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A ROCKY MOUNTAIN SCIENCE SAMPLER

Bruce Chesebro, who heads the Laboratory of Persistent Viral Diseases (LPVD), has a three-ring research focus: on the immunology of mouse Friend leukemia retrovirus, neural HIV infection, and transmissible spongiform encephalopathies or TSE diseases.

Retroviral immunology has been a 25-year interest of Chesebro's. The Friend virus, which is in the same family of viruses as HIV, causes fatal leukemia in a high percentage of susceptible strains of mice. Remarkably, other strains become infected but "cure" their own leukemia. "We know more about a protective response to this virus than to any other retrovirus," Chesebro says. He is closing in from two directions on understanding effective immune response to Friend by attempting to develop a vaccine and by attempting to clone the Rfv-3 gene on mouse chromosome 15 that appears to confer the effective immune response. Ultimately, Chesebro expects, there will be three essential components: correct responses in CD8+ cells and CD4+ cells and in humoral antibody production.

For his work on HIV-dementia, Chesebro collaborates with colleagues at the Department of Neurology at Johns Hopkins University School of Medicine in Baltimore, *continued on page 8*

THE LAST BEST PLACE FOR RESEARCH: NIAID'S BIG SKY LABORATORY

by Celia Hooper

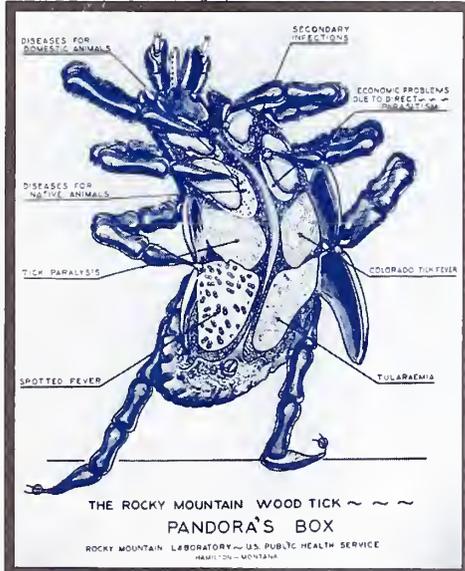
Imagine living in Shangri-La—a shimmering, legendary trout-stream river valley poised between two spectacular mountain ranges that make the winters mild and the summers temperate . . . A place where people don't lock their houses or even bother to roll up their car windows, much less install The Club . . . A place where you can find parking after 9:30 a.m. and you don't even need a sticker or a hanger. Now imagine that, in this paradise, you also get all the perks of being an intramural scientist—the chance to do excellent research with good support services and bright, energetic colleagues.

It's not a daydream; it's the Rocky Mountain Laboratories.

RML, a Hamilton, Montana, outpost of NIAID, celebrated that institute's 50th anniversary this summer. *The NIH Catalyst* used this as an excuse to visit the place and find out, if you will pardon the

pun, what makes it tick.

As RML scientist-emeritus Willy Burgdorfer (who discovered *Borrelia burgdorferi*, the spirochete that causes Lyme disease) tells it, the facility that would eventually become RML owes its origins to a mysterious western Montana outbreak at the turn of the century of what was called black measles or spotted fever. As dozens of settlers and pioneers moving through the Bitterroot Valley perished, Howard Taylor Ricketts was summoned from the University of Chi-



John Moore (circa 1955)



Celia Hooper

Above the Montana Lab: the Bitterroots

cago and determined that the ailment was being spread by infected wood ticks. State and federal public health officials, working out of a shack in the area, launched prevention and control

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IT'S AS GOOD AS IT GETS: VERY PERSONAL REFLECTIONS ON NIH AND ITS RESEARCH FESTIVAL



Arthur Levine

The Twelfth Annual NIH Research Festival arrives—with all due pomp and circumstance—on October 6–9. As chairman of this year's festival, I have the opportunity to continue what has become a wonderfully satisfying and still evolving tradition. However, this Research Festival will have a bittersweet flavor for me personally, as I shall be leaving NIH immediately after the festival to become senior vice chancellor for the health sciences and dean of the School of Medicine at the University of Pittsburgh. After 31 years at NIH, I cannot imagine a better way to say hail and farewell to this great institution than by celebrating its intramural science.

The Research Festival has changed over the years, in both style and content. My good friend Abner Notkins, then NIDR scientific director, proposed the idea to the Board of Scientific Directors in 1986. Abner now recalls that back then, "We had 15 very separate, self-contained, and often isolated institutes. More than a little of the very good work going on in the different institutes was similar or even overlapping, especially at the basic level, but investigators often had no sense of this common ground because scientists in the various institutes simply didn't have much contact with one another." In addition, Notkins felt that the breadth and depth of excellent intramural science offered the critical mass needed for a rich and robust scientific meeting—a true celebration of our work. At least some of Notkins' colleagues were dubious about the likely success of such a meeting, or even territorial about their science, and many felt that just the usual listing of lab and branch seminars on the Yellow Sheet was sufficient for scientific exchange. Fortunately, Ed Rall, then the deputy director for intramural research, thought that the festival idea was worth a try.

The first year, Abner organized a one-day festival and decided to turn the usual protocol for scientific meetings on its ear. Instead of having the "superstars" present the plenary symposia, and postdocs their posters, he asked Rall to invite NIH's most prominent senior scientists to present the posters. Thus, it was midcareer and even younger scientists who headlined the morning program, with plenary symposia on topics that at the time were at the cutting edge: *Prospects in Gene Therapy and Oncogenes and Growth Factors*. Notkins recalls one Nobel laureate struggling to assemble his poster—something he'd never done before or, at least, not for decades! The festival's afternoon featured 20 workshops, with a gala picnic concluding "Research Day" in the evening. Hardly the typical federal event!

I chaired the second NIH Research Festival. Still just one day, this one included plenary symposia on *Signal Transduction, Gene Structure and Expression*, and the *Molecular and Cellular Biology of the Nervous System*. Again, we made time for a picnic and even a jazz concert in the evening. Getting from one event to the next proved daunting, given that the workshops were so widely scattered across the campus.

In 1990, the festival joined forces with the Technical Sales Association (an equipment vendors' trade organization), which mounted a display of the latest scientific equipment in the tent that had earlier housed the posters. (The association's generous role in the festival was the brainchild of Jim Bahre, for many years a manufacturer's representative on this campus and so inextricably a part of our culture that he eventually received an NIH Director's Award!) Successive festivals followed this model more or less intact through 1994. In 1995, all festival events were consolidated in the new

Natcher Building, making it easy to move between talks and workshops but forcing a cutback in the number of workshops and posters—although we were still offered an amount and diversity of science that one could barely metabolize. That year also, we began to involve NIH's growing library of "special interest groups" in festival organizing. In 1996, to celebrate the Tenth Research Festival, we revived Abner Notkins' notion of inviting NIH's most senior scientists—including several institute and scientific directors—to present posters. Despite the vast resources available to this august group, their posters—while scintillating, perhaps, scientifically—tended to lack the aesthetic of their younger but more Mac-proficient colleagues. That year, too, after years of tolerating the September rains, and with a science-based consult (*Poor Richard's Almanac*), we moved the festival to early October; and last year, obeying Poor Richard and remembering not to schedule the festival on Yom Kippur, we were rewarded by sunshine. Last year saw the birth of a Postdoctoral Job Fair, run by the Office of Education, bringing together job-hunting postdocs and representatives of pharmaceutical and biotechnology companies.

I have again fine-tuned the formula for this year's festival (the program is available at: <http://silk.nih.gov/silk/fest90/>): a more leisurely three-day format, a revival of picnics and concerts, a tighter focus of the workshops (now called "mini-symposia") to cutting-edge topics, and morning plenaries that should have very wide appeal. The now all-day Job Fair is slated for Tuesday, October 6. The festival itself begins Wednesday with a plenary symposium on *The Origins of Life*, featuring NIH Director Harold Varmus and NASA Director Dan Goldin. I believe this will be one of the most exciting scientific sessions ever held at our festivals (talks on astrobiology, planetary origins and prebiotic life, and the earliest events both in prokaryotic and eukaryotic evolution).

The Thursday plenary symposium offers a nontraditional view of translational research: bedside-to-bench, rather than the more customary bench-to-bedside. The last morning symposium is devoted to a subject now pursued aggressively in virtually every institute: *Apoptosis*.

Mini-symposia on cross-cutting topics of interest to both basic and clinical researchers fill the mornings and poster sessions the afternoons. The latest lab equipment is on display throughout Thursday and Friday. The challenge will be to choose from the engaging menu of competing sessions, including, for example, "Cell Biology of the Nucleus" (chaired by Mary Dasso and John Hanover), "Molecular, Cellular, and Tissue Imaging" (Peter Basser and Carolyn Smith), "HIV Biology: Bridging the Gap Between *In Vitro* and *In Vivo*" (Edward Berger and Leonid Margolis), and "The Molecular and Cellular Biology of Diabetes Mellitus" (Abner Notkins and Phillip Gorden).

I hope you enjoy this thoroughly groaning board, filled with the fruits of our best basic and clinical science. For myself, I know that the delight I shall take in this festival will mirror the joy of my three decades at this magnificent institution. I may be moving on, but my deep affection and respect for my many NIH colleagues will endure. Despite the frustrations that we may feel (e.g., campus space so supersaturated that we may all soon crystallize and seemingly limitless government forms to complete), surely there has not in history been a better place than this one in which to do research—"it's as good as it gets"—and in the Twelfth Annual NIH Research Festival, we'll know this still again. ■

—Arthur S. Levine, Scientific Director, NICHD

NEW NIDDK LAB CONCENTRATES THE SPOTLIGHT ON NORMAL AND ONCOGENIC MAMMARY GLAND DEVELOPMENT

by Sharon Ricks,
technical writer,
NIDDK

May 11 was moving day for 11 NIDDK researchers and 400 mice—out of their friendly but modest quarters in the upper reaches of the Clinical Center and into the new NIDDK Laboratory of Genetics and Physiology (LGP).

The new lab spans rooms 101 through 115 of Building 8 and boasts a new laser-capture microscope (see "Hot Methods: Laser Capture Microdissection," *NIH Catalyst*, November-December, 1997, page 12) and new video imaging equipment. It officially opened June 11, replacing the developmental biology section of the Laboratory of Biochemistry and Metabolism.

The lab explores genetic switches and biochemical pathways that control normal and oncogenic mammary gland development—and it's a tribute to 16 years of study of mammary gland development and physiology. (Though the lab is dedicated to the study of the mammary gland, other projects, such as the study of germ-cell development in the testes, are also on the agenda.)

The research originated in the quest of a graduate student in Cologne, Germany, who was

working on his thesis project in the genetics lab in which the lysozyme gene, a relative of the milk protein, α -lactalbumin, had been cloned. The student wanted to isolate the α -lactalbumin gene in the mouse to identify the gene's structure and to determine

whether the structure and functional domain were conserved through evolution. Instead, he discovered what would prove to be a powerful new research tool.

"I did not manage to isolate the α -lactalbumin gene," says the chief of the new NIDDK lab, Lothar Hennighausen, reminiscing on his early work. "It tricked us. We were surprised to find that the milk protein is expressed 100-fold less in the mammary tissue of mice than in that of all other species. Instead, I isolated for the first time mammary-specific genes for the mouse, including a

novel gene called the whey acidic protein (*Wap*).

When Hennighausen came to the NIDDK Laboratory of Biochemistry and Metabolism in 1985, he picked up the research again and discovered that the *Wap* gene was almost exclusively expressed in mammary tissue and that its control switches targeted other

genes to mammary tissue for expression in transgenic animals. The new promoter could therefore be used to target oncogenes to mammary epithelial cells and to create mouse models of human breast cancer, Hennighausen recalls. It could also be applied to the creation of "mammary bioreactors" to express pharmaceuticals in the milk of transgenic mice and livestock, such as are now used commercially to produce blood-clotting factors in sheep and goats.

These days, says Kay-Uwe Wagner, a postdoc in the lab, "we are doing tissue-specific gene knock-outs," linking the *Wap* gene with an enzyme specific for whatever gene is slated for removal from the mammary gland, such as the *bcl-X*

gene, and determining its culpability in tumorigenesis. The lab is also creating technologies to deregulate gene expression at specific times during development.

To Hennighausen, the mammary gland harbors fundamental lessons of how organs are built. "In the virgin gland you just see ducts, and as soon as pregnancy sets in, the gland takes off," he observes, noting that many rounds of cell proliferation and differentiation lead to an organ designed to produce large amounts of milk. "After weaning," he adds, "the gland completely regresses,



Bill Branson

Lothar Hennighausen (seated), encircled by labmates (left to right): Ulrike Wagner, Svetlana Stegalkina, Kay-Uwe Wagner, Patricia Dierisseau, Justin McSbane, Ed Rucker, Nataly Strunnikova, Robin Humphreys, Jonathan Shillingford, Gertraud Robinson, Annie Guerrero, and Marta Gallego.



Bill Branson

Lothar Hennighausen and the fruits of his new lab: a laser-capture view of mammary gland mysteries

and in a short time, 99 percent of the epithelial cells die." He says the lab will explore the signals that trigger cell death for clues on how to destroy tumors.

NIDDK Scientific Director Allen Spiegel says Hennighausen's work has illuminated the role of several hormones, growth factors, and their signal-transduction path-

ways in the complex changes that occur in the breast during normal pubertal development, pregnancy, lactation, and involution, as well as in the neoplastic process that leads to breast cancer.

Colleagues at NCI are quite interested in the work of the LGP. "Lothar's lab is working to identify all the genes that are expressed during normal mammary gland development and to define when they're expressed," says Bob Callahan, chief of the Oncogenetics Section in NCI's Laboratory of Tumor Immunology and Biology. "His is probably the only lab doing that for any particular tissue," Callahan says, "and it provides a basis for understanding where things go wrong during mammary tumorigenesis."

NCI supports two related Web sites: NIDDK's Mammary Gland Anatomy Project at

<<http://mammary.nih.gov/mgap>> and the Biology of the Mammary Gland at

<<http://mammary.nih.gov>>, both of which are managed by Hennighausen and supported by CIT's Jai Evans. ■

NIDCD: Ten Years!

Friday, **October 2**, 1998, 10:30 a.m., Natcher Conference Center, NIH.

Celebrate the decade's research in human communication with the NIH and NIDCD directors and other speakers.

For more info, call 496-7243 or 402-0252 (TTY); for agenda and luncheon reservation form, visit

<<http://www.nih.gov/nidcd/tenanniv.htm>>.

MENTORING ROUNDTABLE: FOCUS ON CULTURAL DIFFERENCES

by Marc Horowitz, Director,
Office of Loan Repayment and
Scholarship

The subject of mentoring commands a lot of attention at NIH; this summer, at a specially convened Mentoring Roundtable—the first of its kind at NIH—the focus was on mentoring students from disadvantaged or minority-group backgrounds.

Sponsored by the Office of Loan Repayment and Scholarship (OLRS), whose Undergraduate Scholarship Program (UGSP)* supports students from disadvantaged backgrounds, the roundtable featured invited university faculty with more than 90 years of combined mentoring expertise and substantial experience mentoring disadvantaged and minority science students. More than 100 NIH denizens—undergraduate and postdoctoral students, scientists, and administrators—attended the roundtable.

Guest panelists were Lawrence K. Alfred, professor of biology at San Diego State University; Frank J. Talamantes, professor of biology at the University of California at Santa Cruz; and Uri Treisman, professor of mathematics at the University of Texas at Austin. The roundtable was moderated by John F. Alderete, professor of microbiology at the University of Texas Health Science Center at San Antonio and president of the Society for the Advancement of Chicanos and Native Americans in the Sciences.

In his 25 years of working with Chicano students, Talamantes said, he'd observed in many a deference to authority, a subdued demeanor in the presence of a generally acknowledged leader in the field. Such characteristics, he noted, could be a handicap in the world of scientific research. The mentor's challenge with such students is to help them question authority without disrespecting their cultural values. In general, Talamantes emphasized, mentors need to take students' concerns and problems seriously, listen carefully, and respect students' individuality. But they also need to challenge students' ideas of what they want to do and help them explore other options.

Treisman pointed to the learning environment as the critical factor in minority students' achieving their science career goals. Successful mentoring, he said, is most often accomplished in educational programs in which mentoring is a group enterprise with strong support and leadership from the department chair and administration. Good mentors, he said, are able to define excellence in their field, know how to achieve it, and share that information with their students. The most important mentoring tasks senior scientists can perform are to monitor student progress, publicly ask questions, and scrutinize students' lab practices, he said.

Alfred emphasized "nurturing" to help students overcome fears and to foster in them a belief in their own academic abilities. He also recommended that links be established between NIH scientists and the university mentors of students in NIH programs. He posed two key questions: How can we get more faculty members, especially those with NIH research grants, involved in mentoring? How can mentoring outcomes be measured more effectively? Panel members agreed that mentoring must be a part of the broader mission of an institution and the responsibility of mainstream faculty members, especially if disadvantaged students are to succeed in the field of biomedical research.

Michael Gottesman, deputy director for intramural research, noted that NIH leadership—including Director Harold Varmus and NIDR Director Harold Slavkin, who chairs the Committee for the Recruitment of Ethnically Diverse Young Talent into Biomedical Research (also known as the Slavkin Committee), are working to close the gap between students' expectations and the reality of the NIH research experience. A committee report and recommendations—a mentoring handbook—are expected by year's end. ■

* Each student in the UGSP is assigned an NIH researcher to serve as a mentor. This mentoring relationship is initiated during a 10-week summer program, when students work as paid employees in NIH research laboratories. A goal of the UGSP is continuation of the mentoring relationship into all seasons. Marc Horowitz, director of the Office of Loan Repayment and Scholarship, Office of Intramural Research, oversees the UGSP and is always eager to identify intramural scientists willing to take active roles in mentoring his program participants, especially beyond the time spent in NIH's labs. Information on the UGSP can be found at <http://ugsp.info.nih.gov> or by calling Horowitz at 402-5666.



Ernie Branson

Uri Treisman holds aloft
mentoring guidebook

SURGEON GENERAL REVIEWS SUMMER RESEARCH AT NIH



Adm. David Satcher, Surgeon General, and Rear Adm. Arthur Lawrence, senior advisor, upon arrival at NIH's Summer Research Program Poster Day, August 6. For more than two hours, the surgeon general reviewed the research efforts of nearly 400 NIH summer research students, including the 23 who had come to NIH under the Undergraduate Scholarship Program (UGSP; see story this page), for whom Poster Day was the culmination of their 10-week experience here.



At
Poster
#139:

Audrey
Ramirez,
UGSP
scholar,
San
Francisco
State
University



"My heart is in my throat. I just told the surgeon general about my research project," Ramirez whispered moments later. Her poster depicting "Mobilization of CD8+ dendritic cells in response to microbial products as visualized by immunofluorescence microscopy" reflected her research in the NAID Laboratory of Immunology (with preceptor Ronald Germain). With her fresh SFSU degree in cell molecular biology, Ramirez will pursue a doctorate at the UCSF Program in Biological Sciences beginning this fall. She learned of the UGSP through the Society for the Advancement of Chicanos and Native Americans in Science.

FOUNDATION FOR THE NIH SETS OFF ON SOLID GROUND

The National Foundation for Biomedical Research, also known as the Foundation for the National Institutes of Health, is living up to the promise for which it was designed by Congress.

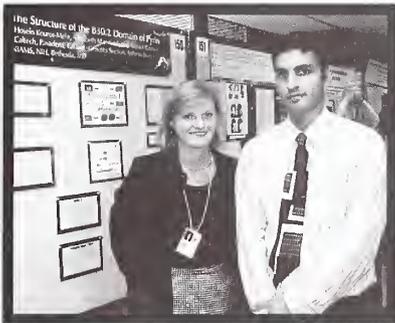
In the past year, the Foundation has started to become a magnet for donations from private-sector entities with an inherent interest in biomedical research, as well as from individual scientists who cherish NIH.

■ Contributions approaching \$2 million have been made to the Clinical Research Training Program (CRTP), the Foundation's first major initiative in collaboration with NIH, which aims to expose medical and dental students to the rigors and rewards of a career in clinical research. The CRTP is accommodating nearly twice as many students in its second academic year (1998-1999) as it did the first time around, thanks to grants of \$572,000 from Pfizer, Inc., to support 16 fellows, and \$35,000 from the Ruch family foundation in New York, in honor of Foundation Board member Mrs. William McCormick Blair, Jr., to sponsor one student. The Pfizer gift extends over two subsequent years for a total commitment of \$1.6 million.

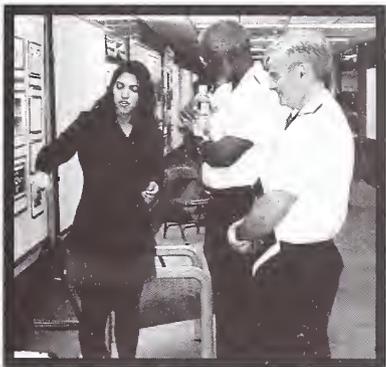
■ The Foundation has received two grants from the pharmaceutical industry in support of the National Coalition for Health Professional Education in Genetics—\$25,000 from Novartis and \$10,000 from Pharma. The Coalition includes more than 100 professional organizations, government agencies, and consumer groups intent on ensuring that health professionals systematically keep pace with advances in human genetics. NHGRI, the American Medical Association, and the American Nurses Association are among the coalition's members. NHGRI director Francis Collins is a coalition co-chair. Moreover, the Merck Company Foundation has given a grant of 25,000 to support the foundation's operations, a critical need as it grows.

■ The family of virologist Norman P. Salzman has established the Foundation's first endowed memorial fund—the Norman P. Salzman Memorial Award in Virology, which will be awarded on a regular basis to an outstanding young postdoctoral investigator in virology at NIH. Salzman's research career spanned 40 years, many of them spent at NIH's Bethesda and Frederick campuses. The Salzman family has donated \$15,000 to start the fund, and Salzman's colleagues and friends have contributed another \$15,000, for a total of \$30,000 thus far. Details about the award and the nominations process will be forthcoming; the first award will be made in 1999.

For further information regarding the Salzman award, the CRTP, or making a donation to the Foundation, contact Anne Alexander, executive director, Building 60, Room 152, 1 Cloister Court, Bethesda, MD 20814; 301-402-5311. ■



Marguerite Rippy (left), UGSP acting director, and Hosein Kouros-Mehr, a biochemistry major at CalTech, where he starts his sophomore year this fall. This is the UGSP's third year, Rippy said, and the first year the program is at "full strength." About one in 12 applicants qualify for the program, which awards full tuition on a yearly basis for successful candidates. After they earn their advanced degree, participants provide a "one-year payback," working at NIH for each year of support they received as an undergraduate. Kouros-Mehr, who did research on the "structure of the B30.2 domain of pyrin" (#150), under Daniel Kastner and Elizabeth Mansfield in the NIAMS Arthritis and Rheumatism Branch, aspires to a research career (PhD or MD/PhD) and a fiction-writing sideline. He's already published short stories and is working on a novel.



Andrea Borgbese, who's entering her senior year at Lehman College, City University of New York, explains her research to the surgeon general and Michael Gottesman, NIH deputy director for intramural research. Her poster (#148) on "inducible transgenic mouse models for autoimmune myositis" captures her work in the NIAMS Arthritis and Rheumatism branch with preceptors Paul Plotz and Kanneboyina Nagaraju. "Amazing," Satcher said, as he wished her well. "He's been impressed," commented Gottesman, who'd invited Satcher to spend the day.

—photos and text by Fran Pollner

CATALYTIC REACTIONS

More Slide Tips

Make multiple copies of a slide if it is to be used more than once in a presentation. Avoid flipping back and forth during your talk. When at all possible, find out the size of the room you're talking in and preview your slides in a similarly sized room. Stand in the back and look at your own slides. Always mark your slides so you can easily place them in a cassette. As you hold the slide up to light to see it, make sure you can read it with your naked eye. Then mark the lower left corner. When filling the cassette, the mark is in the upper right corner.

—Barbara Vonderhaar, NCI

On Teamwork

I'd like to endorse, with enthusiasm, Michael Gottesman's emphasis on the role of group dynamics in optimizing today's biomedical research environment ("Fostering Collaboration and Teamwork at NIH," *Catalyst*, July-August 1998, p. 2).

Not only is the creative exchange among multidisciplinary teams of strategic importance in conquering diseases, those teams are expanding beyond the usual government-academia research collaborations to include corporate partners, as "inventions" are viewed more as an integral part than a byproduct of biomedical research. Indeed, public demands for practical applications are often tied to funding authorizations. Along with the advice that younger scientists working with more senior investigators "work cooperatively but carve a distinctive niche within the team," I would add that they acknowledge the creative integrity of the contributions of their colleagues as well as their own and readily credit the works of others—whether they are collaborators or not—that served as sparks to their own creativity.

One hopes that young investigators are introduced early in their NIH experience to mentors who pay attention to group dynamics and foster teamwork in achieving research goals—not to mention strict adherence to ethical principles. The value of the process and the people involved cannot be overstated.

—Wanda Darwin, OD/OHRM

THE LAST BEST PLACE
continued from page 1

efforts. They went on to break important ground in understanding ticks and their anatomy and role in spreading diseases, as well as vector-parasite relationships. These health officials eventually produced a vaccine that prevented death from Rocky Mountain spotted fever. In the first three decades of the century, the lab pursued studies of five additional tick-borne diseases: tick paralysis, tularemia, Colorado tick fever, tick-borne relapsing fever, and Q fever. In 1928, the lab—by then housed in a more modern research building—was sold to the federal government. As far as Burgdorfer is concerned, “Tick-borne diseases were and always will be the prime reason the [Rocky Mountain] Lab exists.”

But in the past 50 years, the lab’s focus of research has expanded beyond tick-borne diseases. RML’s fortunes have waxed and waned and right now seem to be in ascendance: With a current staff of about 160, a massive \$25 million renovation of the laboratories and animal facilities is underway to bring them up to modern building codes. New staff, including a new lab chief, are being recruited. RML scientists are excited about their research, and visitors and would-be collaborators are venturing out to NIAID’s loveliest summering grounds. For example, in mid-July, Anthony Basile, a neuropharmacologist from NIDDK was out at RML to give a talk on his work and explore the possibilities of collaborating with RML’s Bruce Chesebro on studies of AIDS dementia using a mouse model Basile has developed. Basile’s lecture—one of five at RML that week—was enthusiastically attended by a roomful of interested scientists. “These people are all really top-flight,” Basile said. “The best in their fields. I’ve been pleasantly surprised by the high quality of the work.”

NIAID Scientific Director Thomas



Yesterday: Tick-borne disease researchers, circa 1915, at precursor lab near Victor, Montana, run by the state and the Public Health Service.



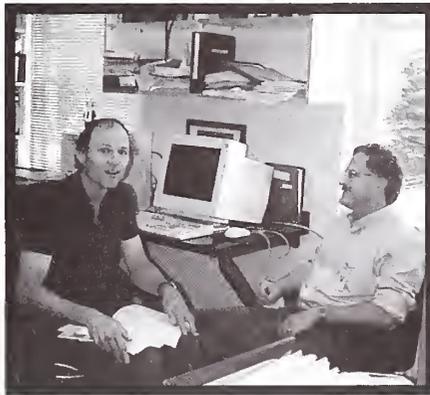
Vaccine development, circa 1925, in old schoolhouse lab. (Caption information provided by Marshall Bloom.)

Kindt defines the focus of RML labs fairly broadly as being infectious disease, often involving animal models. But beyond that, he is loath to shoe-horn the research into a narrower slot. Kindt says, as with the new lab chief being recruited in the area of bacteriology, NIAID picks outstanding scientists “with their field in mind, but then we give them the freedom to follow the best research oppor-

tunities” just as would be the case in Bethesda. The result is a slightly eclectic mix (see “RML Science Sampler,” page 1) of bacteriology, virology, and some immunology. “We like to keep the emphasis on fewer rather than many things so that there is a synergy among the groups” at RML, Kindt says. “They

work on Aleutian mink disease, “couldn’t have been done elsewhere—certainly not in Bethesda. For the bulk of the animal work, this was the ideal place. You had or could get facilities [for research animals] right at the back door.” Several senior scientists interviewed by *The Catalyst* cited the outstanding animal research facilities as a key factor in the success of their work.

To other scientists, various aspects of the locale are a definite advantage. Investigator Tom Schwan, who studies molecular adaptations of disease-causing bacteria as they move from ticks to mammals, says the best thing about RML is “having this type of research facility in this type of environment.” Chesebro says if he lived and worked elsewhere, he’d probably use up more of his personal leave for vacation each year, whereas in Hamilton he can strike out for prime recreation areas and be there in a matter of minutes after work or on the weekends. Chesebro is one of the favorite rock-climbing companions of Steve Porcella, a research fellow in the



Bruce Chesebro (left) and Antony Basile

don’t cover every area that we do here in Bethesda.”

If you ask scientists at RML what they like about the place, for the most part their answers are similar to the answers you’d get from satisfied researchers anywhere. For tenure-track investigator Sue Priola, the best thing about RML is “the scrapie research group. We get along and interact well,” she says. “It is small, productive, with great exchange of ideas. The science is the biggest plus.” Retired veterinary pathologist Bill Hadlow says his research, including

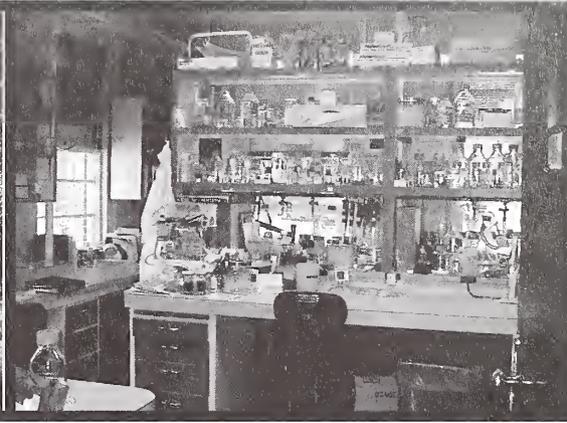


Bill Hadlow

because of the proximity of skiing and other outdoor attractions, or because an



Today: RML Main Entrance



Modern Lab

Celia Hooper

NIH stipend goes farther in Montana than Maryland.

But other staff—including librarian Kate Oliver who moved to Hamilton a year ago from Bethesda for the broad challenges of running her own scientific library—are happy enough to live in lovely surroundings, but haven't become enmeshed in outdoor pursuits. Says Kindt, "If it is necessary for you to go to the opera every week, you would not live there, but otherwise RML has pretty much the same people" as Bethesda. "There may be more intense interest in the out-of-doors," he adds, "but that is not a necessary trait."

Although Hamilton, with a population of about 4,500, may lack first-rate cultural attractions and Bethesda's diverse selection of great restaurants, there are compensatory features, according to RML scientists. Bloom points out that more academic and cultural opportunities are available in Missoula, about a 45-minute drive from Hamilton. And when artists and celebrities do come to the area—as did Pulitzer Prize-winning author Jared Diamond in mid-July—there's a much better chance of getting close to them and having a meaningful personal exchange. "You don't get that at the Kennedy Center," Bloom observes.

Bloom sees the real advantage of RML's setting in the fact that its scientists are very visible in the tiny community and thus have a unique opportunity to communicate science to the public. "You talk about your work with people at the gas station, the grocery, the bait shop," Bloom says. "You are in a good position to communicate with the community at large about what science is good for. With so much anti-intellectualism in the world . . . we need to communicate about science. Here we have a better opportunity to do that, compared with either a university or Bethesda." Other scientists find Hamilton is much less stressful than

big cities, with a low crime rate and good public schools enlivened by energetic parent and teacher involvement.

From all signs, says Kindt, the community returns the lab's affection, despite the fact that RML scientists study deadly diseases and rely on research animals. Bloom believes that Montana culture, grounded in ranching, farming, hunting, and fishing, fosters an understanding of the importance of disease research and the correct presumption that research animals will be treated humanely. "The nice thing about [Hamilton] is that there is a community involvement that is very strong," Kindt says. Local newspapers give extensive—and favorable—coverage to lab events, including groundbreaking a year ago for the lab's renovation, at which the mayor of Hamilton spoke. Kindt says RML staff have been updating the community progress on the renovation and how construction may affect them.

There are some disadvantages to life at RML. A key concern for Kindt is keeping RML scientists from being isolated in their Shangri-La. Through frequent videoconferenced staff meetings, lab chiefs' meetings, and other formal and ad-hoc connections and an NIAID-wide principal investigators' meeting every 18 months, RML scientists seem to be reasonably well plugged-in to NIAID. Broadcasts of the Wednesday Afternoon Lectures are available but poorly attended at the lab. More popular is RML's own lecture series and an open invitation to all RML staff to attend the an-

nual lab meeting of Stanford's hematopoiesis pioneer, Irv Weissman. Weissman's lab meeting is held on a nearby ranch that he shares with University of Washington (Seattle) scientist Leroy Hood and Nobel laureate David Baltimore, president of the California Institute of Technology in Pasadena. Kindt makes funds available to bring

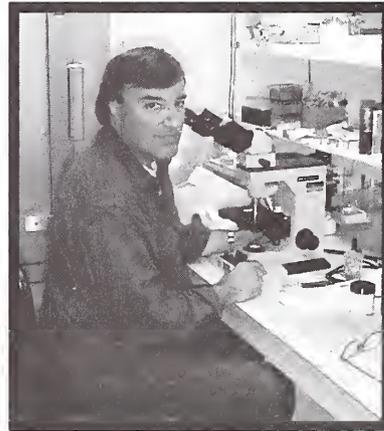
RML postdocs to Bethesda for the Research Festival and other meetings. "I strongly encourage every fellow to come to campus at least once during their tour at RML," says Kindt, who personally visits Hamilton two or three times per year.

As a result of these efforts, scientists at RML say that connectedness to professional colleagues has been reduced to a question of personality, just as elsewhere. "With the electronic technology—e-mail, videoconferencing—and travel, isolation is now self-imposed,"

says Bloom. "I know people at the NIH Bethesda campus who are more isolated from what's going on around them than people here. . . . It's possible to be fully connected here or totally isolated there." Librarian Oliver says she has managed to get the RML library well connected to electronic and interlibrary loan resources from academic libraries in the region as well as the NIH Li-

brary in Bethesda. The real problem is that for her personally, western Montana is remote from friends and family—pretty much a full day's journey away. "There's quite some expense getting in and out of Montana," says Oliver. Researcher Schwan concurs: "The worst thing is the distance you have to travel to get to colleagues. But I don't let it stop me."

Chesebro says it would be nice to have the luxuriant selection of colleagues from all scientific disciplines that are represented at a major medical center—clinicians, chemists, neurobiologists, and mathematical modelers, for



Tom Schwan

Celia Hooper

example. Water-fountain meetings with a diverse range of people can lead to serendipitous discoveries of solutions. But he notes that there's only so much time; if he had a greater diversity of colleagues with whom to chat, he'd probably have less time for each.

A better setting for casual conversation is among the improvements planned in the renovation that will include an interior courtyard connecting individual lab buildings. The original plan targeted only electrical and air-handling infrastructure, Kindt says, but when it was discovered that none of the labs' walls were up to modern code for earthquake-prone regions and that there was lead paint and asbestos to remove, the project grew into the present plan, which will replace or overhaul every lab by the year 2001.

But Burgdorfer says even the present facilities are hardly a drawback. "The renovation will add to our comfortable quarters, though I am one of the few who appreciate the research facilities out here" as they are. "I have set up labs under conditions you wouldn't believe," he recalls. "I've dissected mosquitoes with a toothpick in the tropics. . . . Here, everything is furnished for you."

Ultimately, Burgdorfer says, it is not fancy facilities or great hiking and waterfalls that determine the fate of NIAID's Montana outpost. It's "the intellectual fascination" and the lab's ability to recruit and retain scientists who will sustain the fascination and serve as magnets, attracting ideas and collaborators from all over. RML has been for Burgdorfer what the unofficial slogan for the Bitterroot Valley claims the area is: "The Last Best Place." "I wouldn't trade this for any other area," Burgdorfer says, referring as much to the lab's research as the place where it is conducted. "I've gone abroad a lot (with extended stays in Egypt, London, and Czechoslovakia), "but I would always come back." ■



Celia Hooper

Willy Burgdorfer
"I would always come back."

ROCKY MOUNTAIN SCIENCE

continued from page 1

who have used careful cognitive testing to differentiate HIV patients with true AIDS dementia from those with other neurological deficits caused by opportunistic infections or other factors in the disease. Through long-term studies, they have collected blood and virus samples from living patients and brain samples from deceased participants. These materials have revealed that although almost 100 percent of patients die with active virus present in their brains, just 20 percent have AIDS dementia. Cloning of the virus from these patients has revealed that there are clear sequence differences in the virus from demented and nondemented patients. Because the indirect viral effects on neuronal cultures correlate with effects in

living patients, Chesebro is exploring, in vitro, what specific changes in HIV envelope sequence—or the host's response to the virus—result in damage to neurons. "It could be a combination of cytokines, lipids, and envelope proteins produced by infected microglia that leads to damage to neurons," Chesebro speculates.

Two other scientists in the LPVD interviewed by *The Catalyst*—Byron Caughey and tenure-track investigator Sue Priola—join Chesebro in his third interest in TSE diseases. While the three appear to be very collegial, they don't even start out with the same opinion of the prion hypothesis, namely that abnormal prion protein, PrP-res, is sufficient to transmit TSEs, which include bovine spongiform encephalopathy, scrapie in sheep and goats, and kuru and Creutzfeldt-Jakob disease in humans. Caughey comes closest to being a believer: "I don't be-



Celia Hooper

Nestled 'neath the Bitterroots, the RML parking lot is serene and spacious at 9 a.m.

lieve it's proven, but it might be the case," he says. Priola, a virologist, acknowledges that there is a lot of supporting evidence for the hypothesis, "But it is not entirely convincing. . . . It is hard to find viruses sometimes, but in this case, no one is even looking." Chesebro comes down gently on the side of the nonbelievers: "I'm not convinced that the transmissible agent is a protein only. In the case of the genetic TSE diseases, where people express mutant PrP genes, these genes may be a susceptibility factor, but by no means do I believe we know the agent. I be-

lieve the causative agent of TSE diseases is a virus; the fact that normal PrP interacts with PrP-res to form amyloid is like processes that occur in many amyloid diseases, including Alzheimer's. But in those diseases the protein alone won't transmit the disease," as seems to be the case in TSE diseases—at least under artificial conditions in which injection of the appropriate

PrP-res directly into the brains of animals will lead to disease.

One of the most important breakthroughs in TSE research was made in 1994 by Caughey, who first induced self-

propagating conversion of normally folded PrP to abnormally folded PrP-res (so called because it is resistant to proteases) in the test tube. This achievement was simultaneously an important proof-of-principle for the prion hypothesis and the basis for fundamental techniques for working with PrP. The lab is now exploiting these techniques in basic and applied research. Caughey used this approach to

demonstrate that the in vitro reaction is "incredibly specific." In some instances in the test tube, PrP-res derived from one species of animal will convert PrP



Celia Hooper

Sue Priola



Celia Hooper

Byron Caughey

derived from a different species—but only in instances in which the same is true *in vivo*, and cross-species transmission of disease is possible. The lab is finding that single-amino-acid differences between different species' strains of PrP are sufficient to block cross-species reactions. Now using infrared spectroscopy, Caughey has identified different β -sheet conformations in PrP-res that might account for different strains of TSE agents. He is now trying to increase the efficiency of the test-tube reaction so that a measurement can be made of whether new infectivity is generated by PrP-res formation. The TSE research group is also studying inhibitors of the reaction, including Congo red, sulfated glycans, peptide fragments of PrP, and phthalocyanines. These might yield clues to therapeutic targets in TSE diseases and possibly other amyloidoses.

Priola is using scrapie-infected cell cultures and the *in-vitro* reaction to study the control of the passage of TSE from one animal to another and to look at the effects of human familial TSE-associated PrP mutations. Working with mouse and hamster versions of TSE as models, Priola has pinpointed parts of the PrP amino-acid sequence that are critical in determining the compatibility of PrP isoforms from different species. In addition, Priola has described aberrations in the metabolism of mutant PrP molecules that may underlie pathogenesis in familial TSE diseases. Currently one of Priola's goals is to develop a diagnostic test based on Caughey's test-tube reaction that could be used to identify animals that have BSE very early, before they show behavioral signs of mad cow disease.

Marshall Bloom, also of the LPVD, has studied diverse aspects of the immunologically peculiar Aleutian mink disease parvovirus (ADV). ADV produces different types of disease in newborn kits vs. adult mink. Infected kits typically succumb to fulminant respiratory infection, similar to hyaline membrane disease of premature human infants. Adults develop a persistent infection, forming massive numbers of lymphocytes and extremely high concen-

trations of gamma globulin and antibody to the virus. Virus-antibody complexes deposit in the kidneys, leading to kidney failure and death.

Bloom expects various aspects of the ADV system could shed light on chronic infection states and autoimmune diseases—including human diseases such as lupus. In the mink system, the viral capsid plays a key role in the disease. In sharp contrast with other parvoviruses, "inoculating" mink with empty capsid of ADV not only fails to protect the animals—it actually leads to accelerated, hyperacute disease when the animals are challenged with live virus. Bloom's research group is now comparing nonpathogenic and pathogenic ADV isolates to understand precisely what structural features of the capsid convert the disease into such a bizarre killer. As with Dengue fever, a key to

the disease's pathogenesis is ADV's ability to infect macrophages in the presence of antibody, and Bloom and his colleagues are studying the mink's cytokine responses—especially an IL-6 homologue—for clues to this phenomenon. As much as he still has to learn, Bloom reckons ADV is the best-studied of all parvovirus diseases, and he values the collegial relations of a small field.

"The advantage of working on Aleutian mink disease is that everyone working on it in the world came out of or through my lab—all five of them!"

The research of **Tom Schwan**, acting lab chief for the Laboratory of Microbial Structure and Function (LMSF), carries on the historic focus of RML on blood-feeding arthropods and the pathogenic bacteria they transmit to humans. But he gives the work a 21st-century twist by applying contemporary techniques to understanding the bacteria's molecular adaptations as they move from the midgut, salivary glands, and other parts of cold-blooded ticks and fleas into a dramatically different environment: the warm bloodstream of mammals.

A primary interest for Schwan is in spirochetes: developing an improved



Celia Hooper

Bitterroot range serves as backdrop to RML animal facilities (left foreground).

blood test for Lyme disease and relapsing fever and understanding the biology of the spirochete inside the tick. Relapsing fever, like Lyme, results when ticks transmit a spirochete, *Borrelia hermsii*, to humans. Though uncommon, relapsing fever is an insidious foe. Ticks that transmit the bacteria are endemic to the mountains in the West and are "fast feeders" that typically attach to a host at night and complete their feeding in 10 to 90 minutes. Victims are unlikely to know they've been bitten or to attribute their flu-like symptoms three to 10 days later to a tick bite; thus, their doctors are unlikely to take a blood sample, which would reveal the spirochete in the blood. This first stage of the disease passes as antibodies clear the infection. But that is not the last of *Borrelia*. Some days later the bacteria turns to its genetic closet, stuffed with at least 40 different genes for outer surface proteins, switches to an antigenically fresh exterior, and again flourishes in the bloodstream, again making the victim sick. This process has been known to repeat itself up to 12 times. Schwan believes the best hope for a vaccine lies in the surface of the spirochete as it is first transmitted from the tick.

Another research interest for Schwan is how the bacteria that cause plague sense and adapt to the molecular world in their arthropod host—the flea. Key stimuli that turn off and on suites of genes in *Yersinia pestis* are temperature, oxygen concentration, pH, and the arthropod's ingestion of a blood meal. Work with RML postdoc **Joe Hinnebusch** and **Robert Perry** of the University of Kentucky in Lexington, published in *Science*, demonstrated that the bacteria must possess and activate a certain set of genes to successfully infect the flea. Schwan points out that the similar genes and processes—which may present attractive vaccine and diagnostic targets—are also likely to be present other disease-causing agents transmitted by arthropods.

LMSF tenure-track investigator **Patti Rosa** says that to begin to understand gene regulation and adaptation in *Borrelia burgdorferi*, the agent that causes Lyme disease, will first require devel-



Celia Hooper

Marshall Bloom

oping molecular tools for manipulating the spirochete's genome similar to tools that have made *Escherichia coli* and *Y. pestis* tractable. An important step is finding a plasmid that replicates reliably in the spirochete and can serve as a ferry for genes.



Celia Hooper
Patti Rosa

With a small set of genetic tools in hand, Rosa has begun to knock out genes to answer biological questions: What genes play a critical role in the ability of the Lyme disease spirochete to adapt to various environments? How does its gene expression change between tick and mammalian hosts?

Postdoc **Steve Porcella** works on bacterial expression and host response in vivo to spirochetes that cause Lyme disease, relapsing fever, and syphilis (*Treponema pallidum*). The latter work is daunting because the spirochete can only be grown in the rabbit testis and development of a molecular genetic system for manipulating the bacteria has proven intractable. The labile bacteria deteriorate rapidly outside of the rabbit testis, which Porcella uses as his model

for exploring how host and spirochete respond to one another. Porcella, a life-long rock-climbing and mountaineering enthusiast, says, "I like big challenges. Working with syphilis is a lot like climbing a big granite wall—it seems impossible at first, yet if you chip away at it, you eventually reach your goal." Another big challenge is a project perfecting what Porcella calls "bionic mice." These animals are implanted interperitoneally with an FM transmitter that provides an instantaneous and continuous record of the animals' activity and body temperature. The system produces an intimate record sensitive enough to demonstrate physiological effects of simply changing the animal's bedding material. If some technical bugs can be ironed out, long-term data from the bionic mice,



Celia Hooper
Steve Porcella

coupled with molecular immunology, could provide a uniquely complete profile of the infectious process for the spirochetes Porcella studies. Porcella adds that for a postdoc at RML, "the senior staff, the support staff, and the facilities—everything is the best. . . . The opportunities to try new, innovative science, or even risky approaches to age-old questions make it a real joy to work here. To me, this place really is Shangri-La." ■

—CH

RML Scientists Develop Anti-Rabies DNA Vaccine

RML scientists have developed a DNA vaccine against rabies that protected all of eight vaccinated monkeys against the disease. This is the first DNA vaccine to show complete protection in nonhuman primates against a virus that attacks the central nervous system.

"The vaccine worked beyond our wildest dreams," commented lead author Donald Lodmell, of the NIAID Laboratory of Persistent Viral Diseases, following publication of a report in the August issue of *Nature Medicine*.

Postdoc Nancy Ray made the vaccine from DNA encoding the surface glycoprotein of the rabies virus. Not only did the vaccine afford perfect protection against lethal doses of the virus, it elicited anti-rabies antibodies that neutralized a global range of rabies viruses, a result that suggests the vaccine will be effective worldwide ■

—from a press release by Laurie Doepel, NIAID

FACES OF SHANGRI-LA



Photos by Celia Hooper

MAKING THE SHORT LIST: HOW TO SUCCEED IN GETTING A JOB INTERVIEW BY REALLY TRYING

by Doug Loftus, NCI

If you've submitted papers for critical peer review, you know that it can be humbling and not a little anxiety provoking. What could be exponentially worse, however, is submitting not just a single paper, but



Fran Pollner

Barry Hoffer and Story Landis

yourself, in your job-seeking postdoc entirety, to the same kind of scrutiny—in other words, submitting your relevant life story to the powers that be as you vie with other candidates for plum positions in academic and corporate job markets.

Crafting a curriculum vitae (vital stats; an outline of accomplishments) and résumé (a more descriptive elaboration of that outline) that stand up to a rigorous, competitive review process can be daunting. To help NIH postdocs improve their chances of success, the NIH Fellows Committee, the Office of Education, and the Office of Research on Women's Health held a CV and Résumé Writing Workshop July 10 in the Lipsett Amphitheatre.

A capacity crowd heard the workshop leaders—NIDA Scientific Director Barry Hoffer, NINDS SD Story Landis, and Randall Kincaid of Veritas, Inc., a Rockville biotech company—hammer out their best advice on how to “make the short list”—be one of the handful of people, often among hundreds of applicants, to survive the first cut and be called in for an interview.

Nothing succeeds like success, so if your postdoctoral career has been legendary, you might have employers clamoring for you. But for the average, or “merely” above-average, candidate, a finely crafted application package is the key to getting your foot in the door. Even if you've done some high-profile work within your field, your application may be reviewed by several people who've never heard of you. As Hoffer suggested, “You sort of have to pretend you've come from Mars, and [all] they're going to know about you is what's in your résumé.”

Although specific application requirements vary with the position, an application should conform to the general format below. And unless an e-mail or HTML format is requested, materials always should be sent by regular U.S. mail.

Your package should include:

■ **A one-page cover letter**, briefly stating why you are writing and what you have enclosed. Avoid redundancy with other enclosed material.

■ **A CV**, consisting of: education (beginning with college degree), research and

teaching experience, any administrative experience, awards, professional society memberships, and grants (if any; postdocs early in their careers might consider applying for a K22 award; see <<http://www.nih.gov/grants/guide/rfa-files/RFA-ES-98-001.html>> for more details). Only professionally relevant items should be included.

As Hoffer noted, “The clock starts ticking in graduate school.” Thus, all awards and positions listed should be from graduate school onward. Be certain that honors or fellowships listed reflect competitive awards (the IRTA is not a competitive award; a FARE award is).

Landis also brought up the matter of “taste.” Using an example of an unnecessarily embellished CV, she pointed out elements that could be a turn-off to a committee member. For example, “Who's Who”-type listings are a bit on the “cheesy” side, she implied, and indiscriminate parading of awards may, to a reviewer, reflect an undesirable trait. Some audience members were dismayed that anyone should incur a penalty for receiving honors, highlighting the fact that there is an arbitrary element to the application review process—subjective judgments.

In general, Landis suggested, your CV is a high-maintenance item, requiring continual updating and shaping, so that it reflects only your most important accomplishments. “You have to think of your CV as a living organism, as a tree that you have to trim,” she advised.

■ **List of publications.** Putting your name in boldface type in your bibliography helps committee members quickly assess if your name is in the “right” place—first or last. Hoffer urged postdocs and their mentors to discuss authorship issues and, ideally, establish that one or two peer-reviewed papers will carry the postdoc as the first author. If you feel you may be deficient in this area, be sure to point out any papers in which you were a corresponding author or perhaps a second author but given an “equal credit shared with first author” footnote.

■ **Résumé.** This is an item on which opinions diverged. Hoffer suggested including a narrative, up to three pages, of your research experience that brings out additional elements that may not be apparent from your CV. This might include administrative duties, supervision of less experienced personnel, supplemental training, and perhaps engagements as a ple-

nary speaker at symposia. For an industry position, this type of narrative can be helpful to the employer and should be included. However, especially for academic positions, Landis advocated a more economical approach: Give them precisely what they ask for—no more, no less.

■ **Research statement.** (for academic jobs) and/or a description of technical skills (for industry). Again, what you send depends on what is requested. Usually this consists of a brief summary of your current work and plans for the future, including plans for funding if possible. Companies frequently do not ask for research statements, because they already have an agenda. According to Kincaid, biotech companies often are interested in what skills or expertise you bring to their efforts, including computer-related experience, and it helps to highlight these capabilities separately. Also, for any research position, include reprints of two or three salient publications.

■ **References.** If letters are requested, have them enclosed or sent under separate cover by referees as soon as possible. If names only are requested, three to five individuals should be listed, ideally including both thesis and postdoctoral mentors.

Finally, attention to production values is critical—eliminate typographical errors, and make sure that grammar and syntax are impeccable. With as many as 200–300 applications flooding academic departments each recruiting season, give search committee members the slightest excuse to can your application, and they will. They have to. For the sake of time and money, employers must limit the number of candidates they interview.

With a good record of research, some attention to detail, and perhaps a bit of luck, your application could end up in the small stack of five or six invitees. Then, all you have to worry about is your job interview. But that's another workshop (let's hope). ■

Need a Job? a Grant?

All NIH fellows are invited to attend a series of workshops on “What They Never Taught You in Graduate/Medical School.” All workshops will be held in Building 10, Lipsett Amphitheater from 8:30 to 11:30 a.m.

September 28, 1998: Job Hunting, Part 1
October 19, 1998: Job Hunting, Part 2
January 11, 1999: Oral Presentations
February 8, 1999: Writing Research Articles
March 8, 1999: Grantspersonship
May 10, 1999: Personnel Skills

RECENTLY TENURED

Toren Finkel received his M.D. and Ph.D. from Harvard Medical School in Boston in 1986. He completed a residency in internal medicine at the Massachusetts General Hospital in Boston and a cardiology fellowship at Johns Hopkins University in Baltimore before joining the NHLBI Cardiology Branch in 1992. He is currently a senior investigator and chief of the Cellular and Molecular Biology Section in that branch.

Atherosclerotic heart disease remains the leading cause of morbidity and mortality in the Western world. Over the past 20 years, many studies have demonstrated the role of blood pressure, smoking, cholesterol, and other factors in disease progression, but relatively little is known about how these systemic factors result in localized plaque formation.

Before the development of atherosclerotic plaque in both animal models and human subjects, however, there appears to be an increase in the production of reactive oxygen species (ROS) from the vessel wall. My lab has focused on how these ROS are generated and regulated in nonphagocytic cells and what intracellular signaling pathways they seem to regulate.

Early in our studies, we observed that vascular smooth muscle cells stimulated by platelet-derived growth factor (PDGF) produce a large and rapid but transient increase in intracellular H_2O_2 . We were able to demonstrate that this increase in ROS was essential for PDGF signal transduction and, in particular, for growth factor-stimulated tyrosine phosphorylation. Results from our lab and others have since suggested that the burst of ROS is not confined to smooth muscle cells or PDGF, but occurs with a variety of ligands in a multitude of cells.

We next were able to demonstrate the role of the small GTPases ras and rac1 in the regulation of ligand-stimulated ROS. This was particularly interesting because rac proteins were already known to regulate ROS production in nonphagocytic cells. Nonetheless, these results suggested that the ras superfamily of proteins might function to regulate the balance of oxidation and reduction, that is, the redox state, of the cell.

Not only does our work suggest that ROS play a role in growth-factor signal-

ing, we have also demonstrated that ROS serve as mediators of apoptosis. Using an adenovirus to deliver wild-type p53, we have demonstrated that p53 expression results in an increase in ROS, which is needed to initiate apoptosis. More recently, we have shown that ROS also mediate certain aspects of senescence.

Taken together, these results suggest that the redox state of the cell is actively regulated and plays an important role in a variety of pathways as diverse as growth, death, and senescence. The mechanism by which small diffusible molecules like H_2O_2 can regulate targeted pathways is not yet fully understood. We are currently seeking to identify specific intracellular protein targets of ROS. Furthermore, we hope to relate these findings back to the vessel wall to understand how continuously elevated concentrations of ROS contribute to atherosclerotic disease progression.



Fran Pollner

Toren Finkel

Klaus Gawrisch received his Ph.D. in physics from Leipzig (Germany) University in 1979. He received further training in membrane biophysics and nuclear magnetic resonance (NMR) at Leipzig University and at NIH—at DCRT and as a visiting scientist at NHLBI. In 1993, he moved to the NIAAA Laboratory of Membrane Biochemistry and Biophysics, where he now heads the NMR section.

My team investigates the influence of the lipid matrix on the function of neural receptor proteins, in particular, the influence of high concentrations of polyunsaturated fatty acids, such as the unsaturated docosa-hexaenoic acid (DHA, 22:6n3) with six double bonds. The phospholipids of brain synaptosomes and the retina contain 30 to 50 mol% DHA as fatty acids. Several lines of evidence suggest that high DHA concentrations are necessary to achieve full activity of certain neural membrane receptors.

I have applied recent developments in NMR spectroscopy to the study of membrane structure and dynamics to obtain a better description of membrane properties that modulate membrane receptor function. Modern NMR techniques require only milligram-size samples of

membrane material and are compatible with investigation of complex biological membranes containing mixtures of lipids and proteins at physiological conditions. With atomic resolution, we are able in many instances to pinpoint the location of membrane molecules in the lipid matrix.

For example, we determined that short-chain alcohols such as ethanol locate preferentially near the membrane-water interface and lower interfacial energy of lipids and proteins. These techniques enable a more detailed description of membrane biophysical properties, including parameters that describe the energy of elastic membrane deformation, that can be linked to the membrane receptors' structural transitions during excitation.

The alteration of membrane mechanical properties is one possible role of lipid polyunsaturation. There has been controversy concerning the nature of the perturbation of membrane elasticity induced by DHA chains. The six methylene-interrupted cis double bonds within DHA's 22-carbon unit reduce the number of degrees of freedom for structural transitions, a finding that has led some investigators to suggest that these chains have a specific, rigid conformation. However, this hypothesis is at variance with experimental results. We determined, for the first time, a large number of parameters that describe orientation and motion of individual DHA chain segments in biomembranes, and

we measured by X-ray diffraction average DHA chain length and the molecular cross-sectional area. The data indicated an unexpected high deformability of DHA chains. This information provided constraints by which to examine DHA conformations proposed by molecular modeling studies to determine their correlation with experimental data.

Our results suggest that DHA chains in membranes prefer looped conformations and undergo rapid structural transitions, providing increased flexibility to receptor-rich neural membranes. Moreover, our research is beginning to uncover a framework within which the biophysical properties and functions of membrane lipids can be understood in terms of their degree of unsaturation, a discrimination that nature clearly makes.



Fran Pollner

Klaus Gawrisch

James Kennison received his Ph.D. from the University of California, San Diego, in 1979 and did postdoctoral work at the Universidad Autonoma de Madrid, the University of Alberta in Edmonton, and the University of Colorado in Boulder before joining the Laboratory of Molecular Genetics of NICHD in 1987. He is now a senior investigator in the Section on Developmental Biology.

I have a long-standing interest in how cellular diversity is established and maintained. As a confirmed *Drosophila* geneticist, I have used the sophisticated genetics of the fruit fly *Drosophila melanogaster* to identify and characterize the genes involved in one particular developmental step, the specification of segmental identity in the fly. Segmental identity is specified by the homeotic genes, the *Drosophila* homologues of the HOX genes of vertebrates. Because the homeotic genes have 100-kb cis-regulatory regions that control their developmental expression patterns, a large number of proteins are required to specify and maintain expression. I have concentrated on identifying and characterizing two groups of genes that function to maintain patterns of gene activity, either repression or activation. These two groups of genes, the Polycomb and trithorax, are conserved between *Drosophila* and humans.

My colleagues and I have identified more than a dozen new Polycomb and trithorax group genes using genetic screens. We have cloned and characterized several of these new genes, including the *brhma* (*brm*) gene. We showed that the BRM protein functions as the ATPase subunit of a 2-megadalton protein complex. This complex is conserved from yeast to humans and appears to be a chromatin remodeling machine. We have shown that BRM is required to maintain expression not only of the homeotic genes but of several other important developmental genes as well. It is not required for expression of all *Drosophila* genes, however.

We are currently trying to understand what recruits this large protein complex to its target genes. We have identified putative *brm*-response elements in the cis-regulatory regions of two of the tar-

get homeotic genes and have used genetic screens to identify other proteins that interact with BRM in regulating these target genes. BRM appears to interact with different sets of proteins at these two cis-regulatory elements.

Complementing our work on the proteins that maintain transcriptional activation of the homeotic genes, we are now also identifying and characterizing proteins required to maintain repression of these genes. One of these new repressors appears to be part of a histone deacetylase complex, which suggests a role for histone deacetylation in maintaining repression of the homeotic genes.

We began exploring fruit fly development in the hope that our observations would elucidate how genes control human development. Because not only the homeotic genes but also the proteins that regulate their function appear to be conserved between flies and humans, we are finding that our hopes have not been misplaced. Moreover, the emergence of increasingly sophisticated molecular genetic approaches in *Drosophila* bolsters our confidence that this research will continue to expand our understanding of human developmental processes, both normal and defective.

Richard Maraia received his M.D. from Cornell University Medical College, New York, in 1985. He completed a pediatric residency at New York Hospital before coming to NIH in 1987, when he was jointly appointed by the Human Genetics Branch, NICHD, and the Interinstitute Medical Genetics Program as a medical staff fellow. In 1990, he became a founding member of the Laboratory of Molecular Growth Regulation, NICHD, where he is now a senior investigator.

My current research uses RNA polymerase (pol) III and its associated factors as a model to explore the mechanisms that control transcription in eukaryotes and to elucidate how the expression of certain small RNA genes—namely tRNA and Alu family retroposons—are regulated. Pol III also synthesizes a variety of other transcripts, including 5S rRNA and U6 small nuclear

(sn) RNA, but their promoter genes are organized differently from those of tRNA and Alu and engage different arrays of pol III transcription factors. Several viruses rely on pol III for the expression of their small RNA genes, most notably adenovirus, whose virus-associated [VA] RNA products modulate the host-cell translational machinery. A growing number of pathogenic viruses not only use pol III for expression of their genes, but also encode proteins that modulate certain host-cell pol III-associated factors.

Nearly one million Alu sequences constitute a complex family of mobile elements that “retro”-transpose through their small RNA transcripts, sometimes causing recognizable genetic disorders in humans. These sequences, like the family of tRNA genes, contain pol III promoters within their transcribed region, a feature that endows newly inserted copies with the potential for transcriptional competence. However, unlike other pol III-transcribed sequences, Alu elements are maintained in a transcriptionally inactive state, becoming activated by viral infection, heat shock, and translational stress. The mechanisms that regulate Alu transcription and the consequences of their expression are largely undefined.

Assembly of a transcription complex on the promoter of a target gene is a key determinant of eukaryotic gene transcription—but it is not the only one. My laboratory has shown that control can also occur at the levels of transcription termination and reinitiation. Efficient

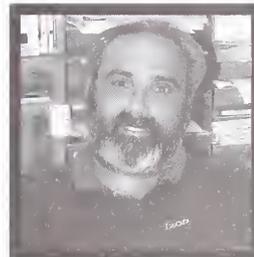
reinitiation is especially important for tRNA and 5S rRNA genes that must be transcribed at high levels. We have focused on the human La protein, an abundant nuclear phosphoprotein that is recognized as a self-antigen in patients suffering from autoimmune disorders such as systemic lupus erythematosus and Sjögren’s syndrome. We have shown that

La facilitates transcriptional termination and reinitiation by pol III. Moreover, as an RNA-binding protein that remains associated with nascent pol III transcripts after their synthesis, La also controls the post-transcriptional processing of these RNAs. We have shown that human La is phosphorylated on serine 366, an evolutionarily conserved casein kinase II phosphorylation site, and that this pro-



Fran Pollner

James Kennison



Fran Pollner

Richard Maraia

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cess can regulate La's ability to modulate transcription as well as RNA processing. Thus, the human La phosphoprotein can coordinate and regulate transcriptional and post-transcriptional steps in RNA biogenesis.

Our team has developed a pol III transcription-termination reporter gene in the fission yeast *Schizosaccharomyces pombe* for use in our continuing studies. We use a tRNA opal suppressor capable of suppressing a nonsense codon so that the mRNA can encode a colorimetric metabolic marker (Ade6-704). We plan to examine intracellular signals that can integrate the phosphorylation status of La with pathways relating to other aspects of cell biology and proliferation. Our goal is to use information gained from this system to advance our understanding of gene regulation and cell growth in humans.

Alex Martin received his Ph.D. from City University of New York in 1978. He did his postdoctoral work at NINCDS (now NINDS) on cognitive dysfunction in patients with Alzheimer's disease before joining the faculty of neurology at DoD's Uniformed Services University of the Health Sciences, where he concentrated on cognitive and motor dysfunction associated with different stages of HIV infection. In 1990, he joined NIMH and is currently a senior investigator in the Laboratory of Brain and Cognition.

My interests lie in the area of cognitive neuroscience, specifically as it relates to understanding perceptual and memory systems. My recent research at NIMH uses functional brain imaging technologies, positron emission tomography, and functional magnetic resonance imaging to evaluate the functional neuroanatomy of semantic memory—a specific type of memory system that includes the information stored in our brain about the meaning of words and objects.

Our earlier studies sought to clarify word comprehension and word-finding problems—such as an inability to retrieve object names—in patients with Alzheimer's disease. We learned that such difficulties are related to a loss of information about the features and attributes that define an object and differ-

entiate it from other objects within the same semantic category (for example, information about the features that distinguish a tiger from a leopard or a pair of pliers from a wrench).

Using functional brain imaging with normal subjects, we have been able to demonstrate that information about different types of features, such as an object's typical shape and color, is not stored as a whole unit in a specific place in the brain. Rather, this information is distributed in the brain and organized into a network of discrete cortical regions: Different features and attributes are stored near the regions of the brain that mediate perception of those attributes. Thus, for example, knowledge of object color is stored in a region of the brain adjacent to the areas that mediate perception of color, whereas knowledge about object motion is stored adjacent to areas that mediate motion perception. These findings demonstrate a close link between areas of the brain that mediate perception of different visual features (form, color, and motion) and the regions of the brain where we store these types of information. Additional studies have shown that a similar link exists between brain regions that subserve motor performance and stored knowledge about how objects are used. Thus, the organization of semantic information parallels the organization of the sensory and motor systems in the primate brain.

These studies have provided us with a deeper understanding of object-recognition, object-naming, and language-comprehension problems in a variety of brain disorders, including Alzheimer's disease and related dementias. They have also provided us with a framework for understanding the etiology of category-specific knowledge disorders that result from focal brain lesions (for example, how one patient can have problems naming and retrieving information about a single category of objects, such as four-legged animals, and another patient can have a deficit limited to naming and knowing about tools). This framework is based on the

premise that the distinction between members of different categories of objects depends on access to information about different types of features. More generally, these studies have provided us with a means for asking questions about the broader issue of how information is stored and organized in the human brain.

Stanko Stojilkovic received his Ph.D. in 1982 from the University of Novi Sad, Yugoslavia, where he was an assistant professor of animal physiology until joining the NICHD's Endocrinology and Reproduction Research Branch in 1985. In 1993, he became an investigator and head of the Unit on Cellular Signaling in that branch.

The research in my laboratory has focused on understanding the mechanisms and functions of calcium signaling in hypothalamic and pituitary cells.

Earlier investigations revealed that two calcium-signaling pathways operate in hypothalamic and pituitary cells: plasma membrane

(PM)- and endoplasmic reticulum (ER)-derived. I have shown that these cells express a set of voltage-gated channels that drive spontaneous action potentials, leading to cytosolic calcium fluctuations (the PM oscillator). The major thrust of these investigations was on the role of dihydropyridine-sensitive channels in calcium signaling and the mechanism of their activation and inactivation.

ER-derived calcium signaling in hypothalamic and pituitary cells is activated by several hypothalamic calcium-mobilizing agonists. Agonist-induced calcium release from the ER is mediated by inositol 1,4,5-trisphosphate and leads to frequency-modulated oscillatory calcium signaling in gonadotrophs (the ER oscillator) and to nonoscillatory amplitude-modulated calcium signaling in lactotrophs (lactotrophs and gonadotrophs are pituitary cells that produce hormones that control lactation and ovulation and spermatogenesis, respectively).

I have characterized the role of several intracellular elements involved in the regulation of the oscillatory vs. nonoscillatory calcium response, such as inositol 1,4,5-trisphosphate receptor channels and the ER calcium pump. I have also studied the coupling of PM



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Stanko Stojilkovic



Fran Pollner

Alex Martin

and ER oscillators during agonist stimulation. These experimental studies led to the development of quantitative mathematical models—one for the PM oscillator and one for the ER oscillator—as well as a coupled model that describes the effect of the PM oscillator on depletion and repletion of the ER calcium pool. Functional studies have shown that both hormone release and gene transcription can be activated by calcium-mobilizing agonists when the PM oscillator is rendered inoperative by the depletion of extracellular calcium. In the absence of an agonist, spontaneous activity of the PM oscillator is sufficient to trigger hormone release and early-response gene expression in lactotrophs but not in gonadotrophs.

Current investigations focus on two families of plasma-membrane calcium channels. We recently found that ATP-gated purinergic-receptor (P2X) channels are expressed in pituitary cells and have the capacity to modulate PM- and ER-derived calcium signals and secretion. The primary P2X gene transcripts in pituitary cells undergo extensive al-

ternative splicing, generating several isoforms. We have identified the amino-acid residues contributing to the desensitization of the P2X₂ subtype of these channels, or the protective attenuation of response during prolonged ATP stimulation. The finding that these residues are also expressed in all slowly (but not rapidly) desensitizing P2X channels suggests that a common mechanism controls the rate of cationic influx through these channels, a hypothesis that will be tested in the near future.

We recently identified a novel calcium-influx pathway in several excitable cells that is activated by depletion of the ER calcium pool in a manner comparable to that observed in nonexcitable cells. In neuroendocrine cells, these calcium-influx channels also depolarize the plasma membrane to generate action potentials or to increase the frequency of spiking in spontaneously active cells. Our current investigations are directed toward characterizing the electrophysiological properties of these channels in hypothalamic and pituitary cells, as well as the mechanism of synchronization of

calcium release from intracellular stores and action-potential-driven calcium influx.

Our recent finding that endothelin, unlike other calcium-mobilizing agonists, induces a prolonged inhibition of electrical activity—with associated decreases in calcium influx and cytosolic calcium, depletion of the ER calcium pool, and inhibition of prolactin release—piqued our interest. Preliminary pharmacological investigations suggest that a novel endothelin receptor is expressed in lactotrophs. We are now attempting to clone this receptor. Functional characterization and coupling of this novel receptor to intracellular messengers will follow.

Another of our objectives is to understand the link between the cellular functions and dynamics of calcium signaling in isolated and interconnected cells. The studies will focus on physiological requirements for the specific pattern of calcium signaling (oscillatory vs. nonoscillatory), the source of calcium (PM- and ER-derived), the threshold calcium concentration needed to activate a specific cellular process, and the role of calcium signals in synchronization of cellular activity among neural and nonneural networks. ■

INTEREST GROUP GAZETTE

A Cold Day with the Mitochondria

"Mitochondria: Genetics, Health, and Disease," an all-day minisymposium **December 2, 1998**, is being held in conjunction with a Wednesday Afternoon Lecture and is sponsored by the NIH Interinstitute **Mitochondria Interest Group (MIG)**. Lectures will be held at Masur Auditorium in the Clinical Center (CC); posters and exhibits will be displayed at the CC Visitor Information Center, CME credit is available.

Meals, breaks, and reception are sponsored by the Technical Sales Association. A block of rooms at a special meeting rate has been reserved at the Bethesda Ramada. Call 800-272-6232, or 301-654-2703, before November 9, 1998. Mention NIH Minisymposium, group # 6210.

Submit advanced registration via Minisymposium Web site at

<<http://www-lecb.ncifcrf.gov/~zullo/mig/DB/symposium.html>>

or via e-mail to: <zullo@helix.nih.gov> (deadline November 8) or regular mail to: Steven Zullo, Building 10, Room 2D54, NIH, Bethesda, MD 20892 (postmark deadline November 2).

An Organism for All Seasons

"Choosing an Organism: The Ins and Outs of Developmental Genetics in the Eukaryotic Hierarchy" is the theme of the fall-winter meetings of the **Genetics Interest Group**. The series is designed to help researchers select their model organism and includes speakers from NIDDK, NICHD, NINDS, NIDCD, and NHGRI. Meetings are held Tuesdays at 4:00 (except December 15, which starts at 4:30) in Building 49, Conference Rooms A & B.

■ September 15: Nematode ■ October 13: Zebrafish ■ November 10: Drosophila ■ December 15: Xenopus ■ January 12: Avian ■ February 9: Mouse ■ March 9: Human

For additional info, contact Beverly Mock at <bey@helix.nih.gov> or Lynn Hudson at <hudson@helix.nih.gov>.

RIGHT INTEREST GROUP WRONG CONTACT NAME

Please correct the spelling of my name as a contact for the **Image Processing Interest Group**.

—Benet Trus, CIT

Phone: 496-2250

E-mail: <trus@helix.nih.gov>



Virgil is amazed to discover that the secret ingredient of a successful *in vitro* transcription is a lobster.

CALL FOR CATALYTIC REACTIONS

In this issue, we are asking for your reactions in four areas: "Catalytic Cauldron," Research Festival ideas, achieving CV perfection, and "hot methods."

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 1, Room 209.**

In Future Issues...

- Al Graeff Helps CIT Find ITself
- Fogarty Scholars Link NIH Labs
- Y2K + U = X

1) The *Catalyst's* Editorial Advisory Board has urged us to present more science tidbits—along the lines of the Rocky Mountain Lab Science Sampler (this issue) or the pieces in the "Recently Tenured" section. What research subjects would you most like to read about in our upcoming "Catalytic Cauldron" section?

2) What innovations would you like to see in the 1999 Research Festival? What worked well (and not so well) in 1997 and 1998?

3) What additional suggestions would you have for postdocs preparing their CVs?

4) What would you like to see elucidated in a future "hot methods" article? What were the "hottest methods," ideas, or research you happened upon at the Research Festival, October 6–9?

The NIH Catalyst is published bimonthly for and by the intramural scientists at NIH. Address correspondence to Building 1, Room 209, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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