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Evans Medicine

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Boston University

EVANS MEDICINE

Evans Memorial Department of Clinical Research and Preventive Medicine

Sixth Annual Event

Research Day fosters spirited competition among participating young investigators

The most recent Research Day, co-sponsored by the Evans Department of Medicine and Boston University School of Medicine's Division of Medicine, marked the climax of one of the most strongly contested research competitions yet.

"There were supposed to be three prizes awarded," said Norman Levinsky, M.D., director of the Evans, in announcing the winners, "but the number of the abstracts and their excellence led the faculty committee that reviewed them to award five prizes instead."

The prizes, which carry a small monetary award, go to fellows in the Evans or in the BUSM Division of Medicine who are lead authors on abstracts submitted for the Research Day competition.

Among the other highlights of Research Day, held this past year on October 24, were lectures by two leading figures in medicine. Howard M. Temin, Ph.D., the Harold P. Rusch Professor of Cancer Research at the University of Wisconsin and co-winner of the 1975 Nobel Prize for Physiology or Medicine, gave the Evans Distinguished Basic Science Lecture. Dr. Temin, co-discoverer of the enzyme reverse transcriptase, spoke on "The Plasticity of the Retrovirus Genome." (For Dr. Temin's views on how the nature of retroviruses affects prospects for an AIDS vaccine, see page 6.)

The Distinguished Alumni/Alumnae Lecture was given by Judith L. Vaitukaitis, M.D., acting deputy director for extramural research resources at the National Center for Research Resources. Dr. Vaitukaitis, until 1986 a member of the Evans Section of Endocrinology, spoke on aspects of her research on follicle-stimulating hormone and other steroid hormones.

Following Dr. Vaitukaitis' noontime talk, which was the first event of the day, there was a poster session and luncheon in BUSM's Hiebert Lounge. There were a total of 78 presentations, a Research Day record, and the session drew a crowd of several hundred. Dr. Temin's address concluded the day's program.

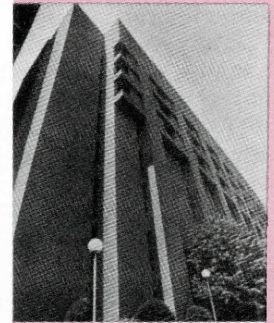
The first Research Day was held in the fall of 1985. The aim of the annual event is to both celebrate and promote the research programs of the sponsoring organizations.



Lead authors on winning Research Day abstracts were (from left), Drs. Conrad Cowan, Jerome Levine, Marcia Katz, Gil Frei and Kyran Bulger.

This year's five winning fellows were, Kyran Bulger, M.D., a member of the Evans Section of Medical Oncology; Conrad Cowan, M.D., Vascular Biology; Gil Frei, M.D., Renal; Marcia Katz, M.D., Pulmonary; and Jerome

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The
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Message from the director

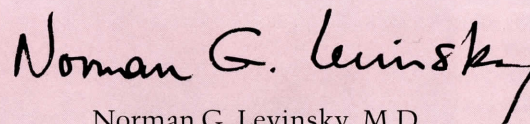
New research and training program

The Evans has been a bastion of clinical research for 78 years. During most of that period, the Evans staff consisted of a relatively small number of investigators focused largely on patient-centered clinical research programs. As in other academic departments of internal medicine, over the past two decades research at the Evans has increasingly involved teams of M.D. and Ph.D. investigators using the concepts and techniques of molecular biology to supplement the approaches of organ and whole animal physiology, clinical epidemiology and clinical trials that made up the spectrum of clinical research in the past. In addition, the size of the Evans/Department of Medicine staff has increased dramatically, to its current level of about 100 at the Evans itself, and over 160 if one includes the closely linked programs at Boston City Hospital and the Boston Veterans Administration Medical Center.

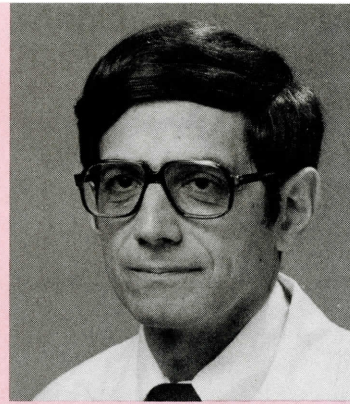
Last year I convened a faculty planning committee to review the research and training environment of the Evans. This committee, chaired by David Salant, M.D., chief of nephrology, developed an innovative and exciting plan to build our established programs to a new level of excellence and to enhance the research and training environment of the Evans. I obtained the support of the Evans Board of Control to devote up to \$500,000 a year to this new program. With the help of a faculty committee, I am currently reviewing candidates to direct the program.

We intend to create an environment especially attractive for the advanced training of postdoctoral fellows, M.D. and Ph.D. alike. Core courses, visiting scientists, hands-on methods courses, revised research seminars, possibly expanded central research facilities, etc., will provide an underpinning for our expanded training program. The director and a standing faculty committee will promote interactive research within the department (and with other departments, as appropriate), and encourage the rigorous intellectual atmosphere associated with basic scientists and the sense of relevance to clinical needs characteristic of M.D. investigators.

We are currently recruiting candidates for Evans-guaranteed fellowship stipends. The array of new activities will be available not only to the specially designated "Evans fellows" but to all postdoctoral trainees at the Evans, including those recruited by traditional routes via the individual subspecialty sections. These are exciting but difficult times for clinical and basic scientists because ideas and talent exceed resources. We are fortunate that, due to Mrs. Evans' original vision, we have internal funds to help us meet the challenge of reaching a new level of excellence.



Norman G. Levinsky, M.D.



Dr. Norman G. Levinsky

'We intend to create an environment especially attractive for the advanced training of post-doctoral fellows, M.D. and Ph.D. alike.'

Research Day

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Levine, M.D., Research Immunology. Their abstracts were:

Bulger, K., Pihan, G., Nichols, J., Murphy, J., McCaffrey, R.: PHA induces high affinity IL-2 receptors and is a potential biological response modifier for an IL-2/diphtheria hybrid toxin;

Cowan, C., Cohen, R.: Bradykinin relaxes pig coronary artery by two distinct mechanisms;

Frei, G.L., Alexander, E.A., Schwartz, J.H.: Pathogenesis of experimental genetic hypertension: role of Na/H exchange;

Katz, M.F., Duquette, D.M., Farber, H.W., Cruikshank, W.W., Beer, D.J.: Elaboration of a novel T-lymphocyte mitogen by aortic endothelial cells; and

Levine, J., Hartwell, D.W., Frenzl, G., Fenton, M., Beller, D.: Aberrant macrophage cytokine expression characterizes several autoimmune-prone mouse strains.

Alumnae Profile

A basic researcher committed to making sure laboratory findings are applied in the clinic

Judith L. Vaitukaitis, M.D., says she set her basic career course when she was about 10 years old.

"I was always fascinated by science, and I knew I'd like working with people," she says, "so I decided I wanted to combine research, teaching and patient care even before I knew you could do that."

For Dr. Vaitukaitis, currently the acting deputy director for extramural research resources of the National Center for Research Resources, a key step toward this goal was to enter Boston University School of Medicine. And it was there, during her initial year, that she was introduced to the field she would soon adopt as her own.

The school, she says, offered an unusual course that covered biochemical, biophysical and clinical aspects of endocrinology. "I was fascinated by endocrinology," she says, "because it seemed to me to be right at the interface of science and medicine."

Her graduation in 1966 ended what would be the first of three associations with Boston University Medical Center, as she left to intern at New York's Bellevue Hospital. Within two years, though, she was back, drawn by an experimental program set up by Robert W. Wilkins, M.D., former director of the Evans.

The idea was to encourage M.D.s to pursue research while continuing their residency training. Dr. Vaitukaitis recalls having had her doubts, but says these were allayed in the course of a two-hour phone conversation with Dr. Wilkins. "There was no opportunity I was aware of that was quite like this one in terms of flexibility," she says.

So, she joined the Evans as a resident in internal medicine and a fellow in the laboratory of James C. Melby, M.D., now head of the Section of Endocrinology. By this time, Dr. Vaitukaitis was committed to reproductive endocrinology. This was then a largely unexplored area, and in setting out to see what light she might be able to shed on the subject, the young investigator soon realized that it could be slow going.

"If you were measuring hormones," she recalls, "it would take two weeks working at the bench to do 25 determinations. You could do 2,000 or so in the same period of time today. And if a contaminant got into the chemicals you were using, all your efforts would be wiped out."

By working long hours, though, she was able to make valuable contributions to the field. Among them was the discovery that ACTH — adrenocorticotrophic hormone — does not, as had been thought, regulate the output of certain major products of the adrenal cortex.

In 1970 Dr. Vaitukaitis left again, this time to take a position at the National Institutes of Health. Four years later, however, she returned once more, rejoining the Section of Endocrinology and also assuming the title of associate professor of medicine at Boston University School of Medicine (BUSM).

It was this phase of her career that cemented her reputation as one of the nation's top endocrinology researchers. Among her major achievements, says Dr. Melby, was describing the hormonal system that underlies the menstrual cycle. "Her figure showing the roles of luteinizing hormone, follicle-stimulating hormone and other hormones in this cycle is in every endocrinology textbook," he says. Equally important, he says, was her discovery of a simple technique for measuring hormone levels in the bloodstream.

Dr. Vaitukaitis' work contributed not only to the understanding of hormonal function but also to clinical medicine. Dr. Melby notes that her studies of polycystic ovary syndrome, whose symptoms include disruption of the menstrual cycle, led to an effective treatment for the condition. Similarly, her discovery that certain cancers secrete measurable amounts of the beta subunit of human chorionic gonadotropin (hCG) — a hormone best known for its role in pregnancy — led to new prognostic tests for these malignancies.

Dr. Vaitukaitis says she sometimes is surprised at how clinically relevant her re-

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Dr. Judith L. Vaitukaitis

'I was fascinated by endocrinology, because it seemed to me to be right at the interface of science and medicine.'



Dr. Vaitukaitis with her former lab director, Dr. Melby (center), and Aram Chobanian, M.D., dean of Boston University School of Medicine.

Dr. Vaitukaitis

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search has turned out to be. She notes, for example, that the applications of her hCG research "have gone way beyond anything we'd initially imagined."

On the other hand, as someone who continued an active practice in addition to running a large-scale research program, she says she always was eager to exploit the clinical potential in research findings. Indeed, while with the Evans she took a formal role in promoting that aim by heading BUSM's General Clinical Research Center (GCRC), a federally backed enterprise whose mission includes transferring research findings from the lab to the bedside.

In 1986, Dr. Vaitukaitis was offered the chance to oversee the GCRC program nationwide for the National Institutes of Health. "It was a hard decision," she says, "because I loved doing research." On the other hand, she was convinced she could help boost the status of

clinical research within the overall universe of biomedical research.

Today, Dr. Vaitukaitis remains head of the GCRC program as well as serving as deputy chief of the Center for Research Resources. It makes for a hectic existence, she concedes, but she adds that there are compensations. "For me, having the chance to see all this work that's at the forefront of biomedical research is like being in a candy store," she notes.

Dr. Vaitukaitis also believes her research experience has enhanced her effectiveness in her current role. "I find I can sometimes help investigators identify problems they don't even know exist," she says, "and can help them prevent those problems from derailing their work."

She adds, however, that there are times when she looks back with nostalgia on her days as a young investigator at the Evans and NIH. "That was probably the happiest period of my life," she says, "because I was able to spend most of my time in the lab. If I'd been independently wealthy, I would have been happy to do it for free."

Her discovery that certain cancers secrete measurable amounts of human chorionic gonadotropin led to new prognostic tests for these malignancies.

Evans/Transition

This year's chief resident is Douglas Mesler, M.D. A graduate of the University of North Carolina School of Medicine, he is specializing in internal medicine and plans a fellowship in nephrology when he finishes his residency.

The new Evans interns, and the medical schools from which they graduated, are:

Lauren Abbate, M.D., Tufts
Alan Berger, M.D., Jefferson University
Steven Brandwein, M.D., Northwestern
Megan Callahan, M.D., Boston University
Steven Cohen, M.D., Georgetown
Paul Conrad, M.D., University of Medicine and Dentistry of New Jersey
Robert DeBiase, M.D., New York Medical College
Alexis Fenton, M.D., University of Texas at Galveston
Ann Sophie Gadenne, M.D., Boston University
Subhash Gumber, M.D., University of Massachusetts
Andra Ibrahim, M.D., University of Minnesota
Mark Joseph, M.D., Georgetown
Donna Katcher, M.D., Boston University
Doreen Konik, M.D., New York University
Patricia Koury, M.D., University of North Carolina
Frannie Kronenberg, M.D., University of Connecticut
John Mashakian, M.D., State University of New York at Stony Brook
Sandra Quintero, M.D., New York University
Ruth Ann Ross, M.D., Bowman-Gray School of Medicine, Wake Forest
Richard Siegel, M.D., Albany Medical College

Margaret Vallen, M.D., Medical College of Pennsylvania.

Last year's graduates, their new institutions and their subspecialties, are:

Scott Beau, M.D., Washington University (cardiology)
Anthony Cannistra, M.D., the University Hospital (cardiology)
Lauralynn Cannistra, M.D., the University Hospital (cardiology)
Stephen Franklin, M.D., the University Hospital (cardiology)
Thomas Greenough, M.D., University of Massachusetts (infectious diseases)
Suzy Kim, M.D., Emory University (gastroenterology)
William King, M.D., the University Hospital (gastroenterology)
Joanne Linevsky, M.D., the University Hospital (gastroenterology)
Lisa Mendes, M.D., the University Hospital (cardiology)
David Porter, M.D., Brigham and Womens Hospital (hematology/oncology)
Howard Safran, M.D., the University Hospital (hematology)
John Saltzman, M.D., New England Medical Center (gastroenterology)
Daniel Sternberg, M.D., National Jewish Hospital (allergy/immunology)
John Wilson, M.D., Duke University (cardiology).

Noteworthy

Eight new staff members have joined the Evans over recent months. Four are members of the Section of Cardiology, two of the Section of Medical Oncology, and one each of the Pulmonary and Renal sections. The new members are:

Bruce Bergelson, M.D., Cardiology — A native of New Jersey, Dr. Bergelson received his bachelor's degree from the University of Pennsylvania, and his medical degree from that university's school of medicine. He did his residency in internal medicine at Boston City Hospital, and was a fellow in cardiology at the Evans and the University Hospital prior to being named a staff member in that specialty. His experience includes working as a cardiologist at a medical center in the Chinese city of Dalian.

Stuart James Bresee, M.D., Cardiology — Dr. Bresee, born in Oak Ridge, Tenn., received his bachelor's degree from the University of Tennessee, and his medical degree from Emory University School of Medicine. The new staff member did his residency at Boston City Hospital. He worked for three years as an internist at a rural health clinic in Tennessee prior to accepting a fellowship in cardiology at the Evans and the University Hospital in 1987.

Kyran N. Bulger, M.D., Medical Oncology — Born in Dublin, Ireland, Dr. Bulger received both his bachelor's and medical degrees from Trinity College of the University of Dublin. He interned at Dublin's St. James Hospital and then became a resident at the University of Dublin. Dr. Bulger accepted a fellowship in medical oncology at the Evans and the University Hospital in 1987. Among his interests are the use of computers in cancer care and research.

Jesse W. Currier, M.D., Cardiology — A native of New Hampshire, Dr. Currier was graduated from Dartmouth College and received his M.D. from the Dartmouth Medical School. He interned and did a residency year at the Dartmouth-Hitchcock Medical Center in Hanover, N.H., and completed his residency at Boston's Beth Israel Hospital. Dr. Currier became a fellow in cardiology at the Evans and the University Hospital in 1986. Among his research interests are methods of preventing artery restenosis following angioplasty.

Ravin Davidoff, M.D., Cardiology — Dr. Davidoff was born in Johannesburg, South Africa. He received both his undergraduate and medical degrees from the University of Witwatersrand in South Africa, and did an internship and residency year in hospitals in that country. He subsequently completed his residency at Boston City Hospital, where he was chief resident in 1984-85. After a fellowship in cardiology at the Massachusetts General Hospital, Dr. Davidoff became a staff cardiologist at the Veterans Administration Medical Center in Albany, N.Y. Among his research interests is the use of echocardiography in assessing the damage done by heart attacks.

Michael A. Shia, Ph.D., Renal — Dr. Shia received his B.A. degree from Reed College in Oregon, and his Ph.D. in biochemistry from Boston University. Following his doctoral training he spent five years as a fellow at the Whitehead Institute for Biomedical Research in Cambridge, Mass. While there, Dr. Shia developed a system for studying the assembly, structure and functional relationships of complex cell-membrane receptor proteins.

Mary C. Williams, Ph.D., Pulmonary — Dr. Williams received her bachelor's degree from the University of Illinois and her doctorate from the University of California at San Francisco (UCSF). Following her graduation from the latter, she held several positions at UCSF, and in 1984 was named professor of anatomy at the school. She was a visiting professor at Harvard Medical School in 1988-89. Dr. Williams has held numerous important positions in pulmonary medicine, including membership on the Pulmonary Diseases Advisory Committee of the National Institutes of Health and chair of the 1982 Gordon Conference on Non-ventilatory Functions of the Lung. Dr. Williams, currently co-editor of the *American Journal of Respiratory Cell and Molecular Biology*, has extensively explored the nature and role of Type II alveolar cells in the lung.

Yuk-Chor Wong, Ph.D., Medical Oncology — Born in Hong Kong, Dr. Wong received his bachelor's degree from the University of Toronto and his doctorate from Harvard University. After graduating from Harvard in 1985, he accepted a research fellowship at the Dana-Farber Cancer Institute. In 1989, he became a research associate in medical oncology at the Evans and the University Hospital. Dr. Wong's research interests include the regulation of gene expression, and differentiation of normal and transformed epithelial cells.

Nobelist

Continued from page 6

protein. Like all the genes in a retrovirus, the gene for this protein is mutation prone. Beyond that, there is evidence that even vaccines targeted to specific sub-segments of such a protein may have to accommodate changes anywhere in the protein's gene.

"It appears," he says, "that changes in one region result in changes in others, so the whole gene is important."

Realities such as these make Dr. Temin cautious in appraising the outlook for an effective vaccine. "I'd say there's a 50-50 chance of developing such a vaccine," he says, "but we don't know enough yet to say even that with much assurance. It might take 5 to 10 years before we can tell whether a vaccine is possible."

Evans Memorial Department
of Clinical Research
The University Hospital
88 East Newton Street
Boston, MA 02118-2393

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Nobelist Temin sees retrovirus mutability as a major barrier to an AIDS vaccine

Although many have suggested that the AIDS virus represents a tough challenge for vaccine developers, Howard M. Temin, Ph.D., speaks with special authority on the topic.

Dr. Temin, the Harold Rusch Professor of Cancer Research at the University of Wisconsin, has studied retroviruses — a category that includes the human acquired immunodeficiency virus (HIV), the cause of AIDS — for more than 30 years. His lab's work, with that of other labs, shows that such viruses generate very high rates of genetic variation. This translates into a high rate of evolution, says Dr. Temin, which in turn means that "when there are new opportunities for a virus, a retrovirus is often able to take advantage of them."

The genetic changes in these viruses take one of two basic forms. In one — by far the rarer of the two — the virus genome picks up genetic material from the host organism. If that material turns out to be a gene with certain types of properties, the result may be a new kind of cancer-causing virus.

On the other hand, the genetic changes may not involve the host's DNA, but rather mutations within the virus's own genetic material. Changes of this type can occasionally produce a new kind of virus able to infect a human cell, as HIV does. "When that happens, the result may be a virus that causes AIDS," notes Dr. Temin.

Retroviruses contain only RNA, the so-called messenger molecule, not DNA. The genetic mutations such viruses undergo almost always occur during the phase when their RNA is being reverse-transcribed into DNA prior to becoming part of the host's genome. This is the process catalyzed by reverse transcriptase, the enzyme whose discovery led to the Nobel Prize for Dr. Temin and for another scientist working independently, Dr. David Baltimore. It also is turning out to be a process marked by a massive potential for mutation.

"If you take a regular retrovirus," says Dr. Temin, "and ask how often it varies in the

course of a single replication, you find that about two percent have RNA deletions and seven percent have base-pair substitutions." There are other minor sources of genetic alteration as well.

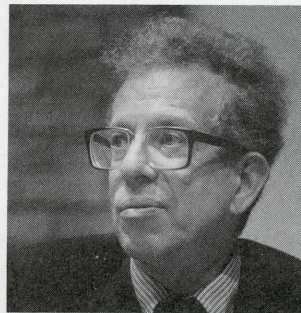
But by far the most critical process in making for a mutable genome is a phenomenon called recombination.

In recombination, the virus's replication machinery works together with that of the cell to produce new DNA based on stretches from two different virus RNAs. This occurs, says Dr. Temin, when the growing DNA strand "jumps around" from one retrovirus RNA genome to another in the process of adding new bases.

What would explain such unusual behavior? Dr. Temin thinks that, in part, it's a repair mechanism. "We believe the primary role of recombination is to compensate for breaks in the RNA," he says. Dr. Temin and his associates, though, have discovered another form of recombination that occurs even when there are no RNA breaks.

Recombination, when added to other sources of genetic alteration, means that retroviruses have an astounding capacity for generating genetic changes. "We estimate that roughly half of retrovirus replications produce altered progeny," says Dr. Temin.

In the context of developing a workable vaccine to a retrovirus-induced disease such as AIDS, this may spell serious trouble ahead. Much of the vaccine work focuses on the HIV's outer coating — its so-called envelope



Dr. Howard Temin

Evans Medicine is published by the Evans Memorial Department of Clinical Research and Preventive Medicine at The University Hospital, a member of Boston University Medical Center. Editor is Jay D. Coffman, M.D., associate director of the department; associate editor is Richard P. Anthony. Staff designer is Catherine LeBlanc. *Evans Medicine* is produced by Boston University Medical Center's Office of Publication Services, Owen J. McNamara, director. Send any correspondence to the Evans Memorial Department of Clinical Research, 88 East Newton Street, Boston, MA 02118. Norman G. Levinsky, M.D., is director of the department.

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