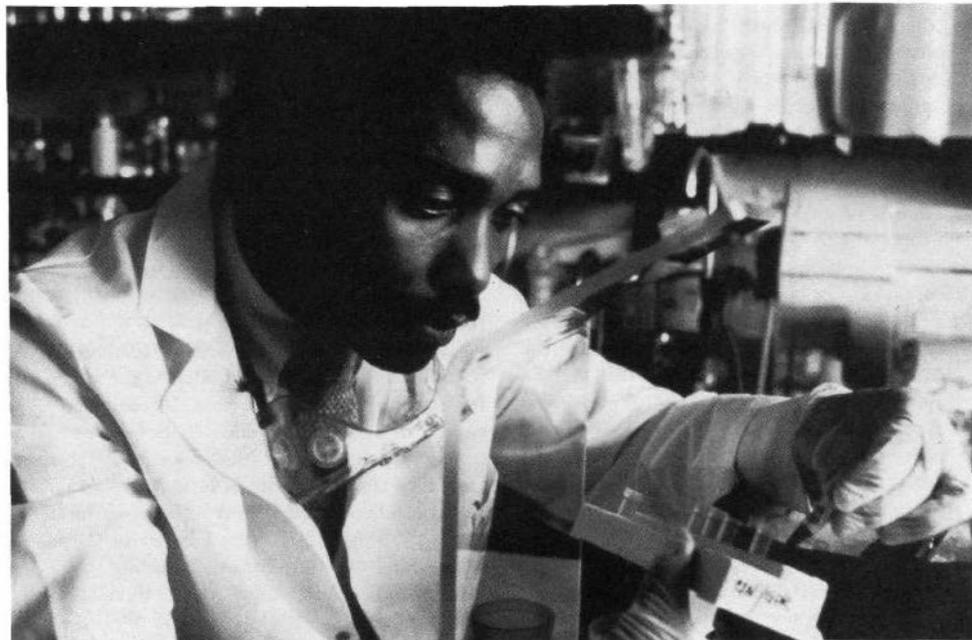


The NIH Record

NIDDK Celebrates 40th Year With Focus on Future



Dr. Griffin Rodgers, a researcher in NIDDK's Laboratory of Chemical Biology, searches for ways to treat sickle cell disease. See pages 8-13 for more 40th anniversary feature stories and photographs.

NIDDK Clinical Research

The Well-Beaten Path Between Bedside and Bench

By Kathy Kranzfelder

In her postcard to the National Institute of Diabetes and Digestive and Kidney Diseases, the woman wrote, "Please send me information on your diseases. I've been diagnosed with all of them."

Surely she was mistaken. Maybe she has diabetes, perhaps with kidney complications, but could she also have a thyroid condition? sickle cell disease? hepatitis? ulcers? kidney stones, gallstones, cystic fibrosis, and a long list of metabolic disorders?

Like the postcard's author, most people have no idea of the breadth of disorders being studied by NIDDK scientists. NIDDK clinical investigations involve hematologists, endocrinologists, hepatologists, gastroenterologists, pathologists, even neurologists. Varied as these studies are, however, they have one thing in common: the constant traffic they create between bedside and bench.

Severe Forms of Disorders Studied

NIDDK clinical studies, particularly into rare, severe forms of disease, have often given insight into basic biological mechanisms. For example, studies of a severe form of insulin resistance have led to an understanding of how healthy insulin receptors function.

According to Dr. Simeon Taylor, chief of the NIDDK Diabetes Branch, the advantage

of studying an extreme form of a disorder is that a pattern of symptoms specific to the disorder tends to emerge. If investigators looked only at milder forms of the disorder, such a pattern might take many more years and resources to identify.

Taylor's group has been investigating severe insulin resistance type A, a syndrome that often leads to non-insulin-dependent diabetes and is marked by dark, velvet-like rashes in the folds of skin, called acanthosis nigricans, and, in young women, high androgen (testosterone) levels, leading to facial hair and menstrual disorders. People with severe insulin resistance have plenty of insulin circulating in their blood, but defective insulin receptors prevent cells from responding efficiently to the hormone, which leads to impaired glucose metabolism. Investigators believe that high levels of insulin have adverse effects on some organs, including the skin and ovaries, thus causing the acanthosis nigricans and hyperandrogenism.

The dark rash can cause patients considerable distress and is often their main reason for seeking medical attention, said Taylor. A topical cream used to treat acne is frequently effective in relieving acanthosis nigricans.

The changes caused by hyperandrogenism,

(See CLINIC, Page 4)

Discovery of CF Gene Spurs Windfall of Research

By Jane DeMouy

"SOLD OUT" read the banner pasted over the poster in a Crystal City hotel lobby. Upstairs, the crowd had already filled a ballroom. New arrivals spilled into adjacent rooms, where they crowded around TV monitors.

The headliners for these standing-room-only crowds were not Madonna or Paul McCartney, but the cystic fibrosis gene, its mutation, Delta F508, and the cystic fibrosis transmembrane regulator (CFTR). Backing them up was the Molecule of 1989, the DNA polymerase, which helped make the last two possible. The occasion was the 1990 North American and International Cystic Fibrosis Conference and the speakers, Dr. Francis Collins of the University of Michigan (Ann Arbor) and Drs. Lap-Chee Tsui and Jack Riordan of the Hospital for Sick Children in Toronto, were the three NIDDK grantees who only a year ago discovered the mutation that causes cystic fibrosis (CF) to occur in 70 per-

(See CF GENE, Page 6)

NIH To Observe World AIDS Day, Nov. 30

The National Institutes of Health will commemorate World AIDS Day on Friday, Nov. 30. Officially, Dec. 1 (Saturday) has been declared by the World Health Organization (WHO) Global Programme on AIDS as a day to focus on the concerns and problems of women, to support programs that specifically promote the health of women and children, and to assist women in their crucial role in AIDS prevention and care. The first World AIDS Day, held in December 1988, was proposed by the World Summit of Ministers of Health on AIDS Prevention in recognition of the need for wide dissemination and exchange of information and educational messages on AIDS prevention.

The NIH World AIDS Day program, "Women and AIDS," will be held at noon in Lipsett Amphitheater, Bldg. 10. The program, cosponsored by the Office of AIDS Research and the Fogarty International Center, will feature addresses by Dr. William F. Raub, acting NIH director; Dr. Anthony S. Fauci, NIH associate director for AIDS research and director, NIAID; S. Denise Rouse, a commander in the PHS Commissioned Corps; and LaShaun Evans, a woman living with HIV disease.

Rouse has held various positions in the

(See AIDS DAY, Page 2)

AIDS DAY

(Continued from Page 1)

Bureau of Health Care Delivery and Assistance at the Health Resources and Services Administration. She was the recipient of a PHS award in 1989, and an outstanding unit citation for planning the National Conference on HIV Infection and AIDS among Racial and Ethnic Populations. In 1987 she was the recipient of the Southern Christian Leadership Coalition's Black Achievers of Alabama Award. She holds a master's degree in public health, in addition to her undergraduate degree in biology. She is presently on a special assignment to Community Health Care, Inc., a federally funded health center in the District of Columbia.

Additionally, Rouse serves as the volunteer director of the D.C. Women's Council on AIDS. The council, founded in 1987, is a private nonprofit organization dedicated to the prevention of HIV infection in women, as well as providing compassionate support to women



S. Denise Rouse

infected by HIV. "The council exists because AIDS is now one of the top 10 causes of death for women in their childbearing years. The proportion of female cases of AIDS in two D.C. wards significantly exceeds the national average," stated Rouse, who also serves as a "buddy" to several Black women, offering them her friendship and support.

Rouse will talk about one of the council's several programs, the Sister Care Support Network. Sister Care, as its all-volunteer membership calls it, holds weekly support group meetings that provide peer support, companionship and information on how to live with HIV for infected women. Segments of a soon-to-be released film of a support group meeting will be shown. In the film, Rouse serves as facilitator for three HIV-infected women.

The film, tentatively named *Women and AIDS*, is "real and strong," said Rouse, and "tells it like it is." One of the support group participants, Evans, will also speak at the NIH commemoration. Evans, a 35-year-old single mother, is the HIV program director at

'Names' Quilt To Be Displayed During World AIDS Day at NIH

The Names Project Foundation is responsible for the Names Project Quilt, a quilt made of thousands of 3' x 6' panels, each one commemorating the life of someone who has died from complications associated with the human immunodeficiency virus (HIV) that causes AIDS. The idea of a quilt as an AIDS memorial originated with Cleve Jones in November 1985. A year and a half later, in June 1987, he teamed up with several others to organize the Names Project Foundation. Jones, who served as executive director of the Names project until last spring, spoke at the 1989 NIH commemoration of World AIDS Day.

Two important goals of the Names project relate well to the commemoration activities planned at NIH—to confront individuals and governments with the urgency and enormity of the AIDS pandemic and the need for a compassionate response, and, by revealing the names and the lives behind the global statistics, to build a powerful, positive, creative symbol of remembrance worldwide.

The sections of the quilt displayed at NIH are part of more than 13,300 panels that comprise it. The quilt, in its entirety, was first displayed on Oct. 11, 1987, on the Capitol Mall. At that time, it covered a space larger

than two football fields, included 1,920 panels, and was seen by an estimated half million people.

The entire AIDS quilt returned to the Washington area in October 1988, having grown to 8,288 memorial panels when it was displayed on the Ellipse behind the White House. It grew to more than 10,900 panels when it was displayed for the last time, again on the Ellipse, the weekend of Oct. 6-8, 1989. It has grown too large to ever be displayed in its entirety again.

The Names project estimates that more than 2 million people have visited the quilt. It presently weighs more than 14 tons, consists of more than 227,000 square feet, contains more than 4 miles of walkway fabric and more than 78 miles of total seams. Panels have been contributed from individuals in all 50 states, Puerto Rico, the District of Columbia, as well as 23 countries, including Australia, Belgium, Israel, Italy, Uganda and New Zealand.

Materials in the quilt include afghans, cremation ashes, dresses, flags, jeans, merit badges, stuffed animals and wedding rings—all representative of the diverse lives commemorated by the quilt.

the Washington Free Clinic, when she is not spending "quality time" with her 9-year-old daughter or serving on the advisory committee of *Positive Woman*, a newsletter for HIV positive women. Evans, in a recent telephone interview, said, "Don't call me a victim, and don't give me your sympathy—I feel good about myself, about my life, and about how I am living with HIV disease."

A *Visible Symbol*, a videotape produced by the Names Project Foundation to explain the educational and memorial nature of the AIDS memorial quilt, will be shown during the presentation. This film, shown during last year's World AIDS Day program, moved many in the audience to tears. In addition, sections of the AIDS quilt (see related story) will be shown. The entire quilt contains more than 13,300 panels.—Marc Horowitz □

Subjects Needed for Herpes Study

NIAID is seeking healthy men and women, ages 18 to 45, with confirmed genital herpes for a placebo-controlled study. You must have had genital herpes for more than 1 year to qualify for this study. For more information, call 496-1836. □

The NIH Record

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NIAID To Test New AIDS Vaccine in Humans

The NIAID has received FDA approval to begin human clinical trials of a new candidate AIDS vaccine. The trials will take place in NIAID's AIDS Vaccine Evaluation Units located at several major medical centers around the country. This is the sixth AIDS vaccine sanctioned by the Food and Drug Administration for human testing.

The vaccine (IMMUNO-Ag) consists of gp160, the surface protein of the AIDS virus, made by recombinant DNA technology. This particular recombinant gp160 is novel because its three-dimensional shape matches that of the gp160 protein made by native HIV. Experience with other virus vaccines indicates that this match may be important.

"In many cases, retaining the native shape of the viral molecule is crucial to a vaccine's ability to stimulate a strong immune response," said NIAID director Dr. Anthony S. Fauci. "We don't know if this is true for HIV molecules used in vaccines, but these clinical trials will help answer this very important question."

Scientists from NIAID, the National Cancer Institute, and IMMUNO-Ag of Vienna, Austria, collaborated on preclinical development of the vaccine.

The phase I clinical study will evaluate the safety and immunogenicity of the vaccine and will be performed in two phases. In the first phase, a low dose of vaccine (12.5 micrograms) will be evaluated: by random assignment, 20 volunteers will receive the real vaccine and 10 will receive a dummy vaccine, or placebo. Neither the volunteers nor the study physicians will know who is receiving which vaccine.

In the second phase, a high-dose (50-microgram) vaccine preparation and placebo will be compared in a similar manner, with 20 volunteers receiving the real vaccine and 10 receiving placebo. The high-dose study will begin 1 month after the low-dose phase, and only if no serious toxicities are noted in the earlier study. Each of the 60 volunteers will be given a primary immunization and boosters at 30 and 180 days and will be followed for a total of approximately 30 months.

Volunteers must be HIV-negative healthy men and women ages 18 to 60. A comprehensive questionnaire and interview will be administered before admission to the study to determine that neither the potential volunteer nor his or her sex partners have identifiable high-risk behavior for HIV infection.

Work on the IMMUNO-Ag vaccine began several years ago in the laboratory of Dr. Bernard Moss, chief of NIAID's Laboratory of Viral Diseases. He and his colleagues had devised a new way to turn mammalian cells into mini-factories for producing recombinant

proteins. NIAID, IMMUNO-Ag, and NCI scientists initiated a project to make a vaccine with a recombinant gp160 made by this process.

A monkey cell line was coinfecting with two recombinant vaccinia viruses, each acting solely as a carrier. One vaccinia carried the gene for an enzyme from a bacterial virus. This enzyme, RNA polymerase, helps copy DNA into RNA, which is then translated into proteins. The other vaccinia carried a "switch" attached to the gene for gp160. As RNA polymerase was produced, it bound to the switch, initiating the production of gp160 protein. Because this process all took place in a mammalian cell line, the recombinant gp160 protein was properly glycosylated: that is, sugar molecules were attached to its surface in the same way as found on native HIV.

Thus vaccinia, a virus familiar to medical science, was adapted to induce the production of noninfectious HIV envelope proteins that could be purified and formulated into a vaccine.—Laurie K. Doepel □

Seminar Series on Women's Health Continues With Dec. 12 Session

The second session in the seminar series entitled "Women's Childbearing Years and Beyond," begins at 3:30 p.m. in Lipsett Amphitheater, Bldg. 10, on Dec. 12.

The program for seminar II is a multidisciplinary examination of the health and behavior issues across the lifespan of women. Following an introduction by Dr. Vivian Pinn-Wiggins of Howard University, Dr. Nancy Adler of the University of California at San Francisco will present research findings most relevant to women in their teenage years. Dr. Jennifer Niebyl of the University of Iowa Hospitals and Clinics will address health issues related to pregnancy and childbirth and Dr. Sonja McKinlay will talk about menopause. Drs. Jane Norbeck of the University of California at San Francisco and Ruth Faden of Johns Hopkins University will lead the discussion that follows.

All those interested are urged to attend. Until further notice, no tickets are required. Seating will be on a first-come, first-served basis and this session will not be broadcast via closed-circuit television.

Please check *The NIH Record* for future announcements about the remaining sessions (Feb. 6 and Apr. 3) of the 1990-1991 women's health seminar series. □



NIAID director Dr. Anthony S. Fauci recently received the First International Chiron Prize for Biomedical Research during a ceremony in Rome, Italy. The honor was bestowed upon Fauci by the Scuola Superiore di Oncologia e Scienze Biomediche, in Genoa, Italy, and the Scuola Internazionale di Oncologia e Medicina Sperimentale, in Rome. The institutions honored Fauci for his scientific accomplishments in the field of basic and clinical immunology. Fauci also received the degree of doctor of medicine and surgery, *honoris causa*, from the Università di Roma, "La Sapienza," in Rome.



Dr. William E. Paul, chief of the Laboratory of Immunology, NIAID, was one of 24 internationally renowned biomedical scientists who spoke recently at the Irvington Institute for Medical Research 75th anniversary symposium "Immunology in the 21st Century" in New York City. His theme was "Lymphokines: Molecular Mediators of the Immune Response." The symposium focused on new studies that have led to an improved understanding of the basic functions of the immune system and their implications for the practice of medicine today and in the future.

CLINIC*(Continued from Page 1)*

however, are more difficult to reverse. "It's like when you're in a boat that's full of water: it's easier to bail out the water after you've plugged the hole," said Taylor. Thus, the first step is to reduce the patient's androgen level, usually with estrogen and progestin. These hormones suppress the pituitary hormones that signal the ovaries to release androgen. Once the source of androgen is blocked, patients can try electrolysis to remove unwanted facial hair. Losing weight also helps to reduce the masculinizing effects of excess androgen.

The cosmetic problems of severe insulin resistance can be profoundly disturbing to patients, and Diabetes Branch scientists are trying to understand the physiologic mechanisms that trigger these changes. The work of Taylor's group actually began with the discovery of type A insulin resistance by NIDDK investigators Drs. Ron Kahn, Jesse Roth, and Phillip Gorden in 1976. A steady flow of basic science insights has emerged from this line of clinical research ever since.

"In the past decade, we've made great advances in learning how receptors work and in identifying the genes that encode for insulin receptors," said Taylor. NIDDK scientists have identified about 15 mutations associated with insulin resistance. As obstacles to gene therapy are gradually overcome, these findings may lead the way to curing insulin resistance and possibly preventing some forms of diabetes.

Thyroid Hormone's Role Elucidated

Dr. Bruce Weintraub, chief of NIDDK's Molecular, Cellular, and Nutritional Endocrinology Branch, is studying hormones that regulate the thyroid gland. Like the Diabetes Branch researchers, Weintraub's group has found receptor defects that interfere with the body's ability to use vital hormones efficiently. Weintraub has also focused on syndromes of severe hormone resistance before searching for less severe, possibly more common hormonal abnormalities.

Generalized thyroid hormone resistance (GTHR) is one such syndrome, in which thyroid hormone fails to bind properly to its intracellular receptor, leading to mental retardation, attention deficit, and impaired growth. Earlier NIDDK research indicated that this hormone resistance is an inherited syndrome caused by a genetic mutation and has provided the first clearly genetic model for the study of attention deficit disorder, or hyperactivity, in children.

GTHR, like other hormone resistance syndromes, has long baffled physicians because the symptoms led doctors to believe patients lacked thyroid hormone, yet blood tests indicated excess thyroid hormone. Weintraub and

*Dr. Simeon Taylor*

his collaborators were the first to show that this syndrome, and possibly other thyroid hormone abnormalities, could be caused by receptor defects.

"There is an increasing recognition that many endocrine problems studied at NIDDK are caused by problems in receptors," said Weintraub. Since this early speculation, 11 separate molecular defects in the thyroid hormone binding domain have been discovered, and at least four different thyroid hormone receptors have been identified. "We have learned that the various forms of thyroid hormone receptors play an important role in growth, development, behavior and metabolism," said Weintraub.

Defective Cell Intermediaries Targeted

Studies of hormone resistance by Dr. Allen Spiegel, chief of the Molecular Pathophysiology Branch, are also enhancing our understanding of the basic workings of the cell. Spiegel's investigations of pseudohypoparathyroidism helped establish that inherited diseases can be caused by defects in G proteins, which serve as intermediaries between hormone receptors and effectors. Individuals with pseudohypoparathyroidism have short stature, bone abnormalities in hands, feet and face, obesity and mental retardation.

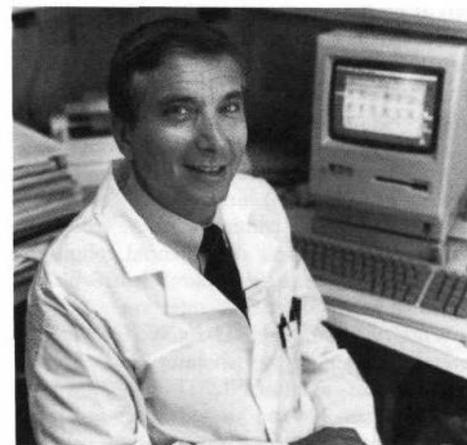
The cellular sequence of events involving G proteins begins when a so-called first messenger such as a hormone binds with a receptor which then attaches to a G protein. The G protein carries a signal to an effector, often an enzyme, before shutting itself off. The effector sends out a second messenger to signal another sequence of events, often the

generation of cyclic AMP, which finally leads to a physiologic effect, for example, the excretion of phosphate ions in urine as occurs in kidney cells.

This receptor-G protein-effector system is very specialized in the first phase, when hormones are bound by their uniquely specific receptors, and in the end, when the specific physiologic effects are triggered. The middle steps involving G protein and effector action are generic. The G protein that binds to an activated parathyroid hormone receptor in the kidney is indistinguishable from the G protein that binds other hormone receptors linked to cyclic AMP production in liver cells, thyroid cells and myriad other cells.

"If you were trying to discover the cause of a disease of PTH resistance, you would not likely be thinking the defect would occur in G proteins, because if the resistance is unique to PTH, you would look to the specific parts of the pathway—in the beginning at the PTH receptor, or possibly in the end where the physiologic effect occurs," explained Spiegel. However, several common features in pseudohypoparathyroidism—obesity, short stature and mental deficiency—cannot be explained by resistance to parathyroid hormone alone; and other hormonal disorders in these individuals have come to light such as abnormal thyroid and gonadal function. These findings led Spiegel, who was working with Dr. Gerald Aurbach in the 1970's, to look for a point of convergence that would tie these characteristics together.

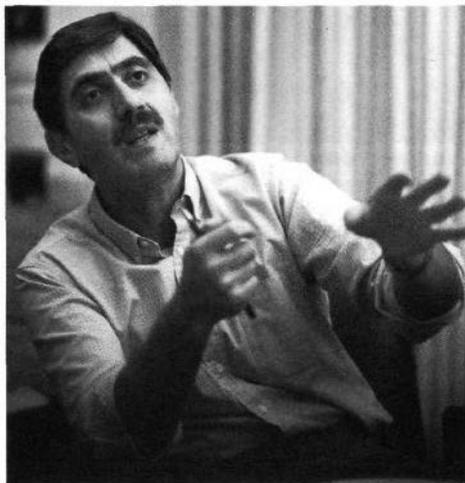
Aurbach, chief of NIDDK's Metabolic Diseases Branch, had already determined that the defect had to occur at or before the point of cyclic AMP production in the cellular pathway, which ruled out the end of the pathway. Spiegel trained his attention on the G protein, which had recently been discovered by NIDDK scientist Dr. Marty Rodbell. "A defect in the PTH receptor would give a picture of unique PTH resistance," said Spiegel, "but a defect in a common element can give

*Dr. Bruce Weintraub*

you lots of other things going wrong."

Spiegel's hypothesis was easy to test because the G protein is in all kinds of cells. He could measure amounts of G protein in easily accessible red blood cells and skin tissue. "We found about a 50 percent deficiency in the amount of G protein in pseudohypoparathyroid individuals as compared to controls and people with plain old hypoparathyroidism," said Spiegel. These initial results have now been extended to identification of specific mutations in the gene for the G protein in individuals with pseudohypoparathyroidism.

Malfunctioning G proteins have since been suggested as suspects in causing some psychiatric illnesses, acromegaly and other endocrine tumors, and the aging process. Given the ubiquity of G proteins, scientists are very interested in knowing all the functions and influences of these intracellular coupling pro-



Dr. Allen Spiegel

teins. About 16 different G proteins have been discovered to date.

Basic Findings Lead to Sickle Cell Drug

About as often as clinical findings demystify fundamental mechanisms, bench findings can spur new treatment approaches. Such was the case when NIDDK Laboratory of Chemical Biology researchers Drs. Griffin Rodgers and Alan Schechter and others decided to try hydroxyurea, a widely used leukemia drug, to treat sickle cell disease.

"The observation that individuals with high levels of fetal hemoglobin have mild sickle cell disease, combined with what molecular biologists had learned about turning on fetal genes, led to the idea of increasing the levels of fetal hemoglobin in sickle cell patients to try to improve their clinical condition," said Rodgers. Hydroxyurea promised to "turn on" the fetal hemoglobin genes as desired, though scientists do not fully understand how this happens.

Schechter, Rodgers and collaborators found that hydroxyurea raised fetal hemoglobin levels two- to ten-fold in more than half the patients they treated. This increase curbed by 25 percent the tendency of hemoglobin molecules to polymerize, or link up in long chains, which leads to the red cells' distortion, the hallmark of the hereditary blood disease. This "sickling" of red cells can lead to clogged blood vessels, causing excruciating pain, and, in severe cases, strokes and sudden death.

Rodgers and Schechter believe that the more they can reduce the polymerization tendency, the fewer complications their patients will suffer. They are currently studying the potential of treating patients with hydroxyurea in combination with erythropoietin, an anti-anemia drug. Anemia is another common complication of sickle cell disease because sickled red blood cells tend to "wear out" faster than normal red blood cells.

Opiate Blockers May Relieve Itching

Another example of applying basic concepts to a clinical problem comes from the liver diseases section of NIDDK's Digestive Diseases Branch. Investigators here are exploring the problem of severe pruritus, or itching, associated with obstructive liver disease (cholastasis) such as primary biliary cirrhosis in which bile secretion is impaired.

The itching was originally thought to be caused by the accumulation of bile acids because skin biopsies from patients with cholastasis showed high levels of bile salts. The conventional therapy was to administer oral resins that bound bile acids in the intestine and increased their fecal excretion. "Anti-histamines have been prescribed, though they generally didn't work. Ultraviolet light has also been tried. In fact, many treatments have been given in an attempt to relieve this distressing symptom without any strong scientific rationale," said Dr. Nora Bergasa of the liver diseases section. When all else fails and the itching becomes intractable, a liver transplantation is the final option.

Bergasa was working with section chief Dr. E. Anthony Jones on other research when they hypothesized that this form of pruritus might be mediated by opiate substances that are somehow present in increased amounts or made more available to the brain in cholestatic liver disease.

"Opiate-like substances have been reported to accumulate in patients with chronic liver disease, and pruritus is a recognized side effect of opiates such as morphine," Bergasa explained. These findings, along with results of a study published in England, provide support for Bergasa's postulate. In the British study, patients with cirrhosis had a reaction similar to narcotic drug withdrawal when they were given nalmefene, a powerful opiate-receptor antagonist. Nalmefene, which com-

petes with opiates for the same receptors, caused only minor side effects in the study's healthy control group. These observations suggest that patients with cirrhosis have increased levels of internally produced opiate-like substances.

Bergasa and her colleagues conducted a pilot study to see if another opiate-receptor antagonist, naloxone, would alleviate itching caused by primary biliary cirrhosis. Naloxone is often used in hospital emergency wards to awaken unconscious heroin abusers.

Eight patients received either naloxone or saline infusions without being told which they were receiving. Scratching was then measured with a "scratch transducer," developed by NIH's National Center for Research Resources' Biomedical Engineering and Instrumentation Program, which recorded the vibrations of a fingernail as it crossed skin. Naloxone reduced scratching by 50 percent overall, according to Bergasa. She is now seeking additional patients with itching caused by liver disease to further test the benefits of naloxone and nalmefene. Bergasa has also gone back to the lab where she is studying how opiate systems behave in animal models of cholestatic liver disease.

Back to Basics

Many other clinical investigations are under way in NIDDK, yet they represent only part of what goes on in the Division of Intramural Research. NIDDK has one of the largest, most varied basic science programs on campus.

While NIDDK clinical investigators often hear words of gratitude from their patients, the basic scientists toil in relative obscurity to the general public. Most people are unaware of the seemingly unimportant basic findings that underlie so many widely known clinical therapies and discoveries.

In the world scientific community, however, NIDDK has a well established reputation as an extremely productive and influential basic research institution. Half a dozen Nobel laureates in chemistry and physiology or medicine since 1956 can trace roots to the NIDDK Division of Intramural Research. □

SIDS Seminar Set for Dec. 6

The NIH Disease Prevention Seminar Series will present, "SIDS: Working Toward Preventive Strategies," on Thursday, Dec. 6, in Wilson Hall, Bldg. 1, at 11:30 a.m. Dr. Marion Willinger, Center for Research for Mothers and Children, NICHD, will make the presentation. All NIH employees are invited to attend. No preregistration is necessary. For more information, contact Janet Wetmore, 496-1105. □

CF GENE*(Continued from Page 1)*

cent of the 30,000 Americans who have the disease.

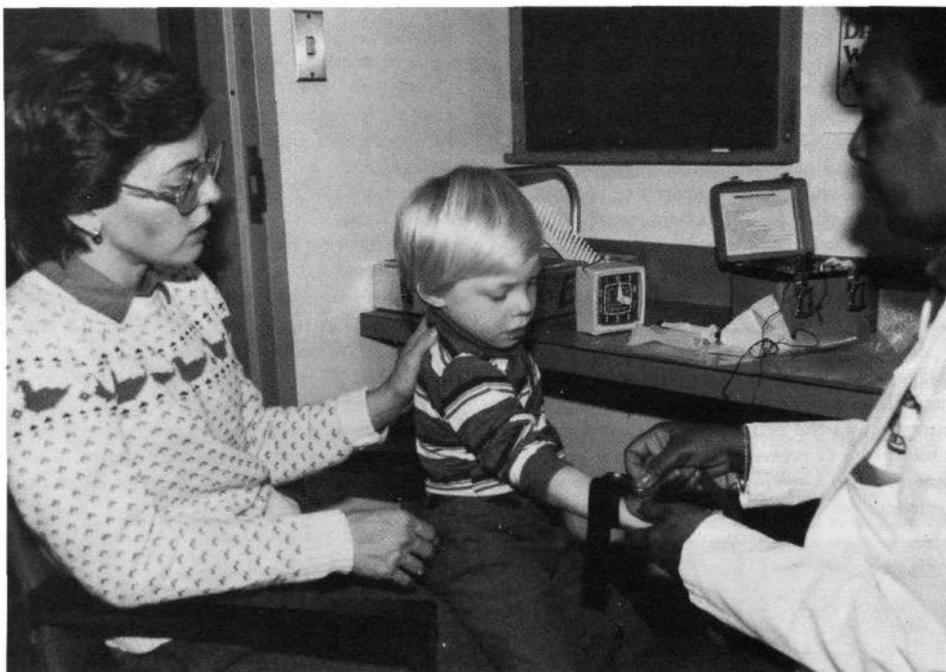
Recently, the three researchers and their colleagues succeeded in correcting the CF defect *in vitro* by replacing it with a normal gene. Their work has energized conference attendees, who attentively examine slide after slide of DNA and Southern blots, hoping to decipher whether the CFTR protein plays a role in the faulty ion transport that can cause the lungs of CF patients to clog with mucus, and whether drugs such as DNase, which breaks down the mucus in test tubes, will provide safe and effective treatment.

CF research wasn't always like this. NIDDK scientist emeritus Dr. Paul Di Sant'Agnes discovered an abnormality in the sweat of CF patients, leading to the first diagnostic test for CF in 1953. In the next decade, NIDDK-trained scientists made Nobel Prize-winning discoveries that would make the eventual identification of the gene possible: Dr. Arthur Kornberg discovered the enzyme that could copy DNA; Dr. Christian Anfinsen identified the mechanisms of protein folding; and Dr. Marshall Nirenberg helped unravel the code that DNA uses to translate itself into the protein building blocks of the body.

Then for some years, CF seemed stalled in a sleepy backwater of research. Luckily, and largely through NIH support, scientific tools were being developed that would change that: NIDDK-supported researcher Dr. Paul Quinton used greatly refined techniques for culturing and studying cells and their functions to report that the sweat gland ducts of CF patients did not allow normal chloride transport. Simultaneously, geneticists were developing new methods to study genes, the blueprints of proteins. Now cystic fibrosis research is advancing by coupling basic research in cell biology with recombinant DNA technology. Methods such as restriction fragment length polymorphism (RFLP) analysis and gene walking and jumping, techniques that once might have seemed science fiction fantasies, are yielding answers.

Using RFLP analysis, for example, scientists are able to cut sequences of chemical bases in DNA structure with restriction enzymes to create a gene library. With this technique, NIDDK-supported researcher Tsui and colleagues began to identify markers linked to the disease, narrowing its location to the long arm of chromosome 7. By mid-1987, several research teams had submitted proposals for NIDDK support to find the gene, and NIDDK staff facilitated a collaboration between Tsui in Canada and Collins in Michigan that resulted in their cooperative hunt.

Even for seasoned researchers, the task was daunting: chromosome 7 contained



A young patient receives sweat test to determine whether he has cystic fibrosis.

150,000,000 base pairs. But by 1988, researchers knew that the CF gene lay somewhere between two markers, MET and J3.11. That narrowed the territory to 2,000,000 base pairs, making a systematic search possible. Using DNA probes from a library of CF sweat glands developed by Riordan, Tsui began to "walk" that segment of the chromosome with overlapping segments of DNA in search of the CF trait, covering lengths of 20,000 bases at a time. Meanwhile, Collins and the University of Michigan team used an analogous technique, gene "jumping," which covered 100,000 base pairs at a time. In effect, Collins' team could scout the territory rapidly, looking for broad signs, knowing that Tsui's team was following up, scrutinizing all the nooks and crannies.

As they narrowed the field, the Collins team mapped a promising region, using probes and pulsed field gel electrophoresis, while the Tsui team screened thousands of probes from a chromosome 7 library to label the section of the chromosome near the CF gene. With this combined persistence and inventiveness, they brought home the prize.

"Finding the gene opened a bottleneck," Collins told the crowd at the CF conference. Since then, scientists in several labs have cooperated to identify other mutations of CFTR, totaling 50 to date. Collins and Tsui have already succeeded in replacing a defective gene with a normal one in a cell culture system. They are also trying to understand how the gene and its protein function.

"The protein is there to pump something

unidentified; what is that something?" Collins queries. "The chloride channel doesn't seem to be the issue, but maybe regulation of it is." Researchers currently assume that several domains regulate the movement of sodium and chloride across the epithelial membrane.

Search for Diabetes Genes Sparked by CF Success

The success of CF research has generated its own clones. Other scientists were encouraged to begin tracking the genes responsible for both insulin-dependent and non-insulin-dependent diabetes (NIDDM). NIDDM, believed to begin from the interaction of multiple genes and environmental triggers, presents a particularly complex genetic puzzle.

It is that very complexity that has intrigued molecular biologists such as NIDDK's Dr. Simeon Taylor and Dr. Graeme Bell, a University of Chicago researcher and a member of the NIDDK-supported team at the University of California at San Francisco (UCSF) that cloned the insulin gene in 1979. A physician friend at UCSF began to educate him about diabetes while he shared his knowledge of biochemistry and molecular biology in a mutual effort to "see what we could do with this information."

What Bell, now working with his own team, has done with the information has revitalized research in glucose metabolism. Research has shown that glucose transporters are likely to be involved in the pathology of diabetes, and by cloning and sequencing the DNA encoding the proteins in a family of

glucose transporters, Bell's team has put "faces" on them, helping to illuminate their specific roles in glucose metabolism. "There are five proteins that are able to transport glucose across the plasma membrane," Bell explains. "We now know the sequences of all of them, so it's like having a signature."

Other benefits accrue when molecular techniques are applied to the physiological problems of a specific disease. Knowing the identity of each protein allows scientists to develop specific antibodies for each and to study each in isolation. A protein's precise molecular identity provides a base for more sophisticated assays to measure it, and researchers are then able to work with small amounts of tissue from human subjects under various metabolic conditions. "You can use an RNA sample, and do a needle biopsy for fat and for muscle," Bell says, in some instances bypassing animal studies and providing information that applies directly to people. "Molecular approaches allow a greater range of experiments," with more applications for clinicians, he says.

Currently, Bell's lab is using two approaches to identify genes that contribute to diabetes susceptibility. In one direction, they continue to clone candidate genes expressed in beta cells and in insulin target tissues such as muscle, adipose tissue, and the liver. A second approach that appears to be paying off is to ignore assumptions about gene products that might be involved and to look for DNA markers using segregation analysis.

Building on NIDDK-supported work done by emeritus researcher Dr. Stefan Fajans at the University of Michigan in Ann Arbor, Bell's group has been studying a large family with Maturity Onset Diabetes of the Young (MODY). This form of non-insulin-dependent diabetes has a clear mode of inheritance, Bell explains, allowing the same kind of genetic experimentation used to identify DNA markers for cystic fibrosis.

They've already identified a DNA marker tightly linked to the MODY gene in one family, Bell says. Working with Dr. William Knowler's group at the NIDDK labs in Phoenix, Bell's team is now trying to determine if this marker might be responsible for diabetes in other families by looking at DNA samples from 100 Pima Indians. Developing more genetic data will help his team develop a strategy for cloning the diabetes genes.

Encouraged by research successes expedited by scientific cooperation, CF patients have begun to anticipate treatment, prevention, and cure. Diabetes patients have been watching, too. They hope it won't be long before Bell and his colleagues can do the same for them. □



On Oct. 22, the NIDDK EEO advisory committee presented a \$375 check to Andrew Tartler, executive director of the Children's Inn, marking the last event celebrating the institute's 40th anniversary. Seated are (front row, from l) Karen Howard, Tartler and Mary Jane Zarnowski. Seated in back row are (from l) Dorothy Banks, Lois Lipsett (cochair), Ludlow McKay, James Scherbenske, Nancy Cummings (cochair), Rao Thotakura and Sharon Frazier.

Research Subjects Needed

Earn up to \$378 for participating in a psychopharmacology experiment relating to the effects of commonly prescribed drugs. Minimum time required over a 7-week period. Must be between ages 21 and 50, in good health, and not active-duty military. For more information, call 295-0972 weekdays between 9 a.m. and 12 noon, Uniformed Services University. □

NIMH Needs Volunteers

The Laboratory of Psychology and Psychopathology, NIMH, is seeking healthy women and men between the ages of 20 and 45 to participate as control subjects in studies of cognitive processes in different types of mental illness. No drugs or invasive procedures are involved. Volunteers will be paid. For information, call 496-7674 between 9 a.m. and 4:30 p.m., Monday-Thursday. □



NIDDK celebrated its 40th anniversary with a dinner in September at the National Naval Medical Command Commissioned Officers' Club. Seated are (from l) Dr. Daniel J. Koshland Jr., guest speaker and editor of Science magazine, Dr. William F. Raub, acting director of NIH, and Mrs. Raub. Standing are (from l) NIDDK director Dr. Phillip Gordon, Mrs. Gordon, assistant secretary for health Dr. James O. Mason, Mrs. Mason, and Dr. John T. Farrar, chairman of the Digestive Disease National Coalition and host of the event.

High Blood Pressure Is Major Culprit

Blacks Struck by High Rate of Kidney Disease

By Mary Harris

Four hours a day, 3 days a week, and probably for the rest of his life, 39-year-old Joe Henderson Jr. goes to his "job" at Walter Reed Army Medical Center's dialysis clinic. There he is joined to a machine that removes his blood a pint at a time, cleans it, and returns it to his body.

Joe Henderson's kidneys don't work. His job is dialysis, and it keeps him alive. Maybe long enough to receive a donated kidney. Maybe not.

"Kidney failure is no longer fatal, thanks to maintenance dialysis and kidney transplantation," said Dr. Lawrence Agodoa, who directs NIDDK's research program in chronic kidney failure and treats patients with kidney disease at Walter Reed Army Medical Center. "But even with these effective treatments, most people with chronic kidney failure have a vastly shortened lifespan, with survival rates comparable to those for prostate, colon and lung cancers."

The main reason for this shortened survival is heart disease. Heart-related problems were the immediate cause of death in 65 percent of kidney failure patients who died in 1988. "Some of the deaths were due to an accelerated buildup of cholesterol in the arteries," said Agodoa. But cholesterol is not the heart's only enemy. Because dialysis is not a perfect replacement for the kidneys, patients with kidney failure must control the amount of potassium-rich foods they eat. Too much or too little potassium can disrupt the heart's rhythm, causing sudden heart failure.

Under normal conditions, the kidneys, nestled on each side of the body under the rib cage, remove waste and regulate blood pressure. They also balance body fluids and salts and release erythropoietin, a hormone that tells the bone marrow to produce red blood cells.

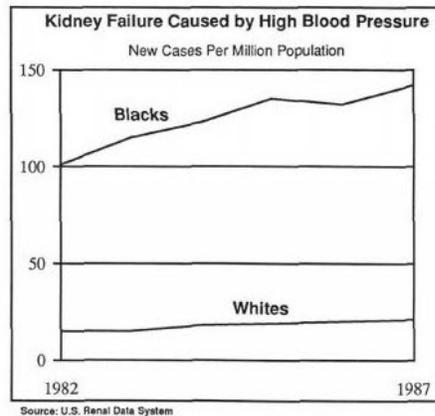
The filtering units of the kidney, called glomeruli, are made up of clusters of microscopic blood vessels. When these units are damaged by a disease such as diabetes or high blood pressure, the remaining healthy units work harder to compensate for the loss. As the disease progresses, more units are destroyed until the kidneys are working at only 5 or 10 percent of capacity. At this point, a person is diagnosed with end-stage kidney disease, or kidney failure, and must have dialysis or a kidney transplant to survive.

During 1988, 172,506 people in the United States were treated for kidney failure. More than 36,000 were newly diagnosed cases—nearly a 9 percent increase over 1987. Whites accounted for 67 percent of those treated for kidney failure, and Blacks

accounted for 29 percent—more than double their representation in the U.S. population, which is only 12 percent. Most patients with kidney failure have access to treatment—dialysis and transplantation—through the Medicare program administered by the Health Care Financing Administration (HCFA). According to a report from the U.S. Renal Data System, an NIDDK-supported program, treatment for chronic kidney failure cost more than \$5.4 billion in 1988.

The four main causes of kidney failure are diabetes, hypertension, glomerulonephritis and polycystic kidney disease. Blacks are at higher risk than whites for all causes except polycystic kidney disease, but researchers are finding that Blacks are hit especially hard by high blood pressure, which they tend to get at a younger age than whites. Between ages 25 to 44, Blacks have nearly 20 times the rate of kidney failure from high blood pressure as whites, and between ages 45 to 64, their risk is about 11 times higher.

"High blood pressure is basically what did my kidneys in," said Joe Henderson. "My feet and legs started swelling, so I went to the doctor." By the time Henderson found out he had high blood pressure, his kidneys had already been severely damaged. Fifteen years later he had kidney failure.



As treatment for high blood pressure has improved, death rates for stroke and heart disease have declined. In contrast, kidney failure due to high blood pressure is on the rise, particularly in Blacks. As one researcher pointed out, doctors know how to protect the heart and brain from hypertension but not the kidneys.

An NIDDK research initiative on kidney disease in Blacks is aimed at filling this gap of information. "We need to find out why Blacks

(See **BLOOD PRESSURE**, Page 10)



NIDDK Celebrates 4



Kidney failure patient receives hemodialysis.

Liver Transplantation Becomes

By Jim Fordham

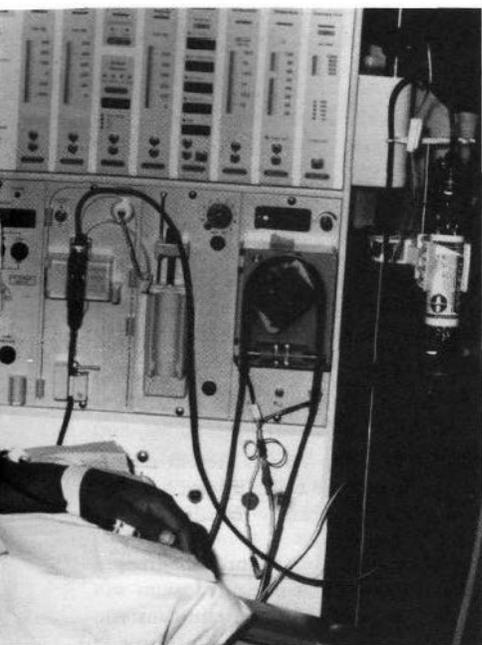
Liver transplantation is heroic surgery that offers patients with fatal forms of liver disease a new chance to pursue a full and active life. This ultimate step in the treatment of liver failure is exceptionally difficult surgery that only recently has evolved from an experimental and often disappointing procedure into an established, usually successful, treatment.

More than 2,100 liver transplants were performed in 1989 in 79 hospitals in the United States, almost double the number done 3 years ago, and more than 20 times the number done 10 years ago. In fact, more than half of all liver transplants have been done in the last 2 years.

Before the landmark 1983 NIH Consensus Development Conference on Liver Transplantation, fewer than 350 livers had been grafted in the U.S. At that meeting, the consensus panel concluded that "liver transplantation is a therapeutic modality for end-stage liver disease that deserves broader application," and in the years since, this life-saving therapy has come of age.

This important achievement began with crucial research on experimental animals in the 1950's and 1960's. By the early 1960's, the first extended survival after liver transplanta-

10th Anniversary



Established Therapy

tion in dogs was achieved using the anti-rejection agent azathioprine, with one dog surviving more than 10 years.

The first liver transplant in man was performed in 1963 by NIDDK grantee Dr. Thomas E. Starzl at the Colorado Medical School in Denver. During the next 20 years, about 540 of the operations were done at four major medical centers in the U.S. and in Europe. Long-term survival of patients who underwent the surgery was uncommon. Nearly 300 of the transplants done in the U.S. were performed by Starzl, who in February 1981 moved to the University of Pittsburgh School of Medicine to establish a transplant program at the Presbyterian-University Hospital. There, in 1984, Starzl did the first human combined heart-liver transplant.

In the beginning, successes were few, but Starzl and his colleagues persisted, gradually improving the surgical technique and means of controlling rejection. Eventually survival rates improved. The challenge and excitement surrounding liver transplantation attracted talented young investigators to the field. The work of Starzl and his many young trainees eventually led to successful surgical techniques

(See LIVER, Page 10)

NIDDK Researchers Probe Causes of Diabetes, Obesity

By Joan Chamberlain

Luggage in hand, Dr. Peter Bennett hurries into one last meeting at NIH before leaving for the airport. In an unmistakably British accent, he jokes about the 120-degree welcome awaiting him in Phoenix, Ariz., where he oversees an NIDDK intramural research program in diabetes. Bennett went to Phoenix 25 years ago to organize the first epidemiologic research on diabetes in the Pima Indians. As chief of NIDDK's Phoenix Epidemiology and Clinical Research Branch, he leads a team of researchers who continue to search for the causes and treatment of insulin resistance, obesity and diabetes in the Pimas.

Pima Indians have the highest rate of diabetes in the world: 50 percent of adults ages 35 and older have non-insulin-dependent (also known as type II or adult onset) diabetes, the most common form of the disease. Although diabetes was rare in the Pimas early this century, it had become common by the 1950's. In just the last decade, incidence has climbed by 50 percent.

Diabetes is caused by a defect in the body's ability to convert food to energy, a process that depends on the hormone insulin. People with non-insulin-dependent diabetes produce insulin, but their cells do not respond to the hormone efficiently. This condition, called insulin resistance, often precedes diabetes, making it a strong risk factor for the disease. To regulate glucose levels in the blood, the pancreas releases more and more insulin. Eventually, though, the pancreas can no longer keep up with the body's demand for insulin, and diabetes sets in. Treatment consists of weight loss through diet and exercise and, in some cases, insulin injections or oral drugs that lower blood glucose. But even with treatment, diabetes slowly damages nerves and small blood vessels and, in time, often leads to heart, kidney, nerve and eye disease.

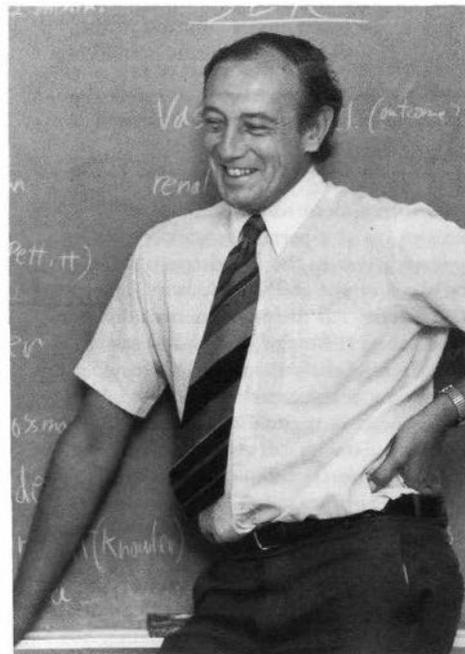
Genes Contribute to Diabetes

NIDDK researchers believe that genes play a major role in diabetes and have been studying insulin resistance as a key to understanding what goes wrong with glucose metabolism. Insulin resistance worsens as a person gains weight, but cells' sluggish response to insulin has more to do with genes than obesity.

"We're interested in insulin resistance because non-insulin-dependent diabetes is clearly a genetic disease. Since insulin resistance is one of the early abnormalities seen in the disease, it's natural to ask if insulin resistance is also genetically determined, and several pieces of evidence suggest that it is," said Dr. Clifton Bogardus III, chief of the clinical diabetes and nutrition section.

"In the Pimas, insulin resistance shows strong familial clustering, independent of obesity. Also, the Pimas tend to cluster into three groups—with low, medium and high levels of insulin resistance—rather than in the typical bell-shaped distribution. This three-pronged pattern of insulin resistance suggests that in the Pimas there may be a major autosomal gene inherited in a codominant manner," said Bogardus. That is, a person could inherit two copies of a normal gene, enabling a normal response to insulin; two abnormal genes, resulting in severe insulin resistance; or one of each, causing moderate insulin resistance.

Bolstering the case for a genetic basis of insulin resistance is a recent study conducted by NIDDK researcher Dr. Dave Pettitt, showing that Pima children have insulin resistance decades before the onset of diabetes. In a study comparing 439 nondiabetic Pima youngsters ages 6 to 19 with age-matched



Dr. Peter Bennett directs NIDDK's Phoenix Epidemiology and Clinical Research Branch.

white children from Rochester, Minn., Pima children had blood insulin levels 15 to 20 percent higher than their Midwestern peers.

Diabetes is most common in offspring who have two diabetic parents, less so in those with one diabetic parent, and least common in those with nondiabetic parents. Another risk factor is diabetes during pregnancy. Offspring of a diabetic mother are much more likely to develop diabetes than the offspring of a

(See DIABETES, Page 11)

BLOOD PRESSURE*(Continued from Page 8)*

seem more vulnerable to renal injury from high blood pressure, if some drugs are better than others in preventing blood pressure-related renal injury in Blacks, and if the target blood pressure should be lower for Blacks than whites," said Dr. Gary Striker, director of NIDDK's Division of Kidney, Urologic, and Hematologic Diseases.

People with kidney failure must decide, with the help of their doctors and families, which treatment—dialysis or transplantation—is best for them. Factors such as age, other illnesses, emotional support of family and friends, religious beliefs and trust in the medical profession influence a patient's decision.

Dialysis is a life-saving procedure and the treatment choice of most chronic kidney failure patients. Hemodialysis, done three times a week, uses a machine connected to a special filter to remove, clean and return the patient's blood minus wastes. Various forms of peritoneal dialysis, done three times a week to four times a day, depending on the form, use the patient's abdominal wall to filter wastes from the bloodstream into a solution in the abdomen. The waste-filled fluid is periodically

Blacks and whites differ in treatment choice and results.

replaced with a clean solution. Surgery is required to insert a permanent device that allows easy access to the bloodstream for hemodialysis or the abdominal cavity for peritoneal dialysis. All dialysis patients must cut down on calories, fluids, protein and salts.

Side effects of dialysis include blood clots and infections of the access site and the abdominal wall in peritoneal dialysis. New hemodialysis patients can also experience headache, nausea, muscle cramps, anorexia, dizziness and seizures.

Blacks most often opt to remain on dialysis, possibly because they tend to do well on it. Among Blacks with kidney failure at the end of 1988, 86 percent were on dialysis compared to 69 percent of their white counterparts. Blacks on dialysis have fewer complications that require hospitalization, and they live longer than whites on dialysis. According to Henderson, "It's not a physically active life, but I don't have any noticeable problems. If I didn't tell you that I was on dialysis, you wouldn't know. I feel well and I have adjusted well to the diet and regular visits to the dialysis center."

Kidney transplantation has important advantages over dialysis that, for many people, outweigh the risk of organ rejection, infection, osteoporosis and kidney damage. Although transplant patients must take immunosuppres-

sive drugs to prevent rejection, they are freed from dialysis and tend to have an improved quality of life, close to that experienced before the onset of kidney disease.

In 1989, 8,882 people got their wish for a new kidney. Unfortunately, another 14,669 were still waiting. Kidney donations have not kept pace with need, so most patients wait a year or more for a kidney transplant, according to the U.S. Renal Data System.

Henderson does not want a kidney transplant. "Maybe if I was to get worse I would think about it," he said. But even if he wanted a transplant, he would not accept a kidney from a family member. "It would be too much to put on them. What if they got sick and died, and I was still alive? I couldn't live with that."

But for patients who receive a transplant, the success rate is encouraging. Blacks and whites who received a transplant in 1987 had about the same 2-year survival. Up to 96 percent of patients who received a kidney from a living relative and up to 93 percent of those who received a kidney from a deceased, unrelated donor lived at least 2 years.

Graft survival, or survival of the new kidney, is lower in Blacks than whites regardless of whether the kidney came from a living relative or deceased, unrelated donor. Researchers do not know why some patients keep a transplant when others who seem as well matched reject the transplant. Why graft survival is lower in Blacks compared to whites is not well understood, but researchers are beginning to find genetic clues.

A donor kidney is matched with a recipient on the basis of six antigens, or tissue types, found on the HLA gene of each person. These antigens are part of the immune system and have been linked to kidney rejection. According to Agodoa, "Graft survival is best when all six antigens match. The next best is when five of six match. Beyond that, graft survival is similar for four or fewer matching antigens."

Researchers have found that Blacks have a more diverse genetic makeup and a wider range of HLA antigens than whites. This diversity decreases the chances of finding a donor kidney with matching antigens.

Finding Answers

In recommendations to NIDDK, a panel of researchers in epidemiology, genetics, immunogenetics, hypertension and nephrology has called for more studies, including a clinical trial to help answer questions about kidney disease in hypertensive Blacks. The NIDDK is now planning a pilot clinical trial that will test the feasibility of a full-scale study of kidney disease in hypertensive Blacks.

The NIDDK is also supporting the U.S. Renal Data System, the source of most of the

data presented in this article. The data system began collecting and analyzing data in 1988 with the help of the HCFA and is now the largest database on kidney disease in the U.S. Current studies are comparing patient and

For many, transplantation improves quality of life.

graft survival considering severity of illness at the onset of treatment; prognosis based on renal biopsy results; and quality of life of patients treated with erythropoietin, which relieves the anemia of kidney failure.

These and other NIDDK-supported studies will improve the understanding of kidney disease and, one day, will lead to the treatment and prevention of kidney failure. □

LIVER*(Continued from Page 9)*

and methods of followup care to prevent rejection that have made liver transplantation a well-accepted, effective therapy for advanced liver disease.

Over the years, Starzl has trained hundreds of transplant surgeons from dozens of countries, including most of the liver transplant surgeons in the U.S. According to Dr. Oscar Salvatierra Jr., past president of the United Network for Organ Sharing (UNOS), Starzl "has contributed more to the field of transplantation than any other individual." (UNOS is the national voluntary organization that sets standards of quality in organ procurement, distribution, data collection, testing and patient access.)

The liver is the largest of the body's organs and is essential to life. It acts as a chemical factory, regulating the blood levels and distribution of nutrients. The liver synthesizes glucose for energy and produces proteins for metabolic functions. The liver makes most of the clotting factors that prevent a person from bleeding to death. It also metabolizes drugs and toxins and secretes fluids such as bile that aid in digestion. Without a viable liver, a person would soon die. Liver transplantation is the only alternative.

Transplanting a liver is a monumental challenge that draws on all of a surgeon's skill and intelligence. The operation on the liver recipient can take 10 hours or longer, during which the surgeon often works blind, suturing many vessels behind the large, awkward organ, and coping with numerous other technical difficulties and complications.

Important advances in liver replacement have included development of more effective surgical techniques for the management of bile duct connections and the introduction of the "veno-venous bypass," which allows blood that would normally go to the liver to circulate to the other organs while the liver is being



Dr. Thomas Starzl, pioneer of liver transplantation removed.

A basic problem encountered in organ transplantation is the natural tendency of the body's immune system to reject the donor organ. Since the beginnings of organ replacement, scientists have searched for safe and effective methods of suppressing the immune response. At first, irradiation and bone marrow transplantation were tried, but were unsuccessful. Since then, scientists have focused their efforts to prevent graft rejection on the use of either drugs or antibodies.

The drug azathioprine was first used clinically in 1962 and marked the beginning of the modern era of immunosuppression. Nearly two decades passed before another drug, cyclosporine A, was found to be more effective than azathioprine in suppressing immune response. By the 1980's, cyclosporine had become the mainstay of therapy to prevent transplant rejection, although it was necessary to combine it with prednisone, an anti-inflammatory corticosteroid hormone.

Scientists soon found, however, that toxic effects, particularly to the kidneys, occur when cyclosporine A is given in a high-dose, two-drug regimen. So in recent years, many centers have used three-drug regimens that combine lower-dose cyclosporine A with prednisone and azathioprine to prevent rejection.

This approach is highly successful compared to early efforts to suppress immunity, but problems remain. Amounts of the drugs that can be used are constrained by toxic effects on vital organs, and thus make it difficult to balance the risks of infection from immunosuppression against the need to prevent graft rejection.

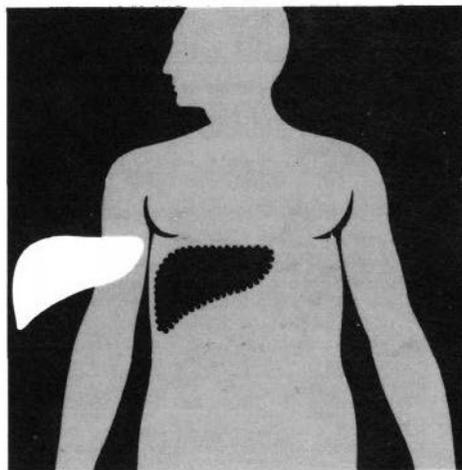
For this reason, researchers are excited over the prospects of a new immunosuppressive drug known as FK506, a natural product of soil fungi, that is now being tested at several transplant centers in a clinical trial sponsored by the manufacturer, Fujisawa Pharmaceutical Company, Ltd., of Japan. So far, the drug appears to rival cyclosporine A in its mode of

action and efficacy, and seems to have fewer side effects. Scientists believe it may also prove to offer other advantages, such as permitting use of lower doses of prednisone, improving survival and the quality of life of transplant recipients.

Another advance in antirejection therapy has been the use of monoclonal antibodies against certain lymphocytes. These help reverse rejection, but they have been found to induce allergic reactions when used repeatedly. At present their use is limited to episodes of severe rejection.

Unlike kidney transplantation, where kidney dialysis can usually maintain the patient's life until surgery, liver transplantation is generally an emergency operation in which a critical factor is the limited time that a donor liver can be preserved. Until just a few years ago, a cold storage solution could preserve a donor liver for about 8 hours or so. There was a vital need to find better methods to extend preservation time of donor livers before transplantation.

In the late 1980's, NIDDK grantees Dr. Folkert O. Belzer and Dr. James Southard at the University of Wisconsin developed and tested a new solution that can preserve a donor liver for up to 20 hours. The investigators tested the new solution, known as "UW" solution (for the University of Wisconsin), on hundreds of donor livers and found that the average preservation time was nearly double that for the standard solution. The researchers also found that the livers preserved with UW survived at a significantly higher rate.



Liver Transplantation

Extended preservation time provides important benefits for the safety of patients, the timing of surgery, better coordination of surgical teams, and cross-matching between donor and recipient. The added time also allows for organ retrieval from more distant locations, and it permits more preparation time for staff in anesthesia, nursing, operating room, blood bank and intensive care units.

At present, the survival rates of patients receiving new livers are about 75 to 80 percent at 1 year and 60 to 65 percent at 5 years. Researchers hope, however, that long-term survival soon will be increased through advances in immunosuppressive therapy to stop rejection, developments in surgical technology, and through improved preservation that yields better matches of donor organs and better functioning grafts in recipients.

One of the most urgent and difficult problems facing liver transplantation in the U.S. is shortage of organs. While the number of livers transplanted increases each year, so does the waiting list of patients who need the operation. In a recent month, more than a thousand people were waiting. It is estimated that a quarter of them will die before a donor is found. At the same time, only a small proportion of the livers that could be donated are obtained. UNOS and numerous other voluntary health organizations are conducting campaigns to encourage Americans to donate organs at their death (call 800-24-DONOR).

There is hope that some day the need for donor organs might be less urgent as artificial livers are developed, as researchers gain experience implanting portions of liver from living donors, and as improved therapies prevent complications of liver disease, reducing the need for organ replacement. □

DIABETES

(Continued from Page 9)

mother with normal glucose tolerance during pregnancy, even if that mother later develops diabetes.

NIDDK researchers think the genetic defect underlying insulin resistance might be found in the pathway to the activation of glycogen synthase, an enzyme necessary for normal glucose metabolism. "In normal people, most glucose is taken up by the skeletal muscle," said Bogardus. "The cell does one of two things with glucose: either it burns it—oxidizes it to carbon dioxide and water—or it stores it as glycogen. In an insulin-resistant person, there are probably defects in both these pathways, but the most serious defect is in the glycogen storage pathway. We don't think the genetic defect is in the glycogen synthase molecule itself, but we've found significant abnormalities in the insulin regulation of one of the enzymes back from glycogen synthase—glycogen synthase phosphatase."

Doctors have long known that obesity adds to the problem of insulin resistance and the chances of getting diabetes. Often a modest 10-pound weight loss can increase a person's sensitivity to insulin, even forestalling diabetes. On the other hand, as an insulin-resistant person gains weight, insulin resistance increases. NIDDK researchers speculate that

(Continued on Page 12)

(Continued from Page 11)

the added fat causes muscle cells to enlarge, increasing the distance between capillaries that carry insulin to its site of action.

The type of muscle fiber a person inherits may also play a role in insulin resistance, according to Bogardus. "The two major classes of muscle fibers are type 1 and type 2, and each fiber type has different metabolic characteristics. For example, a type 2 fiber is more insulin resistant than a type 1 fiber. Also, the amount of each fiber that an individual has appears to be genetically determined. A person who inherits a lot of type 1 fibers, for example, would make a good long-distance runner, while a person born with a lot of type 2 fibers would make a good weight lifter."

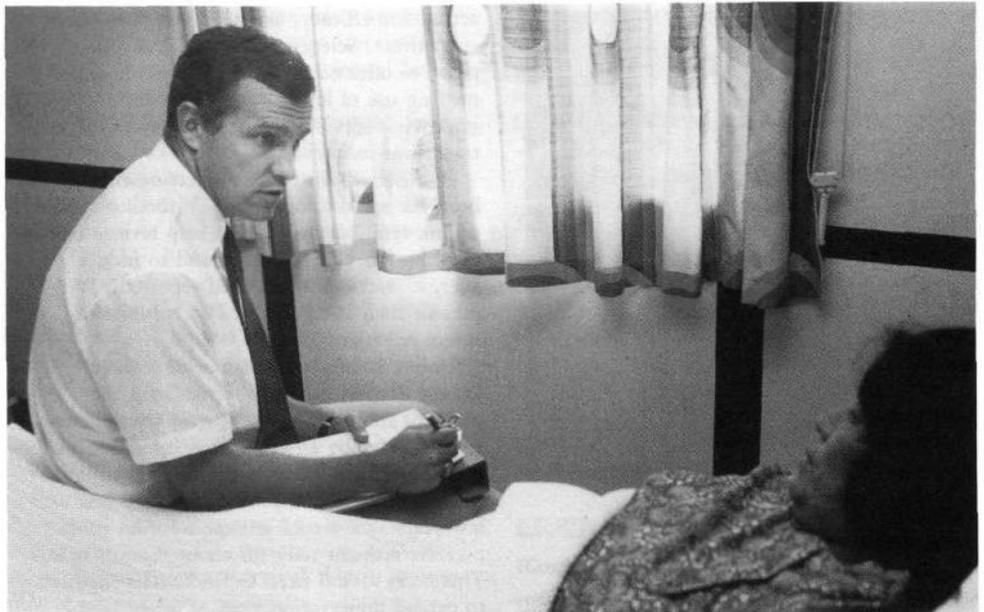
Dr. Eric Ravussin of the Phoenix branch has been exploring metabolic rate in muscle. "In the past, muscle has been quite neglected because in resting conditions it doesn't require a lot of energy per unit of weight. Yet, it's a large tissue mass, about 30 or 40 percent of your weight. One observation that we have made is that overall metabolic rate is related to muscle metabolic rate; that is, the differences in metabolic rate among people might reside in muscle tissue."

Studies of Metabolic Rate Shed Light

Obesity, another risk factor for diabetes, is common in the Pimas, who are about 30 percent heavier than the general U.S. population. Like insulin resistance, obesity appears to have strong genetic influences. For example, family members are likely to share the same metabolic rate. In studies using highly sensitive equipment to measure energy expenditure, the Phoenix investigators found that the risk of gaining 22 pounds over a 4-year period was eight times higher in individuals whose resting metabolic rates were lowest.

Despite the strong role of genes, environmental factors also play a role in weight gain, and dietary changes over the years have clearly added to the Pimas' obesity problem. The traditional Pima diet consisted of high-carbohydrate, low-fat, high-fiber foods such as maize, pumpkins, beans, gourds, and fruits supplemented by rabbit, deer, and fish. By 1969, however, this diet had been replaced by a high-fat, high-calorie diet, with the average Pima woman between ages 25 and 44 eating 3,163 calories a day. The average intake for a woman in the same age group in the U.S. population is 1,600 calories a day.

"It's difficult to understand why a disease like diabetes is so prevalent if it is not linked to a survival advantage. In fact, a low metabolic rate has probably been a survival advantage for centuries," said Ravussin. "The 'thrifty gene' hypothesis suggests that, in the past, populations like the Pima Indians have been subjected to periods of famine and peri-



Dr. Clifton Bogardus III counsels Pima volunteer at NIDDK research clinic.

ods of feast. During the periods of famine, babies who were better at storing fat were more likely to survive—they were more thrifty in their metabolism. Over the centuries, there was a natural selection for this thrifty gene or group of genes, which may turn out to be the same gene for diabetes and low metabolic rate.

"We have observed under very standardized conditions that people who are better at burning fat are less likely to gain weight. We've found that there are differences among people in the fuel mix they oxidize and that these

Often a modest 10-pound weight loss can increase a person's sensitivity to insulin, even forestalling diabetes.

differences run in families. Now we're studying the enzyme lipoprotein lipase to try to understand the mechanism of high versus low fat oxidation. There are possible differences in the activity of lipoprotein lipase in muscle versus fat tissue, which might explain differences in fat deposition and oxidation. If you have a high activity of this enzyme in your fat tissue and a low activity in your muscle, you are going to direct ingested fat directly to fat tissue," Ravussin explained.

In the 25 years since NIDDK scientists began studying the health problems of the Pima Indians, researchers have gained valuable insights into the biological mechanisms underlying diabetes and obesity. Such longitudinal and prospective studies are essential in obesity research. "We need more prospective studies to learn what happens before the obese state when the damage is already done," said Ravussin. "We need longitudinal studies and

studies in children. So much research in this field has compared obese to nonobese people in cross-sectional studies. The problem is that obesity is so heterogenous. When you compare obese to nonobese people, you can't learn much because everything tends to normalize in response to weight gain: your metabolic rate goes up, beyond the increase in body weight. You also start to burn more fat when you reach the obese state, thus correcting for the initial defect."

Diabetes Causes Wide Range of Complications

Living with diabetes has become a part of everyday life for the Pima Indians. Young people talk about when, not if, they will get it. They know all too well that once they have diabetes, they are likely to lose their eyesight, kidneys or a limb to the disease. Some will lose all three.

"People used to say the Pimas don't have



The Sonora Desert is the traditional homeland of the Pima Indians.

the rate of diabetic complications that Caucasians do, but clearly they get nephropathy in abundance and retinopathy at least as frequently as Caucasian populations. They also have a high rate of amputations, although we haven't followed neuropathy as closely. But for reasons we don't understand, the Pimas don't have as high an incidence of heart disease as might be expected, and which diabetes often causes," Bennett explained.

The research of Dr. William Knowler, chief of the diabetes and arthritis epidemiology section in Phoenix, and others has shown that blood pressure is a predictor of many complications of diabetes. As a result, doctors now focus more attention on controlling their patients' blood pressure to prevent complications.

The longer a person lives with diabetes, the greater the chances of developing severe complications. Because diabetes strikes the Pimas so early in life, they are as likely to suffer serious kidney and eye problems as a person who has type 1 or insulin-dependent diabetes. This less common form of diabetes, which usually occurs in children, is caused by an autoimmune attack on the insulin-producing cells of the pancreas.

"If Pima Indians who have diabetes lived 20 years after the onset of the disease, we estimate that half would develop nephropathy—kidney disease that is marked by an abnormal amount of protein in the urine. The actual percentage who have nephropathy is less than

"A low metabolic rate has probably been a survival advantage for centuries."

—Dr. Eric Ravussin

this, however, because so many people with nephropathy have already died," said Knowler.

"The real tragedy of nephropathy is that it leads to kidney failure, which means that a person must go on dialysis or have kidney transplantation. In a community of 5,000 to 6,000 Pimas, between 60 to 80 people are living on dialysis at any given time. That's an astronomical number of people on dialysis compared to anywhere else," said Knowler.

To learn how diabetes damages the kidneys, researchers from the Phoenix group, Stanford University and the Cleveland Clinic are studying kidney function in the Pimas before and after diabetes begins. Early findings suggest that diabetes quickly disrupts the way the kidney's filtering units, the glomeruli, filter particles such as protein.

"Normally, the glomerulus acts like a screen that lets water and waste products filter through but holds back most of the protein. Early in the course of diabetes, we are seeing changes in the size of the pores of the screen, so that more protein filters through. This may



Dr. William Knowler examines Pima volunteer's eyes for signs of diabetic retinopathy.

be due to high glucose levels rather than small blood vessel disease, which takes longer to develop," said Knowler.

While the Phoenix researchers know that diabetes is a genetic disease, the number of genes involved may remain a mystery for a while. In Knowler's view, "It's likely that one gene has a very large influence on insulin resistance, and there may be other genes that influence the beta cell's ability to cope with insulin resistance. There is also evidence that genes influence which persons with diabetes get nephropathy. But I don't believe that one or two genes will explain everything about the causes of diabetes, because the patterns of diabetes inheritance in families are just not that

simple."

Following their hunch that one or two genes play a key role, the Phoenix team and their collaborators have begun a large-scale search of DNA from families with diabetes. As their attention turns to finding the diabetes genes, the researchers foresee a time when they may be able to identify persons who are susceptible to the disease and prevent it from gaining a foothold. They speak of gene therapy as a cure on the horizon. For many Pima Indians, however, the prospects for genetic therapy are still too distant. For them, NIH research can be appreciated most for the good medical care it has given them in the past 25 years.



Aerial view of NIDDK research facility on the campus of the Phoenix Indian Medical Center

Employee Counseling Service Starts 1990-91 Lectures

The theme for the 1990-91 Employee Counseling Services Guest Lecture Series, "Intersections: Health and Illness Issues in the Workplace," centers around work and health issues and the impact of health stressors on the workplace. Topics include the varied issues and interests that come to the attention of ECS throughout the year and that speak to the eclectic needs of the NIH community.

Each month ECS will present a lecture one week and a film and small group discussion the next week.

All sessions will meet from noon until 1 p.m. on the dates indicated below.

December

"Drawing the Line: Drug and Alcohol Recovery and Relapse Issues in the Workplace," Dr. George Kolodner, Thursday, Dec. 13, Conf. Rm. 4, Bldg. 31.

Working The Program: film and discussion, Thursday, Dec. 27, Little Theater, Bldg. 10.

January

"Taking Control: Depression and Anxiety Disorders in the Workplace," Dr. Norman Wilson, Thursday, Jan. 24, Conf. Rm. 4, Bldg. 31.

Dealing With Depression: film and discussion, Thursday, Jan. 24, Little Theater, Bldg. 10.

February

"Financial Health: The Psychology of Money and Money Management," Olive Mellon, Wednesday, Feb. 14, Conf. Rm. 7, Bldg. 31.

Making Money Count: film and discussion, Thursday, Feb. 21, Little Theater, Bldg. 10.

March

"The Other Side of Wellness: Dealing With Chronic Illness," Carol Weiss and Ann Mahony, Thursday, Mar. 14, Conf. Rm. 4, Bldg. 31.

Fight For Your Life: Survival Techniques in Living With Cancer: film and discussion, Thursday, Mar. 21, Little Theater, Bldg. 10.

April

"Anger in the Workplace," Dr. Dale Berman, Wednesday, Apr. 11, Conf. Rm. 4, Bldg. 31.

Defusing Hostility: film and discussion, Thursday, Apr. 18, Little Theater, Bldg. 10.

May

"Walking the Tightrope: Balancing Out Work and Family Life Health Issues," Dr. Michael Bowler, Thursday, May 11, Conf. Rm. 4, Bldg. 31.

Vital Balance: Work and Family Conflicts: film and discussion, Thursday, May 16, Little Theater, Bldg. 10.

June

"Changing Currents: Dealing With Disabilities in the Workplace," Dr. Dave Gray and panel, Thursday, June 13, Conf. Rm. 4, Bldg. 31.

Disabilities: film and discussion, Thursday, June 20, Little Theater, Bldg. 10.

FAES Announces Spring Classes

The FAES Graduate School at NIH announces the schedule of courses for the spring semester. The evening classes sponsored by the Foundation for Advanced Education in the Sciences will be given on the NIH campus.

Tuition is \$50 per credit hour, and courses may be taken for credit or audit. Courses that qualify for institute support as training should be cleared with the supervisors and administrative officers as soon as possible.

Courses are offered in biochemistry, biology, biotechnology, chemistry, computer science, mathematics, medicine, pharmacology, immunology, microbiology, psychology, psychiatry, statistics, languages, administration and courses of general interest.

It is often possible to transfer credits earned to other institutions for degree work, and many courses are approved for AMA category 1 credit.

Classes will begin Jan. 28, and registration will be held from Jan. 14 through 18. Spring schedules will be available mid-December in the graduate school office in Bldg. 60, Suite 230, the foundation bookstore, Bldg. 10, Rm. B1L101 and the business office in Bldg. 10, Rm. B1C18. To have a schedule sent call 496-7977. □

Lecture on 'Seeing Diseases'

Dr. Sander L. Gilman, currently NLM's visiting historical scholar, will present an illustrated lecture on "Seeing Diseases: Visual Sources and the Meaning of History," Dec. 5, at 3:30 p.m. in the Lister Hill Auditorium, Bldg. 38A. All are invited.

Gilman is on leave from Cornell University, where he is professor of humane studies and professor of psychiatry. His numerous publications reflect a long-term interest in the portrayal of disease in art throughout history. He is the author of *Difference and Pathology: Stereotypes of Sexuality, Race, and Madness* (1985); and *Disease and Representation: Images of Illness from Madness to AIDS* (1988).

For further information call 496-5405. □

Toastmasters To Honor Mylander

The NIH Toastmasters Club will hold its annual Communication Achievement Award ceremony Dec. 7 at noon in Wilson Hall, Bldg. 1. This year's recipient is Maureen Mylander, special assistant for health information in OD's Office of Communications. She is also the author of the book, *The Healthy Male*, and a former member of the NIH Toastmasters Club.

Everyone is invited to attend. For more information, call Jasper Cummings, 496-5635. □

Human Rights Day Observed

The NIH medical scientists committee is sponsoring two short films, *The Colors of Hope* and *You Could Be Arrested* to observe Human Rights Day. The films, which are produced by the human rights organization Amnesty International, will be shown Dec. 10, 12:30-1:30 p.m. in the Visitor Information Center, Bldg. 10. NIH'ers and their guests are invited to attend. Refreshments will be served.

Human Rights Day commemorates the anniversary of the passage of the United Nations Universal Declaration of Human Rights. The medical scientists committee is an NIH employee group affiliated with Amnesty International that works for the release of prisoners of conscience worldwide. The committee meets every Thursday from 12:30 to 1:30 p.m. in Bldg. 10, Rm. B1D25. For more information, call Dr. Pat McKinley, 496-9291. □



NIGMS director Dr. Ruth L. Kirschstein (c) meets with NIH Merit Award recipients Crystal Jenkins (l), an administrative assistant, and Marcia Cohn, a grants management specialist.

Madrigal Singers To Perform

The NIH R&W Madrigal Singers will present a program of sacred and secular works from the 16th century, mostly from England, followed by a 20th century segment featuring works by British composer Ralph Vaughan Williams and American songster Mel Torme. The program will be given in Masur Auditorium, Tuesday, Dec. 11 at 12 noon. □



TRAINING TIPS

The NIH Training Center of the Division of Personnel Management offers the following:

Courses and Programs Starting Dates

Management and Supervisory 496-6371

Efficient Reading for Professionals	12/13
Working It Out	1/7
Good Starts: Transition Planning	1/10
How To Write and Publish Scientific Papers	1/14
Time Management	1/16
Managing Workforce Diversity: Skills for Utilizing Differences	1/23
Getting Results in Task-Oriented Groups	1/28
Projecting an Effective Executive Image	1/28

Special Courses 496-6211

Career Assessment and Life Planning	1/9
Basic Employee Relations	1/14
American Sign Language Level 1	1/15
Breaking the Smoking Habit	1/17

Personal Computing Training 496-6211

Intro to Keyboarding	1/9
Introduction to Personal Computing for New Users	11/29
Intro to DOS	11/30, 1/3
Word Perfect 5.1 — Advanced Topics	12/3
Word Perfect 5.0 to 5.1 Transition	12/7, 12/17, 1/4
Introduction to Word Perfect 5.1	12/10, 12/19
Introduction to Harvard Graphics	12/12 & 1/7
Printing With Word Perfect and Laser Printing	1/10
dBase III Plus Advanced Topics	12/4
Intro to dBase III Plus	12/18
Welcome to Mac	12/3, 12/14, 1/8, 1/18
Intro to Microsoft Word	12/5, 12/7
Excel — Level 1	1/4
Excel — Level 2	12/10, 1/14
Excel — Level 3	1/29
Mac Draw II	12/6
Intro to Power Point	12/13
Introduction to Delta Graph	1/6
Hypercard-Level 1	1/31
Hypercard Programming-Level 1	1/15
3Com Network — Level 1	12/4, 1/7, 1/17
3Com Network — Level 2	12/11, 12/12, 1/23, 1/24
3Com Network Management-Level 1	1/28, 1/29

Training and Development Services 496-6211

Personal Computer training is available through User Resources Center (URC) self study courses. There is no cost to NIH employees for these hands-on sessions.

The URC hours are:

Mon.-Thurs.	8:30 a.m. — 7 p.m.
Friday	8:30 a.m. — 4:30 p.m.
Saturday	9 a.m. — 1 p.m.

Training Center, DCRT, and other training information is available on WYLBUR. Logon to WYLBUR and type ENTER TRAINING

Preschool Eligible for CFC

The preschool at NIH run by Parents of Preschoolers Inc. (POPI) is eligible for Combined Federal Campaign funds. Any CFC funding received by POPI is used exclusively for lowering tuition costs. The program maintains a sliding-fee scale to assure financial accessibility to the entire NIH community. □

Friends Offer NLM Calendar

A colorful 1991 National Library of Medicine wall calendar—featuring 12 illustrations, mostly drawn from the library's historical collections—is now available from the Friends of the National Library of Medicine, 1527 Wisconsin Ave., NW, Washington, DC 20007.

The price is \$10 per calendar (\$8 for members of the Friends and staff of NIH and



"The Alchemist," a 17th century etching from NLM's History of Medicine collection, is one of the illustrations in the 1991 NLM calendar, offered by the Friends of the NLM.

NLM). Please add \$2 for shipping and handling; if ordering more than one calendar, add an additional \$1 per calendar.

Among the illustrations in the calendar, most of which are in full color, are a 1514 engraving on melancholy by Albrecht Durer, an 1825 etching caricaturing indigestion, an 1887 lithography of Louis Pasteur, and a 1987 AIDS conference poster. Important anniversary dates in medical history are given for each month, as well as interesting anecdotes and quotations related to the themes represented in the pictures.

The calendar was produced by Pomegranate Calendars and Books of Peraluma, Calif., in conjunction with the library and the Friends. It is being sold in bookstores for \$10.95. □

NIH Historian To Address Science Writers Guild, Dec. 4

The first transfer of foreign genes into humans and the first clinical trial of gene therapy are recent examples of NIH's prominent role in making medical history. As head of NIH's Historical Office and curator of the DeWitt Stetten Jr. Museum of Medical Research at NIH, Dr. Victoria Harden plays a key role in documenting and preserving NIH's great moments in history. She will present an overview of the work and goals of the office and museum and discuss how science writers—and other members of the NIH community—can help contribute to this effort at a meeting of the NIH Science Writers Guild on Tuesday, Dec. 4, in Bldg. 31, Rm. 4C32, from 11:30 a.m. to 12:30 p.m.

Harden became NIH's historian and the museum curator in 1987. Prior to that she worked at NIAID for 3 years doing the research for her latest book, *Rocky Mountain Spotted Fever: History of a Twentieth Century Disease*. She is cochair of the AIDS History Group for the American Association for the History of Medicine and is also coauthoring a chapter of a book, *Discovering New Worlds in Medicine*, for the Columbus Quincentennial in 1992.

Harden received her Ph.D. in American history from Emory University in 1983. She had a fellowship at the Smithsonian Institution and did her postdoctoral work at the Johns Hopkins University School of Medicine's Institute of the History of Medicine. During that time, she wrote her first book, *Inventing the NIH: Federal Biomedical Research Policy, 1887-1937*.

For additional information, contact Bobbi Bennett, 496-8855. □

STEP Sponsors Forum on Integrity in Science

A forum titled "Integrity in Science," sponsored by the Staff Training in Extramural Programs (STEP) committee will be held on Tuesday, Dec. 11, from 1:30 to 4 p.m. in Wilson Hall, Bldg. 1.

A panel of speakers will discuss issues relating to policies and procedures being developed by the PHS/NIH Office of Scientific Integrity in response to concerns raised by Congress, the media and others. Are the policies and procedures effective? Are changes needed? Can scientists/universities/grantees continue to be involved in resolving the complex technical issues raised or is the process too sensitive to be left to them? What is the impact on grantees and how have they responded? What are the continuing congressional concerns? These are a few of the questions to be addressed by the panelists. There will also be

an opportunity for the audience to ask questions.

Featured speakers will be: Dr. Jules Hal-lum, director, Office of Scientific Integrity, NIH; Dr. Leslie Russell, staff member, energy and commerce committee, U.S. House of Representatives; Robert Charrow, attorney with Crowell and Moring; Dr. David Blake, senior associate dean, Johns Hopkins University School of Medicine. The forum moderator will be Dr. Thomas Malone, vice president for research, Association of American Medical Colleges.

STEP forums do not require advanced registration and are open to all NIH personnel. Attendance will be on a space-available basis. Additional information is available from the STEP program office, Bldg. 31, Rm. 5B44, 496-1493.

Second Trial To Start Soon**Gene Therapy Approved for Melanoma Patients**

The NIH has received final approval from FDA to begin the first study using human gene therapy to treat cancer.

Drs. Steven A. Rosenberg and R. Michael Blaese of NCI, and Dr. W. French Anderson of NHLBI expect to treat the first patients next month. These patients have advanced melanoma, a skin cancer for which there is no effective treatment. The scientists have received approval to treat up to 50 patients with this disease.

"This approach that uses gene therapy to treat patients with advanced cancer is experimental and in an early stage of development," said Rosenberg, who leads the study.

Patients in this study will receive transfusions of special cancer-killing cells called tumor-infiltrating lymphocytes, or TILs, that have been altered in the laboratory by insertion of the human gene for tumor necrosis factor (TNF). The NIH scientists grow the gene-altered TILs in the laboratory for 4 to 6 weeks before returning them to the patient by transfusion.

TILs are white blood cells that have migrated from other parts of the body to the cancer site. After invading the tumor, they develop the ability to target and destroy the tumor tissue from which they were derived.

Since 1987, Rosenberg has been using unaltered TILs to treat cancer. Only about half the patients with advanced melanoma show some improvement after therapy with unaltered TILs.

"There has been a need to improve this therapy, and one way may be with the addition of the TNF gene," said Rosenberg.

"In mice, TNF is one of the most powerful antitumor agents we have seen. Humans, however, cannot tolerate the large doses necessary to achieve this potent cancer-killing effect," he added.

TNF is a protein that is produced by the body in the course of bacterial infections. Although initially recognized for its cancer-killing activity in mice, TNF also regulates inflammation and immunity by signaling the body to repair injuries and fight infection. However, if TNF is active in the body for too long, it can cause shock and body wasting.

At the tumor site, TNF appears to work effectively by cutting off the developing blood supply in that region. By using TILs to target the tumor and carry the TNF gene directly to the tumor site, scientists hope to maximize the gene's benefit and also minimize the potential toxicity that could result if TNF were distributed throughout the body.

Said Rosenberg, "At this time, we are giving TILs that have some anticancer activity.

With the addition of the TNF gene, we hope to enhance the ability of TILs to destroy tumor cells."

This trial will be the first to apply gene therapy to cancer, which, in its many forms, affects millions of people.

On Sept. 14, under the leadership of Blaese, the research team of Anderson, Rosenberg, and another NCI investigator, Dr. Kenneth W. Culver, began a study using human gene therapy to treat an extremely rare, inherited immune system disorder known as adenosine deaminase (ADA) deficiency disease. The first patient in that study was a 4-year-old girl who received a transfusion of her own white blood cells that had been altered in the laboratory by insertion of the human ADA gene.

This patient lacks a crucial enzyme for immune system functioning known as ADA. Untreated, ADA deficiency disease often results in death within the first years of life.

Foreign genes cannot be directly inserted into the cell, but certain viruses have the ability to enter the cell and insert their genes into the cell's DNA. In both the cancer and the ADA deficiency trials, the virus that is used to deliver the gene has been crippled so that it cannot reproduce in the patient.

"Ultimately, this new technique could lead to the use of gene therapy to correct or ameliorate a wide range of diseases, including cancers other than melanoma; heart disease; diabetes; and other inherited disorders such as hemophilia and cystic fibrosis," Rosenberg said. □

Former CC Surgical Wing Becomes Animal Facility

Bldg. 10A, the 5-level round structure formerly housing the surgical wing of the NIH Clinical Center, was dedicated on Nov. 6 as NIH's newest, state-of-the-art laboratory animal facility. The new rodent and rabbit unit will consolidate most of the 33 animal holding and procedure rooms scattered throughout the Clinical Center.

A large group of NIH investigators, administrators and laboratory animal care staff toured the new facility after the dedication ceremony and ribbon cutting.

Opening of the unit, scheduled for February, is part of NIH's concentrated effort to obtain accreditation of the entire NIH intramural animal research program by the American Association for Accreditation of Laboratory Animal Care.

"It is fortunate that a move of the surgery to new, technologically advanced facilities was already under way when the need to consolidate the animal facilities became clear," said Dr. J. Edward Rall, NIH deputy director for intramural research. Renovations began in 1987.

A committee of the intramural scientists who will use the facility took part in the design decisions. The shared facility will be managed by the Veterinary Resources Program, NCRR; participating ICDs will share in operating expenses.

The unit has 49 animal holding rooms and 15 research procedure rooms. It is equipped with computer-monitored environmental and air circulation controls, radioisotope rooms, and the latest technology for maintaining the health and well-being of the animals.



A tour of the new Bldg. 10A rodent and rabbit unit followed the ribbon cutting by Dr. J. Edward Rall (r), NIH deputy director for intramural research, along with (from l) Dr. Richard Wyatt, NIH assistant director for intramural affairs; Dr. Robert A. Whitney Jr., director, NCRR; Dr. Wayne O'Brien, manager of the new facility; Jerry Lawson, Division of Engineering Services; and Dr. Stephen Potkay, director, Veterinary Resources Program, NCRR.