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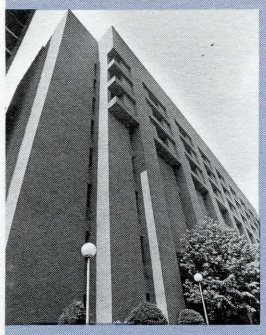


Evans Memorial Department of Clinical Research and Preventive Medicine

VOLUME 4, NUMBER 1
SUMMER 1988

Enthusiasm and a broad research program characterize growing Dermatology Department

In just three years the Department of Dermatology has grown from one to 11 members and its research programs and clinical activities have been expanded to make it one of the top dermatology groups in the nation. The force behind this growth is Dermatology chief Barbara A. Gilchrest, M.D., who joined the Department in 1985 from Tufts University and the New England Medical Center (where she still heads a laboratory at the USDA Human Nutrition Research Center on Aging). Her energy and innovation have made the Department a great place to be, according to one member who feels "very lucky to be a part of it."

A sampling of the types of research and clinical activities under way in the Department includes:

- Exploration of new laser applications in dermatology.
- Treatment of difficult skin cancers by a new microscopically controlled surgical technique known as Mohs surgery.
- The establishment of a Clinical Test Center for studies of new dermatologic treatments, including a trial of retin A for photoaged skin.
- Formation of two innovative training programs: A unique joint training program in dermatology with Tufts University and the New England Medical Center and a new year-long certificate program in dermatology for foreign health-care professionals, scheduled to begin this summer.

Crucial to the success of the Department, says Dr. Gilchrest, are three factors: the quality of its members, the strong interactive links between laboratory research and clinical practice, and the multidisciplinary character of projects under way.

This issue of *Evans Medicine* highlights three members of the Department of Dermatology whose work symbolizes important aspects of the discipline and the Evans in general: basic research, education and patient care. □

Monica Peacocke, M.D., discusses her research on melanocytes and nerve growth factor.

Laboratory group at forefront of human melanocyte biology

As principal investigator of a program project grant on the cellular basis of aging, one of Dr. Gilchrest's principal interests has been the biology of the human melanocyte, an area to which she has made some pioneering contributions. Although melanocytes are a minority cell type in the epidermis after keratinocytes and fibroblasts, they nevertheless play a key role in photoprotection, photoaging and photocarcinogenesis. It is in this last capacity that molecular biologist Monica Peacocke, M.D., recruited to pursue research in this area, finds them so interesting.

Dr. Peacocke, who joined the Department last year, heads the laboratory group on cuta-

Continued on page 2

The Department capitalizes on members' innovation and collaborative projects with other Evans groups.

The University Hospital

neous gerontology. She is posing questions—many for the first time—about the growth and differentiation of normal melanocytes and the possible mechanisms involved in malignant transformation.

"The most interesting thing about melanocytes for us is not their role in tanning, but the fact that they can become malignant," says Dr. Peacocke, "and melanoma is a cancer that is galloping in terms of incidence. We are probably the first group to investigate aspects of melanocyte gene expression—examining which genes are involved in normal growth and which may be involved in transformation."

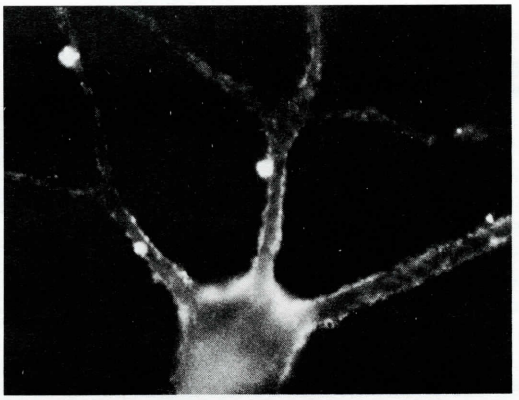
Thanks to breakthrough contributions by Dr. Gilchrest over the past several years, the ability to culture melanocytes has been vastly improved. Using these techniques, Dr. Peacocke and her colleagues are looking closely at the role of nerve growth factor in melanocyte biology and at the cell-cell interactions between keratinocytes and melanocytes. According to Dr. Gilchrest, the group was the first to demonstrate in culture that keratinocytes produce a series of substances that influence melanocyte morphology, pigment production and growth rate. Melanocytes are attracted by what keratinocytes make and these factors are critical to melanocyte survival. Exactly what these mediators are and how they work on melanocytes are the subjects of further studies in Dr. Peacocke's lab.

Dr. Peacocke's current studies began serendipitously, she says. When, working with Dr. Mina Yaar at Tufts University, she noticed that melanocytes treated with the tumor promoting phorbol ester, TPA, differentiated to look like nerve cells. (As neural crest-derived cells, melanocytes migrate early in embryonic development to the skin where, in contact with keratinocytes, they assume a polygonal, somewhat dendritic character.)

This nerve cell-like morphology suggested to Dr. Peacocke that receptors for nerve growth factor (NGF) could be found on melanocytes. Collaborating with a colleague at Cornell University who had cloned the human NGF receptor, Dr. Peacocke found that normal melanocytes were negative for NGF receptor. However, cells that had been exposed to the tumor promoter made the receptor protein. Further experiments revealed both the presence of protein of the correct molecular weight for the NGF receptor and the expression of the gene for the receptor in TPA-stimulated cells.

"If you give nerve growth factor to an unstimulated melanocyte, nothing happens; NGF cannot interact with the cell because there is no receptor. What we are discovering now is that we can induce the receptor in a variety of ways," says Dr. Peacocke. By removing for a period of time the serum or basic fibroblast growth factor—the major melanocyte mitogen—needed to grow melanocytes in culture, and *then* giving the melanocytes NGF, she found that the cells grew better. "Not as well as if they had serum or basic fibroblast growth factor, but clearly there is an effect of NGF on melanocytes at certain points in their life cycle." Ultraviolet irradiation, a stimulus for tanning of normal skin, also stimulates NGF receptor production in cultured melanocytes.

Nerve growth factor receptors have been found on many human melanoma cell lines, but it is not clear whether NGF is related to the malignant transformation or is just a marker of cellular maturity. To explore this question, Dr. Peacocke is beginning a series of experiments that involve inserting an amplified version of the gene for nerve growth factor receptor into normal melanocytes and observing the changes. After three weeks of growth, Dr. Peacocke hopes to notice changes in morphology to the nerve cell type and unusual growth patterns, particularly clumping, which is generally the first sign of malignancy. As a final step, the abnormal cells will be injected into nude mice to see if tumors develop.



TPA-stimulated melanocytes stain positive for NGF receptors with immuno fluorescent monoclonal antibody.

In collaboration with Dr. Yaar, Dr. Peacocke has shown that keratinocytes produce NGF as well, and she is pursuing investigations to elucidate the complex relationships between keratinocytes and melanocytes. For instance, if skin is exposed to sunlight in amounts necessary to produce a tan, do the keratinocytes make more NGF, and is increased NGF production involved in melanocyte transformation? She also is interested in the proteins that enable melanocytes to maintain their long dendritic processes and is looking especially at fibronectin and laminin, which are two large extracellular matrix proteins synthesized by neighboring keratinocytes. The hypothesis is that as melanocytes encounter these proteins, the melanocytes differentiate and a sequence of genes involved in the differentiation program are induced.

Although Dr. Peacocke is looking at the specific genetic steps involved in the melanocyte differentiation from normal polygonal to dendritic nerve-cell form, particularly the events that occur in the first 30 minutes to one hour after exposure to TPA, she also is looking at the sequence of gene activation in normal melanocytes.

"Only through a meticulous exploration of normal growth and differentiation can we come to understand the abnormal growth involved in malignancy," she says. □

Dermatologist studies melanoma prevention, blood cancer treatment

Research in the Department of Dermatology is not restricted to the laboratory bench, and the work of Howard Koh, M.D., is a case in point. Dr. Koh is board certified in internal medicine, hematology, oncology and dermatology and presently has appointments in the School of Public Health and the Departments of Medicine and Dermatology. He is putting his broad training to good use in the study of skin cancer, particularly melanoma, and its prevention.

"My overall interest is in the public-health aspects of cancer and the early detection and prevention of cancer. Melanoma is an excellent tumor model to study because even though the rate of incidence is increasing faster than any other cancer, except for lung cancer in women, and the number of deaths from melanoma is increasing, the potential for early detection and prevention is great."

Dr. Koh and colleagues in the School of Public Health are researching how to improve the early detection and prevention of melanoma and whether screening helps to control the number of deaths. Dr. Koh is a member of a national committee of the American Academy of Dermatology (AAD) that is looking into skin cancer prevention. The AAD has organized yearly nationwide screening clinics as part of this effort.

According to Dr. Koh, more than 100,000 people, including approximately 2,500 in Massachusetts, have been screened in the past three years during limited screening campaigns. Such clinics will be held again this year at a number of sites, including at BUMC, where dermatologists in the Evans Medical Group have donated their time to conduct examinations for skin cancer. (Last year, 116 people were screened during two days at the Evans Medical Group; 25 percent were thought to have clinically suspicious lesions and were referred to their own physicians for follow-up.) Dr. Koh is active in coordinating the Massachusetts melanoma screening efforts in order to obtain hard data on whether the screening programs work. This effort includes tracking what happens to individuals following the screening—whether cancer was diagnosed and what the pathology and outcomes were.

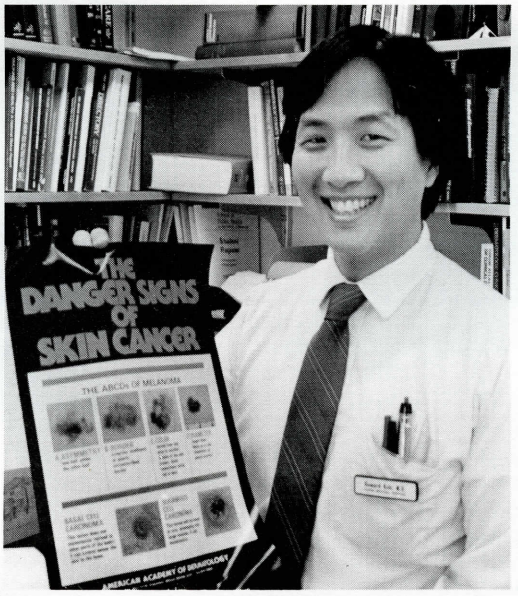
Dr. Koh uses the term "applied epidemiology" to describe his prevention efforts, which involve using all available data on melanoma, including who is at risk for it and what the risk factors are, in order to prevent the disease or at least keep it from reaching an incurable stage.

In addition to screening, educational efforts have been aimed at teaching individuals, primary care physicians and nurse practitioners to routinely check for signs of melanoma. Dr. Koh has contributed to these efforts as a member of the board of directors of the Massachusetts Chapter of the American Cancer Society. Similar campaigns have proved effective for breast cancer detection and prevention and, according to Dr. Koh, should work as well for melanoma.

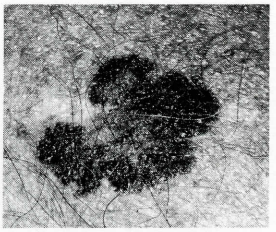
In addition to his public health work, Dr. Koh is the director of photopheresis at the University Hospital. Photopheresis is a new technique used to treat people with a severe form of the skin cancer cutaneous T cell lymphoma. Cutaneous T cell lymphoma is a relatively uncommon tumor compared to melanoma, but it can appear in a wide range of forms. The most advanced phase, called Sezary's syndrome, occurs when malignant T cells in the skin move into the bloodstream and the patient develops leukemia as well. (Dr. Koh recently was awarded a Whitaker Health Sciences Fund grant in collaboration with Dr. Herman Eisen of the Massachusetts Institute of Technology to explore the basis of photopheresis' beneficial effect.)

The University Hospital is one of 10 centers in the country offering photopheresis. The technique involves removing a patient's blood by a dialysis machine, separating out the malignant T cells and shining long wave ultraviolet light on these cells, which activates the drug, psoralen, that the patients have taken prior to the procedure. The photoactivated drug affects the malignant cells and the blood is then returned to the patient. Exactly how the process works is unknown, but it is thought that by damaging cells with light, photopheresis allows for more rapid destruction of the malignant cells, conceivably through an immunologic mechanism.

The treatment helped approximately 75 percent of the patients in a first series studied at Yale University. "In theory this might work with other, more common diseases, such as chronic lymphocytic leukemia and chronic rheumatoid arthritis," says Dr. Koh, who plans to start protocols this summer with collaborators in the Evans Sections of Hematology and Arthritis. □



Howard Koh, M.D., is pursuing research in melanoma prevention and photopheresis, a new therapy for patients with Sezary's syndrome.



Screening has the potential to catch melanoma before it becomes deadly.

'Although the number of deaths from melanoma is rising, the potential for early detection and prevention is great.'

Noteworthy

Internationally known expert on hypertension **Aram Chobanian, M.D.**, chief of the Evans Hypertension Section and professor of medicine and pharmacology, became the 16th dean of Boston University School of Medicine, effective May 1.

Among other recent achievements, Dr. Chobanian presented the 1988 Report of the Joint National Committee (JNC IV) on the Detection, Evaluation and Treatment of Hypertension at an April press conference in Bethesda, Md., sponsored by NHLBI. Dr. Chobanian is chairman of the JNC IV committee, and the report was scheduled to appear as a special article in the May 1988 issue of the *Archives of Internal Medicine*.

Dr. Chobanian also received the 1987 Eastman Kodak Award of the National Academy of Clinical Biochemistry for his research on the relationships between hypertension and atherosclerosis.

David Beller, Ph.D., who heads the Evans Research Immunology Unit, has been invited to speak at the Second International Workshop on Macrophage Biology and Activation this July.

Richard D. Diamond, M.D., chief of the Infectious Disease Section, recently was elected a member of the American Association of Physicians. **Richard A. Cohen, M.D.**, of the Peripheral Vascular Section, and **Thomas Rothstein, M.D., Ph.D.**, of the Hematology Section, were elected to membership in the American Society for Clinical Investigation. Both organizations encompass all specialties and election to them recognizes outstanding research accomplishments and national and international reputation.

Matt Fenton, Ph.D., recently joined the Evans as a research professor of medicine in the Immunology Section. His interest is in molecular mechanisms of regulating IL-1 expression.

William Kannel, M.D., chief of the Section of Preventive Medicine and Epidemiology, received a Distinguished Service Award this spring from the American College of Cardiology at the College's annual meeting in Atlanta.

Evans Director **Norman G. Levinsky, M.D.**, Wade Professor of Medicine and chairman of the Division of Medicine at BUSM, recently was elected a Master of the American College of Physicians. He also is serving as president of the Association of Professors of Medicine for the 1988-89 term.

Ronald McCaffrey, M.D., chief of the Section of Medical Oncology, served as chairman of the Leukemia Society of America's annual meeting in New Orleans in March. **Paul Hesketh, M.D.**, an assistant professor of medicine in the same Section, presented a lecture on the increasing frequency of adenocarcinoma of the esophagus in Massachusetts at the recent annual meeting of the American Society of Clinical Oncology, also in New Orleans.

Mark Moskowitz, M.D., has been appointed chief of the Evans General Internal Medicine Section. Dr. Moskowitz previously had been in charge of the Health Care Research Unit in that Section.

Karen Freund, M.D., also of the General Internal Medicine Section, has been named director of the Women's Health Group, effective July 1, 1988. She replaces **Linda Lesky, M.D.**, who is leaving to pursue research in clinical epidemiology at Harvard Medical School.

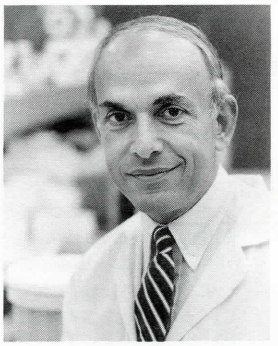
Evans member **Michael Rosenbaum, M.D.**, an associate clinical professor of dermatology, has been elected secretary-treasurer of the New England Dermatological Society.

Neil Ruderman, M.D., Ph.D., head of the Diabetes-Metabolism Unit in the Evans Section of Endocrinology and Metabolism, was a visiting professor at Louisiana State University and the University of Tennessee Schools of Medicine in March. **Anthony McCall, M.D.**, an assistant professor of medicine and physiology in the same Section, is an invited speaker for the Symposium on Hypoglycemi organized by the International Diabetes Federation, to be held in Sydney, Australia, in November.

David Salant, M.D., a professor of medicine and pharmacology, was named head of the Renal Unit and the Renal Section of the Department of Medicine in 1987.

R. Knight Steel, M.D., chief of the Evans Geriatric Section, is serving as chairman of the Certifying Examination Committee in Geriatric Medicine of the American Board of Internal Medicine and the American Board o Family Practice. In April, Dr. Steel was among a panel of experts discussing issues related to aging and health care during an interactive video teleconference, moderated by Ted Koppel of ABC. The program, entitled "Aging in America: Dignity or Despair," was broadcast live to special conference centers across the country.

Joseph Stokes, M.D., a member of the Section of Preventive Medicine and Epidemiology, received medals from the Swedish Society of Medicine and the Society for Prospective Medicine in recognition of his research in preventive medicine and epidemiology. In addition, Dr. Stokes, who directs the Framingham Offspring Study, presented a lecture in April on the National Cholesterol Education Program at Prevention '88.



Aram V. Chobanian, M.D.

Skin graft technique holds promise for patients with chronic wounds

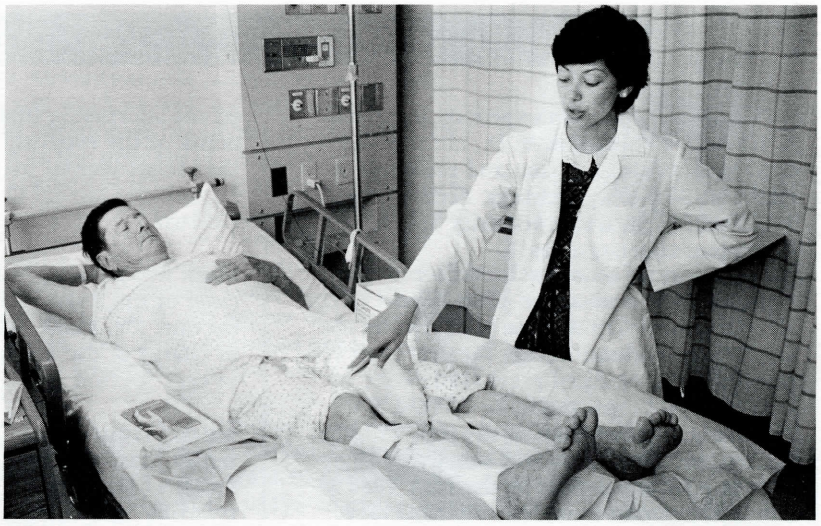
Since joining the Department a year and a half ago, geriatric dermatology fellow Tania Phillips, M.D., has been heading a clinical research program using cultured skin allografts to treat intractable skin ulcers. It has been estimated that 1.5 million Americans suffer from chronic, nonhealing wounds. People with diabetes, older people with poor circulation and cancer chemotherapy patients may be especially prone to delayed or failed healing. Dr. Phillips' approach involves culturing small pieces of discarded foreskins from newborns into large sheets of cells that can be placed directly onto wounds.

Before coming to the United States, explains Dr. Phillips, she was a clinical dermatologist at the London Hospital in London, England, where she treated many patients with persistent leg ulcers. "One of the ways to treat these problems is with a split-thickness skin graft, using skin from the thigh to cover the wound. The problem with this approach, especially with older patients, is that you leave a wound in the thigh, which itself can be painful and take a long time to heal." The split-thickness approach also limits the size of the wound that can be treated.

When she arrived in Boston, Dr. Phillips spent time in the laboratory of Dr. Howard Green of Harvard University, where she learned how to grow the cells in culture. "Dr. Green developed the method of taking a tiny piece of skin from a person, growing it to many times its original size and then using this bigger piece to treat the wound. In early trials this worked pretty well, but the problem again was that with older patients the skin cells are older and just don't grow as well," Dr. Phillips explains, "so people wondered what else could be tried."

Drawing on Dr. Gilchrest's findings of age-related losses in the proliferative potential of skin cells, Dr. Phillips decided that a good possibility might be to use newborn foreskins because young cells grow so much better in culture than older skin and because newborn cells generate large amounts of growth factors.

She has treated about 40 patients so far at the University Hospital using cultured neonatal cells, and has been getting excellent results—over 70 percent of patients' wounds have healed completely and most of the rest have shown improvement. First, the ulcer is cleaned with conventional topical treatments, then the layer of cultured cells attached to a gauze backing is applied and bandaged over. If the patient can rest at home and stay off his or her feet for the first week, there is no need for hospitalization; if not, Dr. Phillips does her best to have the patient admitted. After the first week, the gauze is removed and the patients can continue to dress the wound themselves until healing is complete.



With patient looking on, Tania Phillips, M.D., describes cultured allograft procedures.

"The interesting thing," says Dr. Phillips, "is the way the allograft works, because this is foreign tissue." At first, she says, the results were so dramatic that she thought the graft must be taking. Further studies have indicated, however, that the allografts do not remain in place permanently, but are slowly rejected as the host tissue repairs itself. Biopsies performed after three or four weeks do not reveal any foreign tissue at all.

"We think the combination of a biological dressing, which keeps the wound moist and protects it from the air, and the rich mix of growth factors secreted by the neonatal cells stimulate the patient's own skin cells to be more active and fill in the wound, which they couldn't do before," says Dr. Phillips.

It also is possible that the loss of the donor skin's Langerhans cells during the culture process makes the graft much less antigenic than a conventional graft of noncultured tissue.

Another positive aspect of the allograft treatment, according to Dr. Phillips, is the almost immediate relief from pain that many patients experience—pain that for many has been constant during the months or years during which the ulcer has failed to heal.

Until now, Dr. Phillips has been doing an uncontrolled trial of this treatment, following the wound healing process in each patient, tracking the time the process takes and the pattern of healing. A comparison of ulcers that heal completely and those that don't showed a pattern of dramatic improvement in both during the first two weeks, followed by a tapering off in some cases. "If a wound is going to heal at all, you can usually tell in the first four weeks," she says.

Beginning this summer, she will head a large randomized study in collaboration with groups at the Boston Veterans Administration Medical Center and Brown University's Roger Williams Hospital in which some patients will receive cultured allografts while others will only receive the gauze dressing. At the moment, she is seeking patients to include in this next phase of research. □

So far, more than 70 percent of her patients treated with cultured allografts experienced complete wound healing.

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Kenneth Steinberg, M.D., has been named chief resident for the 1988-1989 academic year. Born in Brooklyn, N.Y., and raised in Stamford, Conn., Dr. Steinberg received his medical degree from New York Medical College. He is just finishing his third year as a resident in internal medicine and will start his chief residency July 1.

Following his year as chief medical resident, Dr. Steinberg expects to begin a pulmonary medicine fellowship, although he is not yet sure where. His research interests focus on vascular mediators and their role in pulmonary vascular disease. Dr. Steinberg also is interested in the development and treatment of interstitial lung disease.

In addition to patient-care duties, Dr. Steinberg helps teach the advanced cardiopulmonary life support course of the American Heart Association to nurses, interns and other residents at the Medical Center, and he instructs second-year medical students in physical diagnosis.

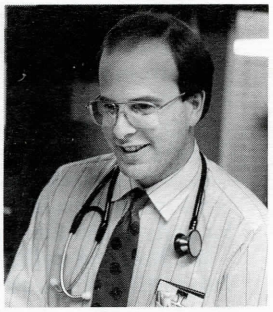
"I definitely would like to get a position in academic medicine. I enjoy teaching, thrive on patient care and have research interests as well, so I would prefer a situation that combines all three."

A total of 20 interns have joined the Evans this year. They are:

Christopher diFilippi, M.D., University of Rochester School of Medicine
Judy Fine, M.D., Tufts University School of Medicine
John Freedman, M.D., University of Pennsylvania School of Medicine
Howard Goldberg, M.D., Albert Einstein College of Medicine
Robert Goldberg, M.D., University of California-San Diego School of Medicine
James Hoffman, M.D., Boston University School of Medicine
Michael Hollett, M.D., Duke University School of Medicine
Abram Kirschenbaum, M.D., New York University School of Medicine
Glenn Levine, M.D., Columbia College of Physicians and Surgeons
Wendy Livingston, M.D., Columbia College of Physicians and Surgeons
Mary Manning, M.D., George Washington University School of Medicine
Andrew Nichols, M.D., Boston University School of Medicine
Joseph Polito, M.D., Medical College of Virginia
Bruce Randazzo, M.D., State University of New York at Stony Brook School of Medicine
Lisa Renfro, M.D., University of Connecticut School of Medicine
Monique Roth, M.D., University of Connecticut School of Medicine
Jeffrey Silver, M.D., Boston University School of Medicine
Lynn Sydor, M.D., University of Pittsburgh School of Medicine
Robert Tarpy, M.D., University of Massachusetts Medical School
Arthur Zerbey, M.D., University of Minnesota School of Medicine

Thirteen Evans members complete their residencies in July. The graduates and their future pursuits are:

Manuel Anton, M.D., (cardiology)
Andrew Chodos, M.D., Boston University Medical Center (cardiology)
Peter Francis, M.D., National Cancer Institute (oncology)
Russel Gerry, M.D., private practice in Concord, Mass.
Eric Manning, M.D., Boston University Medical Center (research fellowship in biochemistry)
Craig Morita, M.D., Brigham & Women's Hospital, Boston (rheumatology)
Joanne Murabito, M.D., Framingham Heart Study
Margaret O'Donoghue, M.D., Harvard University (neurology)
Alan Steele, M.D., Beth Israel Hospital, Boston (renal medicine)
Kenneth Steinberg, M.D., The University Hospital, Boston (chief medical resident)
Richard Taikowski, M.D., Mt. Sinai Hospital, New York (cardiology)
Robert Weiss, M.D., (gastroenterology)
Anthony White, M.D., (infectious disease) □



New chief medical resident Kenneth Steinberg, M.D.

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