligated to provide a successful drug to the inhabitants of the country in which the drug trial took place. Some attendees in Malawi were asked to be teachers in later courses; others were so excited by the course, they returned to their homes set on arranging to bring it there.

This year, in March, the course was held at two more African sites: Accra, Ghana, and Entebbe, Uganda. Two more sites are on the docket: Seoul, Korea, in June, and Cairo, Egypt, early next year. Another session in Uganda and one in Mali, in preparation for a series of malaria vaccine trials, are also anticipated.

To enhance its resources to build ethics capacity in developing countries and to explore ethical issues in the international context, the CC department recently recruited Reidar Lie, a physician and philosopher from the University of Bergen, Norway, to head a section on international programs. Lie, who has related experience in WHO and the European Union, is also one of the course's lecturers; James Lavery, a bioethicist at the Fogarty International Center, is also among the course's NIH contingent.

In each course, local investigators present a local case that illustrates each of the ethical issues explored in the lectures: randomization, placebo controls, subject recruitment, financial incentives, research with stored biological samples, risk-benefit assessments, conflict of interest, individual and community informed consent, measuring community benefits of clinical research, and the ethics of treating nonresearch-related health conditions. The composition and role of institutional review boards is also addressed. (Emanuel notes that he's found the level of IRB sophistication quite variable among the African nations, with Mali, for instance, practicing a degree of oversight that the United States could do well to emulate.)

Reidar Lie

In Uganda, March 2002

That the flow of information that transpires during the course is very much a two-way street is reflected in how Emanuel describes course objectives:

- To provide African clinical researchers with a systematic framework for thinking about the core ethical issues contained in the course.
- To foster interaction about ethical issues among researchers who often don't know one another.
- To teach the non-African instructors how cultural, economic, social, and political issues impinge on the conduct of clinical research in other countries and how researchers there have navigated these challenges. ("Americans, Emanuel remarks, "can learn an enormous amount from [African researchers] about community education on research, mobilization around research, and community consultation on the structure and design of research. We talk a lot about it. They've done it—for more than a decade in some cases. They have experience and sophistication.")
- Related to the last objective, to induce African clinical researchers who have acquired such wisdom but have not imparted it to people outside their own circles to write papers about these issues and to assume leadership positions on the international stage.

"Many controversies in multinational clinical research are steered by academics sitting in comfortable places who have never visited these countries and don't understand the lay of the land," Emanuel says. "We desperately need people who are from the area who can speak authoritatively—not just because they have experience but because they've actually thought through the ethical issues."

Coming to the Fore

During a telephone conversation in April with the CC's Department of Clinical Bioethics about a joint project involving an ethics substudy of an existing clinical research protocol in his country, Ugandan researcher Ambrose Talisuna spoke with *The NIH Catalyst* about the impact of the department's course, "Ethical and Regulatory Aspects of Clinical Research in Developing Countries."

Reidar Lie

The figure at the head of this class in Entebbe, Uganda—Ambrose Talisuna (at front, facing the microphone-holding participant)—plans to become more visible in the ethics arena

For him personally, Talisuna said, attending the first course and lecturing at the next two inspired a commitment to the discipline of bioethics. Of particular importance in his field of clinical research—malaria—is the handling of stored blood samples for future use; among other compelling ethical issues are distinctions between the ethics of clinical care and the ethics of medical research, financial conflict of interest, and individual consent vs. community consent (viewed differently by NIH and within his country).

Although very little time has elapsed since the course occurred, already there are signs of change to come. "In Entebbe, we will see changes in the IRBs. And there will be better protocols because IRB members will be paying attention to certain things not discussed before. After my presentation in Entebbe," Talisuna said, "I was asked to look at protocol review in Uganda." ■

Ambrose Talisuna, a member of the Multilateral Initiative on Malaria and the Uganda Ministry of Health, Kampala, is an example (see "Coming to the Fore," above). After attending the course in Malawi, Talisuna was prevailed upon to deliver lectures at the next two. "He probably gave the single best lecture—one on conflict of interest—at [the Ghana] meeting. The world could benefit from his being a spokesperson on bioethical issues," Emanuel said, and then quickly started naming other African researchers as he pointed to a list of about 30 coauthors of a newly minted paper on reasonable availability. The paper arose from a spontaneous discussion and ensuing consensus after the Malawi course ended. A draft was circulated to all contributors and over the course of a year was refined to the point of its being submitted to the *New England Journal of Medicine*. David Wendler, of the department, is leading a similar process to reach consensus on whether and to what extent clinical researchers ought to treat the multiple health problems of people enrolled in a clinical trial.

The course itself lasts three days, but teaching, learning, collaborating on new projects, and translating ideas into actions continue indefinitely. ■

Fran Pollner

Maged El Setouhy discusses ethics course during a break from a tropical medicine symposium at NIH in April

Bringing the Course Back Home

Maged El Setouhy attended the CC Department of Clinical Bioethics course in Malawi in March 2001 and has been arranging ever since to bring it to Egypt in March 2003.

A clinical researcher funded by NIAID to conduct studies on filariasis therapies, El Setouhy is chairman of a regional WHO program and an assistant professor of community, environmental, and occupational medicine at the Ain Shams University, Cairo.

For his own country and the four other countries that comprise his region—Yemen, Saudi Arabia, Oman, and Sudan—the establishment of formal national IRBs is an important issue he hopes will be catalyzed by the course (local IRBs, he noted, can be ad hoc panels of the friends of a researcher embarking on a project).

The course will also be a "good way to raise the issue of needing to add bioethics to the medical school curriculum," El Setouhy said. "Students need to know why it is wrong to do liver biopsies on normal people in a case-control study devised to satisfy one's thesis requirement," he said, recalling just such a circumstance.

Like Uganda's Ambrose Talisuna (see above), El Setouhy has encountered differences in NIH's and his own culture's perspective regarding informed consent, with NIH placing more importance on the actual signature of a research subject as opposed to local acceptance of the signature of a close kin (of a minor or someone who cannot read) in the context of true education. "The traditions and values of each region must be respected," he commented, noting that he and NIH have negotiated mutually acceptable compromises when such conflicts arise.

After the Malawi seminar, El Setouhy returned to Egypt with three copies of the ethics coursebook. He keeps one in his office as a reference and as a text for the members of his group, who read and discuss it. He placed another in the library and gave the third to a proposal-writing colleague. ■

NEW NIH DIRECTOR

continued from page 1

Some of Zerhouni's organizational achievements at Hopkins include restructuring the School of Medicine's Clinical Practice Association and working with local government to plan a biotechnology research park and revitalization project near Hopkins' urban medical campus.

As Hopkins' Interim Vice Dean for Research, Zerhouni crafted a comprehensive strategic plan for research and launched new facilities and core technology development projects.

In his chosen field of radiology—a crucible for his talents in math, physics, and clinical medicine—Zerhouni developed innovative approaches and new techniques in both computerized tomography (CT) and magnetic resonance imaging (MRI). He laid the groundwork for the development of CT densitometry, invented a method to enable all scanners to perform such tests, and conducted early clinical trials establishing CT as the standard by which to evaluate lung nodules. He invented a novel MRI cardiac tagging technology to evaluate heart function and was also the co-inventor of vacuum-assisted, image-directed biopsy, a less invasive method for diagnosing suspicious lumps found on mammography that has become the standard of care.

> "... IN MY FIELD, PROGRESS CANNOT BE MADE WITHOUT BIOLOGISTS, PHYSICIANS, AND PHYSICAL SCIENTISTS WORKING TOGETHER. ... PROGRESS INCREASINGLY WILL DEPEND UPON FIELDS OF SCIENCE BEYOND MEDICINE AND BIOLOGY. ... WE NEED TO ENCOURAGE CROSS-CUTTING INITIATIVES."
> *—Elias Zerhouni, 4/30/02*

Zerhouni, 51, was born in Algeria and arrived at Hopkins in 1975 after earning his medical degree from the University of Algiers School of Medicine. In concluding his remarks at the Senate hearing, he described himself as "an immigrant [who is] deeply touched by being here today." ■

Ethics Forum

Preempting Discord: Prenuptial Agreements for Scientists

by Howard Gadlin, NIH ombudsman and Kevin Jessar, associate ombudsman

A recent article in the *Chronicle of Higher Education* entitled "When a Mentor Becomes a Thief" describes a doctoral student who, after working on a project for seven years, found what she thought was her discovery published under the name of her advisor. Her contribution was acknowledged in a footnote. It appears that while she was working on the project she assumed she would be the lead author, but she never did confirm that assumption with her advisor.

"Misunderstandings" like this are not limited to mentors and their postdocs or doctoral students. Conflicts over authorship and a host of other issues also erupt among collaborating scientists who are peers. In the worst situations, not only does the research project suffer, but investigators also wind up leveling accusations against one another, sometimes through formal, adversarial mechanisms. It is painful and somewhat paradoxical to see collaborating scientists neglect such planning and foresight when the scientists devote so much of their intellectual and other energies and resources, often over many years, to make the collaboration successful.

In the Office of the Ombudsman, we hear many stories like the one above. Although we are often able to help people resolve such disputes, we are struck by how many could have been avoided if only the collaborators had taken a few precautionary steps at the outset. People often assume that since they share an interest in the same research area and have complementary skills and areas of expertise, things will just work out. But scientific collaborations, like other important relationships, take some forethought and some ongoing work to succeed.

While scientists most often bring authorship disputes to our office, there is a wide range of issues on which collaboration can falter. We have seen people in dispute over issues of access, sharing, management, and analysis of data; the use and sharing of biological materials; and even the scope and direction of the research project. We have also worked on disputes involving the collaborative relationship itself—sharing research space, the structure and function of research team meetings, decisions about staffing needs of the project, personal and scientific conflicts among members of the research team, and questions regarding who gets to be the public spokesperson for a project if research results attract media attention.

Most often, problems arise in scientific collaborations because the scientists failed to explicitly define their expectations of one another. We believe that framing a partnering agreement at the outset of the research project can help enormously in setting the collaboration on a solid footing. Ideally, the agreement spells out exactly what the roles and contributions of each scientist will be and provides a mechanism for decision making for major issues such as authorship, additional collaborations, and the sharing of biological materials.

Some people prefer written partnering agreements signed by the key collaborators. For others, a written agreement feels too legalistic, too much like a contract. Written agreements may offer the advantage of being less ambiguous than each party's selective recall of what was agreed to, but we believe that it is most important that collaborators commence their project by anticipating, discussing, and resolving possible areas of disagreement. Moreover, the parties can jointly define a process for constructively handling disputes should they arise in the future.

Although each research project has unique features, certain core issues are common to most of them and can be addressed by collaborators posing the following questions:

- What are the scientific issues, goals, and anticipated outcomes or products of the collaboration? When is the project over? Are all members of the research team on the same wavelength regarding these issues?
- What are the expected contributions of each participant?
- Who will write any progress reports and final reports?
- How will you decide about redirecting the research agenda as discoveries are made?
- What will be your mechanism for routine communications among members of the research team (to ensure that all appropriate members of the team are kept fully informed of relevant issues)?
- How will you negotiate the development of new collaborations and spin-off projects, if any?
- How, and by whom, will personnel decisions be made? How and by whom will personnel be supervised?
- What will be the criteria and the process for assigning authorship and credit?
- How will credit be attributed to each collaborator's institution for public presentations, abstracts, and written articles?
- How and by whom will public presentations be made?
- How and by whom will media inquiries be handled?
- When and how will you handle intellectual property and patent applications?
- How and by whom will data be managed? How will access to data be managed? How will you handle long-term storage and access to data after the project is complete?
- Should one of the principals of the research team move to another institution or leave the project, how will you handle, data, specimens, lab books, and authorship and credit? (Keep in mind that data, specimens, and lab books are the property of NIH.)

Of course, it is easy to imagine that for any particular research project there might be additional specific questions that should be added to this list.

Many potential collaborators can answer these questions simply by getting together and talking things out. For some people a neutral third party, with no involvement in the project, can help facilitate such discussions and maximize their effectiveness. Staff in the Office of the Ombudsman are available to facilitate such discussions. For those who would like to translate the results of their discussion into written partnering agreements, we are prepared to help in that way as well. The specific decisions, of course, belong to the scientists.

We recognize that using scientific prenuptials goes against the informal norms of science. But we have seen the damage that can be caused, both scientifically and personally, when scientists at NIH overlook questions like these in their enthusiasm to launch an intellectually exciting collaboration. ■

The NIH Office of the Ombudsman, Center for Cooperative Resolution, is located in Building 31, Room 2B63, and can be reached at (301) 594-7231.

For another treatment of this topic, see "Silence is Not Golden: Making Collaborations Work" (*The NIH Catalyst*, July–August 1997, page 3).

Recently Tenured

Fred Dyda *received his Ph.D. from the University of Pittsburgh in 1992 in protein crystallography. He did his postdoctoral work at the Laboratory of Molecular Biology, NIDDK, where he is now a senior investigator.*

fran poliner

Fred Dyda

I am interested in the function of complexes of macromolecules and why these complexes are always more than the sum of their parts. Our main experimental approach is to determine the three-dimensional structure of complexes using X-ray crystallography—the only experimental method that can resolve the structures of large complexes at near-atomic resolution. Unfortunately, this yields images—or structures—that are static, whereas macromolecules are inherently dynamic. To overcome this limitation, we attempt to determine several structures, representing different conformational forms or steps along a pathway. We then infer dynamics from the resulting array of static structures.

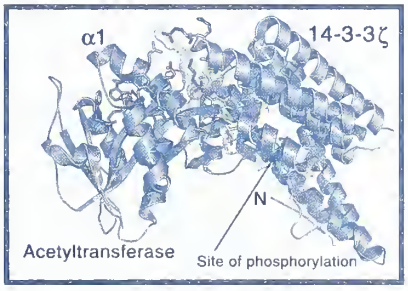
One problem we are studying is how the intracellular adaptor molecules, known as 14-3-3s, modulate conformational state and, through this, the biological activity of numerous binding partners. 14-3-3s bind their binding partners in a phosphorylation-dependent way.

One such binding partner is the melatonin rhythm enzyme, serotonin *N*-acetyltransferase. In collaboration with the laboratory of David Klein at NICHD, we have shown that this enzyme undergoes a major conformational rearrangement during catalysis involving a large movement of a surface loop. When the enzyme is phosphorylated, it forms a stable complex with 14-3-3. We were able to grow diffraction quality crystals of this complex and thus solve its three-dimensional structure. This is still the only structure ever obtained for a 14-3-3 bound to an active protein.

Surprisingly, we found that 14-3-3 conformationally modulates exactly that loop of the enzyme that undergoes structural rearrangement during catalysis. Indeed, 14-3-3 stabilizes a conformational state of the enzyme with its substrate-binding site open, allowing easy access by both its substrates.

Our finding introduced a new way of thinking about the biological action of 14-3-3s, namely that rather than just simple binding to other molecules, their more significant action is changing the structure of their binding partners. It will be important to determine how far our results from serotonin *N*-acetyltransferase can be generalized. If conformational modulation is the rule in 14-3-3 biology, then how can 14-3-3 molecules act on a vast array of very different binding partners? To answer this question, we hope to analyze a series of structures of these 14-3-3 complexes with different enzymes and transcription factors.

We are also studying an elaborate DNA transposon called Tn7, work done in collaboration with the laboratory of Nancy Craig at the Johns Hopkins University (Baltimore)/Howard Hughes Medical Institution. This system is particularly intriguing because it requires the assembly of four different proteins for transposition. Tn7 is a clear example of the rule that a complex is much more than the sum of its parts, as each individual component is inactive for transposition on its own.



Detailed interactions between serotonin N-Acetyltransferase and 14-3-3. The dots (lighter areas) represent that part of 14-3-3's surface that interacts with the enzyme. A large portion of this surface stabilizes helix α1 of the enzyme; several turns of this helix forms from a loop during substrate binding.

Still, even the isolated components are full of surprises. For instance, we have shown that one of the transposase molecules, TnsA, contrary to expectations, does not follow the paradigm that all transpos-ases (such as HIV integrase, for example) share an RNaseH-like fold. Rather, TnsA looks like a type II restriction enzyme, making it a truly unique transposase. Based on what we have learned from TnsA, we are now in the process of assembling other complexes of Tn7 proteins in order to understand how the transposon moves antibiotic resistance genes between cells.

Douglas Fields *received his Ph.D. from the University of California, San Diego, in 1985 and did postdoctoral work at Stanford (Calif.) and Yale (New Haven, Conn.) universities and NICHD. He is now a senior investigator in the Laboratory of Cellular and Synaptic Neurophysiology, NICHD, where he heads the section on Neurocytology and Physiology.*

Driving Mr. Albert, by Michael Paterniti, tells the factual story of pathologist Thomas Harvey, who performed the autopsy on Albert Einstein in 1955 and then irreverently removed Einstein's brain, took it home, and kept it hidden for nearly 40 years. Over the years he doled out slices of it to scientists and pseudoscientists around the world who probed it for clues to Einstein's genius. One respected scientist, Marian Diamond of the University of California at Berkeley, could find nothing unusual about the size or number of neurons in the slice of Einstein's brain, but she noticed a large increase in the number of nonneuronal cells, termed glia. This observation is curious because traditionally glial cells are regarded as having only a passive support role in maintaining the extracellular environment. Research from my lab shows that glia can detect the electrical activity in neurons and respond physiologically and functionally to the signals.

My interest in neuron-glial communication developed from a more general interest in how development of the brain is modified by neural impulse activity in fetal and early postnatal life. I started my reasoning from the fact that information in the nervous system is coded in the pattern of neural impulse activity in the brain. Next I hypothesized that neuronal genes must be regulated by the pattern of impulse firing, because long-term changes in neuronal structure and function must involve the regulated expression of appropriate genes.

By stimulating neurons to fire in different temporal patterns and then measuring the amount of mRNA for genes known to be important in formation of neural circuits or in adaptation to the environment, we found that this was indeed the case. We observed that one could turn a particular gene on or off—for example, a cell adhesion molecule on the surface of axons that bundles them together into cables with other axons—simply by dialing up the correct stimulus frequency on our electrophysiological stimulator. The result was that the microscopic structure of the neurons changed accordingly: The axons either bundled or unbundled, depending upon the stimulus frequency we delivered to regulate the appropriate gene.

Having observed that neuronal genes could be regulated according to the pattern of neural impulse activity in developing neural circuits, we faced a deeper question: How could genes in the nucleus of the neuron be controlled by the pattern of electrical depolarization at the cell membrane? To study this, we used biochemical, molecular, and confocal calcium imaging to trace the stimulus transduction pathways from the cell membrane to the nucleus of the neuron in response to different patterns of impulse activity. What we observed was that temporal patterns of

membrane depolarization are transduced and decoded within the cytoplasm and nucleus of neurons in accordance with differences in the kinetic response of individual signaling reactions comprising the network of intracellular signaling pathways. Some signaling pathways were sluggish and could not respond well to rapid bursts of impulses, but once they were activated, their lethargy in inactivating meant that they could sustain signals between bursts of action potentials that were separated by long intervals of inactivity. Thus, signals of different temporal patterns were propagated through distinct signaling pathways that were favorably tuned to those patterns of activation and ultimately regulated different transcription factors and different genes.

Fran Pollner

Doug Fields

This work helps explain how the nervous system becomes modified by interaction with the environment, including some of the molecular mechanisms involved in encoding memory. Memory comes in two forms—short term and long term—and the transition from one to the other requires gene transcription and new protein synthesis. Your best friend's name is stored in your long-term memory, for example, but the name of a person to whom you have just been introduced is stored in short-term memory and may be gone within a few minutes.

Prior to our work, it was theorized that an unknown signaling molecule must be generated when a synapse fires. The signaling molecule would wend its way from the synapse up the dendritic tree to the nucleus of the neuron to turn on the genes necessary for permanently strengthening the synaptic connection. Our work showed instead that when neurons in the hippocampus of the brain fire, signaling pathways originating from the cell membrane are activated, propagate to the nucleus, and regulate transcription factors and genes associated with permanent increases in synaptic strength and memory formation.

What does this have to do with Einstein's glia? The intimate physical association between glial cells and neurons led me to wonder whether impulse activity in neurons might also be detected by glia and have some influence on their function. Using confocal calcium imaging to detect intracellular calcium fluxes in co-cultures of neurons and glia, our studies showed that when axons were stimulated to fire impulses, the glial cells nearby responded with large increases in cytoplasmic calcium concentration.

Through a series of pharmacological and biochemical experiments, we identified the signaling molecule mediating the communication between neurons and glial cells in the PNS (Schwann cells) and showed that neural impulse activity in axons could regulate glial genes, the mitotic rate of glia, and their differentiation. This would suggest that the distinctive architecture of Einstein's brain resulted from the way his mind worked, rather than vice versa.

One of the key functions of Schwann cells is to form the myelin membrane that wraps around axons and insulates them to enable rapid conduction of nerve impulses. The importance of myelin can be seen in the growing abilities of a baby to hold its head up and eventually walk. It can also be seen in the deficits in adults when myelin is damaged through a disease such as multiple sclerosis. Our studies showed that impulse activity arrested the development of early Schwann cells and prevented the formation of myelin that might otherwise occur prematurely. This provided a way for myelination and development of Schwann cells to be coordinated according to functional activity in the nervous system.

In a series of pharmacological experiments, we identified the molecule that carried the signal from neurons to Schwann cells and concluded that it was ATP. Using the enzyme that allows fireflies to glow—a reaction that requires ATP—we were able to detect the release of ATP into the cell-culture medium when we stimulated axons to fire action potentials.

Stephen Ikeda

Sometimes a small amount of light can illuminate a new landscape.

Stephen Ikeda *received his M.D. and Ph.D. from the University of Maryland School of Medicine, Baltimore, in 1980 and 1983, respectively. He did postdoctoral work at the NIAAA before joining the Department of Pharmacology and Toxicology at the Medical College of Georgia in Augusta and then joining the Guthrie Research Institute in Sayre, Pa., as a senior scientist and director of the Laboratory of Molecular Physiology. He also served as director of the Guthrie cDNA Resource Center and was an adjunct research professor of pharmacology, State University of New York Upstate Medical Center, Syracuse. He returned to NIAAA in February 2002 as chief of the Laboratory of Molecular Physiology.*

The main focus of my laboratory is to understand signal transduction pathways underlying ion-channel modulation in neurons. In recent years, we have concentrated our efforts on understanding the molecular mechanisms involved with neurotransmitter-mediated modulation of N-type ($Ca_v2.2$) Ca^{2+} channels in sympathetic neurons. Because Ca^{2+} flux through the N- and P/Q-type ($Ca_v2.1$) Ca^{2+} channels triggers exocytotic release from presynaptic nerve terminals, modulation of neuronal Ca^{2+} channels is an important mechanism for fine-tuning synaptic transmission at both peripheral and central synapses. A few years ago, we discovered that a well-described mode of N-type Ca^{2+} channel modulation, termed voltage-dependent inhibition, was mediated by G protein βγ subunits. Work from our lab and others defined a compact signaling pathway comprised of G protein coupling receptor (GPCR), G protein heterotrimer (and associated proteins), and the α1 subunit of the Ca^{2+} channel. Within this framework, we pursue several avenues of research, using electrophysiological, molecular, biological, and biochemical techniques.

Specificity of heterotrimeric G protein signaling components. Heterotrimeric G proteins are comprised of three subunits (Gα, Gβ, Gγ). Because there are numerous isoforms of each subunit, we wondered whether N-type Ca^{2+} channel modulation requires discrete Gαβγ combinations to serve specific functions. We are taking two separate, complementary approaches to address this question. The first is to reconstruct the signaling pathway using defined G protein subunits to determine which combinations are capable of supporting modulation. The second is to selectively ablate elements of the signaling pathway to determine the effect on pathways natively expressed in sympathetic neurons.

Role of RGS proteins in ion channel modulation. RGS (for "regulator of G protein signaling") proteins are a large, diverse family of proteins that interact with activated Gα subunits. The main result of this interaction is an acceleration of the GTPase activity of the Gα subunit. However, it is becoming clear that RGS proteins serve different specific roles in regulating the duration and strength of G protein signaling. We are currently investigating how RGS proteins affect modulation of ion channels.

(GPCR) coupling and pharmacology. The sympathetic neuron turns out to be an ideal surrogate for studying GPCRs nor-

mally expressed in central neurons. Heterologous expression of metabotropic glutamate receptors (mGluRs) in sympathetic neurons allows researchers to study molecularly defined mGluR isoforms and also mutated and epitope-tagged mGluRs within a neuronal environment. We are also interested in another GPCR—the CB1 cannabinoid receptor. We have previously shown that expression of CB1 in SCG neurons results in functional coupling to Ca^{2+} channels and that SR141716A acts as an inverse agonist in this system. Our current interest is in determining whether CB1 coupling to specific Gα subunits alters the pharmacology of the receptor. Specifically, we seek to determine whether endocannabinoid efficacy is influenced by the heterotrimeric G protein composition.

We are currently working on new methodologies, such as circularly permutated EYFP-based optical sensors to detect Gβγ interactions and FRET-based approaches to Ca^{2+} channel/Gβγ binding. We hope to extend some of our findings on GPCRs and ion-channel modulation to more complex systems, such as synaptically coupled neurons.

Steven Sollott *received his M.D. from the University of Rochester (N.Y.) School of Medicine and Dentistry in 1984. He completed residency training in internal medicine at Cornell in 1984 and a cardiology fellowship at Johns Hopkins University in 1991. He is board certified in internal medicine and cardiovascular disease. He worked as a fellow in the NIH Medical Staff Fellowship program and as an NIH senior staff fellow before being appointed to NIA's tenure-track program. He also holds an appointment as an assistant professor in the Department of Medicine, Division of Cardiology, at Johns Hopkins. He is now a senior investigator in the Laboratory of Cardiovascular Science (LCS), NIA.*

We are studying structure and function of cells from the cardiovascular system along three principal lines to gain an understanding of basic cell biological processes that may have implications for the pathophysiology and treatment of human disease. These lines are:

- Mechanisms of cardiac contractility
- Nature and control of mitochondrial instability during oxidant stress
- Cellular changes after vascular injury.

How the heart adapts to stress is critical to the quality of life during periods of good health and to the ability to survive during periods of disease. Muscle stretch is a principal determinant of cardiac performance. Cardiac muscle stretch modulates contraction via enhancement of the excitation–Ca^{2+}-release process, but how this occurs was largely unknown prior to our latest work. We found that myocyte stretch modulates the elementary Ca^{2+}-release process from ryanodine-receptor Ca^{2+}-release channels ("Ca^{2+}-sparks") and the electrically stimulated Ca^{2+}-transient.

Stretch induces PI3-kinase–dependent phosphorylation of both Akt and eNOS, resulting in localized NO production and a proportionate increase in Ca^{2+}-spark frequency. We propose that myocyte NO produced by activation of the PI3-kinase–Akt-eNOS axis acts as a second messenger of stretch by enhancing Ca^{2+} release, contributing to myocardial contractile activation. The significance is that this mechanism could serve as a physiologic sensor of cardiac stretch by generating NO, providing a novel link between cardiac muscle length and excitation-contraction coupling.

Steven Sollott

Oxidant stress is an important factor in normal aging as well as in diseases such as atherosclerosis, heart attack, and stroke. Reactive oxygen species (ROS) are major contributors to oxidant stress. Mitochondria are both a major source of ROS and a target for their damaging effects.

A central event in apoptosis is a phenomenon known as the mitochondrial permeability transition (MPT). Various oxidants stimulate apoptosis, whereas antioxidants inhibit it, suggesting a role for ROS as initiators or downstream mediators of apoptosis. Because mitochondria are themselves the major intracellular sources of ROS production, together with the fact that ROS exposure and altered redox state can lead to the MPT, we hypothesized that under certain circumstances this biological system could become self-amplifying and unstable.

We developed a new model using "interactive" confocal microscopy, which enables controlled, incremental ROS photoproduction and accumulation in individual mitochondria inside living cardiac myocytes. Accumulation of ROS levels past a threshold reproducibly triggers abrupt mitochondrial depolarization, which we proved is the result of induction of the MPT. This model enables real-time observation of the initiation and induction of the MPT and its consequences in individual mitochondria inside living cells.

Thus, we were able to observe that this ROS-triggered induction of the MPT coincided with an immediate large burst of additional ROS generated by that same mitochondrion, together with a brief period of unstable Ca^{2+} handling in its immediate vicinity.

This phenomenon could also contribute to pathological disturbances in cardiac excitation and rhythm, for example, during postischemic reperfusion arrythmias, a major cause of sudden death after heart attack. For this newly described phenomenon accompanying induction of the MPT we coined the name mitochondrial ROS-induced ROS release (RIRR). We think that this link between MPT and RIRR could be a fundamental phenomenon in mitochondrial and cell biology and may be related to programmed mitochondrial destruction in cardiac myocytes, as well as programmed cell death (apoptosis).

One of the most common causes of serious heart malfunction—heart attack—is the result of underlying diseases of blood vessels, such as atherosclerosis. Thus, improvements in the treatment of coronary artery disease have had a significant positive effect on overall cardiovascular health. Intraarterial stents have become a primary therapy for treating coronary artery disease. Stents limit the elastic recoil and late vascular wall remodeling after angioplasty. When restenosis occurs in this scenario, it is an iatrogenic complication of the additional arterial injury caused by stent placement itself, causing abnormal migration and proliferation of vascular smooth muscle cells into the artery lumen, which obstructs normal blood flow.

Restenosis rates for patients undergoing stent placement procedures (more than 400,000 annually in the United States) result in clinical failure in about 20 to 30 percent of patients by 6 to 9 months. Thus, the anticipated clinical effect of drug-coated stents that would prevent cellular responses leading to restenosis is very significant.

Perhaps my most noteworthy discovery relates to the finding that paclitaxel (Taxol), a drug used to treat cancer, could markedly attenuate vascular restenosis after angioplasty. Together with colleagues at LCS and Johns Hopkins, we have organized follow-up studies based on the idea that paclitaxel could be of therapeutic value in preventing human restenosis with minimal toxicity. These studies were included in "Selected NIH Intramural Research Accomplishments 1993–2001" (*The NIH Catalyst*, May–June 2001).

Paclitaxel is now one of the two most promising treatments currently being tested in humans to prevent vascular restenosis after angioplasty. Human clinical trials are

currently in progress in Europe, Asia, and the United States. The initial findings from two of the international paclitaxel-coated stent antirestenosis trials, ELUTES and TAXUS I, indicate that paclitaxel may prevent human restenosis without adverse effects.

Looking ahead, I hope to pursue studies that advance the understanding of how to prevent or limit pathological processes damaging to the heart. On the prevention front, we plan to continue to investigate the safety, feasibility, and efficacy of paclitaxel-coated coronary stents for the prevention of restenosis after coronary angioplasty. We will also pursue how to make the heart more resistant to ischemic damage by focusing specifically on mitochondrial protection, because these organelles are particularly susceptible to damage from oxidant stress, with consequences imperiling cell survival and overall health.

Rocky S. Tuan *received his Ph.D. in 1977 from the Rockefeller University in New York and was a postdoctoral fellow at Harvard Medical School in Boston, first in the Department of Orthopaedic Surgery at the Children's Hospital and then in the Developmental Biology Laboratory at the Massachusetts General Hospital. In 1980, he joined the biology faculty at the University of Pennsylvania in Philadelphia, and in 1988 he became professor and director of Orthopaedic Research at the Thomas Jefferson University, Philadelphia, where, in 1997, he established the nation's first Cell and Tissue Engineering Ph.D. program. In the fall of 2001, he joined the Intramural Research Program of NIAMS as chief of the newly created Cartilage Biology and Orthopaedics Branch.*

Orthopaedic research is fundamentally a study of skeletal tissues and the biological activities that are important for their development, growth, function, and health. My lab is currently engaged in a variety of research projects, highlighted below, that focus on multiple aspects of skeletal and related biology. Our experimental approach integrates contemporary technologies of biochemistry, cell and molecular biology, embryology and development, and cellular imaging, as well as principles of bioengineering.

Cellular and Molecular Signaling during Cartilage Development. My lab has been studying the cellular and molecular mechanisms regulating chondrogenesis. A key working hypothesis is that cell-cell and cell-matrix interactions are important for chondrogenic differentiation. Our recent in vitro and in vivo findings show that the cell-cell adhesion molecule N-cadherin plays a critical role in the cellular condensation phase of chondrogenesis. Interestingly, we have also found that bioactive factors, such as BMP-2 and TGF-β1, which affect cartilage development, appear to act via the modulation of N-cadherin interaction with its cytosolic binding proteins, the catenins, which are also the target of the action of the Wnt family of signaling molecules. We are now investigating the exact, chondrogen-ically relevant signal transduction events regulated by the N-cadherin–catenin complex, as well as the signaling crosstalk with growth factors, such as those in the TGF-β superfamily (TGF-β1, BMP-2, and GDF-5), and Wnt family members and their cognate receptors, the Frizzled family.

Rocky Tuan

We are also analyzing the possible involvement of another mode of cell-cell interaction, namely, gap junctional communication, specifically, the role of the gap junction protein connexin 43. We are currently studying limb mesenchymal chondrogenesis and the effect of growth factors of the TGF-β superfamily in transgenic mice harboring various constructs derived from the *connexin 43* gene.

In terms of cell-matrix interactions, our investigations are focused on how fibronectin isoforms, produced sequentially in the developing limb bud, may provide important cell-matrix-mediated cues in the regulation of chondrogenesis and limb morphogenesis.

Molecular Biology of Axial Skeletal Patterning during Development. My lab has been examining the molecular aspects of somite formation—the first segmented patterning event in the early developing embryo—by focusing on the function of the *Pax* genes, a vertebrate gene family structurally related to the pair-rule genes of Drosophila, and of *Paraxis*, a member of the basic helix-loop-helix transcription factor gene family. We have used antisense technology to perturb the level of expression of these genes in the developing chick embryo and demonstrated the importance of *Paraxis* and *Pax* in somite epithelialization and differentiation-segmentation, respectively. We are currently carrying out gene-transfection experiments using the full-length *Pax-1* cDNA to probe the downstream function as well as regulation of expression of the *Pax-1* gene. Antisense experiments have also demonstrated that *Paraxis* expression is crucial for proper somitogenesis from the paraxial mesoderm of the segmental plate, most likely at the epithelialization step after somitomere formation. Currently we are using retroviral expression constructs of *Paraxis* to examine the effect of overexpression on somitogenesis. Finally, we have shown that misexpression of *Pax-1* and/or *Paraxis* is functionally related to teratogen-induced somite dysmorphogenesis, based on our observations of chick embryos exposed to controlled heat shock, valproic acid, and carbon monoxide. This is an exciting finding because it represents the first correlation between somite teratogenesis, a segmentation gene, and a bHLH transcription factor. The potential implication in terms of axial skeletal birth defects, such as congenital scoliosis and Klippel-Feil syndrome, remains to be investigated.

Biology of Mesenchymal Progenitor Cells. On the basis of our previous findings on embryonic tissues, we hypothesize that multipotential mesenchymal progenitor cells reside as an endogenous cell population within a variety of mature, adult connective tissues, in addition to being a part of the marrow stroma. Our recent studies have revealed that mature human trabecular bone, derived from femoral head tissues obtained from total joint arthroplasty, indeed harbor cells with chondroprogenitor potential. This finding is consistent with the known ability of fractured bone to heal via the endochondral pathway, that is, the formation of cartilage, even in the absence of marrow cell proliferation. We are currently developing ways to optimize isolation and expansion of such cell lines, concurrent with clonal analysis and microarray gene expression profiling. With these approaches we hope to study the mechanisms responsible for chondrogenic differentiation in response to specific chondro-inductive environment.

Cartilage Tissue Engineering. Articular cartilage repair is an exciting challenge in musculoskeletal medicine. Using embryonic cell cultures, we have demonstrated proof of concept by using a solvent-leaching method to fabricate a porous, bioresorbable, polylactide (PLA) scaffold and testing it as a delivery vehicle for peptide growth factors and as a cell-composite matrix for three-dimensional cartilage formation. These are exciting steps toward the development of new methodologies for in vitro three-dimensional cartilage tissue engineering that relies on bioresorbable polymers, such as PLA and polycaprolactone. We are pursuing three approaches to fabricating a three-dimensional scaffolding using human bone marrow stroma-derived mesenchymal stem cells: 1) press-coating

to generate a thin hyaline cartilage surface coating for potential articular cartilage applications, 2) fabricating a PLA-alginate amalgam to optimize both mechanical and cellular requirements for chondrogenesis and cartilage formation, and 3) producing nanoscale fibers using electrospinning for cell seeding. We believe these new constructs may lead to the development of tissue-engineered osteochondral graft materials for clinical applications.

Bone-Implant Interaction. The long-term stability of an endoprosthetic device ultimately depends on the appropriate interaction between the implant and the host tissue and cells. My laboratory has been studying the cellular mechanisms involved in bone cell attachment to metallic orthopaedic surfaces. Our working hypothesis is that biomaterials that promote initial osteoblast adhesion will result in better osseointegration and contribute to a longer stability of the implant. In comparing several clinically used metallic alloys using a newly developed cell-adhesion assay, we have indeed observed a higher rate of osteoblast adhesion on Ti64, a titanium alloy commonly used in orthopaedic devices, particularly compared with standard tissue culture polystyrene. Our current research interests are in analyzing the sequence of cellular events responsible for this enhanced interaction between the bone cell and the underlying substratum, including adhesion, focal contact formation, matrix-integrin interactions, and signal transduction. We are studying these interactions via diverse techniques such as laser confocal microscopy, gene transfection, and receptor-ligand analysis. Thus far we have observed differences in the distribution of focal contacts and integrins, the cytoskeletal architecture, and cell spreading. Interestingly, osteoactive factors such as TGF-β1 and BMP-2 significantly enhance the initial cell adhesion event, suggesting that these factors may be candidates for enhanced osseointegration. Interestingly, our recent investigation into the mechanistic aspects shows that TGF-β1 treatment results in an immediate, transient intracellular Ca^{2+} flux, inhibitable by Ca^{2+} channel blockers, that is required in the adhesion enhancement. Preliminary analysis reveals altered phosphorylation of several intermediary signaling molecules. Our long-term goal is to develop a rational, cell-based set of parameters in evaluating bone implant interaction. We believe that this information will be invaluable for the practical design of orthopaedic implants.

Molecular Diagnosis and Experimental Therapeutic Treatment of Bone Infection. Bacterial infection is a major therapeutic challenge in orthopaedic surgery, more often than not complicated by the lack of rapid, sensitive, and reliable diagnosis. The conventional microbiological protocols are inherently slow and inaccurate. We have recently established a novel, rapid processing protocol for orthopaedically relevant tissue and fluid samples and its application in a polymerase chain reaction (PCR)–based detection of bacterial infections. The PCR protocol uses primers panspecific for the bacterial 16S rRNA gene and has the sensitivity to detect as few as 10 bacteria in the inoculum. Clinical studies are currently underway and the results so far support the applicability of the protocol. This method has already generated a great deal of attention in the orthopaedic community and has the potential to serve as a standard, adjunct algorithm for routine clinical diagnosis. Our present objective is to further develop the PCR-based protocol for speciation diagnosis, using gene sequence polymorphisms among different bacterial species.

Finally, despite the success of arthroplasty, periprosthetic infection remains a challenge. Our recent work has demonstrated, using animal models of osteomyelitis and open fracture, the efficacy of a PLA-based antibiotic delivery system for the prophylactic and therapeutic treatment of bone infection. We are currently investigating design modalities for surface modification of metallic implants for the purpose of controlled delivery of antimicrobial compounds to the bone-implant interface. Such materials would be ideal for efficient treatment of deep periprosthetic infections.

Ted Usdin

Ted Usdin *received M.D. and Ph.D. degrees from the Medical Scientist Training Program at Washington University in St. Louis in 1986. In 1990, after completing a residency in psychiatry at Stanford University, he joined the Laboratory of Cell Biology of NIMH. He is now a senior investigator in the Laboratory of Genetics, NIMH.*

I am interested in the biological roles of neurotransmitters and neuromodulators. I am currently investigating the functions of TIP39 and the PTH2 receptor, a new neuropeptide and its receptor discovered in my laboratory. Following up on hints provided by our initial experimental observations, I am starting to investigate the potential roles of this peptide and receptor in pain modulation and endocrine function.

Several years ago, Tom Bonner of NIMH and I identified a receptor we named the PTH2 receptor (because it is the second known receptor activated by parathyroid hormone [PTH]) during a screen for new members of the secretin or Family B group of G-protein coupled receptors that are expressed in the CNS.

Éva Mezey of NINDS and I mapped the tissue and cellular distribution of the PTH2 receptor and found that it is expressed at greatest levels in the brain, where it is concentrated in several hypothalamic and limbic areas. However, we could find no evidence that PTH is synthesized in the brain. This launched me on a search for a different endogenous ligand for the PTH2 receptor. I used stimulation of cAMP production via the PTH2 receptor to screen tissue extracts for a selective receptor-stimulating activity. I found that a bovine hypothalamic extract stimulated the PTH2 receptor with much greater potency than the PTH1 receptor.

At the NCI Natural Products Support Group facility in Frederick, Tom McCloud and I extracted this activity from 50-pound batches of bovine hypothalamus. I purified the protein that produced the activity, determined its amino acid sequence, and used this information to have the peptide chemically synthesized and to determine its gene and cDNA sequences in human and mouse. This new peptide, tuberoinfundibular peptide of 39 residues (TIP39), is a distant relative of PTH and parathyroid hormone related–peptide. It potently simulates the PTH2 receptor and has no effect on the PTH1 receptor.

We have begun testing ideas about the function of TIP39 that are based on the anatomical distribution of the PTH2 receptor. For instance, the PTH2 receptor is expressed at particularly high levels in the outer layers of the dorsal horn of the spinal cord. This suggests that it may be involved in the modulation of pain perception. In collaboration with Hiroshi Ueda of Nagasaki University in Japan, we found that injecting TIP39 into a mouse paw elicits a withdrawal response, presumably by acting on PTH2 receptors in the peripheral terminals of primary afferent fibers. When we inject TIP39 intrathecally, mice scratch, bite, and lick their hindlimbs—a classic pain-avoidance response. Furthermore, intrathecal administration of an antibody that sequesters TIP39 decreases sensitivity to pain in several assays; injecting TIP39 has the opposite effect.

We are now mapping the anatomical distribution of TIP39. There are some TIP39-

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containing fibers in the spinal cord, consistent with its potential role as a supraspinal mediator of spinal pain processing. There are much denser networks of TIP39 fibers in other regions, and we are now beginning to test ideas about TIP39 function in these areas. There are only a small number of TIP39-containing neurons and they are largely concentrated in two brainstem nuclei. We want to find out what type of information reaches these cells and stimulates TIP39 release. We also want to find out whether TIP39 reaches peripheral PTH2 receptors, including those in pancreatic islets, thyroid parafollicular cells, and gastrointestinal peptidergic cells, and what functions it has in these regions.

Descriptive studies of PTH2 receptor distribution have led us to the discovery of a new neuropeptide and to the testing of specific hypotheses about its function. We expect that studying TIP39 will help us to learn more about physiological modulation, and possibly therapeutic intervention, in processes as diverse as pain perception and release of pituitary hormones.

Ji Ming Wang *obtained his M.D. from the Graduate School of Shanghai Second Medical University, People's Republic of China, in 1983. He then obtained his Ph.D. from the Lombardy Regional School for Professional Education in Pharmacology, Milan, Italy, in 1987. In 1990, he joined the Laboratory of Molecular Immunoregulation, Division of Basic Sciences (now the Center for Cancer Research), NCI-Frederick, where he is now a principal investigator.*

Ji Ming Wang

My major research interests are the role of chemotactic factors (chemoattractants) and their cell receptors in health and disease conditions. Chemoattractants are a supergroup of molecules that induce directional migration (chemotaxis) of human cells. Chemotaxis is a crucial step for leukocyte accumulation at the sites of inflammation, bacterial infection, and immune responses where bacterial or tissue-produced chemo-attractants are elevated. Chemoattractants are divided into "classical" and "chemokine" subgroups, and members of both subgroups use cell receptors with a seven-transmembrane structure. Some of the chemokine receptors act as co-receptors used by HIV for infection.

In the early 1990s, as a special volunteer and, later, as a contract scientist, I focused on the study of novel chemoattractants and receptors and the biological significance of these molecules. We were among the first to demonstrate the promiscuous binding nature of chemokines and identified novel receptors. We established with a mouse tumor model that chemokines are involved in the organ-preferential metastasis of malignant tumor cells, a principle that was confirmed by other investigators with human malignant tumor cells.

Since 1997, when I became a tenure-track investigator, my group has discovered that HIV-1 envelope proteins possess the capacity to inhibit the function of chemoattractant receptors on human mononuclear phagocytes. We further identified several peptide domains derived from HIV-1 envelope proteins that directly activate two receptors for the classical bacterial chemotactic peptides FPR and FPRL1. Activation of FPR and FPRL1 on human monocytes results in the deactivation of chemokine receptors, including a key HIV-1 co-receptor CCR5, and interferes with the ability of CCR5 to act as an HIV-1 co-receptor. These results suggest that FPR and FPRL1 on human cells may recognize HIV-1 envelope-derived peptides during the course of infection—perhaps reflecting a defensive host response to invading pathogens. However, prolonged activation of FPR and FPRL1 may lead to the suppression of cell response to stimulation by other chemoattractants, thereby toppling the balance of the immune system. On the bright side, peptides activating FPR and FPRL1—and thus inhibiting HIV-1 co-receptors—may provide a source of new anti–HIV-1 agents.

My group has also revealed an important role of the chemotactic peptide receptor FPRL1 in proinflammatory aspects of Alzheimer's disease (AD). AD is characterized by the appearance of senile plaques in brain tissues, in association with progressive destruction of neurons and the development of dementia. The key causative factor of AD is a 42–amino acid β-amyloid peptide ($A\beta_{42}$). Production of $A\beta_{42}$ is increased in the context of pathologies such as genetic defects and brain injuries. Aggregated $A\beta_{42}$ forms the core of senile plaques and induces inflammatory responses, as shown by infiltration of the AD lesions by activated microglial cells, a cell type comparable to monocytes in the peripheral circulation.

We demonstrated that $A\beta_{42}$ uses FPRL1 as a functional receptor to induce migration and activation of monocytes and microglial cells. In addition, we detected a high level of expression of the FPRL1 gene in phagocytic cells in the lesions of the AD brain tissues. Furthermore, we found that FPRL1 is critical for cell uptake and intracellular accumulation of $A\beta_{42}$, culminating in the formation of amyloid aggregates and cell death. Interestingly, FPRL1 is also a functional receptor for a peptide fragment, Prp106-126, of the human prion protein, which causes kuru, a human version of bovine spongiform encephalopathy. Prp106-126 forms aggregates and promotes chemotaxis and production of neurotoxic mediators by mononuclear phagocytes. Identification of FPRL1 as a receptor for both Prp106-126 and $A\beta_{42}$ suggests similarity in the pathogenesis of prion diseases and AD.

In future studies, we will continue to focus on the elucidation of the molecular mechanisms underlying chemoattractant and receptor interactions. We are especially interested in using animal models to evaluate the contribution of these molecules to the progress of diseases. We hope the information obtained promotes understanding of the disease process and the design of novel therapeutic approaches. ■

Health and Safety Expo

The NIH Health and Safety Expo will be held **June 11** from 10:00 a.m. to 3:00 p.m. Starting in Masur Auditorium with a talk on biodefense by NIAID's Carole Heilman, the Expo will afterward move down one floor to the Visitor's Information Center. ■

GM Awards

The General Motors Cancer Research Foundation Annual Scientific Conference will be held **June 4–5** in the Masur Auditorium. Winners of the 2002 GMCRF awards will present talks on the second day. For details, see **<http://www4.od.nih.gov/gmcrf/>**. For more information, contact GMCRF at (919) 668-8018 or e-mail **<uemk001@surgerytrials.duke.edu>**.

Mouse Phenotyping

The Veterinary Resources Program is now offering standardized gross and histopathologic analyses of genetically engineered mouse strains, including serum chemistries and hematology.

The workup is designed to evaluate the expected and unexpected phenotypes of the gene manipulations. Analysis will be performed on 18 age-matched mice, 6 each of wild-type, homozygote, and heterozygote.

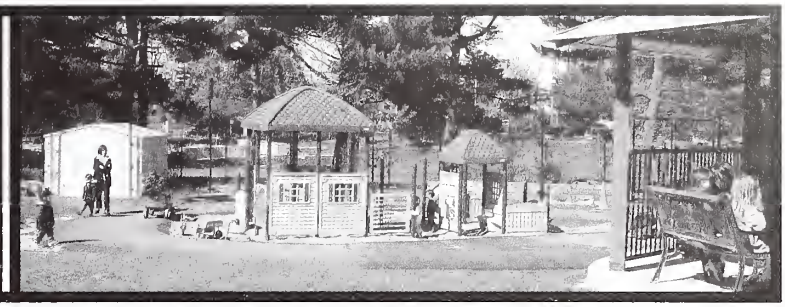
Currently covered by "membership fee," individual investigators will not be charged until FY 2004.

Contact Michael Eckhaus (301-496-4465; **<me18m@nih.gov>**) or Georgina Miller (301-496-4465; **<gm25f@nih.gov>**) for more information or to schedule submissions. ■

Taking Care Of Child Care

text and photos by Rashmi Nemade

Inside . .



. . . and out, at the NIH East Child Care Center, adjacent to Natcher

Lab space is important. So is money. And there's no question that the caliber of the research and the scientists at NIH figure heavily in a decision to take a position here or to remain in one. But the one other issue that can make or break the deal, at least for many people with children, is the availability of child care—ideally on campus or, if not, at least close by, says Mary Ellen Savarese, NIH Child Care Programs specialist in the Office of Research Services (ORS).

The better to present real numbers when negotiating for more child-care resources, ORS engaged the services of Performance Dynamics, Inc. (PDI), and the University of Central Florida in Orlando to develop and conduct the Child Care Needs Assessment Survey.

First, to ascertain the kind of information ORS would seek, PDI created focus groups composed of child-care administrative staff, parents with children at each of the three Bethesda-based NIH child-care facilities (listed this page), and even parents who work at NIH but have chosen other child-care services. A pilot survey was then administered online and questions further refined.

Enjoying the day: *(right) Mary Ellen Savarese, NIH child care specialist, with Mary Haas, director, East Child Care Center*

The final survey was offered in five languages online and two languages on paper. Survey results and the Executive Summary and Report were submitted in January 2002 and can be viewed at **<http://www.nih.gov/od/ors/dss/special/chintro.htm>**.

The survey was completed by 1,441 people out of the approximately 22,000 invited to participate—a 6.6 percent response rate, which is considered within the acceptable range in the field and deemed to adequately reflect the demographics of the NIH population as determined by the NIH Census collected in the year 2000.

The survey provided documentation of what most people at NIH might have intuited or extrapolated based on their individual experiences. As Savarese comments, "much of this was already known, but not in statistical terms.

Having the statistical data to support our requests for more resources is critical to maintaining the excellent quality of child care here—and to improving it further."

The survey concluded that:

- The need for child care greatly surpasses current capacity.
- A plan to assist employees with dependent-care needs should be developed.
- An income-based tuition assistance program should be developed.
- The application procedures for all the existing centers should be standardized and streamlined.

The ORS Worksite Enrichment Programs Branch, under which child-care services and programs are offered, is working to address each of these issues.

Efforts are being directed to increase child care capacity by bringing licensed child care centers close to employees' homes into the NIH system.

The Office of Personnel Management is exploring a Dependent Care Assistance Plan that will enable federal employees to set aside pre-tax dollars for such services as elder care and care for family members with special needs. Tuition assistance for low-income employees already exists in each center, but such funds are quite limited and the goal is to expand them.

Until now, the enormous waiting list to obtain NIH childcare was infamous. Each center had its own waiting list, and parents wanting to obtain a spot would put their names on multiple lists. In collaboration with the Work and Family Life Center Referral Service, the ORS has now centralized this process.

"Now there's only one list," says Savarese, "and staff will be able to advise parents of the wait and offer them alternatives all within one phone call. It's like one-stop shopping." The staff will also call employees on the waiting list quarterly to update them on their list status and to assess their continuing child-care needs. ■

On the Bethesda Campus:

Infant and Toddler Child Care
Provider: ChildKind Inc.
<http://www.nih.gov/od/ors/dss/special/chkind.htm>
Ages served: 6 weeks–3 years
Licensed capacity: 33 children
Location: Building T-46
Hours of operation: 7:30 a.m.–6:00 p.m. (Monday–Friday; closed all federal holidays)
Director: Lee Ettman, (301) 496-8357
Tuition: $494.00 every 2 weeks for children up to 2 years, $389.00 every 2 weeks for children 2–3 years

Preschool Child Care
Provider: Parents Of Preschoolers, Inc.
<http://www.nih.gov/od/ors/dss/special/parents.htm>
Ages served: 2.5 years–6 years
Licensed capacity: 105 children
Location: Building 64 (East Child Care Center)
Hours of operation: 7:30 a.m.–6:00 p.m. (Monday–Friday; closed all federal holidays)
Director: Mary Haas, (301) 496-5144
Tuition: $110.00–$160.00 a week, on a sliding scale based on family income

Off-Campus

Provider: Executive Child Development Center Inc. (ECDC)
<http://www.nih.gov/od/ors/dss/special/ecdc.htm>
Ages served: 6 weeks–12 years (before- and after-school care for older children)
Licensed capacity: 220 children
Location: Executive Boulevard, Rockville
Hours of operation: 7:30 a.m.–6:00 p.m. (Monday–Friday; closed all federal holidays)
Director: Anne Schmitz, (301) 496-9411
Tuition: sliding scale based on family income: infants and toddlers: $424.00–$544.00 every 2 weeks; 2-year-olds: $332.00–$428.00 every 2 weeks; preschool and kindergarten: $272.00–$350.00 every 2 weeks; kindergarten complement: $15.00 a day; surround kindergarten: $254.00–$326.00 every 2 weeks; before and after school: $178.00 every 2 weeks; after school only: $152.00 ■

Two Empty Seats

The NIH Child Care Board seeks two NIH employees to fill upcoming vacancies. The board is advisory and advocates for affordable, high-quality child care for the NIH community. Call Mary Ellen Savarese, 402-8180, or visit **<http://www.nih.gov/od/ors/dss/special/chintro.htm>**.

Call for Catalytic Reactions

In this issue, we are asking for your reactions in four areas: the release of prepublication data, intramural issues of which the new NIH director should be aware, international activities, and the Interest Group Directory.

Send your responses on these topics or your comments on other intramural research concerns to us via e-mail: <catalyst@nih.gov>; fax:402-4303; or mail: Building 2, Room 2W23.

In Future Issues...

- What's New at NCCAM?
- Chemistry at NIH—Or Not?
- Interest Group Directory

1) What is the responsibility of intramural scientists to provide prepublication data to the scientific community?

2) What are the major intramural issues of which the new director of NIH should be aware?

3) Two articles in this issue describe NIH involvement in health education and research in developing countries. Do you think such activities should be expanded?

4) This is not so much a question as **a request to Interest Group contacts.** Each July, the *Catalyst* runs an updated Interest Group Directory. Everyone who was listed as a first contact for any of the 90 Interest Groups included in the July–August 2001 issue will soon receive a copy of last year's listing to verify or change, as needed. If your new group is *not* on the list send the *Catalyst* its name; regular meeting time and place; and the name, phone number, and e-mail of the contact person. **Changes and new information must be received by June 21st to be included in the July-August 2002 issue.**

The NIH Catalyst is published bimonthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2W23, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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