1984

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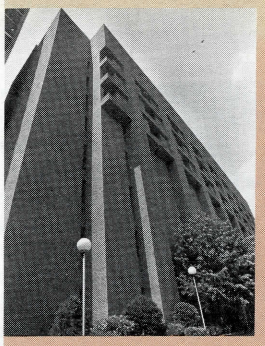
EVANS MEDICINE

Evans Memorial Department of Clinical Research and Preventive Medicine



Volume 1, Number 1
Fall 1984

The Evans has established a new Section of Biomolecular Medicine to help strengthen the bridge between basic and clinical research. See page 4.

John R. Murphy, Ph.D., head of the newly formed Biomolecular Medicine Section of the Evans, examines an autoradiograph of a new form of gene that he and his associates have created.

Tracking the proteins that enable T-cells to amplify their effects

Immune responses depend to an extraordinary degree on the ability of individual T-lymphocytes to amplify their effects.

This is accomplished partly by clonal expansion of individual cells: The T-cells responsive to an antigen produce lymphokines that stimulate cell division.

Equally significant, though, is the fact that sensitized T-cells are able to activate other white-blood cells. These may include not only macrophage-monocytes and polymorphonuclear leukocytes, but also other T-cells. In fact, non-sensitized T-cells are the main participants in many T-cell-mediated inflammatory responses, according to Evans investigator David M. Center, M.D.

"If you take a typical T-cell response to a transplanted kidney, for example, or poison ivy, you'll find that only between 5 and 10 percent of the cells involved are specifically sensitized to the antigens," said Dr. Center. "The rest were activated by lymphokines secreted by the sensitized cells."

The way in which some T-cells attract and temporarily hold other cells, however, is poorly understood. These interactions are the main research interest of Dr. Center, a member of the Evans Pulmonary Medicine Section, head of the Allergy Unit at University Hospital and an associate professor of medicine at Boston University School of Medicine.

"We're looking at the ability of certain T-cell subsets to secrete various types of lymphokines," said Dr. Center, "and trying to determine what effect these lymphokines have on the cellular makeup of T-cell-mediated immune responses.

"For example," the investigator went on, "it is well known that the concentrations of T-cell subsets can vary greatly in different immune responses. You can have one type of response which is very rich in, say, helper T-cells, and another that is enriched for suppressor cells."

Yet paradoxically, noted Dr. Center, responses to various antigens may be difficult to distinguish in pathological terms. "If you were to implant four different kidneys in

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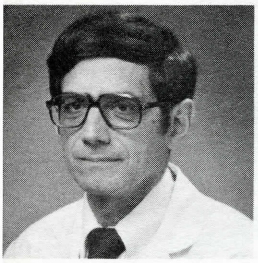
UNIVERSITY HOSPITAL
at Boston University
Medical Center

From the Evans Director



When the Evans was founded in 1912, its research staff of 10 all worked in the original Evans building. Communication among its investigators must have been easy. Even at its golden anniversary in 1962, research faculty had increased only to 20, most of them still housed in the (second) Evans building. As a new member of the staff at that time, I was reasonably well in touch with what was going on at the Evans.

However, in parallel with the rapid growth of Boston University Medical Center and of academic activities as a whole, the Evans staff has doubled and doubled again over the past two decades, to its current roster of 80 to 90. Over the same period, the number of trainees has expanded proportionately. This much larger staff has spread beyond the confines of the (third) Evans Building. Our growth, together with the increasing specialization of research, has made it hard even for those active at the Evans to know what's happening here.

Until now, there has been no way to keep the hundreds of former trainees and staff aware of goings-on at the Evans. This newsletter is an attempt to let our graduates and our friends know about key current events at the Evans: new staff and areas of research, changes in our training programs, news of ongoing activities. We hope you will enjoy *Evans Medicine*, and we welcome feedback.

When the Robert Dawson Evans Memorial Department of Clinical Research and Preventive Medicine—to give it its full official name—was established in 1912, it was one of the few institutions of its kind. Clinical investigation was under way in a number of other centers but separate departments of clinical research were rare. The first building embodied the key elements of Maria Antoinette Evans' remarkably foresighted vision. To quote from the description of the institution's first director, Dr. Frank C. Richardson: "The function of the building is not confined to that of a hospital proper but is divided into three different services. On the main floor...is a large lecture hall...in which popular lectures on hygiene...may be delivered. The fourth floor...contains seven large laboratories for special research. In connection with these laboratories the second and third floors are divided into wards and private rooms, in which those requiring a special study may be cared for."

Thus, from the beginning the purpose of the Evans was laboratory research intertwined with the clinical care of patients, with the intent of bringing advances in medical knowledge to the public. The first building was physically attached to Boston University School of Medicine, emphasizing the close relation of the Evans with education and with the School. As Boston University Medical Center has grown, the Evans has remained a fully integrated member of the Center community. The Evans is not an endowment or a building but an idea, as first defined by the deeds of gift from its donor, Mrs. Evans: support for excellent clinical research, devotion to "truth above everything" (her motto) in finding the causes of human diseases with the ultimate goal of preventing them. We're still working to meet Mrs. Evans' mandate!

Regards from the Evans,

Norman G. Levinsky

Norman G. Levinsky, M.D.

For Maria Antoinette Evans, the basic goal was excellent clinical research that would eventually lead to the prevention of diseases.

'From the beginning the purpose of the Evans was laboratory research intertwined with the clinical care of patients...'

The original Evans Building as it appeared early in its existence. The building, dedicated in 1912, now houses administrative offices of Boston University School of Medicine.

T-cells...

Continued from page 1

me," he explained, "the chances are the major T-cell populations in the inflammatory reponse to all four would be similar even though the antigens involved are obviously very different."

In exploring the mechanisms underlying T-cell responses, Dr. Center and his associates began by seeking to isolate and purify T-cell lymphokines that attract other T-cells, and others that immobilize such cells at the sites of inflammations.

The investigators were aided by the early discovery of ways to stimulate T-cells to produce only a handful of lymphokines, not the 80 to 100 typically produced by a cell in response to an antigen.

"We identified a series of stimuli that will cause T-cells to produce only seven or eight lymphokines," Dr. Center explained. "One of the stimuli with which we've had the most success is histamine. That raises some interesting issues about the biologic links between immediate allergic reactions, in which histamine often plays a key part, and delayed reactions, which often are dominated by T-cells."

So far, said the investigator, his group has purified one lymphokine, is close to purifying another and is making progress on a third. The lymphokine they have purified is a chemoattractant that is produced by a group of cytotoxic/suppressor T-cells, and that targets certain helper/inducer cells. The other two lymphokines are of the type that immobilizes non-sensitized T-cells.

Through their experiments with the three proteins, the investigators have begun to illuminate various aspects of the way in which sensitized T-cells enlist their non-sensitized counterparts in a response to inflammation.

For one thing, said Dr. Center, it is clear that the chemoattractant they have purified, LCF_{56} (lymphocyte chemoattractant factor, molecular weight 56,000 daltons), acts at very low concentrations.

"The concentrations are equivalent to the concentrations at which hormones act," said the investigator. "Nevertheless, the target cells are able to follow the concentration gradient—and this usually means penetrating various barriers, since the target cells come from the bloodstream or the lymphatics."

The research group also has looked at how the immobilizing lymphokines work.

"We have found that these immobilizing lymphokines are highly effective at trapping their target T-cells," said Dr. Center, "but that they don't seem to interfere with normal cell functions. The affected cells are still able to proliferate, and to synthesize their own proteins.

"We also found that when we wash the cells away from the proteins that immobilize them, the cells regain the ability to move. This implies that they're then available to be attracted to the site of another inflammation."

Dr. Center in one of the labs involved in the T-lymphocyte research. (Photo by Bradford F. Herzog)

Besides exploring the nature and functions of the three lymphokines, the investigators also have gained insight into the overall structure of the T-cell-mediated response system. Even when looked at solely in terms of T-cell/T-cell interactions, the system is tremendously complex, suggested Dr. Center.

In the first place, he noted, since not all T-cells produce all lymphokines, the lymphokines generated in any given response reflect the types of T-cells drawn to a specific antigen.

A T-cell's output of lymphokines, moreover, depends not only on its own nature but also on the antigen involved. "It appears that T-cells are preprogrammed to produce certain lymphokines in response to certain antigens, much as B-cells are preprogrammed to produce a single immunoglobulin," said Dr. Center.

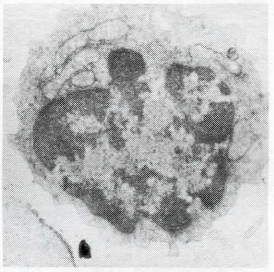
Considering the vast number of potential antigens—and the fact that the T-cell-mediated response to an antigen depends not only on the protein output of the sensitized T-cells but also on the nature of the target T-cells—the potential for highly individualized responses to inflammation would seem great.

In fact, suggested Dr. Center, the phenomenon of the response that is dominated by one T-cell subset reflects this complexity.

"If someone is infected by a tuberculosis mycobacterium," he said, "and if the T-cells sensitive to the bacillus in that person happen to produce lymphokines that target helper cells, then the response will be dominated by helper cells."

From the standpoint of clinical applications, of course, the T-cell-mediated responses that are of most immediate concern are those in which the response itself is the source of the pathology. The response to poison ivy is one example, said Dr. Center.

"The response to poison ivy is a specific, T-cell-induced response," he said. "If you could identify the proteins that attract T-lymphocytes to the site exposed to the allergen, you might be able to find some way of blocking their effects on the target cells." □



A human T-lymphocyte migrating through a nitrocellulose fiber. (Transmission electron micrograph by Charles Vacarro, M.S., and David Center, M.D.)

'It appears that T-cells are preprogrammed to produce certain lymphokines in response to certain antigens, much as B-cells are preprogrammed to produce a single immunoglobulin.'

Biomolecular Medicine Section is established

A new Section of Biomolecular Medicine has been established within the Evans.

Heading the section is John R. Murphy, Ph.D., who previously was an associate professor of microbiology and molecular genetics at Harvard Medical School and the Lawrence J. Henderson Associate Professor of Health Sciences and Technology in the Harvard-MIT Program in Health Sciences, Technology and Management. Dr. Murphy's research interest is the potential treatment of disease with "tailored" molecules; for example, he is seeking to develop model systems for combining altered diphtheria toxin and hormones so that the toxin can be specifically delivered to malignant cells.

Besides heading the new section of the Evans, Dr. Murphy has been named a research professor of medicine and a research professor of biochemistry at BUSM.

The aim of the new section is to help bridge the gap between basic biomedical science and the clinical research that is the chief focus of the Evans.

"We have excellent basic science departments within this Medical Center, and our department has very productive relationships with them," said Norman G. Levinsky, M.D., the Evans director. "The new section is in no sense meant to be a substitute for those departments, but rather is meant to create a closer connection between basic research and clinical research."

That intention will be reflected in the appointments made to the new section. The aim is to find investigators who are interested in basic science, but whose work also has direct clinical relevance.

"We were exceptionally pleased to get Dr. Murphy," added Dr. Levinsky. "His work uses the techniques of molecular biology to develop approaches to therapeutic problems that are of the highest importance. That is exactly the kind of investigator we had in mind when we outlined the requirements of this new position."

Eventually, the section will have four to five faculty-level members. Right now, the other faculty-level member besides Dr. Murphy is James A. Burton, Ph.D., formerly of Massachusetts General Hospital and Harvard Medical School. Dr. Burton also has been named an associate research professor of medicine at BUSM.

According to Dr. Murphy, the new section, in addition to being a center of research in its own right, will help other investigators whose work has a biomolecular dimension. "When you speak of molecular biology or molecular genetics, what you're really talking about is a methodology," he explained. "That methodology is broad enough to be applicable to a very wide range of biologic problems."

Dr. Murphy noted that his section already has established working relationships with other sections. One example, he noted, is the Section of Gastroenterology, headed by J. Thomas LaMont, M.D.

"Dr. LaMont's group is interested in a toxin produced by *Clostridium difficile* that causes gastrointestinal disease," said Dr. Murphy. "We're working together on a study of the molecular biology of that toxin."

As the section grows to its planned complement, its range of expertise will broaden. Dr. Murphy noted that his own background is strongly oriented toward recombinant DNA research. Dr. Burton, meanwhile, has specialized in the biology and synthesis of peptides.

"Dr. Burton has done some very elegant work on the nature of the peptides that specifically inhibit several proteases," said Dr. Murphy. "This has relevance to a wide range of clinical problems, from preventing colonization by particular bacterial pathogens to hypertension."

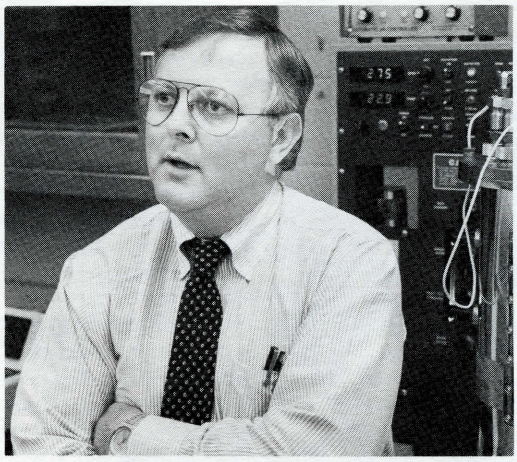
While it has not yet been decided what other types of expertise will be sought in choosing additional staff for the new section, diversity will be emphasized.

Dr. Murphy is a native of Connecticut. He received his B.A. from University of Connecticut in 1968 and his Ph.D. from that university's school of medicine in 1972.

The investigator's interest in the diphtheria toxin as a potential anti-tumor agent dates back to early in his research career. He has focused on two hormones as potential carriers for an altered version of the toxin: thyrotropin-releasing hormone (TRH) and melanocyte-stimulating hormone (MSH).

Dr. Murphy and his associates already have carried out experiments in which altered toxin bonded to TRH has been administered to rodents, with encouraging results. "We have demonstrated that we can destroy almost all of the cells of the pituitary that have TRH receptors, and spare the other cells of the pituitary," he said.

The other model system involves creating, through recombinant DNA technology, a gene that will express molecules that combine the altered diphtheria toxin with MSH. The first of the attempts to create and clone the gene, using a weakened form of *E. coli*, took place this past summer at the Frederick Cancer Research Facility in Frederick, Md. □



Dr. Murphy in one of the Biomolecular Medicine Section labs on third floor of the Evans Building. (Photo by Bradford F. Herzog)

'When you speak of molecular biology or molecular genetics, what you're really talking about is a methodology.... That methodology is broad enough to be applicable to a very wide range of biologic problems.'

Medicine a family affair for new chief resident

For Jonathan A. Fletcher, M.D., chief resident of the house staff in the Evans Department of Medicine, the decision to accept a residency at University Hospital was not a difficult one.

A *magna cum laude* graduate of Boston University School of Medicine in the Class of 1981, he knew what to expect. "As a medical student, I was impressed by University Hospital," said Dr. Fletcher. "Although it's not a large hospital, the entire medical service seemed to have unusual depth."

Dr. Fletcher also anticipated—correctly, as it turned out—that having some experience at the institution meant he might be granted more responsibility earlier than if he went elsewhere. "Once you know people, and they trust you," he explained, "you have more latitude in terms of taking care of their patients."

When he was offered the added responsibilities involved in becoming chief resident in medicine, Dr. Fletcher was delighted. "I plan to stay in academic medicine," said the physician, "and this position offered me an opportunity to gain further experience in administration and teaching."

The Evans' new chief resident, who stands a lean 6'3", entered medicine, as so many do, because he had role models who were doctors. In his case, the models were his father, his uncle and his grandfather.

His father is a pathologist who did his residency at Boston City Hospital and is now in western Massachusetts. His uncle is a hematologist in Binghamton, N.Y. His grandfather was a general practitioner in Binghamton and was also, said Dr. Fletcher, "the type of physician who had evening office hours four or five nights a week and worked every Saturday until he died at the age of 80."

For Dr. Fletcher, therefore, the critical choice was not so much whether to enter medicine as what to specialize in. The Cornell University graduate said that he settled on oncology because he was drawn by the challenges involved in providing effective patient care, as well as the intellectual allure of the field.

"These days, there really are things that you can do for oncology patients, especially at a center like this," he noted. "That applies both to medical therapy and to the kinds of psychological services that you can draw upon.

"Besides that, I'm truly fascinated by cancer. It generally disturbs multiple organ systems, and that's a very challenging aspect of it for me."

Currently, Dr. Fletcher is working on a research project related to his area of interest. The research group is directed by Richard Bell, M.D., a member of the Medical Oncology Section. Its aim is to isolate and purify the different types of proteins expressed by variations of the *ras* oncogene.

Speaking of the residency experience as a whole, Dr. Fletcher said he has not found it as overwhelming as often portrayed.

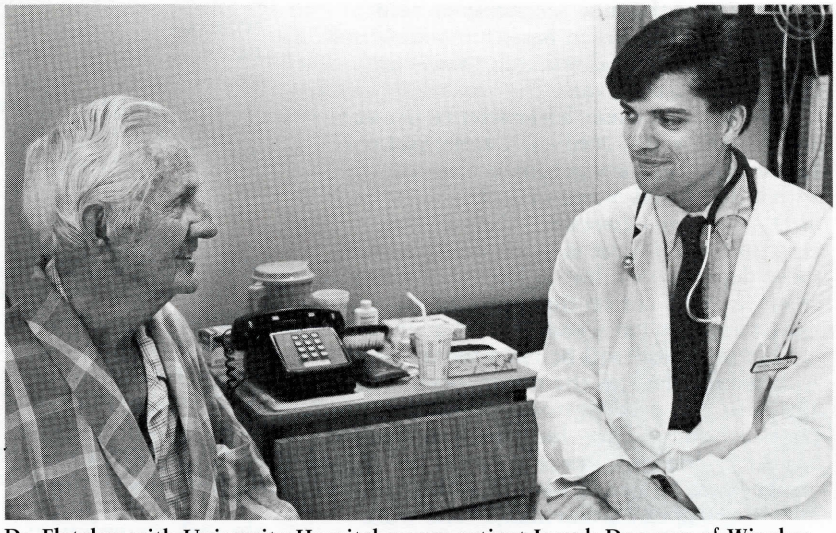
"When compared to my father's training 25 years ago, I don't think the residency these days is exceptionally trying," he said. "On the other hand, for some new house staff the responsibilities involved in using current medical technologies can cause mental strains that are every bit as tough as the physical strains of the long hours."

Whatever the rigors of the modern residency, Dr. Fletcher reported that he has had to put most of his outside interests on hold over the course of his training. The major exception is art collecting. He frequents galleries in Boston, looking for works by younger artists in the region.

"If I had to list the other things I'd like to do if I had the time," he added, "the list would include skiing—I grew up in the Berkshire Hills—sailing, running and reading.

"I also play various instruments, including the violin and piano, and I'd love to have time to do more of that." □

'Once you know people, and they trust you, you have more latitude in terms of taking care of their patients.'



Dr. Fletcher with University Hospital cancer patient Joseph Donovan of Winchester, Mass. (Photo by Bradford F. Herzog)

Noteworthy...

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School of Medicine and received her internal medicine training at Temple University.

Jeffrey L. Hendel, M.D., Cardiology Section, instructor of medicine. Dr. Hendel graduated from the University of Pittsburgh School of Medicine and received his internal medicine training at Boston City Hospital. He recently completed a cardiology fellowship at Boston University Medical Center. His main research interest is the use of lasers to remove atherosclerotic plaques in coronary arteries.

Stuart M. Levitz, M.D., Infectious Disease Section, instructor of medicine. Dr. Levitz graduated from New York University School of Medicine and trained in internal medicine at Case Western Reserve University. He recently completed a fellowship in infectious diseases at University Hospital. His research interest is mycology, with a particular focus on host responses to fungal infections. □

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Noteworthy

The past several months have seen the appointment of a large number of new staff members to the Evans. Following are the new members, their sections and their appointments at Boston University School of Medicine:

Vassilis I. Zannis, Ph.D., Unit of Molecular Genetics of the Cardiovascular Institute, associate research professor of medicine. Dr. Zannis formerly was an assistant professor at Harvard Medical School, and is an established investigator of the American Heart Association. His research interests are the molecular bases of human disease, especially human inborn errors of lipoprotein metabolism.

Elaine J. Alpert, M.D., General Internal Medicine Section, assistant professor of medicine. Dr. Alpert received her degree from the University of Michigan Medical School and trained in internal medicine and rheumatology at Boston University Medical Center.

Patricia Barry, M.D., Geriatric Section, assistant professor of medicine. Dr. Barry graduated from the University of Southern Florida College of Medicine and served her residencies at the University of Southern Florida and Tampa General Hospital. Prior to coming to Boston University Medical Center she developed a program in geriatrics for the University of Southern Florida.

Debbie Beasley, Ph.D., Renal Unit, assistant research professor of medicine. Dr. Beasley did her doctoral work at the University of Michigan. Her research interests center on renal and hypertension physiology.

Harrison W. Farber, M.D., Pulmonary Section, assistant professor of medicine. Dr. Farber is a graduate of the George Washington University School of Medicine and trained in internal medicine at the Medical College of Virginia. He recently completed a pulmonary fellowship at Boston University Medical Center.

Paul J. Hesketh, M.D., Section of Medical Oncology, assistant professor of medicine. Dr. Hesketh graduated from the University of Connecticut School of Medicine and trained in internal medicine at St. Elizabeth's Hospital, Boston. He recently completed a hematology-oncology fellowship at University Hospital. His main research interest is the granulocytic-monocytic colony stimulating factors from lymphocytes.

David A. Melnick, M.D., Infectious Disease Section, assistant professor of medicine. Dr. Melnick graduated from Columbia College of Physicians and Surgeons and trained in internal medicine at Cornell Medical Center. His training in infectious diseases was at Yale University School of Medicine. His main research interests are host defense mechanisms to infection and structure-function relationships in white blood cells.

Robert S. Moreland, Ph.D., Hypertension/Atherosclerosis Section, assistant research professor of medicine. Dr. Moreland did his doctoral work in physiology at the Medical College of Virginia. His main research interest is the mechanisms involved in vascular contraction in hypertension.

Samuel W. Needleman, M.D., Section of Medical Oncology, assistant professor of medicine. Dr. Needleman received his M.D. degree from the University of Pennsylvania and trained in internal medicine at the University of Iowa. Most recently, he completed a two-year fellowship at the National Cancer Institute. His research interests center on arachidonic acid and cellular oncogene interactions, as well as chemotherapeutic approaches to leukemia and lymphomas.

Dean Rodman, M.D., Nuclear Medicine Section, assistant professor of medicine. After receiving his M.D. degree from the University of Chicago, Dr. Rodman trained in radiology and nuclear medicine at Massachusetts General Hospital. His research interests center on magnetic resonance imaging.

Alayn Waldorf, Ph.D., Infectious Disease Section, assistant research professor of medicine. Dr. Waldorf received her Ph.D. at the University of California at Berkeley. Prior to receiving her new appointment she was a postdoctoral research fellow in the Infectious Disease Section. Her research focuses on mucormycosis infections in diabetes mellitus.

Gary J. Balady, M.D., Cardiology Section, instructor of medicine. Dr. Balady graduated from Rutgers Medical School and trained in internal medicine at University Hospital. He recently completed a fellowship in cardiology at Boston University Medical Center. His research interests center on exercise physiology and rehabilitative cardiac medicine.

Laura Coletti, M.D., General Internal Medicine Section, instructor of medicine. Dr. Coletti graduated from Boston University

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Evans Medicine is published by the Evans Memorial Department of Clinical Research and Preventive Medicine of University Hospital at Boston University Medical Center. Editor is Jay D. Coffman, M.D., associate director of the Department; associate editor is Richard P. Anthony; designer is Kredlow & Gonzalez. *Evans Medicine* is produced by Boston University Medical Center's Office of Informational Services, Owen J. McNamara, director. Send any correspondence to the Evans Memorial Department of Clinical Research, 75 East Newton St., Boston, MA 02118. Norman G. Levinsky, M.D., is director of the Department.