EINSTEIN



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NewsReel

VINTAGE AWARD SEASON FOR EINSTEIN FACULTY

Since last spring, Einstein scientists have received 10 major grants from the National Institutes of Health (NIH) totaling \$90 million to support their research in autoimmune diseases, cancer, aging, diabetes, AIDS, kidney disease, and bioterrorism defense research.

Dr. Betty Diamond, Weinstock Professor of Microbiology & Immunology, professor of medicine, and chief of the division of rheumatology, has been awarded a five-year grant totaling \$22.8 million to fund a new NIH-designated "Autoimmunity Center of Excellence at Einstein. It is one of nine such centers in the country, all of which carry out clinical trials and basic research aimed at developing new therapies for autoimmune diseases.

Dr. Leonard Augenlicht, professor of medicine and of cell biology at Einstein and director of Montefiore's Genome Anatomy Laboratory, has been awarded a five-year, \$10million grant to study how a Western-style diet interacts with genetic factors to increase the risk of colorectal cancer.

Dr. Nir Barzilai, director of Einstein's Institute for Aging Research and associate professor of medicine, received a five-year, \$10million grant to support research that will examine the effects of fat and metabolism on aging.

Dr. John Condeelis, co-chair and professor of anatomy & structural biology, was awarded a five-year, \$10million grant to study the signaling pathways and motility responses that allow tumor cells to metastasize.

Dr. Luciano Rossetti, director of the Diabetes Research and Training Center and the Judy and Alfred A. Rosenberg Professor of Diabetes Research, received a \$10-million grant over five years to continue biomedical research into diabetesrelated areas and to promote the translation of research findings into improved health outcomes, especially in underserved and minority populations.

Dr. Harris Goldstein, director of the Center for AIDS Research, professor and vice-chair of research affairs in the department of pediatrics, and professor of microbiology & immunology, has been awarded a five-year, \$7.8 million grant for continued funding of the AIDS research center.

Dr. George Christ, professor of urology and of physiology & biophysics, will receive nearly \$7 million over five years for his research exploring the role of diabetic neuropathy and myopathy in bladder and erectile dysfunction.

Dr. Victor Schuster, chairman and Baumritter Professor of Medicine, received a five-year, \$6million grant to study the critical role of cell signaling in the kidney, with a focus on understanding how cell signaling influences renal disease.

Dr. Arturo Casadevall, Mitrani Professor in Biomedical Research, and professor of medicine (infectious diseases) and of microbiology & immunology, has received \$1.056 million for the first year of an expected five-year \$4.8 million collaboration with the Northeast Biodefense Center, an NIH-funded consortium of regional, academic, and governmental biomedical research organizations and public health agencies. Dr. Casadevall's research will involve bolstering defenses against bioterrorism attacks.

Dr. Jill Crandall, assistant professor of medicine, was awarded a five-year, \$2.5-million grant for the continued follow-up to the long-term Diabetes Prevention Program study, which is evaluating the role of diet and lifestyle changes, such as exercise, in preventing diabetes among people who are glucose intolerant and therefore at risk for developing the disease.

EINSTEIN SYMPOSIUM **CELEBRATES NEW** PRESIDENT OF YESHIVA UNIVERSITY

In celebration of Richard M. Joel's investiture as the fourth president of Yeshiva University, the College of Medicine hosted a special symposium, "The Jewish Genome: Fact or Fancy," on September 16th in Robbins Auditorium. The symposium featured four Einstein scientists whose work involves the study of Jews and their genetic heritage.

Dr. Dominick P. Purpura, The Marilyn and Stanley M. Katz Dean. organized the symposium, noting that "the College of Medicine has been a leader in genetics research for many decades. In fact, the first department of genetics at any medical school in the United States was established at our institution in 1963. We think it is especially appropriate, therefore, that the medical school's participation in the investiture of Yeshiva's new president, Richard Joel, include a special program on the subject of Jewish genetic research."

The symposium speakers and the topics they discussed were: Dr. Susan Gross, associate professor of clinical obstetrics & gynecology and women's health and of clinical pedi atrics, "The Wandering Jewish Genome." An expert on Jewish



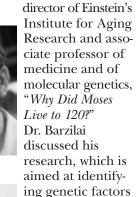
PRESIDENT AND MRS. JOEL AND DEAN PURPURA AT THE SYMPOSIUM RECEPTION.

genetic diseases-and a leader in ongoing efforts to eliminate them-Dr. Gross discussed Jewish migration throughout history.

Dr. Robert Burk, professor of pediatrics, microbiology & immunology, obstetrics & gynecology and women's health, and of epidemiology and population health, "The CLAL Study: Cancer, Longevity, Ancestry and Lifestyle." Dr. Burk focused his talk on one portion of the CLAL study: the Prostate Cancer Research Project, which he directs. The project aims to identify genetic differences



within population groups that are especially susceptible to prostate cancer, including lews, Finns and the Amish. Dr. Nir Barzilai,



that may explain

why some excep-

tionally old people

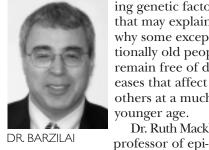
remain free of dis-

eases that affect

younger age.

others at a much

Dr. Ruth Macklin,





ical Ethics, "Studying the Jewish Genome: Ethical Implications." A renowned bioethicist, Dr. Macklin discussed the ethical issues surrounding studies that focus on Jews and other population groups.

Prior to his election as the fourth president of Yeshiva, Richard Joel was president and international director of Hillel, the organization for Jewish college students, for 14 years.

His connections to the University, however, run deep. He is an alumnus of a Yeshiva high school, and as a very young man he headed the University's alumni affairs office. An attorney who received his bachelor's and law degrees from New York University, he also served as an associate dean and professor at the Cardozo School of Law. Two of his children are Yeshiva graduates and a third is currently attending Stern College.

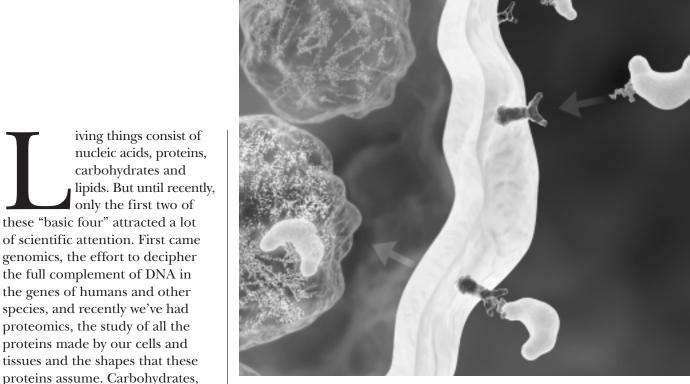
His presence at Einstein marked a homecoming of sorts. Earlier in his career Mr. Joel served as an assistant district attorney in the Bronx

ROSSETTI HEADS DIABETES RESEARCH CENTER

Dr. Luciano Rossetti, professor of medicine and of molecular pharmacology, and The Judy R. and Alfred A. Rosenberg Professor of Diabetes Research, has become director of the Diabetes Research Center at Einstein and principal investigator of the NIH-funded Diabetes Research and Training Center (DRTC).

In both of these roles he succeeded Dr. Norman Fleischer, professor of medicine, who led these programs with great distinction for more than 25 years. Dr. Fleischer continues his important involvement in the diabetes center and DRTC as co-

The Sweet Science of Glycomics



Sugars combine with lipids and proteins to form the glycolipids and glycoproteins that bristle from cell surfaces. Pictured throughout this article are these cell-surface glycoconjugates and molecules that bind to them to trigger cell signaling, inflammation, cancer and other biological activities.

building blocks and the position of the chemical bonds that hold them together—can be exceedingly difficult. And while research labs using automated equipment can readily synthesize protein and DNA molecules containing hundreds of individual building blocks, only recently have the most specialized labs synthesized oligosaccharides of 12 units in length.

by contrast, have been a biological

recently invoked Rodney Dangerfield

when describing how little respect

Sugar's neglect is due partly to

an image problem: When we

consider carbohydrates at all, we

think of molecules that do little

more than provide energy (e.g.

glucose) or store it (starch in

potatoes, glycogen in animals),

offer some structural support

of us gas (oligosaccharides in

beans). But perhaps the main

(cellulose in plants) or give some

reason researchers have shunned

sugars is their daunting complexity.

The four nucleotides that com-

prise DNA, and the 20 amino acids

in proteins, connect like cars on a

subway train to form genes and

proteins that always have simple

linear structures. By contrast, the

10 or so simple sugars (monosac-

charides) found in mammals can

combine with each other at numer-

ous points to form huge branching

Deciphering the primary structures

composition and sequence of their

molecules in which one sugar

of these polysaccharides—the

may be joined to several others.

the field has garnered.

backwater. Indeed, one scientist

Researchers have long known that carbohydrates combine with proteins to form glycoproteins or with lipids to form glycolipids and that cell surfaces bristle with these "glycoconjugates." But the sugary components of these lipids and proteins were often dismissed as decorations—almost literally as icing on the cake.

Now it's clear that the carbohydrates festooning cell-surface proteins and lipids can profoundly influence their three-dimensional structure as well as their function. Studies in recent years have shown that carbohydrates play key roles in many important biological activities including cell signaling, the

immune response, inflammation, embryo implantation and development and cancer progression.

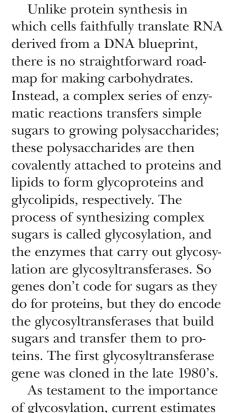
Biologists with a sweet tooth for carbohydrates have carved out a specialty of their own called glycobiology. The effort by glycobiologists to identify all of an organism's glycans (the sugar polymers attached to proteins or lipids) is called glycomics. There's no doubt that glycomics is still in its infancy, perhaps where genomics was in the 1960s. But in a sign of the field's growing importance, the National Institutes of Health in October 2001 awarded a five-year, \$37-million grant to create and fund the Consortium for Functional Glycomics, an international group of some 70 investigators who are carrying out research in this area.

The consortium is focusing its research efforts on carbohydrates involved in cell signaling—in particular, the sugar portion of glyocoprotein and glycolipid cellsurface receptors. When activated by ligands (molecules on the surfaces of other cells or in the extracellular milieu), these cellsurface receptors transmit a signal cascade to the nucleus that tells the cell what to do. Some sugar groupings are crucial to cell signaling because they provide glycoproteins with the all-important "active sites" to which the signaltriggering ligands bind.

Three of the consortium's investigators are Einstein faculty members-Drs. Pamela Stanley, Fred Brewer and Steven Porcelli. Although they approach glycomics from different directions, each studies the role that carbohydrates play in the all-important task of signaling.

r. Pamela Stanley, professor of cell biology, plays a leading role in the Consortium for Functional Glycomics. She's a member of the consortium steering committee, which meets every two weeks via videoconference - and is in a good position to answer the question: Why is the \$37-million NIH grant that created the glycomics consortium referred to as a "glue grant"? "The idea is that gluing together a group of scientists into a consortium should speed progress in the field," she explains.

Dr. Stanley studies glycoprotein cell-surface receptors that mediate cell-to-cell signaling, with a particular focus on how mutations that affect the sugar component of these receptors can in turn affect normal development. Her research clearly shows that constructing a carbohydrate is no simple task.



As testament to the importance of glycosylation, current estimates suggest that more than 300 genes—at least one percent of the entire genome—encode enzymes involved in this process. Dr. Stanley's group at Einstein has cloned several of these glycosyltransferases.

The process of glycosylation has much in common with an assembly line, featuring numerous enzymes that carry out specialized tasks: Each enzyme transfers just one sugar (e.g., fucose)—and only to a particular linkage (e.g., fucose added to

galactose). So synthesizing a typical branched-chain carbohydrate may require the expression of 50 or so glycosyltransferase genes. And like cars on an assembly line, carbohydrates are built on the move: Membrane-bound glycosyltransferases in the endoplasmic reticulum, and later in the Golgi apparatus, sequentially add sugars to (or trim them from) a carbohydrate as it travels through these organelles. (Just how this multienzyme task force is recruited to build a particular carbohydrate remains unclear. But some credit goes to transcription factors, the proteins that regulate the expres-

Among the many types of molecules formed through glycosylation are the glycoproteins destined to become cell-surface receptors.

Once synthesized, these glycoproteins migrate to the cell surface, ready to perform their job of detecting signals and transmitting them to the cell nucleus.

sion of genes.)

One of the most important receptors in all of biology is Notch, a large receptor on the cell surfaces of Drosophila (where it was first discovered) as well as all other multi-cellular creatures including humans. Notch receptors play key roles in sending signals that control cell growth and determine cell fate—telling some cells to prolifer-

ate, for example, and others to undergo programmed cell death.

It has been known for a decade that a protein called Fringe influences Notch signaling during embryonic development and profoundly affects the way tissues are organized. Fringe "directs" Notch signaling by modulating the ability of ligands on adjacent cells to activate Notch receptors. Notch signaling via these cell-cell interactions, for example, guides the formation of somites in developing mammals.

An entirely new paradigm was revealed for how Notch signaling is regulated.

In a study published in 2000 in the journal *Nature*, Dr. Stanley's group, along with colleagues from three other institutions, revealed the mechanism by which Fringe controls Notch signaling: by functioning as a glycosyltransferase. Fringe transfers the sugar N-acetylglucosamine to the sugar fucose, which in turn is attached to about 24 of the 36 epidermal growth factor-like repeats that form a large portion of the Notch receptor. "In showing that Fringe's activity depends on its ability to put a sugar onto the Notch receptor," says Dr. Stanley, "an entirely new paradigm for how Notch signaling is regulated was revealed."

Fringe's transfer of N-acetylglucosamine to fucose on Notch turns out to be necessary—but not sufficient—for Fringe to modulate Notch signaling in a co-culture test assay. In a study published in 2001 in the *Proceedings of the National* Academy of Sciences, Dr. Stanley and colleagues showed that the "Fringe effect" depends on yet another sugar being transferred to the Notch receptor-this time, galactose added to the N-acetylglucosamine already provided by Fringe. "This work identified a new glycosyltransferase that is involved in modulating Notch signaling," Dr. Stanley says.

One way to study glycosyltransferases is to induce mutations in genes that code for them and then examine the impact on the structure and function of cell-surface receptors. To that end, Dr. Stanley has developed Chinese hamster ovary (CHO) cell lines containing a variety of defective glycosyltransferases. These cell lines have yielded much information about glycosyltransferases and have proven useful for testing the role of glycosyltransferases in human disease.

In the 1980's, a Belgian pediatrician named Jaak Jaeken identified a new set of glycosylation defects implicated in human diseases. Jaeken was treating children who were mentally retarded and unable to walk. On a hunch, he did liver function tests on these children and found that their serum glycoproteins were "underglycosylated," meaning the normal number of sugars hadn't been transferred to them. In 1995, Jaeken and collaborators found the cause: a defect in an enzyme called phosphomannomutase that helps to synthesize the carbohydrate portion of cellsurface glycoproteins.

Twelve such disorders, all quite rare, have now been identified. Each involves a defect in a different glycosylation enzyme, and collectively they are known as Congenital Disorders of Glycosylation (CDG's). All CDG's are autosomal recessive disorders, occurring only when both parents contribute a gene carrying a mutation.

Dr. Stanley has used her mutant CHO tissue cultures—created well before CDG's were known to exist—to test whether mutations suspected of causing CDG's are truly responsible for the observed health problems. She uses a technique that resembles gene therapy.

Each CHO cell line has a mutation that alters the activity of a particular glycosylation enzyme. Dr. Stanley had previously shown that a cell line can be "repaired" by transfecting its cells with "normal" DNA that is known to code for that enzyme. Now, when a new CDG is discovered, Dr. Stanley can perform the same sort of transfection, this time taking DNA that codes for the putatively defective enzyme and transfecting it into a CHO cell line that's defective for the same enzyme. "If the DNA from the CDG patient fails to repair the mutant cell line, then this provides good evidence that the mutation

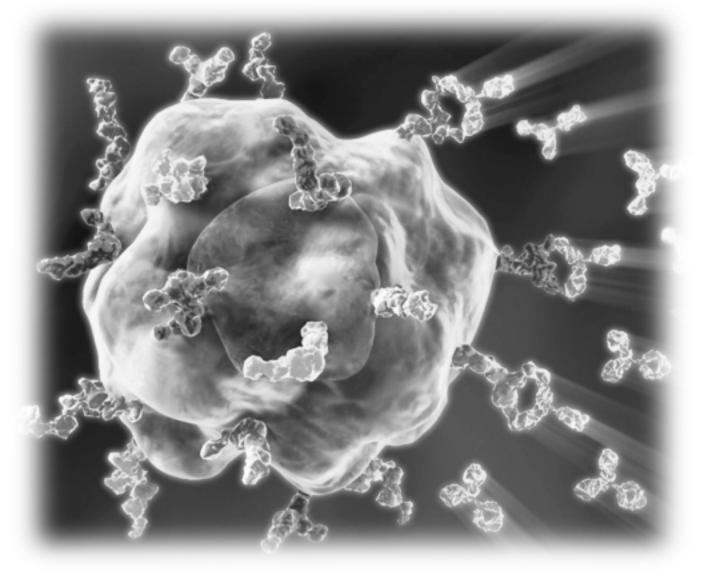
was indeed the reason that the person was sick," Dr. Stanley explains. "New CDG's are being discovered all the time," says Dr. Stanley. She also notes that, just in the past year, researchers have shown that two subclasses of muscular dystrophy are caused by defective glycosyltransferases and have tentatively linked two other subclasses to such defects. "We've never understood the role of sugars in muscle development, and now we may be learning the answer," she says.

Dr. Stanley. "Now we can start thinking about drugs or possibly even gene therapies that can help people with such problems."

he receptors on cell surfaces account for only half the cell-signaling story:
Something else must come along and initiate the signal. As noted earlier, a molecule that binds to and activates a cell-surface receptor is known as a ligand. And arguably the most important ligands are the lectins. Found on the surfaces of

also animal lectins, the first of which was purified in 1974 by two Einstein researchers—Drs. Anatol Morell (now retired) and Richard Stockert, professor of medicine—along with collaborators at the NIH. Dr. Fred Brewer, professor in the department of molecular pharmacology, has continued Einstein's notable tradition of lectin research. He started out studying plant lectins and more recently has worked with the animal variety.

Dr. Brewer's studies have provided important insights into lectin-



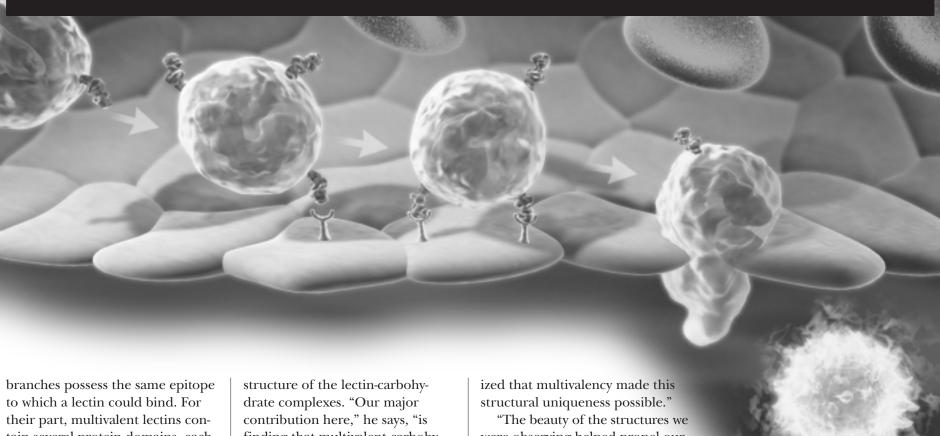
So far, diseases known to be associated with glycosylation are relatively rare. But Dr. Stanley wouldn't be at all surprised if defective glycosyltransferases are implicated in more common health problems. She mentions psoriasis and other inflammatory diseases as leading candidates, since glycoprotein receptors are intimately involved in the body's inflammatory response.

"It's clear that human disease can result if glycosyltransferases don't build the right sugars," says both plant and animal cells, lectins are "carbohydrate recognition proteins." A section of the lectin molecule, known as its "domain," activates the receptor on another cell by binding to one or more of its carbohydrate molecules. More specifically, the binding is between the lectin domain and the "active" portion of the carbohydrate molecule, referred to as its epitope.

Researchers have studied plant lectins for many years. One of the world's most notorious toxins—ricin, derived from castor beans and much in the news recently—is actually a plant lectin. There are

carbohydrate binding. He has focused on the phenomenon of "multivalency," which refers to the fact that lectins, and the carbohydrates they bind to, often possess more than one binding site as part of their molecular makeup. For example, the carbohydrate component of a glycoprotein will often sprout several different branches, with each branch containing the same epitope. A glycoprotein with two carbohydrate branches will have a valence of two if both those

4



tain several protein domains, each of which can bind to the same carbohydrate epitope.

Dr. Brewer describes his research this way: "What we've been doing are the very fundamental studies of the physical interactions that occur between multivalent lectins and multivalent carbohydrates. This involves looking at such basic properties as the thermodynamics of these interactions as well as the structures formed as a result of these physical interactions."

For their thermodynamic studies, Dr. Brewer and his colleagues systematically measured the energy transfers that result from these interactions. "We're fortunate here at Einstein to have state-of-the-art instruments that measure the thermodynamics of molecules binding to each other. These instruments allow us to quantitate the energy released when lectins bind to carbohydrates."

A "wonderful thing" about thermodynamics, says Dr. Brewer, is its universality: "If plant lectins are similar in structure to animal lectins—and they are—then what is true thermodynamically in plants must also be occurring in animal systems. Then there's the fact that thermodynamics doesn't know the difference between in vitro and in vivo. So you know that any interactions that you measure in a test tube will also be happening in plants and animals."

Almost as fundamental as his thermodynamics work is Dr. Brewer's nearly 20 years of research into the finding that multivalent carbohydrates and multivalent lectins interact to form highly organized cross-linked lattice structures. Some of these lattices are in two dimensions, others are in three. but the really intriguing aspect is their uniqueness."

He describes a typical experiment: "We would take a tetravalent lectin and combine it in a test tube with three bivalent carbohydrates that have the same two epitopes

"It's going to be a real challenge to understand how that complexity relates to the function of carbohydrates. But once we do that, we'll be able to put this field onto a really strong footing."

but different structures with respect to their branching. After allowing time for the ingredients to equilibrate, we'd find that three distinct precipitates had formed. Examining the precipitates using electron microscopy and x-ray crystallography, we would see that each had a different crosslinked lattice structure that was specific for the individual carbohydrate and the individual lectin that formed it. We observed similar results for every class of plant lectin we could put our hands on and real-

were observing helped propel our research, and so did the growing evidence that cross-linked lattices were ubiquitous in nature and doing something of fundamental biological importance," says Dr. Brewer. Indeed, Dr. Brewer's "latticework" would help show that lectins play a starring role in one of the most important of all biological activities: the programmed cell death of T lymphocytes.

This T-cell phase of Dr. Brewer's research began in the mid 1990's, when an assistant professor of pathology at the UCLA School of Medicine named Linda Baum visited Dr. Brewer's lab at Einstein. "I was telling her about our crosslinking findings with plant lectins, and she was very interested in our work," Dr. Brewer recalled. "She said, 'I'm going to see if that's occurring in our biological system, but I had no idea what system she was looking at and lost track of her. A few years later, I went to a meeting where one of her students was giving a poster presentation and I just about fell over. Lo and behold, she had found evidence suggesting that lectin/carbohydrate crosslinking caused programmed cell death in T lymphocytes."

T lymphocytes, or T cells, help generate the body's immune response via surface receptor molecules that recognize foreign antigens. The vast majority of T cells aren't needed for immune surveillance, and some of them may trigger unwanted immune reactions. These unnecessary and unwanted T cells are eliminated within the thymus gland through programmed cell death, the process also known as apoptosis.

Dr. Baum found that an animal lectin known as galectin-1 induces T-cell apoptosis. And she has gathered evidence suggesting that apoptosis is triggered by the lattice that forms when galectin-1 binds with glycoproteins on the T-cell surface.

Galectin-1 is secreted by epithelial cells of the thymus gland, where T cells develop. It can bind to four different T-cell glycoprotein receptors, which normally are distributed uniformly over the cell surface. In studies using fluorescent antibodies, Dr. Baum made the surprising observation that exposing T cells to galectin-1 makes the four glycoprotein receptors segregate into two types of discrete clusters. She has hypothesized that the cross-linking has caused this striking shift in cell-surface receptors and the apoptosis that later ensues.

"Here we'd spent years studying crosslinking having no idea how it would affect the biology of these molecules," says Dr. Brewer. "Now, research based on our biophysical studies had provided the first good indication that lattices form on cell surfaces and that they influence a

very important biological process, namely the apoptosis of susceptible T cells. This finding has spawned an enormous research effort to find crosslinked lattices in other biological systems."

Galectins, one of several subclasses of animal lectins, are so named because these proteins bind to the carbohydrate galactose. Dr. Brewer began working with galectins before learning of Dr. Baum's work with galectin-1 and now studies how other galectins—there are 14 of them in all—may be influencing T-cell apoptosis.

"We now know the molecular structure of most of the galectins, says Dr. Brewer, "and they've all turned out to be multivalent principally bivalent, meaning they have two subunits, each capable of recognizing galactose. What makes them fascinating is their biological activity: Nearly all of them are involved in inducing apoptosis." But one member of the galectin family has long been known to inhibit apoptosis. That's galectin-3, notorious for encouraging tumor growth by deflecting signals telling tumor cells to kill themselves. Now it turns out that galectin-3 interferes with T-cell apoptosis.

"If you expose T cells to both galectin-3 and galectin-1, apoptosis won't happen," says Dr. Brewer. "We've been studying how galectin-3 counteracts galectin-1 and prevents apoptosis from occurring." Dr. Brewer believes the explanation lies in galectin-3's valency. "We've found that galectin-3 has much the same binding specificity as galectin-1, meaning that both of them bind

to the same T-cell glycoproteins. But in contrast to the bivalent structure of galectin-1 and the other galectins, galectin-3 can be a tetramer. Having four branches rather than two would give galectin-3 an advantage over galectin-1 in competing for the same receptors."

Even more interesting, says Dr. Brewer, is the nature of the crosslinking caused by the antiapoptotic galectin-3. "Instead of forming organized cross-linked lattices like galectin-1, our biophysical studies have shown that galectin-3 forms disorganized cross-linked complexes. So when galectin-3 binds to receptors on the surface of T cells, it probably holds them in one large aggregate structure rather than induce them to segregate into clusters like we see with galectin-1. If so, then galectin-3 prevents apoptosis by actively suppressing organized cross-linking from occurring. It's essentially a disorganizing protein."

"We've always believed that if you pay enough attention to the physical properties of molecules, they'll tell you what they're doing," he says. "So all along, we've felt strongly that the structures of the lattices we were observing must be fundamentally influencing biological function. The recent findings regarding T lymphocytes have helped to confirm this belief."

Much remains to be learned about structure/activity relationships in glycobiology, Dr. Brewer says, since the carbohydrate structures are very complex. "It's going to be a real challenge to understand how that complexity relates

to the function of carbohydrates," he says. "But once we do that, we'll be able to put this field onto a really solid footing."

professor of medicine at r. Steven Porcelli, associate Einstein, also works with T lymphocytes. He studies how T cells that recognize lipids and glycolipids influence a wide spectrum of immune-system responses-combating infections, shrinking tumors and regulating autoimmune reactions.

"T cells have gained a high profile in recent years, because they're attacked by the AIDS virus, HIV," says Dr. Porcelli. "As a result of AIDS, we now know that the T cell is a very important component of the immune system: Once we lose T cells, everything falls apart, and we lose the ability to ward off even those microbes that normally would be

innocuous.' Dr. Porcelli explains that all creatures possess what's known as innate cellular immunity: white cells equipped with cell-surface receptors that can recognize certain fixed molecular "patterns" associated with pathogens. But only vertebrates possess the more sophisticated adaptive (acquired) cellular immunity.

The T cell, says Dr. Porcelli, is "the master regulatory cell" of the adaptive immune response. T cells are the white cells that recognize bacterial or viral antigens from previous encounters, says Dr. Porcelli. "They then respond by recruiting other cells that flood in to kill the pathogens. In addition, the T cell itself can attack the pathogens directly."

Researchers had long assumed that the antigens recognized by T cells were proteins. But in a paper published in 1994, when Dr. Porcelli was at Harvard, he and his colleagues showed that this assumption was incorrect. "We were studying how T cells isolated from human blood responded to mycobacteria and found evidence that some of the T cells responding to these bacteria were recognizing something else besides protein antigens," he says. "On further

investigation, we found that these T cells were recognizing lipids and glycolipids." For the past 15 years, Dr. Porcelli has been studying this novel family of T lymphocytes that

respond to lipid

and glycolipid anti-

gens. Known as

CD1-dependent T cells, they're found in men as well as mice—and are emerging as a normal and reasonably abundant component of the immune system.

At first, says Dr. Porcelli, he and other researchers had "absolutely no idea" what this family of T cells did in the body. But whatever their

role, their presence certainly implied that they conveyed a survival advantage.

"Mice and men diverged from each other some 70 million years ago," notes Dr. Porcelli, "so the fact that these T cells have been conserved in both species suggested they were likely to have some important functions." Studies show that CD1-dependent T cells respond to foreign lipids and glycolipids found prominently in the cell walls and membranes of pathogenic mycobacteria—strong evidence that they help fight infections. But in addition, they may also influence autoimmune diseases.

Before a CD1-dependent T cell can recognize an antigen, that antigen must first go through a process called presentation, which involves antigen-presenting immune cells, commonly referred to as dendritic cells. On the surface of these dendritic cells are specialized antigen-presenting proteins that bind the antigen to form a stable protein/antigen complex, which can now be "presented" to T cells. Finally, this protein/antigen complex can be recognized by T cells possessing receptors that can bind specifically to the complex.

This mechanism by which CD1dependent T cells recognize lipids and glycolipids closely resembles the classic "presentation-recognition" pathway already well established for T cells that react to protein antigens. In that classic pathway, peptide-specific T cells "see" peptide antigens bound to class I or class II antigen-presenting proteins encoded by the major histocompatibility complex (MHC) of genes. But in the case of lipid and glycolipid antigens, CD1 proteins perform the job of binding antigens and presenting them to T cells.

T lymphocytes can be classified according to the proteins that present antigens to them—hence the name CD1-dependent T cells for this family of T lymphocytes that recognize CD1 proteins and the complexes they form with lipid and glycolipid antigens. Humans express five different forms of CD1 proteins on their antigen-presenting cells, which together can bind many different lipid and glycoprotein antigens.

"We were originally focused mainly on how CD1 molecules were involved in getting immune responses started, especially against foreign glycoprotein antigens like those on the surface of bacteria," says Dr. Porcelli. "But now we're looking more closely at their role in stopping the immune response—which is actually very important, since if you're unable to shut off the immune response, you may end up with an autoimmune disease caused by T cells attacking other cells of the body."

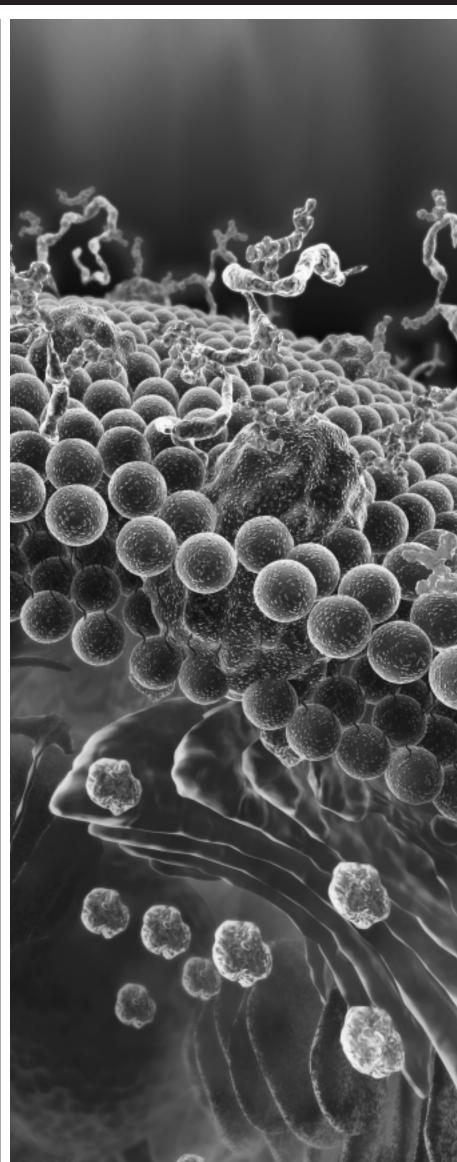
According to Dr. Porcelli, we all possess T cells capable of reacting to the proteins, lipids and glycolipids that are normal parts of our bodies. "You can show that these T cells respond to 'self' constituents when you put them in a Petri dish," he says. "But the fact that T cells don't normally cause autoimmune problems in vivo suggests that something is suppressing them." Evidence from Dr. Porcelli's lab and others suggests that CD1-dependent T cells help in quelling these autoimmune reactions.

"T lymphocytes that respond to CD1 must go through a phase early in their development called selection," Dr. Porcelli explains. "During this phase, the T lymphocyte expresses its antigen receptor on its surface. But if the T cell's receptor doesn't 'see' a CD1 molecule in its vicinity, that T cell never becomes active but instead dies from neglect. Most T cells develop in the thymus gland, and normally up to 90 percent of them will die this way [i.e., through T-cell apoptosis, the same process that Dr. Brewer is investigating]."

Accumulating evidence suggests that losing the wrong CD1-dependent T cells—those responsible for tamping down immune responses—may lead to autoimmune diseases. This evidence comes in part from studies in which the gene that codes for CD1 proteins in mice has been knocked out. "By taking out that gene, you cause the mouse to lose the T cells that respond to CD1 proteins, which leads to unwanted autoimmune responses," says Dr. Porcelli.

On the plus side, glycolipids can provoke a T-cell response that prevents autoimmune diseases. "There's a mouse model of type 1 diabetes called the non-obese diabetic mouse that replicates much of the immunology of the human disease in that it's caused by an autoimmune attack that destroys the

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Scoping Out the Causes of Birth Defects



Dr. Cohen at her laser microdissection scope.

t may not seem obvious, but learning how a single, fertilized cell becomes a fully formed human baby can be useful in cancer research. Both processes involve cells that multiply rapidly—a normal occurrence in embryonic development, but destructive in cancer. And in both processes, the same genes may be implicated in the rapid cell division. In her developmental genetics research, Dr. Paula Cohen is studying a family of genes involved in both colorectal cancer and the development of sperm and ova.

Dr. Cohen, assistant professor of molecular genetics, has always been fascinated by the complexities of pregnancy—especially how pregnancy usually goes right when so much can go wrong. Her graduate studies at King's College in London focused on developmental defects in early pregnancy. After completing her studies in England, Dr. Cohen arrived at Einstein's Belfer Institute for Postdoctoral Studies in 1993 to continue her training and to work with Dr. Jeffrey Pollard.

More recently, Dr. Cohen's research has involved meiosis, the process by which germ cells in the ovaries and testes convey genetic

material to eggs and sperm. Errors during meiosis can lead to miscarriages and to serious birth defects-and little is known about why those errors occur. One approach to studying meiosis is to isolate individual eggs (from mice) as they are formed in the ovary, characterize their genetic content and note how the cells are conducting their housekeeping at each stage of development.

Isolating such individual cells from a mass of tissue can be a technological nightmare:
Locating the cells is difficult, and then comes the problem of plucking out a single cell that is less than a thousandth

of an inch across without dragging unwanted additional tissue with it. But a new technology—an instrument known as a laser capture microdissection system—has come to the rescue.

Originally designed for cancer research, laser capture can be used during the earliest stages of tumor formation, when just a few cancer cells may be bobbing in an ocean of a thousand normal cells. After "capturing" early cancer cells through laser microdissection, researchers can assess their genetic and protein makeup even before a tumor is evident, or compare the gene expression/protein profiles of a cancer cell and its neighboring normal cell. They can also "microdissect out" and study cancer cells in biopsy samples that were taken from cancer patients years ago.

In the spirit of one field of science borrowing from another, Dr. Cohen has adapted laser microdissection for her research in developmental biology. She is jubilant about the technology, which allows her, for example, to view germ cells undergoing meiosis and then extract them from tissue one by one.

The principle behind laser capture microdissection is cunningly simple: a traditional high-power microscope for viewing is coupled to a laser that can precisely target an individual cell in a sample. A thin polymer film, resembling a sheet of plastic, coats the sample on the slide. The operator views the sample under the microscope, locates the cell of interest and directs the laser to cut around that specific cell (or group of cells). The heat of the laser causes the chosen cell to stick to the film; and when gravity induces the piece of film to fall into a collection tube, the cell comes with it.

"For the first time we can look at these different cells with this technique and it's just very exciting," says Dr. Cohen.

She is studying mismatch repair genes-a family of crucially important DNA repair genes involved in both cancer and meiosis. Mutations that damage these repair genes can cause a hereditary form of cancer known as human non-polyposis colon cancer, and Dr. Cohen is investigating their possible involvement in meiotic errors that lead to Down syndrome and other maternal agerelated birth defects. She credits another Einstein faculty member-associate professor of biology

"Winfried has led the effort to investigate how mutations in this family of DNA repair genes contribute to hereditary colon cancer," says Dr. Cohen. "His lab generated knock-out mouse models for six of the 11 members of this gene family, which were some of the first mouse models ever developed for colon cancer." These repair genes are highly conserved, she notes, and perform very similar gene-repair functions in yeast, mice and

Winfried Edelmann—for

guiding her into meiosis

research.

humans.

"In 1995, Winfried noted that yeast strains harboring mutations in the repair gene MLH1 not only had repair defects-many genetic defects had accumulated that weren't being repaired-but also had sporulation abnormalities," says Dr. Cohen. "And since sporulation is a meiotic event, he predicted that the mammalian homolog of this gene might regulate meiosis as well as participate in colon cancer. Winfried knew that Jeff Pollard and I were the reproductive biologists at Einstein, so he asked us to look into this gene's possible role in mammalian meiosis."

"I wasn't a meiosis expert then, but that's how I got involved in the field," says Dr. Cohen. She recalls her excitement upon first examining the testis of an MLH1 knockout mouse: "My reaction was Wow! It was amazing—there were no sperm whatever. I believe this was the first-ever mouse to have zero sperm as a result of knocking out a single gene."

Her collaboration with Dr.
Edelmann has been extreme-

ly fruitful. Subsequent research has shown that five of the 11 genes in the mismatch repair family are involved in meiosis, a field in which Dr. Cohen is now a nationally recognized authority.

"Colon cancer and developmental biology are very separate fields," observes

Dr. Cohen, "and I don't know whether such a convergence of interests—focusing on the same gene family from two different perspectives—could have occurred anywhere else. And that really exemplifies Einstein.

The collaborative environment here is fantastic."

Pictured above are sections of mouse testis before and after laser capture. In the bottom image, the laser has cut out five different cells, and each shows a unique profile of gene and protein expression.

Up Close Personal

Stephen Atwood, M.D., Class of '72

n January, when Dr. Stephen Atwood (class of '72) returned Lto the Albert Einstein College of Medicine to receive the 2002 Alumni Association's Life Achievement Award, he made a presentation about global medicine. At the time he could not have imagined that, within a few months, the region where he serves as UNICEF's regional advisor for health and nutrition-East Asia and the Pacific-would become the epicenter for a disease, severe acute respiratory syndrome (SARS), that would bring worldwide attention to the very issue.

Dr. Atwood's talk offered insights into the "globalization" of health issues as well as suggestions for how the medical profession can better address these issues.

Through his travels on behalf of UNICEF, Dr. Atwood visits 23 developing nations that typically have limited resources. He has seen, firsthand, the challenges these nations face in promoting good health and providing adequate health care to their people. These challenges have included vaccinating the children of India against polio while also combating tribal distrust; assuring that insecticide to protect villagers in Papua New Guinea against malaria gets used to good effect; and providing educational and medical tools to healthcare givers within marginalized communities, which are often many miles from the nearest roads or hospitals.

While these examples may not themselves pose a risk globally, our shrinking world does, Dr. Atwood noted.

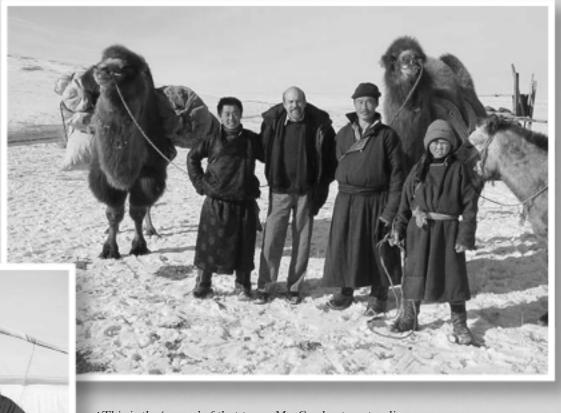
"Each day, one million people cross borders and travel between nations or even continents. Boundaries are disappearing, augmenting the potential for the

The editors thank roving physician-photographer Steve Atwood for the photoessay accompanying this story.



▲ This photo was taken in a village near the town of Atemble on the northern side of Papua New Guinea. This is a riverside village that is reached by dug-out canoe with an outboard motor, so it's actually more accessible than other villages in the interior. We had gone there to see a community self-help program where families actually assessed their own homes for health, sanitation, and education and then developed a plan on how to improve their self-rating. Villages in PNG tend to be pretty self-sufficient. Just a note: the kids in this village dress in the grass skirts and fruit necklaces for festivals rather than everyday wear. (I guess I was considered a festival!)

▼ On the way back from Khenti Aimag (an Aimag is an administrative division similar to a Province) travel is by 4-wheel drive vehicle over unpaved tracks across the steppes. We slowed down to talk to this group bringing back supplies to their house (called a Gir). The camels are characteristic of Mongolia and the Gobi Desert, which was south of this Aimag. The horses are famous, and the people of the town I had stayed in (Galshir Suom) boasted that Genghis Khan was known to have raised his fastest horses in their town.



◆This is the 'mayor' of that town, Mr. Ganbaatar, standing with me in front of the Gir that we stayed in. The Gir is a circular tent-like structure that a family can raise or strike in 30 minutes. It's got a wooden frame, with felt and canvas over the outside. There are no windows in it, but a stove in the center is vented through a hole in the center of the roof.

spread of diseases or viruses globally, whereas before they remained more localized," he said. "While the poor-mostly women and children –are most directly affected by this 'small world syndrome,' ultimately, we are all at risk."

The spread of SARS, with many of those diagnosed in North America and Europe having recently traveled in Asia, poignantly illustrates this very point.

"We need to recognize that diseases are not so isolated and to globalize medical education. To do this, we need to expand opportunities for research, conduct situational analyses, and thoroughly assess each nation's resource needs. We also need to go into the lab and direct technology at addressing global needs, and we need to make global medicine an integral part of the medical education our future doctors receive."

With the education of future doctors in mind, Dr. Atwood has a vision of setting up a graduate student exchange program where a student from a U.S. (or Canadian or European) graduate school would work with a graduate student from an Asian university on a research problem that they would define along with UNICEF. These problems could address a broad range of medically related issues including medicine, public health, and even economics.

"The importance of the pairing would be to allow each student to learn from the skills of his/her collaborator," Dr. Atwood explains. "It would also be important to pair up faculty advisors from each institution. And the end result would be a Masters or Doctoral thesis, or publication."

În his address, Dr. Atwood also stressed the role that prestigious institutions, such as Einstein, could play in drawing connections

between what is going on in health in developing countries and how it affects health care in the U.S. (Again, the recent emergence of SARS as a threat to health worldwide underscores the relevance of this issue.)

While Dr. Atwood noted that training students and involving leading institutions in the addressing of global medical issues is critical, he also spoke about the importance of educating the general population about health. During his career he has traveled far and wide and witnessed the healing power that knowledge can provide.

"I really enjoy being involved in training and working with people who are struggling with real problems of life and death in the field," he said. "When you apply participatory methods and ask the kind of questions that raise people's

awareness and ability to analyze their own situation, you can watch people absolutely unfold and take off. It gave me my first understanding of what the word empowerment meant."

Dr. Atwood's most important "take home" message about globalizing medicine, stemming from the experiences he has had during nearly three decades of work abroad, was: "It cannot be done alone."

"Everything in this business is working with others, bringing each individual's expertise and skill to bear on solving the problem at hand," he said.

His selection for the Einstein Alumni Life Achievement Award recognized his role in such team efforts-namely his life of service to medicine for the under-served populations of East Asia and the Pacific, and acting as an exemplary model for future generations of physicians.



▲ This is what the inside of a Gir looks like. The stove is in the foreground. People burn coal, wood, or cow dung. It's amazingly warm inside despite the inhospitable temperature outside.

▼Couldn't resist a little advertising for UNICEF. This is, afterall, what it's really all about.



What's Ahead for Med Ed?

by Albert S. Kuperman, Ph.D. Associate Dean for Educational Affairs



hile the medical students here today were on the path to cians, the scientific foundation of clinical medicine continued to expand. New clinical applications of biomedical science and technology were discovered and deployed. The cultural, economic and demographic environment in which medicine is practiced continued the transformation begun in the '70s. These changes will continue even after students graduate and proceed through the years of graduate medical education and beyond. This is why, whether they be practitioners or teachers of medicine, physicians must be independent, self-directed and effective learners throughout their professional lives.

How does medical education respond to biomedical science discoveries and changes in the practice environment? It, too, must change in both evolutionary and revolutionary ways, sometimes by adding new learning goals; sometimes by integrating whole new disciplines; sometimes by

The transition from genomic science to clinical genomics will not come quickly or easily. It will probably be another decade or two before genomics takes center stage of clinical practice ... but still well within the professional lifetime of the graduating students here today.

altering the strategies of teaching and learning. Obviously and emphatically, medical education cannot be allowed to develop static cling.

I would like to discuss just a few areas of educational change that are likely to be addressed with some vigor while the graduating seniors sitting here today are in their residency training. These students will need to figure out how to learn what their medical student successors will be learning. Faculty in the audience will need to integrate new knowledge and approaches into their teaching. And for everyone out there, what more do your physicians need to know?

So, without further delay: What's ahead for Med Ed? First on my list is genomic medicine.

It was only about 15 years ago that the term "genomics" joined the medical vocabulary. The science of genomics takes us beyond the era when medical genetics was a tool for diagnosing only a few relatively rare diseases inherited in simple Mendelian fashion. Rather

than being the study of single genes and their effects, genomics is the study of functions and interactions of all genes in the entire genome, whose sequence in man, other animals, and microbes, we now know.

Unlike the relatively uncommon nature of single gene disorders, abnormalities in the interactions of multiple genes plus the influence of environmental factors are already known to play a role in such common diseases as breast cancer, colorectal cancer, Parkinson's disease, HIV infection and Alzheimer's disease. And this is probably just the tip of the iceberg.

Except for monozygotic twins, each of us has a unique genome, and this has enormous implications for patient care. Knowledge of a person's genome will enable us to predict that person's risk of common diseases and undesirable responses to the environment and to drugs. Thus, we have the potential for a genomically based practice of primary preventive medicine. We also have the potential for development of genomically based diagnostic medicine and therapeutics. Knowledge of microbial genomics will lead to better methods for preventing, diagnosing and treating infectious disease and will also contribute to methods of bioterrorism defense.

The transition from genomic science to clinical genomics will not come easily or quickly. It will probably be another decade or two before genomics takes center stage of clinical practice. But this is still well within the professional lifetime of the graduating students here today.

Drug and medical diagnostic companies are not waiting for a fully grown genomic medicine to happen. They are already developing novel human protein and antibody drugs through genomics-

based research. They are already developing new diagnostic tests based on abnormal proteins that are the consequence of genomic dysfunction. We are beginning to see gene-testing and proteintesting methods that flag patients with genetically based risks, identify persons at risk for developing adverse responses to certain drugs, and spot diseases before they are associated with symptoms. Gene chip diagnostics using DNA microarrays is already well established in diagnosing the most common form of non-Hodgkin's lymphoma; and just think, it was three years ago that the so-called lymphochip was invented, with its more than 18,000 snippets of genes associated with normal and abnormal lymphocyte development. Protein chips using antibody microarrays to detect abnormal

proteins are not far behind.

I hope I have made the case for beginning immediately to greatly expand the teaching of genetic medicine in general—and genomics in particular—to the physicians of tomorrow. Indeed, at Einstein, this process is already well underway.

Text on my list of items for educational change is pre-I have already mentioned how knowledge of a person's genome can serve as the scientific basis for practicing preventive medicine, albeit at the level of the individual patient. This still begs the question: What kinds of knowledge and communication skills should a physician have in order to practice effective health promotion and disease prevention with individual patients? And what is the role of the physician in contributing to the health of populations?

From Paul Marantz, a colleague here at Einstein, I learned about a 19th century English physician named John Snow. In 1854, Dr. Snow traced the source of London's huge cholera epidemic to a single pump on Broad Street that was leaking sewage into the public's drinking water. He thus ended the epidemic by forcefully putting the pump out of commission. A few years later, still savoring his epidemiologic victory, Snow was among the first to rec-

ommend that preventive medicine be taught in medical schools. One hundred and fifty years later, we are still waiting for Dr. Snow's recommendation to be implemented. We should do it now.

Just imagine if each physician in the United States was trained appropriately in the science and clinical application of prevention. What could be achieved in preventing the adverse medical, economic or social consequences of smoking, inadequate diet, lack of exercise, accidents, domestic violence, lack of immunizations, occupational hazards, toxic environmental exposure and substance abuse? And moving beyond the individual patient, just imagine how physicians could influence positively the health of populations if they were educated in principles of disease prevention and behavioral change appropriate for specific patient populations; if they learned the importance of respecting cultural and economic diversity; if they were willing to work as part of systems and as collaborators in health care teams; if they accepted at least some responsibility for the health of populations?

Most physicians of today would probably not oppose Medicare and Medicaid the way individual physicians and the AMA did when these programs were first proposed by the White House in the 1960's. On the other hand, I don't see too many of today's physicians or medical students taking robust stands against a White House economic policy that will cause a huge reduction in health care financing during the next 10 years. I'm also concerned with the medical community's increasing tolerance for a health care non-system that permits more than 40 million uninsured individuals, including an enormous number of children. Need I remind you, we are still the only Western industrialized nation that does not have a national health insurance program except for the elderly or impoverished. We seem even further from the goal of universal health insurance today than when such a system was proposed by the White House in early 1993.

I am postulating that a pervasive and persuasive education in prevention and population sci-

ences will stimulate more medical students to become the socially responsible and responsive physicians they should be. Perhaps from the large number of students here at Einstein who participate in myriad community-based health programs, some will emerge to lead the way to a medicine of the future that embraces prevention, population health and greater social concern.

prevention and behavioral change appropriate for specific populations; if inked with development of educational programs in they learned the imporpreventive medicine, but in tance of respecting many ways standing on its own, is education in *global medicine*. cultural and economic There is no need for me to convince you of the interconnectedness diversity; if they were of all peoples on this planet and willing to work as part how poverty, poor public health and sanitation, contagious diseases of systems and as collaband ecological disasters any place in the world can have orators in health care medical consequences teams; if they accepted anywhere and everywhere. at least some

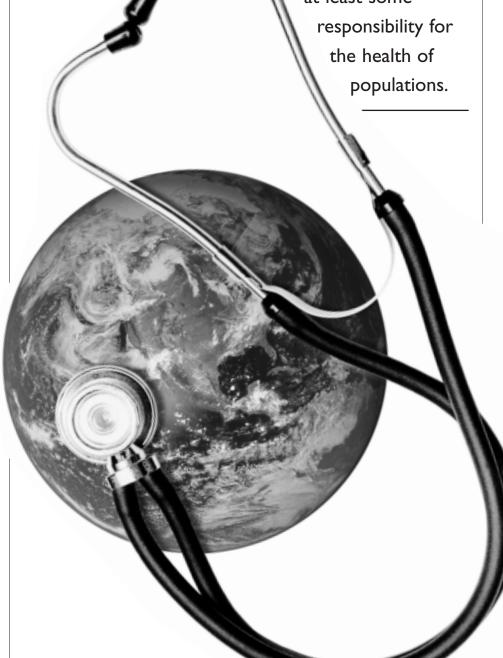
Imagine how physicians

could influence positively

the health of populations

if they were educated in

principles of disease



This keynote address was delivered by Dr. Kuperman on May 1, 2003, at the ceremony inducting Einstein students into the medical school honor society, Alpha Omega Alpha.

Aside from the practical necessity of educating future physicians in global health issues, such education should also include humanitarian medicine. The aim here is to motivate more physicians to bring the benefits of their knowledge and expertise to the cause of improving human health in less developed and emerging nations. This nation, with its great workforce of superbly trained physicians, should lead the way in global health efforts. Should we even imagine that global outreach in the health arena might one day become public policy, or is this an impossible dream?

rom genomics, preventive medicine and global medicine, I would now like to discuss *integrative medicine* as another topic for educational change. This new concept and approach to clinical medicine grew out of recognition by physicians that many practices and modalities of alternative medicine can, and should, be combined with the best of conventional therapies.

Integrative medical practice does not accept unconventional, alternative modalities uncritically; such acceptance requires scientific evaluation within the context of informed skepticism. Nevertheless, integrative medicine is open to ideas and views that, compared to conventional medical practice, offer a wider array of possibilities for health care with interventions that are more natural, less invasive, less toxic and less costly.

An essential feature of the integrative medicine approach is that patients are viewed as whole persons with minds, spiritual needs and abundant mechanisms for innate healing. Mind-body medicine plays a huge role in the practice of integrative medicine.



Largely due to the work of John Kabat-Zin and his colleagues at the University of Massachusetts Medical Center, mind-body medicine has a substantial scientific foundation and evidence base compared not only to other forms of alternative medicine but even compared to many widely used conventional medical treatments.

Most important, integrative medicine places great emphasis on something that conventional medical practice is losing

sight of, and this loss
has not gone
unnoticed by

Integrative medicine...
is about restoring caring,
trust, communication,
patient participation and
commitment to the
relationship between
physician and patient.

patients. The loss I refer to has nothing to do with state-of-the-art drugs, technology, or life-saving procedures. I refer simply to the loss of primacy of the doctorpatient relationship, the caring bond and superb communication between caregiver and patient, a sense by the patient of the caregiver's commitment to his or her health, the responsibility of the physician to engage the patient's participation in his or her health care. Viewed from this perspective, integrative medical practice is not just about herbs, biofeedback, acupuncture, nutritional supplementation, imagery and visualization, ethnic and cultural healing rituals and the like. It is about much more. It is about restoring trust, caring, communication, patient participation and commitment to the relationship

between physician and patient. And this is why we should start educating students in the principles, concepts and practices of integrative medicine.

he last item for educational change that I want to discuss is the need to be more successful in *promoting the values and behaviors of professionalism and humanism* in our students. In its 1995 "Project Professionalism," the American Board of Internal Medicine specified some of the essential elements of professionalism. They included: altruism, duty and service, integrity and honor, accountability, empathy, compassion, respect for others, and excellence.

Within the academic community and among the public, there is growing concern that physicians' historical commitment to professionalism and humanism is withering. Indeed, there is ample evidence of the public's increasing skepticism about the commitment of physicians to place their patients' interests above their own. Despite many studies about causes of erosion of the doctor-patient relationship, a satisfactory explanation has been elusive. This is not to say that managed care, capitation, constraints in health care funding and the increased need for documentation and productivity have not played any role in the decline of professionalism; but individually or collectively, these factors are not the complete story.

In the search for more compelling explanations for the decline of professionalism and humanism, we should examine what happens during the process of becoming a physician. The educational and cultural environment of medical schools has long been suspect with regard to nurturing students' professional and humanistic behaviors. In fact, medical schools are often seen as having a harmful influence on such behavior. I realize this can be overdone. I am not in the "chicken little" camp of educational reform. I do not think the sky is falling. But I do see it full of gray clouds with respect to the influence of medical education on student behavior, especially in the

hidden curriculum and the socialization process. To quote from one student who graduated recently not from Einstein but from another excellent medical school:

"For two years lecturers parade up and down describing their own particular niche as if it were the most important thing for a student to learn. And then, during the clinical years, life is brutal. People are rude. The hours are long. And there is always a test at the end of the rotation. After a while, I reasoned that the most important thing I could do for my patients, for my fellow human beings, was to assure myself some peaceful time. I made a point of hoarding my extra time for simple pleasures. I read Perri Klass's novel in which she describes how physicians must relearn the ability to appreciate the mundane. Her point is that physicians must regain their humanity after they complete their training. For my part I tried hard not to lose it, or at least to hold on to it as long as possible."

hatever inadequacies of medical education **V** in promoting professionalism and humanism in its students may have existed in the past, they have been greatly exacerbated in recent years. Teaching hospitals across the land have been struggling to survive financially while still maintaining their educational and service missions. Much of the decline in hospitals' income is attributable to the growing unwillingness of private and governmental payers to factor education time into their reimbursement fees. The hospitals' response has been to require clinical teaching faculty to be more clinically productive, to devote ever-increasing amounts of time to reimbursable patient care in order to compensate for revenue shortfall. This reduces the time faculty can give to teaching, research or community service, thus creating a more business-like ethos. In this kind of clinical environment, it becomes more challenging than ever to make certain that the attitudes and behaviors characterizing professionalism are manifested on a consistent basis.

Let me give you one example of a program developed to nurture a few qualities of professionalism and humanism, especially the quality of compassion. It is a program originally conceived and produced by someone who I view as one of the great people in American medicine. Her name is Rachel Naomi Remen and she is at the University of California at San Francisco. She calls her program "Healing Arts." Originally developed for physicians experiencing burnout and the need to refresh mind and spirit, Dr. Remen then offered the program as an elective to medical students at UCSF. It was tremendously popular among the students and was soon replicated at Stanford and Dartmouth. This year, for the first time, a group of faculty in Einstein's Department of Family Medicine gave the program to a group of 40 first-year students who signed up for it. They participated in five four-hour sessions during January and February with not a

Here are some of the written comments from students when asked about the most valuable personal or professional insights gained from the course:

single dropout along the way.

"Not to lose my heart and compassion."

"The importance of not losing yourself in the process of becoming a physician."

"Sharing emotion (crying, hugging) can be beneficial for patients."

"Confidence in what I will bring to my medical practice—not just science and diagnosis, but also relationships, caring, even fun."

Remember, these comments were from students who had completed only five months of medical school!

In this talk, I've discussed very briefly five different items for educational change at Einstein and at medical schools across the land: Genomics, Preventive Medicine, Global Medicine, Integrative Medicine, and Professionalism. There are several, just as important, that I did not have time to discuss: Geriatric Medicine, Women's Health, Palliative Care, and Cultural Competency. But they are no less important.

I am not in the "chicken little" camp of educational reform. I do not think the sky is falling. But I do see it full of gray clouds with respect to the influence of medical education on student behavior; especially in the hidden curriculum and the socialization process.

With each passing year, new items may be added to the list and, of course, as we implement change successfully, some listed items may be removed. Different items will be put into practice at different rates. We have three-year plans, five-year plans, even 10-year plans. Items associated exclusively with knowledge and skills, such as genomics, will be implemented faster. Items associated mainly with attitudes and non-cognitive behaviors, such as professionalism and humanism, take much longer for change to occur. The major point is that we make an institutional commitment to addressing these items and actually produce change! If we make this commitment and

if you, the students, make a commitment to continue to learn, I think the namesake of our medical college would be very pleased.

One of the perks we in the

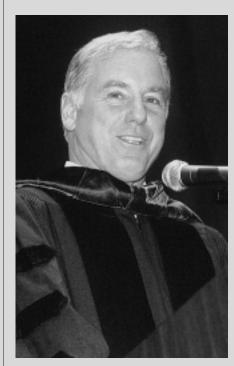
Dean's Office have is the chance to chat with Albert Einstein during moments when he takes muchneeded pauses to relax from his journeys through the universe at the speed of light. I asked him to listen to this talk, though he did seem rather annoyed with me for disturbing his rest and didn't seem particularly interested in what I have to say about the future of medical education. After all, this is the man who said he only wanted to know God's thoughts and that all the rest are details. But I reminded him about the medical college to which he gave his name, and that seemed to arouse him. So he asked me to accompany him to his beloved office at the Institute for Advanced Studies in Princeton. There he listened to my ideas for educational change and read through my notes, which he complained about because there were no mathematical equations. He reminded me that he never thinks in words at all. He also hated the printed images of PowerPoint slides that I showed him and was amazed when I told him that students absolutely adore them.

In the end, however, he smiled, expressed satisfaction, and encouraged me to go ahead with the plan for educational change. He told me that he would visit the school again in about five years to see how much we accomplished. What more motivation do we need?



A Dean's View of Dean

by Dominick P. Purpura, M.D. The Marilyn and Stanley M. Katz Dean



n a recent interview for "Bert's Digest," an independent student publication of the Albert Einstein College of Medicine, Dr. Howard Dean, a former student of ours ('78), was asked: Governor Dean, we understand that you met your wife at Einstein. Dean: "We met in Dom Purpura's class, which is the most frightening class for any medical student. She got 99 on the final exam, I got a 35, and passing was 34. So it is very clear who has the brains in the family."

Howard did indeed pass my course but did considerably better than he recalls. As a matter of fact, in reviewing his academic record as a medical student at Einstein, I noticed that he received honors in psychiatry, neurology, surgery, obstetrics/gynecology, hematology, community medicine and human behavior. As I probed further into his academic file, I discovered that the Howard Dean we knew was not the same person who graduated from Yale in 1971.

applying to a top tier medical school to do very well in both science and liberal arts courses, do extremely well on the Medical College Admissions Test and have a sterling record of extracurricular activities ranging from community service to ife sciences research. And, still some don't make it. Howard Dean was a political science major at Yale who could have done very much better as a student than he did. He graduated in 1971 and endured the life of a stockbroker for two years before taking off to Colorado to think and ski. He worked at a number of odd iobs, one of which took him to a Denver hospital where he worked for six months as a night volunteer. What struck him, he writes in the essay accompanying his application to Einstein, was the dedication of the interns, residents and nurses working together, their sense of commitment, that rekindled a similar type of motivation in himself. This epiphanous experience had to be tested, so he took another volunteer job at St. Vincent's Hospital in New York City while reorganizing his life as a putative premedical student at Columbia University's School of General Studies, nearly three years after graduation from Yale. It is a fact that no student can be considered for medical school without having performed satisfactorily in general and organic chemistry, physics and mathematics. Howard had been exposed to none of these subjects. Despite this, the official record from Columbia shows that in 1973 and 1974 he received no less than an A- in these science subjects and (to my astonishment) A+ in organic chemistry and A+ in biology lab. Such is the power of motivation

and dedication to a new life.

It is common for most students

All applicants to medical school are requested to write a personal statement summarizing their reasons for studying medicine. Howard chose to ask himself two questions in his essay and attempt to answer them—to wit: "How should I use my talents, and what do I want to be able to look back on as my accomplishments when I'm 50?" The answer: "At 50 I would like to look back at a career that provided, and would continue to provide, service to others and was rewarded with the warmth and strength that comes from serving interests other than one's own."

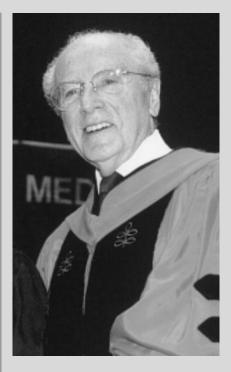
The Albert Einstein College of Medicine places great weight on the personal interview of a candidate for admission. Howard was interviewed by one of our most experienced physicians. The interview lasted over an hour. The

We accepted Howard

Dean in 1975 and graduated him in 1978 in an accelerated program.

He has never left "home."

faculty member's letter sent to the Admissions Committee detailed Howard's experience from the day of his admission to Yale to the date of the interview—a period of 6.5 years. It chronicled the sometimes erratic course of an unfocused young man unable to find his purpose in life—until his epiphany working in a hospital. Our senior faculty member concluded: "Throughout a long interview with this lad, I appreciated his direct and



what seemed to be frank answers to direct and specific questions, some of which are given in this report. He demonstrated a mature demeanor of a man twice his age. He convinced me of his sincerity and affinity for the sick, seldom seen with frequency anymore. Howard B. Dean no longer represents a lost soul, but you can count him a winner, for he has indeed come home."

And so it came to pass that we accepted Howard Dean in 1975 and graduated him in 1978 in an accelerated program. He has never left "home."

Dr. Dean (left) returned to Einstein in June to give the commencement address to the Class of 2003. Dr. Purpura (above) introduced him.

NEWSREEL

continued from page 2

director and remains director of the division of endocrinology.

Dr. Rossetti is internationally recognized as a leading physician/scientist in the field of metabolism. His research centers on understanding the abnormalities that underlie the pathophysiology of type 2 diabetes and the mechanisms by which hyperglycemia causes resistance to the action of insulin. This latter phenomenon, termed "glucose toxicity," is a major reason for treatment failures in both type 1 and type 2 diabetes. He has pioneered research



DR. ROSSETT

bridging fundamental advancements in biochemistry, cell and molecular biology, with state-of-theart physiology in the intact organism. For his groundbreaking work he has received numerous honors, including the Irma T. Hirschl Career Scientist Award. In 2000 he received the Outstanding Scientific Achievement Award of the American Diabetes Association (ADA) and delivered the Lilly Lecture at the ADA's annual scientific meeting. He recently served as chair of the ADA's Policy Committee. Dr. Rossetti is a member of the editorial board of Diabetes and of the Journal of Clinical Investigation, and is associate editor of the American Journal of Physiology: Endocrinology and

Dr. Rossetti received his M.D. degree from Trieste University Medical School in Italy and completed postgraduate training and a postdoctoral fellowship in internal medicine at the Rome University Medical School. He then came to the United States where he served for four years as a postdoctoral fellow in endocrinology at Yale University School of Medicine. He arrived at Einstein in 1991, following three years at the University of Texas Health Science Center at San Antonio. He advanced to professor of medicine in 1996 and was appointed professor of molecular pharmacology in 1998. He has served as co-director of the DRTC since 1997.



From left: Drs. Elizabeth Lee-Rey and Nereida Correa, co-directors of Einstein's Hispanic Center of Excellence, accept a special proclamation from Bronx Borough President Adolfo Carrion along with Dr. A. Hal Strelnick, the Center's director, at the inaugural celebration marking the Center's establishment.

HISPANIC CENTER OF EXCELLENCE ESTABLISHED

The College of Medicine has established the first—and currently only—Hispanic Center of Excellence in New York State. The new Center, funded by a \$1.2 million grant from the U.S. Department of Health and Human Services, is one of just 31 such centers nationwide. The grant recognizes Einstein's leadership in research, education and service to underrepresented communities.

Through the Hispanic Center, a number of programs and courses have been structured to improve the resources available to the communities served by Einstein physicians, and to foster further understanding among students and faculty of the diverse health concerns of the people of the Bronx. The Center seeks to expand the number of qualified Hispanic applicants interested in attending medical school or pursuing research opportunities.

"The Hispanic Center of
Excellence at Einstein will reflect
the diversity of cultures and nationalities that make up the Bronx," said
Dr. Elizabeth Lee-Rey, who, along
with Dr. Nereida Correa, is a codirector of the center.

"We are thrilled to have this opportunity to set an example for our students and faculty, as well as for other medical institutions in New York," added the Center's program director, Dr. A. Hal Strelnick.

WOLKOFF NAMED DIRECTOR OF BELFER INSTITUTE

Dr. Allan Wolkoff, Class of '72, professor of medicine and of anatomy & structural biology, was appointed director of the Belfer Institute for Advanced Biomedical Studies. He succeeded Dr. Dennis Shields, professor of developmental & molecular biology, and of anatomy & structural biology. Dr. Shields, who directed the Belfer Institute from 1996-2002, is credited with developing innovations in the Belfer program that have turned the Institute into a model postdoctoral training program.



DR.WOLKOFF

Dr. Wolkoff has the distinction of being the first Einstein alumnus to head the Belfer Institute. A Dartmouth graduate, he earned a B.M.S. degree from Dartmouth Medical School before coming to Einstein as a medical student. Graduating in 1972, he stayed in the Bronx to complete a residency in medicine at Bronx Municipal Hospital Center (now Jacobi). He then went to the National Institute of Arthritis, Metabolism, and Digestive Diseases as a clinical associate in gastroenterologyhepatology. He returned to Einstein in 1976.

Dr. Wolkoff is director of the program project on liver cell membrane proteins, program director of the gastroenterology-hepatology training grant, and director of research training for the division of gastroenterology, liver disease and nutrition.

He is on the editorial board of the *Journal of Hepatology* and has served both as a member and chair of various study sections for the National Institutes of Health and the Veterans Administration.

Laurels

Dr. Steven Almo, professor of biochemistry and of physiology and biophysics, received the American Society for Biochemistry and Molecular Biology-Amgen Award for significant achievements by a young investigator in the application of biochemistry and molecular biology to the understanding of disease.

Dr. E. Stephen Amis, Jr., professor and chair of radiology, was named chairman of the American College of Radiology Board of Chancellors.

Dr. Nir Barzilai, director of the Einstein Institute for Aging Research and associate professor of medicine (endocrinology), has been elected to serve on the editorial boards of the *Journal of Gerontology* and of *Diabetes*.

Dr. Olga Blumenfeld, professor emeritus of biochemistry, was the recipient of the 2002 Morton Grove-Rasmussen Memorial Award presented by the American Association of Blood Banks. The award recognizes her many contributions—in the study of transfusion medicine and blood group antigen polymorphisms, in the establishment of a human mutation database documenting antigen DNA variation in 14 blood group systems, and to the field of glycobiology.

Drs. Erwin Bottinger, assistant professor of medicine (nephrology) and of molecular genetics; John Condeelis, co-chair and professor of anatomy and structural biology; Jeffrey Segall, professor of anatomy and structural biology; and Robert **Singer**, co-chair and professor of anatomy and structural biology and professor of cell biology, were among the authors of a paper in Cancer Research describing the first successful combination of intravital imaging with molecular profiling as an approach to the discovery of genes involved in tumor invasion.

Dr. Michael Brownlee, the Anita and Jack Saltz Professor of Diabetes Research, has been awarded the Claude Bernard Medal, the highest scientific award of the European Association for the Study of Diabetes (EASD). As the award recipient, Dr. Brownlee received the medal and delivered the Claude Bernard Lecture at the 2003 EASD/International Diabetes Federation meeting in Paris.

Dr. Neil Calman, clinical professor of family and social medicine and assistant clinical professor of epidemiology and population health, is featured in two books that address developing and extending health care: *Big Doctoring in America: Profiles in Primary Care*, by Fitzhugh S.M. Mullan, M.D. (University of California Press) and *To Give Their Gifts: Health, Community and Democracy*, by Richard A. Couto, Ph.D. (Vanderbilt University Press).

The laboratories of **Drs. John** Condeelis, professor and co-chair of anatomy and structural biology, and **Jeffrey E. Segall**, professor of anatomy and structural biology, provided the images of metastatic cancer cells featured on the cover and inside front page of the National Cancer Institute's Plan and Budget Proposal for 2004, entitled "The Nation's Investment in Cancer Research." Jeffrey Wyckoff, director of Intra-Vital Imaging at Einstein, and Frank **Macaluso**, director of Einstein's Analytical Imaging Facility, were also involved in preparing the image.

Dr. Pablo Castillo, assistant professor of neuroscience, was selected as a 2003 Pew Scholar in the Biomedical Sciences.

Dr. Herbert Cohen, professor of pediatrics and of rehabilitation medicine, and director of Einstein's Children's Evaluation & Rehabilitation Center, has been named the first holder of the newly established Ruth L. Gottesman Chair. Dr. Gottesman, a member of the Einstein faculty for more than 30 years, is clinical professor emeritus of pediatrics.

Dr. Ana Maria Cuervo, assistant professor of anatomy and structural biology and of medicine, was selected as an Ellison Medical Foundation New Scholar in Aging. The award supports Dr. Cuervo's studies in protein degradation to determine how to improve the removal of damaged protein that occurs as part of the aging process.

Dr. Ales Cvekl, associate professor of molecular genetics and of ophthalmology & visual sciences, has been selected to receive the 2003 Cataract Research Award from the National Foundation for Eye Research.

Dr. Peter Davies, the Judith and Burton P. Resnick Professor of Alzheimer's Disease Research, has been selected by the National Advisory Council on Aging to receive an NIH MERIT Award in recognition of his outstanding record of scientific achievement as a principal investigator on National Institute on Aging research projects. This is Dr. Davies' second NIH MERIT Award.

Dr. David Fidock, assistant professor of microbiology and immunology, was selected by the Burroughs Wellcome Fund to receive a 2003 Investigators in Pathogenesis of Infectious Diseases Award.

Dr. E. John Gallagher, professor and chair of emergency medicine, has been elected to the Institute of Medicine of the National Academy of Sciences. He is one of only a handful of physicians who specialize in Emergency Medicine to be selected for this honor.

Francine Garrett, an M.D.-Ph.D. candidate at Einstein, was named chairperson emeritus of the Student National Medical Association. She also is the recipient of a National Medical Fellowship and has been nominated for a Herbert Nickens Memorial Fund Scholarship, given by the Association of American Medical Colleges.

Dr. Jeffrey Gold, professor and chair of cardiothoracic surgery and professor of pediatrics, was elected vice president and president elect of the Thoracic Surgery Directors Association and to the board of directors of the Society of Thoracic Surgeons. He also has been invited to serve as an editor of *The Annals of Thoracic Surgery*.

Dr. Susan Horwitz, co-chair of molecular pharmacology and the Rose C. Falkenstein Professor of Cancer Research, has been nominated Doctor Honoris Causa of the Université de la Mediterranée, in Marseille, France. Her honor was marked at a special ceremony during the University's "Journée Scientifique et Academique." She also received the Medal of Distinction from Barnard College, which is the highest honor bestowed by that institution. And she is immediate past president of the American Association of Cancer Research.

Dr. Gloria Huang, instructor of obstetrics & gynecology and women's health, and a fellow in the laboratory of Dr. Susan Horwitz, received the 2003-04 American College of Obstetrics and Gynecology/Solvay Pharmaceutical Research Award in Menopause, for her work exploring chemotherapeutic agents and new drug combinations for treating ovarian cancer.

Dr. William Jacobs, Jr., professor of microbiology and immunology and of molecular genetics, and Howard Hughes Medical Institute Investigator, has been elected to Fellowship in the American Academy of Microbiology.

Dr. Anne Johnson, associate professor emeritus of pathology and of neuroscience, participated in a presentation on the findings of a genetic defect in the rare childhood disorder Alexander's disease, at the second annual Neurobiology of Disease in Children Symposium, sponsored by the Child Neurology Society. She also contributed an article on the disorder to be included in a book, Encyclopedia of the Neurological Sciences (Elsevier, March 2003). Additional Einstein contributors to the *Encyclopedia* include: **Dr.** James Tate Goodrich, professor of clinical neurological surgery and of clinical pediatrics, who wrote a biography of William MacEwen; **Dr. Mark Mehler**, professor of

neurology, of neuroscience, and of psychiatry and behavioral sciences, on hematolymphopoietic growth factors; **Dr. Herbert Schaumberg**, professor and Edwin S. Lowe Chair of Neurology and professor of pathology, on toxic neuropathy; and **Dr. David Spray**, professor of medicine and of neuroscience, on gap junctions.

Dr. T. Byram Karasu, Silverman Professor and chair of psychiatry and behavioral sciences, has authored *The Art of Serenity: The Path to a Joyful Life in the Best and Worst of Times* (Simon & Schuster).

Dr. Leopold Koss, professor emeritus of pathology, was awarded an honorary degree from the Pomeranian Academy of Medicine in Szczecin, Poland.

Dr. Jeffrey Levsky, M.D.-Ph.D. candidate, Class of 2004, who recently completed his doctorate in the laboratory of Dr. Robert Singer, professor and co-chair of anatomy and structural biology, received a 2003 Harold M. Weintraub Graduate Student Award, presented

by the Basic Sciences Division of the Fred Hutchinson Cancer Research Center. The award, given annually to 16 graduate students from North America and Europe, recognizes young scientists whose research demonstrates quality, originality and scientific significance.

David Li, an M.D.-Ph.D. candidate in the laboratory of Dr. Denis Rousseau, professor and chair of physiology and biophysics, is the recipient of a 2003 Student Research Achievement Award, presented by the Biophysical Society. Mr. Li, whose work was selected under the category of bioenergetics, was one of just six students selected for the award.

Dr. Thomas Leyh, professor of biochemistry, is serving as a member of the Biochemistry Study Section for the Center of Scientific Review, of the National Institutes of Health.

Dr. Michael Lisanti, professor of molecular pharmacology, is listed in the "100 Most-Cited Researchers in Biochemistry" from 1992 to 2002.

Dr. Meggan Mackay, assistant professor of medicine, was the selected honoree of the Lupus Benefit Showcase, put on by the Lupus Foundation of America (Bronx Chapter). The honor recognizes Dr. Mackay's research and work with lupus patients.

Dr. Solomon Moshe, professor of pediatrics, of neurology, and of neuroscience, is the recipient of a 2003 research award from the Rett Syndrome Research Foundation for his work helping to improve understanding of the debilitating, often disabling, neurological disorder.

Dr. Peter Mundel, associate professor of medicine and of anatomy and structural biology, received the 2003 Young Investigator Award from the Council on the Kidney of the American Heart Association.

Dr. Seiji Ogawa, visiting professor of biophysics and physiology, is a recipient of the 2003 Japan Prize, presented by The Science and Technology Foundation of Japan. The award, which is widely regarded as the Japanese equivalent of the Nobel Prize, recognizes Dr. Ogawa's "Discovery of the Principle for Functional Magnetic Resonance Imaging."

Dr. Demitri Papolos, associate clinical professor of psychiatry and behavioral sciences, was a panelist for a discussion on bipolar disorder in children, at the symposium of the National Alliance for Research on Schizophrenia and Depression.

Dr. Dominick P. Purpura, the Marilyn and Stanley M. Katz Dean, received a special medallion in recognition of his years of service as chairperson of the Robert Wood Johnson Foundation's National Advisory Committee of the Minority Medical Faculty Development Program. Dr. Purpura served as the committee chair from 1989 to 2002.

Dr. Michael Reichgott, Class of '65, Associate Dean for Clinical Affairs and Graduate Medical Education, has been invited to serve as an American Medical Association representative to the Liaison Committee on Medical Education.

Dr. Matthew Scharff, Harry Eagle Professor of Cancer Research and professor of cell biology and of medicine, received the Mayor's Lifetime Achievement Award for Excellence in Biological & Medical Sciences from Mayor Bloomberg. The award is the highest honor for such achievement given by the City of New York. Dr. Scharff also is the first recipient of the Donald A. Rowley Award for Outstanding Mentoring, presented by the University of Chicago. The award recognizes his contributions to the training of a long line of investigators in the field of immunology.

Dr. Edward Schwartz, professor of medicine (oncology), served as chair of a Pathobiology Study Section for the Department of Defense Breast Cancer Research Program. The program will provide \$150 million to support innovative research directed toward the eradication of breast cancer.

Dr. Sylvia Smoller, professor of epidemiology and population health, was a panel member at a writer's conference sponsored by the National Osteoporosis Foundation, the Partnership for Long-Term Health for Women, and Eli Lilly Company. The purpose of the conference was to provide media with information for telling the "whole" story with regard to hormone therapy and the Women's Health Initiative (WHI). Dr. Smoller is a principal investigator of the WHI at Einstein.

Dr. Pamela Stanley, professor of cell biology, has been awarded the International Glycoconjugate Organization Award for 2003, in recognition of her numerous and important contributions to the glycosciences. She also is past president of the Society of Glycobiology.

Dr. Bettie Steinberg, professor of otolaryngology, chaired the NIH-sponsored 6th Research Workshop on the Biology, Prevention and Treatment of Head and Neck Cancer.

Dr. Martin I. Surks, professor of medicine, received the 2002 Distinguished Service Award of the American Thyroid Association, for his continuing contributions to the Association, of which he has been a member since 1969.

Dr. Weigang Wang, a postdoctoral fellow in the laboratory of Dr. John Condeelis, professor and co-chair of anatomy and structural biology, has been named a 2003 Inglenook Scholar-in-Training. Twenty promising young scientists, all conducting research in breast cancer, are awarded the designation each year by Inglenook Vineyards.

Dr. Thomas Wills, associate professor of epidemiology and population health, was recognized by the Institute for Scientific Information for his authorship of the top half of 1% of papers cited in the fields of psychology and psychiatry in the Science Citation and the Social Science Citation Index.

Dr. Zhong-Yin Zhang, associate professor of biochemistry and of molecular pharmacology, has accepted an invitation to serve as a member of the Biochemistry Study Section at the National Institutes of Health's Center for Scientific Review.

Shi Zhong, a fourth-year Ph.D. candidate working with **Dr. Syun-Ru**Yeh, assistant professor of physiology and biophysics, and **Dr. Denis**Rousseau, chair and professor of physiology and biophysics, received a Student Travel Award from the Biophysical Society for his poster presentation, "The Role of the Molten Globule State in the Folding of Horse Heart Cytochrome C."

IN MEMORIAM

Dr. Edward J. Hehre, founding



chairman of microbiology & immunology, died on August 6, 2002 at his home in Bronxville, NY. Born in New York City in 1912, Dr. Hehre

received his bachelor's degree from Cornell University in 1934 and his medical degree from the university's medical college in 1937. He then joined the medical college's faculty, in the department of microbiology, in 1938. In 1956, he moved to the then newly established Albert Einstein College of Medicine, where he founded the medical school's department of microbiology and immunology. He became emeritus professor of microbiology and immunology in 1978.

During a career that spanned more than 60 years, Dr. Hehre worked in the field of carbohydrate enzymology, biology and immunochemistry. His early work led to the discovery of glycosyltransferases, and later identified the scope and mechanisms of these enzymes. His work received many honors, including the John Simon Guggenheim Fellowship, John Polachek Fellowship, Fogarty Senior International Research Fellowship, Medal of Merit of the Japanese Society for Starch Science, and the 2002 Melville L. Wolfrom Award in Carbohydrate Chemistry.

Dr. Hehre is survived by his wife, Florence, their three children and seven grandchildren.

The editors wish to thank Dr. Fred Brewer, professor of molecular pharmacology and of microbiology & immunology, for providing this remembrance of Dr. Hehre.

IN MEMORIAM

It is with much sadness that we



report the passing of **Raymond Chiu** (1972-2003), an MD-PhD student in the department of developmental and molecular biology, who car-

ried out his thesis research in the laboratory of Dr. Dennis Shields. Raymond passed away on August 16th as a result of acute lymphoblastic leukemia, less than five weeks after the initial diagnosis. He was an outstanding student who graduated from New York University magna cum laude in 1994 with a degree in biology.

He joined our MD-PhD program in 1996. His thesis research was to investigate the mechanism of programmed cell death or apoptosis, a process that occurs when a cell's normal processes malfunction. Raymond identified a series of proteins that are degraded specifically during the cell death process and discovered a novel mechanism by which the so-called "death pathway" can be activated. His research made an immediate impact on the field and has been the subject of several important review articles. His scientific career was far too short and there is no doubt he would have been a leader in his chosen field. He leaves a wonderful legacy in his work, which is being pursued not only at Einstein, but also by investigators around the world.

To commemorate Raymond's memory, the department has established an annual memorial seminar in his name. Raymond will be greatly missed by his wife Kyung Hee, his parents, brother Simon and sister Pamela and their families as well as by all his colleagues and friends.

The editors wish to thank Dr. Dennis Shields, professor of developmental and molecular biology for this remembrance of Raymond Chiu.

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GLYCOMICS

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mouse's insulin-producing cells," says Dr Porcelli. "Injecting a glycolipid compound into these mice will activate their CD1-dependent T cell response and prevent them from developing diabetes. We're real interested in that, because we think we can fairly quickly develop a therapeutic approach to human autoimmune diseases by exploiting the CD1 immune response."

Credit for preventing autoimmune reactions in the diabetesprone mouse goes to an unlikely source: a sea sponge. A pharmaceutical company searching for anti-cancer drugs in sponges happened upon a glycolipid named alpha galactosylceramide, which was synthesized once its structure was determined. Injecting this compound into a tumor-bearing mouse makes the tumor regress significantly-somewhat like chemotherapy but without the usual side effects. Rather than poison the tumor as chemo does, alpha glactosylceramide instead

directs the immune system to attack it.

"What's interesting is that this same glycolipid that provokes an immune response against tumors can also shut down harmful immune responses in the non-obese diabetic mouse," says Dr. Porcelli.

Research has shown that alpha galactosylceramide acts in men and mice through the same mechanism: It binds specifically to CD1d proteins, one of the five different forms of CD1 protein found on antigen-presenting cells. Then, in both species, this "CD1d protein/ glycolipid antigen" complex is recognized by CD1d-dependent T cells, which respond by either attacking tumors or suppressing autoimmune activity. Most of the responding T cells are a major subpopulation of CD1d-dependent T cells called natural killer T cells.

"One problem with alpha galactosylceramide is that it's sort of a blunt instrument that activates anti-inflammatory and pro-inflammatory mechanisms—even both at the same time," says Dr. Porcelli.

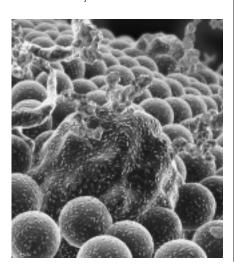
"We're now working with chemists to find variants of this glycolipid that more precisely induce one type of immune response or the other."

As new compounds are synthesized, Dr. Porcelli's lab tests their effects on various strains of mice. Initial experiments are done with standard healthy mice. A few hours after injecting the compound into the mouse, researchers measure blood levels of two cytokines: interleukin 4, which suppresses many types of immune responses including inflammation; and interferon gamma, which is associated with tumor rejection.

"If you find lots of interleukin 4 and little interferon gamma, then you know this compound might be good for treating autoimmune diseases," says Dr. Porcelli. "On the other hand, high levels of interferon gamma and very little interleukin 4 means you might have a cancer treatment." The interleukin-4 is released by the natural killer T cells that recognize alpha galactosylceramide; by contrast, interferon gamma is released mainly by differ-

ent (but similar sounding) immune cells known as natural killer cells, which are recruited by natural killer T cells to help fight infections.

The research is going well: "In the next few weeks, we hope to test about 50 new derivatives of the original glycolipid," says Dr. Porcelli. "We've already found at least two compounds that seem to preferentially produce an anti-inflammatory reaction, so they might be especially good for treating or preventing autoimmune diseases," says Dr. Porcelli. ■



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