Growing Cells a Snafu

Gene Transfer Therapies Envisioned Soon at NIH

By Rich McManus

As the hoopla from the first approved human experiment involving gene transfer, accomplished last spring, dies down, real progress is being made in gene therapy that may actually cure disease.

Among the leaders in the race to use transfer techniques to correct human gene defects is Dr. R. Michael Blaese, deputy chief of NCI's Metabolism Branch. Armed with 23 years of experience in the branch and an enthusiastic cadre of college and medical students, he looks forward to clinical trials aimed at treating ADA deficiency, a disorder caused by an error in a single gene.

Ironically, the technique of engineering genes to carry new DNA is not the scientists' most daunting technical hurdle.

"The real trick in our approach to treating these diseases is growing patients' cells, not gene transfer," Blaese said. "We showed 4 years ago that ADA gene transfer could 'cure' the biochemical defect in the cells of these patients in tissue culture. Today the problem is working out the biology of growing lymphocytes in large volume, sorting out what they do and making sure no harm is done when the cultured cells are given back to a patient."

Blaese's team is using lymphocytes as the medium for introducing altered genes into patients. He and coworkers were part of a triumvirate including Dr. W. French Anderson of NHLBI and NCI's Dr. Steven A. Rosenberg that pioneered the first human gene.

The structure of the Children's Inn, which will house 36 pediatric patients and their families, is becoming recognizable with the completion date estimated for February 1990.
shops. Shuttle bus service will be available throughout the day.

On Thursday and Friday, Sept. 28 and 29, more than 250 companies will display scientific research equipment in the Research Day tent for an exhibit sponsored by the Technical Sales Association. The demonstration is open to all Research Day participants.

The Circus for Caring, sponsored by the R&W association as a benefit for the Children's Inn at NIH, will occupy the tent on Sunday, Oct. 1 (see announcement on page 7).

Tent activities conclude on Tuesday, Oct. 3

with the second NIH/ADAMHA Industry Collaboration Forum. Contact the Office of Invention Development, 496-0750, for more information.

A detailed program of all Research Day activities, including schedules and locations of symposia, workshops and posters, may be obtained from institute scientific directors and NIH information desks. Questions regarding Research Day events should be directed to organizing committee chair Dr. Alan N. Schechter, Bldg. 10, Rm. 9N307.

NIH Research Day Scientific Symposia Schedule

Masur Auditorium

A. Diversity in the Mechanisms of Gene Expression
Chair: Joram Piatigorsky, NEI
8:30 a.m. Opening Remarks — J. Edward Rall, OD
8:45 Regulation of Oct-2, a Human Homeobox Protein
Louis Srauldr, NCI
9:15 Regulation of Collagen Gene Expression
Yoshi Yamada, NIDR
9:45 Regulation of Gene Expression in the Yeast Saccharomyces by Translational Control of the Transcriptional Activator Gcn4
Alan Hinnebusch, NICHD
10:15 Break
10:30 Regulation of Elk2@ gene Expression
Brian Safer, NHLBI
11:00 Gene Sharing Among Enzyme Crystallins: Surprises in Regulation and Evolution of Lens Genes
Joram Piatigorsky, NEI

Masur Auditorium

C. Oncogenesis
Chair: Heiner Westphal, NICHD
2:30 p.m. Differentiation vs. Oncogenesis: Observations from Transgenic Mice
Heiner Westphal, NICHD
3:10 Determination of the Two Proto-oncogene Function
George Vanderwoude, NCI
3:50 Growth Factor Activated Pathways in Human Malignancy
Stuart Aaronson, NCI
4:10 Molecular Approaches to Therapeutic Intervention
Mark Israel, NCI

Lipsett Amphitheater

D. Cellular Differentiation and Development
Chair: Ronald Schwartz, NIAID
2:30 p.m. Tryptic Factors and Neural System Development
Philip G. Nelson, NIDDK
3:00 Signal Transduction and Gene Expression in the Development of Dicyostelium
Alan Kimmel, NIDDK
The Zona Pellucida Genes: Modulators of Fertilization and Early Mammalian Development
Jurrien Dean, NIDDK
4:00 Break
4:10 The Role of the Immune System in the Development of Malignancy
B. J. Fowles, NIAID
4:50 Break
5:00 Molecular Studies on Embryonic Induction in Xenopus
Igor Dawid, NICHD
5:30 Molecular Genetics of Human Malignancy
Louis Staudt, NCI
6:00 Break
6:15 Molecular Approaches to Therapeutic Intervention
Mark Israel, NCI
6:45 Break
7:00 The Role of the Immune System in the Development of Malignancy
B. J. Fowles, NIAID
7:45 Break
8:00 The Zona Pellucida Genes: Modulators of Fertilization and Early Mammalian Development
Jurrien Dean, NIDDK
8:30 Break
9:00 Signal Transduction and Gene Expression in the Development of Dicyostelium
Alan Kimmel, NIDDK
9:30 Break
10:00 The Zona Pellucida Genes: Modulators of Fertilization and Early Mammalian Development
Jurrien Dean, NIDDK
10:30 Break
11:00 Molecular Approaches to Therapeutic Intervention
Mark Israel, NCI
11:30 The Role of the Immune System in the Development of Malignancy
B. J. Fowles, NIAID
12:00 Break
12:30 Signal Transduction and Gene Expression in the Development of Dicyostelium
Alan Kimmel, NIDDK
13:00 Break
13:30 The Zona Pellucida Genes: Modulators of Fertilization and Early Mammalian Development
Jurrien Dean, NIDDK
14:00 Break
14:30 The Role of the Immune System in the Development of Malignancy
B. J. Fowles, NIAID
15:00 Break
15:30 The Zona Pellucida Genes: Modulators of Fertilization and Early Mammalian Development
Jurrien Dean, NIDDK
16:00 The Role of the Immune System in the Development of Malignancy
B. J. Fowles, NIAID
16:30 Break
17:00 The Zona Pellucida Genes: Modulators of Fertilization and Early Mammalian Development
Jurrien Dean, NIDDK
17:30 Break
18:00 The Role of the Immune System in the Development of Malignancy
B. J. Fowles, NIAID
18:30 Break
19:00 The Zona Pellucida Genes: Modulators of Fertilization and Early Mammalian Development
Jurrien Dean, NIDDK
19:30 Break
20:00 The Role of the Immune System in the Development of Malignancy
B. J. Fowles, NIAID
20:30 Break
21:00 The Zona Pellucida Genes: Modulators of Fertilization and Early Mammalian Development
Jurrien Dean, NIDDK
21:30 Break
22:00 The Role of the Immune System in the Development of Malignancy
B. J. Fowles, NIAID
22:30 Break
23:00 The Zona Pellucida Genes: Modulators of Fertilization and Early Mammalian Development
Jurrien Dean, NIDDK
23:30 Break
The NIH Record

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Pollack Accredited by PRSA

Ellyn J. Pollack, a public affairs specialist in the Office of Clinical Center Communications, recently passed the Public Relations Society of America accreditation exam.

Culminating in a day-long exam that includes written and oral tests judged by a panel of PR professionals, the accreditation program was initiated in 1964 to recognize those who have demonstrated broad knowledge, experience and professional judgment in the field. More than 4,000 PRSA members have successfully completed the exam since its initiation.

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‘Help Someone Have a Better Tomorrow’

**Combined Federal Campaign Opens on Oct. 4**

By Carol R. Cronin

“Help Someone Have a Better Tomorrow” is the 1990 theme of the Combined Federal Campaign (CFC). More than 1,200 voluntary agencies will participate in this season’s CFC, allowing NIH employees to contribute to services provided to millions of people who suffer the ravages of illness and disease here in our community and throughout the world.

The NIH Health’s Angels will lead the pack at the Oct. 4 Walk/Run, a 3-mile run and 1-mile walk commencing at 11:30 a.m. in front of Bldg. 1. Organized through a joint effort with the NIH R&W Association and the CFC, the Walk/Run marks the kick-off of a CFC campaign scheduled to run through Nov. 17. Registration forms for the race will be available through R&W gift shops. First and second place awards will be presented to winners in four different divisions: male, 39 and under; female, 39 and under; male, 40 and over; and female, 40 and over. Certificates will be presented to all participants. The Walk/Run is open to all who run or walk for fun, fitness or competition.

If you don’t run or walk, that doesn’t mean you have to miss out on all the fun. Hard Times Cafe will be serving three kinds of chili, corn bread, cole slaw and soda, topped off with ice cream. Lunch tickets are $5 and can be purchased at any R&W store.

You can also enter a free raffle. Prizes include a Sony camcorder (donated by Geico), weekends for two at the Holiday Inn Georgetown and the Crowne Plaza Rockville, tickets to a Capitals game, an autographed hockey stick and an autographed Bullets basketball.

Dr. William F. Raub, NIH acting director, will serve as the NIH CFC chairman. John D. Mahoney, NIH associate director for administration, will serve as NIH’s CFC coordinator. Marian Dawson, executive officer of the Division of Computer Research and Technology, will serve as NIH’s CFC BID coordinator.

BID directors will be providing a special message through this year's promotional video, entitled, “Chain of Caring,” featuring Channel 5 anchorman James Adams.

The CFC donor who pledges a minimum of $26, by payroll deduction or cash contribution, will reap the dividend. A special R&W drawing, to be announced at the close of the campaign, will present the winner with two free round-trip tickets to anywhere in the continental U.S., courtesy of USAir. A special raffle—just for keyworkers—will also be featured.

NIH’s goal for this season’s CFC is $632,000. Ten dollars feeds a starving refugee child in the Sudan for a year. Fifty dollars provides a wheelchair to a handicapped child. Whether by cash contribution or payroll deduction, the combined effort of all of us does more than any one of us can do alone. "Help Someone Have a Better Tomorrow."
Minority Biomedical Research Program Moves to NIGMS

By Doris Brody

Beginning Oct. 1, the Minority Biomedical Research Support (MBRS) program will become part of the National Institute of General Medical Sciences.

The $39 million MBRS program, about $10 million of which is provided by other components of NIH and the Alcohol, Drug Abuse, and Mental Health Administration, addresses the need to increase the participation of minority scientists in biomedical research, the need to strengthen institutions that have significant numbers of minority students, and the overall underrepresentation in biomedical research of scientists who are members of minority groups. Such individuals constitute a vast, largely untapped source of the scientists needed to help the United States maintain its scientific and technological competitiveness.

"I am proud of the longstanding commitment of NIGMS to the goal of increasing research and research training opportunities for underrepresented minorities," said Dr. Ruth L. Kirschstein, director of NIGMS. "Having the MBRS program join NIGMS, which already administers the Minority Access to Research Careers (MARC) program, will further our goal more rapidly."

The MBRS program provides research grants to colleges, universities, and health professional schools with substantial minority enrollments, as well as to tribally controlled institutions on Indian reservations. These grants support research by faculty members, strengthen the institutions' biomedical research capabilities and provide opportunities for students to work as part of a research team.

MBRS program director Dr. Ciriaco Gonzales notes that "this move will permit the program to benefit from NIGMS' vast experience with basic research and research training."

During its 17 years of operation in the Division of Research Resources, the MBRS program has contributed to the development of research programs at more than 90 minority institutions. Most of these institutions had previously conducted little or no research. In addition, many of the more than 14,000 students who have participated in MBRS-supported research projects have become or are now working to become biomedical researchers.

The transfer of MBRS will establish NIGMS as the lead institute within NIH for the administration of minority research and research training grant programs. The NIGMS MARC program awards research training grants that help increase the number and capabilities of minority biomedical research scientists and strengthen science curricula and research opportunities at minority institutions.

One of 83 children who attended the largest Camp Fantastic ever takes a swing during a softball playoff among "tribes." Now in its seventh year, the summer camp for kids with cancer featured new classes in cycling and art. Also for the first time, the camp included a blind youngster and one with Down syndrome in addition to cancer. Some 25 NIH employees, including 15 medical staff, worked to make the recent weeklong session a success.

Dr. Arthur J. Atkinson, Jr., a professor in the department of medicine and pharmacology at Northwestern University Medical School and an NIGMS grantee, recently received the 1989 Harry Gold Award from the American Society for Pharmacology and Experimental Therapeutics. The award recognizes Atkinson's excellence in research and teaching in clinical pharmacology.

Hydrofluoric First Aid Correction

The Aug. 22 issue of the Record contained an error in the first aid procedure for cutaneous hydrofluoric acid exposures. Please note the following correct procedure:

For any accident involving hydrofluoric acid, immediately call the NIH Fire Department emergency number, 116. The Fire Department responds to all hazardous chemical spills and provides ambulance service to the Occupational Medical Service and to local hospitals. For off-campus emergency medical and chemical spill response, call 9-911.

While a coworker is reporting the emergency the injured person should be treated as follows:

For skin exposures, irrigate the area with water for 5 minutes, then apply 2.5 percent calcium gluconate gel. If the calcium gluconate gel is not available, continue washing until the ambulance arrives.

For ocular exposures, immediately flood the eye with copious volumes of water at the eye wash station and continue until ambulance personnel arrive. During the procedure, hold the eyelids apart to increase exposure of the eye surface and the conjunctival sac to the water. Do not use calcium gluconate in the eye.

The NIH Fire Department ambulance carries irrigating solutions and calcium gluconate gel to facilitate expeditious pre-hospital treatment. All hydrofluoric acid users are strongly encouraged to contact the Occupational Medical Service triage nurse at 496-4411 to obtain a hydrofluoric acid first aid kit.

Hydrofluoric acid burns are serious, so please be careful.
STEP Forum on AIDS Policy

The staff training in extramural programs (STEP) committee is holding a forum entitled "AIDS—Policy Update." AIDS has changed and continues to change the ways in which NIH and the extramural community think about and perform epidemiological and clinical research. Confidentiality, infection and disease tracking, what preclinical drug data are necessary, whom to treat and where to treat are all important issues at various stages of discussion and action. What influences resolution of these issues? How are they resolved? What will they have on epidemiological and clinical research immediately and down the road? How will we know if the approaches are working?

These issues and questions are of intense interest to health scientist administrators, research investigators, political activists and concerned individuals. A set of involved experts will address these topics.

Speaking on "Legal and Ethical Issues in the AIDS Epidemic" is Dr. Joan P. Porter of the Office for Protection from Research Risks, NIH. She has recently completed an assignment at the National AIDS Program Office of the PHS and is executive secretary of the working group on legal and ethical issues in AIDS of the PHS AIDS executive task force.

Dr. Jack Killen, deputy director of the Division of Acquired Immunodeficiency Syndrome, NIAID, will discuss "Drug Development and Access to Experimental Therapies." Covering "Community Programs for Clinical Research on AIDS" is Dr. Lawrence Deyton, assistant director for community clinical research and chief, community clinical research section, NIAID. He has spearheaded NIAID program efforts in community research initiatives.

This STEP Forum will be held in Wilson Hall, Shannon Bldg. from 1:30 to 4 p.m., Oct. 4. As with all STEP forums, there will be an opportunity for discussion and interaction with the audience. The forum is open to all interested NIH personnel. No preregistration is required. For additional information contact the STEP program office, 496-1493.

Healthy Men Needed

The Child Psychiatry Branch of NIMH seeks men, ages 18-40, with a high school diploma, or no more than 1 year of college to participate in neuropsychological studies. Participation involves completing paper and pencil tests and/or MRI scans of brain anatomy. Studies are noninvasive and volunteers are compensated. For more information, call Tracy Aquino, 496-3175.

Cohen To Give NIH Lecture on Sept. 20

Dr. Stanley N. Cohen, professor of genetics and medicine at Stanford University, will deliver the NIH Lecture on Sept. 20 at 3 p.m. in Masur Auditorium. He will speak on the “Analysis of Mammalian Gene Regulation in situ Using Retrovirus-based Portable Exons.”

Cohen is probably best known for devising methods that are today the foundation of recombinant DNA methodology, or so-called genetic engineering. Prior to this work, he was well recognized for his pioneering research in 1960 and completed a residency at Duke University Hospital and a postdoctoral fellowship at the Albert Einstein College of Medicine. Also, early in his career he was a clinical associate in the National Institute of Arthritis and Metabolic Diseases, forebearer of the present day NIDDK and NIAMS. Since 1968, Cohen has been on the faculty of Stanford University.

The NIH Lectures were established in 1953 to recognize outstanding scientific accomplishment and to contribute to the vital exchange of information among researchers. The lecture-ships are awarded by the NIH director on the advice of the scientific directors.—Kathy Kranzfelder

Lecture on Genes and Chromosomes

The first lecture in the 1989-90 STEP program "Science for All" series will be held on Thursday, Sept. 28 from 1 to 3 p.m. in Wilson Hall, Shannon Bldg. Dr. Bert Vogelstein of Johns Hopkins University oncology center will present again his popular lecture on "Genes and Chromosomes."

What are genes and chromosomes? How do they function to control heredity? How do they cause disease? Can genetic disease be corrected? What are the exciting research breakthroughs that may affect our lives in the future?

These and other questions will be answered in easy-to-understand language, and ample time will be allowed for questions from the audience. This lecture generated lively discussion 2 years ago, and Vogelstein will again present the basics of genetics, along with updates of current findings.

All are invited to attend this event. Advanced registration is not required nor is continuing education credit available. For additional information, contact the STEP program office, 496-1493.

History of Medicine Talks Planned

The Washington Society for the History of Medicine will sponsor two lectures on Thursday, Sept. 21 at 8 p.m. in classroom 1N30B of the Lister Hill Center, National Library of Medicine. Dr. Victoria Harden, NIH historian, will discuss "Rocky Mountain Spotted Fever Research After the Advent of Antibiotics," and Dr. Diana Long, NLM visiting scholar, will present "Medicine Redefines Sex in the Twentieth Century: the Index Catalog of the Surgeon General's Library 1880-1950." Suburban Hospital has certified this program as acceptable for 2 hours Category 1, CME.
CONSTRUCTION
(Continued from Page 1)

mental retardation, the seven-story structure will also house a modern primate facility. Investigators from seven institutes will work in Bldg. 49, which is slated for completion in late 1992.

Perhaps the most widely anticipated construction project, because it will involve the most people, is still confined to the drawing board. Dubbed the Consolidated Office Building (COB), this project will return some 3,000 employees currently occupying rental buildings in the area to the campus. It will include nine stories of office space, four floors of parking and cost about $120 million. The COB, scheduled for completion in 1994, will stand near Stone House and the Medical Center Metro station.

Also on the drawing board are additions to Bldgs. 14 and 29. Currently awaiting funding, Bldg. 14D-1 will stand between 14C and D, and contain laboratories, offices and animal surgery rooms. Bldg. 29B will be built next to FDA's Bldg. 29A and host the Center for Biologies Evaluation and Research, an integral component of the FDA regulatory mission. Construction is slated for completion in September 1993. At Bldg. 30, the dental institute plans a five-story tower addition on the east side to house cage washing, mechanical and support space in addition to three floors of laboratory space.

The so-called “Round Robin” renovation of aging NIH laboratory buildings continues with Bldg. 5 undergoing a $17.5 million, 2-year restoration. Bldgs. 8 and 4 are already complete, and Bldgs. 2, 3, and 7 will be done in that order after 5 is finished. Employees from Bldg. 5 have moved into Bldg. 4.

Animal holding will also be expanded with the construction of Bldg. 6B, which should be finished in March 1991. Built as a six-story facility adjacent to Bldg. 6, 6B includes 56,000 square feet of space. Two basement levels and the ground floor of the structure will be divided into 23 holding rooms for small animals. The upper floors will be laboratories, primarily serving NICHD.

Bldg. 6B, a six-story addition to Bldg. 6, is scheduled for completion by March 1991.

Over at the Clinical Center, which has undergone renovation almost continually since its cornerstone was laid in June 1951, a new three-story surgery wing is nearing completion on the hospital's west side. Woven almost seamlessly into the red brick of the main structure, the addition will house heart and neurology operating suites as well as the CC's department of transfusion medicine and blood bank. The $8.5 million project has been under way for the past 5 years.

“What is so unique about these two new heart surgery suites is that 50 air changes an hour are required to perform new kinds of surgery,” says Leon Pheder, engineer and project officer in the DES Design and Construction Branch. Normal room air changes range from 5 to 10 per hour. The units also have computerized light systems that allow surgeons remote control over the lights.

“A lot of engineering work was done in designing an air and light system to meet the surgeons’ requirements. We worked on some territory that has never been tested before,” Pheder states.

The former surgery suite in Bldg. 10A (the round building appended to the west portal of the CC) is now being renovated into an animal holding facility with completion slated for this fall.

Future additions to Bldg. 10 include a new medical intensive care unit to be constructed over the existing library patio and three new A-wing floors to accommodate AIDS researchers from several institutes. Since the A wing is located on the east extremity of Bldg. 10 (though, oddly, on the opposite side of the hospital from 10A), it is now possible to state truthfully that the CC is undergoing renovation from the east unto the west.

As if new buildings and renovations to existing structures were not enough to keep the builders busy, the 30 to 40 year-old utility systems on campus are in need of extensive modernization and improvement. A comprehensive program, estimated to span the next two decades, is being developed to meet these “infrastructure” needs. Included in the program will be new heating and refrigeration equipment for the NIH central power plants, the replacement of central distribution piping systems carrying steam and chilled water to the NIH buildings, and, in the case of Bldg. 10, improvements to the infrastructure of the Clinical Center itself.

“This will be the first major improvement in the central supply system on the campus in 37 years,” states John Jenkins of DES's Facilities Engineering Branch. “And, the Clinical Center,” he continues, “will be the biggest problem — how to keep it operational while working on it at the same time.”

“It is a Herculean job,” noted Clifford. And one that is literally changing the face of NIH.
Preparing drywall for the next step — painting, is Debbie Evans, a carpenter in the Shops Branch.

program. Michelle White, assistant foreman in the paint shop, also used the program to get her job.

“Our shops fabricate for anything needed here on campus,” says Burton. A sampling of the work done by the Shops Branch includes cabinet work, laboratory tops, specialty items required by scientists, instruments, metal cages and ladders.

Last year, the Shops Branch handled 13,400 jobs along with 4,757 trouble calls.

“I love it,” says Evans. “It’s never the same job — they are constantly changing. Each job is different. I love a challenge.” — Anne Barber

Renee Poussaint To Speak at NIH

The NIH women’s advisory committee, a component of the Division of Equal Opportunity, is sponsoring a presentation by Renee Poussaint entitled, “A Personal Story,” on Thursday, Sept. 28, from 11:30 a.m. to 12:30 p.m. in Masur Auditorium, Bldg. 10. This program was originally scheduled in March for Women’s History Month.

Poussaint, anchor of WJLA-TV’s evening news programs, received a B.A. from Sarah Lawrence College in New York and an M.A. from UCLA. She did postgraduate work at Yale Law School and Indiana University. She received an honorary doctorate from Mount Vernon College in Washington, D.C., and studied at the Sorbonne in Paris. She is also a graduate of the Michele Clark Program for Minority Journalists at Columbia University.

Poussaint has earned numerous awards for her reporting, including six Emmys, and for her community service. “I tend to gravitate to issues and people who don’t have a voice,” she has said.

Sign language interpretation and reserved seating will be provided for the deaf. If accommodations for disabling conditions are needed, contact Linda Dugger in the Division of Equal Opportunity, 496-2112. For further information, call Bonnie Douglas, DCRT, chairperson of the women’s advisory committee, 496-2847.

Musicians To Play History of the String Quartet

The Manchester String Quartet will present an educational three-part chamber music series for the NIH community. The series, sponsored by Merck & Co., Inc., will explore the birth and development of the classical string quartet through performances of works by Haydn, Mozart and Beethoven. Samples of the musical score and program notes will be provided for each performance, as well as a brief discussion of each work.

The 1-hour lunchtime concerts are free to all. They will take place Sept. 25, Oct. 30, and Nov. 27 in Masur Auditorium, Clinical Center, beginning at 12:30 p.m.

The Manchester String Quartet was established in 1981, and consists of members of the National Symphony Orchestra. The quartet is well-known to Washington music lovers through its concert, radio and television performances. These include appearances at the Kennedy Center’s Terrace Theater, the National Gallery, WGMS, WAMU, WETA radio, and WETA-TV’s “Embassy Concert Series.” In addition the quartet has developed several educational programs, and were members of the artist faculty at the 1985 and 1987 American Congress of Strings.

For further information, call the NIH Visitor Information Center, 496-4713.

NIMH Needs Volunteers

The Laboratory of Socioenvironmental Studies, National Institute of Mental Health, is seeking healthy normal volunteers for a study of memory for textual material. Volunteers should be at least 18 years old, and should speak English as their first language. The study takes approximately 2 hours to complete; volunteers will be paid. Call Leslie Caplan or Zita Givens, 496-3383, for further information.
GENE TRANSFER
(Continued from Page 1)

transfer experiment last May. Though data from that study have not yet been analyzed, three of the five cancer patients who got the new gene—used solely as a marker and not as a tumor killer—have undergone tumor shrinkage. And, quite heartening to the researchers, there appear to be no side effects in patients who received engineered genes.

"That's great," says Dr. Kenneth Culver, a pediatric immunologist in Blaese's laboratory who is helping the team toward its ultimate goal of fixing genes in patients (see sidebar); all of the researchers are mindful of society's suspicion of experiments involving recombinant DNA in humans.

Sitting in the Metabolism Branch library on a recent afternoon, Blaese recounted the advances that have left his laboratory on the brink of bold new generic therapies.

"The history dates back to about 5 years ago," he said. "Gene therapy evolved from molecular hematolgy. The gene defects in such diseases as sickle cell anemia and thalassemia were defined and seemed amenable to correction."

In sickle cell disease, a single amino acid mutation causes cells that should normally be flexible to become rigid. The resulting illness, Blaese said, is sometimes called "sick-as-hell" anemia.

"To correct this problem, you need a gene for the right molecule," he explained, "but you also need a mechanism to shut down the gene producing the wrong molecule. The problem, as with some of the other hemoglobin diseases, was too difficult for current technology and a search for alternatives began."

Researchers settled on a new target—severe combined immune deficiency (SCID), a disease that seemed reversible through bone marrow transplantation combined with gene therapy. About one-quarter of all SCID cases are caused by a lack of adenosine deaminase (ADA), an enzyme important for eliminating wastes that accumulate during normal metabolism. If science could find a way to put a gene that makes ADA into bone marrow stem cells, then many SCID cases could be cured.

Enter the "French" connection.

Blaese had long been interested in treating patients with severe immune deficiency diseases and thrombocytopenia (low levels of blood platelets). In 1979 he initiated studies proving that spleen removal could help patients with these illnesses. One of his patients with Wiskott-Aldrich syndrome needed splenectomy but was too young to be operated on at NIH. Blaese had heard of the good reputation that Dr. Kathryn Anderson, a pediatric surgeon at Children's Hospital, enjoyed.

"She agreed to the surgery and thus began a close collaboration involving more than 25 patients," Blaese said. Anderson told her husband, NHLBI's W. French Anderson, about Blaese's work with immune deficiencies. When French began considering work on ADA gene transfer, he called Blaese, who had never met French at NIH before.

French Anderson, in collaboration with investigators at Princeton University, had devised a gene transfer system during the summer of 1985. They used a retrovirus vector to add a corrective gene to cell cultures that were lacking a certain gene. Blaese's lab was able to develop T cell lines from an ADA deficient SCID patient and then Anderson and Blaese's labs showed that gene transfer would correct the defect in these cells.

"The next step was to apply the technique in vivo, using animals," said Blaese. Joining with Dr. Arthur Nienhuis of NHLBI and Richard O'Reilly at Memorial Sloan-Kettering Cancer Center, he inserted the ADA gene into the marrow of monkeys.

"We got mixed results," he said. "The monkeys made the product of the foreign gene (human ADA) but the expression was far too low and only lasted 3 or 4 months. The transient effect was very discouraging."

Had the experiment worked perfectly, the monkeys would have produced 50 percent monkey ADA and 50 percent human ADA; the best studies yielded only 1-3 percent human ADA.

Scientists next looked for ways to improve the efficiency of inserting new genes into bone marrow, an effort that continues to this day.

Meanwhile, in the summer of 1987, a new medical staff fellow named Dr. Kenneth Culver joined Blaese's staff. His project was to develop a way of using lymphocytes rather than bone marrow as a gene insertion medium.

"Ken put genes into lymphocytes using a murine (mouse) retrovirus," Blaese said. "It worked very well in both mice and monkeys. Suddenly the stage was set to think of human trials about a year and a half ago."

A promising new method in hand, the lab then asked, "Where in the world do you use lymphocytes (to treat) disease?" Blaese recalls. The answer? In Dr. Steven Rosenberg's cellular immunotherapy for cancer.

"I approached Steve with the idea of combining our method of putting genes in T cells with his lymphocyte therapy."

Future experiments with Rosenberg call for inserting genes that will make TILs (tumor infiltrating lymphocytes) even more potent cancer fighters. The goal will be to enlist a variety of cytokines (substances produced by lymphocytes), including tumor necrosis factor and interferon, in the battle against tumors.

"We're all working on that now," he said. "Before that happens, however, the first therapeutic application of gene transfer is"
likely to be against ADA deficiency. Three SCID patients with ADA deficiency are currently enrolled in a Blaese study aimed at growing lymphocytes from the patients, inserting the ADA gene, then seeing if the cells express that gene in a significant way. “SCID patients have almost no lymphocytes,” he explained. “The challenge is to get enough cells to start the experiment.”

Using monoclonal antibodies that react to part of the T cell receptor, Blaese’s team has had striking success in stimulating lymphocytes from these immune deficient patients to divide and proliferate. Starting with 5 ml of blood, they have been able to grow more than 100 million T cells which can then be corrected by gene transfer and given back to treat the patient’s basic disease. They also intend one day to use genetically altered lymphocytes to treat other diseases such as hemophilia.

“The liver normally makes clotting factors 8 and 9 (which prevent the uncontrolled bleeding characteristic of hemophilia). Injection of clotting factor is the current therapy for hemophilia. But we’re trying to put the genes for factors 8 and 9 in lymphocytes. That way we could give patients their own cells back (rather than rely on possibly contaminated factor transfusions). There’s no reason the liver has to...”

(Continued on Page 10)

A Portrait of the Gene Transferer—NCI’s Dr. Kenneth Culver

Dr. Kenneth Culver of NCI’s cellular immunology section is having the time of his life. And that means patients may some day have the time of their lives, too.

A medical staff fellow who joined Dr. R. Michael Blaese’s laboratory in July 1987, Culver had been a fellow in pediatric immunology at the University of California, San Francisco, for 2 years when he came to NIH. Blaese hired him to do work that led directly to the first approved gene transfer experiment in humans, which was performed here last May.

“I came specifically to do gene transfer of ADA (adenosine deaminase, an enzyme critical in normal T-lymphocyte metabolism) into mouse lymphocytes,” he says. “The first experiments worked fantastically, beautifully.”

The initial in vivo experiments involved “nude” mice, a breed with no immune system.

“We could recover T cells proving that the transferred ADA genes were still working 3 months after injection into the mice,” he said.

The next step was to insert genes into T cells of other animals, including normal mice, rabbits and monkeys, and prove that they worked in their new environment.

Culver’s specialty, rigging lymphocytes to carry genes of special interest, was leading directly toward the first human gene transfer trial conducted by Blaese, NCI’s Dr. Steven A. Rosenberg and Dr. W. French Anderson of NHLBI.

Currently, Culver, technician Cindy Able, two medical students and two college students for whom he is a mentor are conducting some dozen projects involving gene transfer. They are using primary (normal noncancerous) lymphocyte lines to carry altered genes into various animals. Their eventual goal is to conduct a clinical trial focusing on ADA deficiency in humans.

“My goal is to get the ADA clinical trial to go while I’m still here,” Culver stated. “I told French that, publications aside, if we can’t treat patients successfully, then we’ve failed.”

Along with Scott Freeman, another fellow who has worked with Blaese and Anderson for the past 3 years, Culver has been studying transfer of a variety of genes. Using calcium phosphate precipitation—“a common way to get big pieces of DNA into cells”—they are building designer gene constructs in retroviral vectors.

The method is not unlike constructing an automobile on an assembly line. A wild type virus, in this case Moloney murine leukemia virus, is converted into a “packaging construct” by deleting what’s known as a psi packaging sequence from its genetic parts. Without that sequence, the virus can make proteins but cannot package its genome and is therefore noninfectious. In this state, the viral genes are a mere builder of “empty virions”; its products are like parts on an assembly line that has no foreman to organize how they fit together.

“All the proteins are being made, but they aren’t being assembled with viral genes inside,” Culver explains. “It can’t get its act together.”

Enter the foreman, in the form of a gene transfer construct. This sequence resembles the packaging construct but differs in two important ways. First, it has a psi packaging sequence, which is the brains of the outfit. And second, it is carrying the “good” gene. By inserting this gene transfer construct along with the packaging construct into fibroblasts, the good gene can get on with its work of expressing infectious virions containing the good gene that are incapable of replication after infecting the initial host cell.

The whole process is just a way to trick a retrovirus into carrying something good into a person or animal instead of something harmful.

Like his lab chief Blaese, Culver enjoys the pedagogical side of his work at NIH. “It’s a privilege to be here, but not just for the research,” he said. “I also enjoy the opportunity to teach.”

Several of his charges have gone on to careers in medicine and many are still friends, though separated by miles and, in one case, an ocean.

“One of my students is working for the Peace Corps in Kenya,” he says proudly. “It’s neat to see the great things people end up doing.”

Culver remembers well the turmoil of his undergraduate days at Drake University in Iowa. “I didn’t know what I wanted to major in at first. I tried business but it bored me. Then I tried teaching but I feared I couldn’t handle a roomful of rampaging kids. A mentor of mine kept insisting that I try medicine. I’m glad he did.”

Culver got his M.D. from the University of Iowa. While doing a fellowship in pediatric immunology he “fell in love with treating sick kids. I found I developed a very personal relationship with some of the families of my patients. You become more than their doctor. You become their friend and sometimes their pastor.” Culver has journeyed to Canada and southern California with his wife and children to visit grateful parents who have appreciated his care.

“The joy of being a physician is being able to put the pieces together,” he said. “You have the personal relationships, the clinic and the laboratory. I’m having the time of my life.”

Adding perspective to Culver’s admiredly privileged view of the world are summer trips to Third World nations where he volunteers his medical expertise. A recent visit to a barrio in the Dominican Republic tempered his esoteric gene research.

“I don’t want to get lost in personal goals and paper-publishing goals,” he said. “I have an obligation beyond gene therapy in my life. Because human gene therapy won’t affect the way people live in the Dominican Republic—not soon anyway.”

Culver hopes to remain at NIH long enough to see gene therapy used successfully. Asked about future plans, he admitted, “I’m still trying to find out where I fit in.”

Given his skill in persuading genes to fit in, there’s little doubt that he will find his place in the world.
Protein May OverACT

Is Alzheimer's a Result of a Protective Mechanism Gone Awry?

By Anne A. Oplinger

At first, it may be such things as forgetting to turn off the stove or getting lost in the shopping mall, but later, people who suffer from Alzheimer's disease also lose the ability to tell time, communicate, recognize their families, find their way around their own homes, and, ultimately, to live independently. The cause of this neurological disorder is unknown and there is no cure. Although many cases of Alzheimer's disease are thought to arise spontaneously, between 20 and 50 percent of the time the disease appears to be inherited. This familial form of the disease is being studied by scientists who are attempting to understand both its genetic origins and the cellular events that erode the brain's functioning. One such scientist is NIGMS grantee Dr. Huntington Potter of Harvard University, who has uncovered tantalizing new clues about the genetics and progression of Alzheimer's.

The brains of elderly persons who have died of Alzheimer's disease are characterized by large numbers of deposits—called senile plaques—composed of at least two different proteins. Several years ago, when researchers identified the gene for one of these proteins (called the beta amyloid protein) and learned that it is located on chromosome 21, there was great optimism that many of the mysteries of Alzheimer's disease might be solved.

Investigators knew that persons with Down syndrome—who have three, rather than the normal two, copies of chromosome 21—sometimes develop senile plaques and Alzheimer-like symptoms in their 30's and 40's. Because they have three copies of the gene for the beta amyloid protein (one on each chromosome), people with Down syndrome can produce excessive amounts of the protein. Some researchers thought that a duplication of the part of chromosome 21 that contains the amyloid gene could lead to excessive amyloid protein production and, therefore, Alzheimer's disease in persons who develop the condition. Could it be, scientists wondered, that the beta amyloid-coding gene is the Alzheimer's disease gene?

Unfortunately, continued study dashed this speculation and researchers have had to seek alternative explanations for the cause (or causes) of Alzheimer's disease. Work in Potter's laboratory is currently directed at understanding another component of senile plaques—a protein called alpha-1 antichymotrypsin (ACT).

ACT is a protease inhibitor produced primarily in the liver. Like all protease inhibitors, ACT hinders the activity of certain enzymes (proteases) whose job is to break down other proteins. Proteases and their inhibitors exist in equilibrium in many body systems. In the blood, for example, proteases are involved in clotting, certain immune responses and inflammation. But whenever proteases begin to work, protease inhibitors are also activated, thereby preventing unchecked protein degradation.

Using sophisticated staining techniques, Potter's group discovered that, besides being present in the liver, ACT is also an integral part of Alzheimer's disease plaques. Subsequently, the scientists showed that ACT in senile plaques does not enter the brain via the bloodstream, but instead is produced by certain brain cells.

Turning next to the genetics of ACT production, Potter measured the amount of ACT messenger RNA (mRNA) in the brains of people who had died of Alzheimer's disease. (Messenger RNA molecules carry instructions for making proteins from the genes in the nucleus to the cell organelles where proteins are manufactured.) ACT mRNA, they learned, is present in higher-than-normal amounts at the sites of senile plaques. In other words, there is an "overexpression" of ACT mRNA which, in turn, leads to an excess of the protein.

How does ACT overproduction in Alzheimer's arise, and how does this manifest itself as senile plaques? Potter and his colleagues have examined the known functions of ACT for clues to its role in Alzheimer's disease. The liver, they point out, increases its production of ACT in response to a number of circumstances, including viral infection and inflammation elsewhere in the body. Perhaps, the scientists suggest, a similar increase in ACT might occur in the brain following a cellular injury there. Ordinarily, the level of any protease produced in response to injury or inflammation slowly decreases as the system returns to normal.

However, in Alzheimer's disease, this return to the status quo may not occur. An excess of ACT, Potter's group hypothesizes, might prevent brain proteases from performing their usual job of clearing away other proteins (including the beta amyloid protein) produced in response to some cellular injury. Ironically, instead of protecting the brain from uncontrollable protease breakdown, an overzealous response by ACT upsets the delicate balance between proteases and inhibitors and may contribute to Alzheimer's disease.
**TRAINING TIPS**

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

**Courses and Programs**

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**Training and Development Services**

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

The URC hours are:

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

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**Long-Term Hormone Therapy Increases Breast Cancer Risk**

By Kara Smigel

A group of 23,244 Swedish women who used replacement hormones (both estrogens and estrogen-progestin combinations) for menopausal symptoms experienced overall about 10 percent more breast cancers than expected, Swedish and American researchers reported recently. A more detailed study based on all 208 women who developed breast cancer and a random sample of 653 disease-free women showed that the risk increased to 70 percent above expected levels among women who used the medications for 9 years or more.

The study was published in the Aug. 3, 1989, issue of the *New England Journal of Medicine*.

Reports in the mid-1970's of increased incidence of endometrial cancer due to use of estrogens led to the addition of progestin to estrogen treatments for menopausal symptoms. An earlier analysis of Swedish women showed that the risk of endometrial cancer did not increase with the combination therapy of estrogen-progestin. The current analysis defines its effect on breast cancer risk. The two studies of Swedish women have been the first research to evaluate long-term use of combination estrogen-progestin therapy—which has only been extensively prescribed in the United States since the early to mid-1980's.

**Short-term vs. Long-term Use**

"Women and prescribing doctors will have to consider the risks and benefits when choosing whether or not to use or prescribe menopausal replacement hormones," said coauthor Dr. Robert Hoover of NCI. "Short-term use, typically sufficient for effective treatment of severe menopausal symptoms such as hot flashes and night sweats, does not seem to be associated with any observable increase in breast cancer risk," he said.

"However, long-term use, currently being widely promoted to decrease the risk of osteoporosis and perhaps cardiovascular disease, presents more of a dilemma," said Hoover, who is chief of NCI's Environmental Epidemiology Branch. "At this time, it is difficult to know how to quantify and weigh the established and suggested benefits against the established and suggested risks."

Among those women in the random sample who used only estrogen-progestin combinations for 6 or more years, breast cancer risk was more than four times higher than for women not prescribed hormones during this time period. In addition, women who switched to estrogen-progestin combination treatments for at least 3 years after having used estrogen alone had greater than twice the expected breast cancer risk. However, Hoover advised caution in interpreting these estimates of risk since they could be unreliable due to the small numbers of women in these groups.

"While these high risks are worrisome, we currently interpret our findings conservatively as showing that estrogen-progestin combinations do not reduce the excess risk of breast cancer that has been associated with long-term estrogen use," said Hoover. Use of the combination therapy for up to 6 years was not associated with any increased breast cancer risk.

"Only with continued research will we learn whether the addition of progestins to estrogen therapy really increases the risk of breast cancer further," said Hoover.

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**Former NCI Research Physiologist**

**Dr. Willie White Smith, Dies**

Dr. Willie White Smith, 82, a retired research physiologist with the National Cancer Institute, died of pneumonia Aug. 29 at Holy Cross Hospital in Silver Spring, Md.

Smith, who had lived at the Chevy Chase Retirement and Nursing Center since 1983, was a native of Georgia where she graduated from Agnes Scott College. She received both her master's and doctoral degrees in physiology from Columbia University in New York.

She was a research physiologist with the Du Pont Co. in Wilmington, Del., from 1939 until 1943, when she moved to the Washington area to join NIH. She retired in 1977.

Survivors include a sister, Carolyn White of Perry, Ga.

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Dr. Eugene M. Zimmerman has been named to the newly created position of special assistant to the director, Division of Allergy, Immunology and Transplantation, at NIAID. Since 1981, Zimmerman has served as executive secretary of the allergy and immunology study section for DRG. He previously had served as the executive secretary of the cause and prevention scientific review committee at NCI from 1979 to 1981. Zimmerman joined NIH in 1976 as a grants associate in the Division of Grants. He received his Ph.D. from the University of Maryland in 1968 and is a member of the American Society for Microbiology and American Association for the Advancement of Science.
Mammography Screening Offered to Women at NIH

According to studies conducted by the National Cancer Institute, mammography is the best way to detect breast cancer early—up to 2 years before a lump can be felt. The good news is that if breast cancer is detected early, 90 percent of the cases can be treated successfully.

The Occupational Medical Service (OMS) of the Division of Safety has planned, as part of National Breast Cancer Awareness Month, a low-cost mammography screening program Oct. 16-20. A mobile van equipped for mammography screening and operated by registered female technologists will be provided by Drs. Groover, Christie and Merritt, Washington area radiologists. The equipment meets quality and exposure standards developed by the American College of Radiology and the mammograms are read by board-certified radiologists; results are given to the screening participants.

There are good reasons to participate in this program:

- All women are at risk for breast cancer, not just women with a history of breast cancer in their families;
- A woman’s chances of getting breast cancer rise greatly as she gets older;
- A mammogram is simple and not painful;
- All results are confidential.

The life-saving benefits of mammography are made clear by an NIH employee who volunteered to share the results of her February 1989 mammogram.

"I felt fine, expecting good news about the mammogram which I had done at the OMS screening," she said. "I expected to gain peace of mind as most women do when they have mammograms.

"When my doctor phoned me about the report, asking me to have more detailed mammograms and an exam, I was surprised. Still, I felt fine and there was no evident lump. That mammogram set off a course of action which saved my life. Long before it could be felt by self-examination, I had early breast cancer removed and I’m on treatment to prevent recurrence.

"This early detection was good news after all. It gave me time to consult with many doctors, to find the best surgeon, and it gave me a choice about the extent of the surgery and treatment. It saved my breast and my life. The only thing worse than having cancer is having it and not knowing about it early enough.”

To participate in the program, women must:
- Be age 40 or older unless there is a family history of breast cancer. Younger women who have a physician’s order (prescription) will be accommodated.
- Be asymptomatic—experiencing no current breast problems (example: pain in one breast, lump or nipple discharge).
- Have a physician to whom the report will be sent (participant will also receive a copy).
- Not have had a mammogram within the last 12 months.
- Not have breast implants.
- Not be pregnant or nursing.

The cost of the mammography screening program is $55 to be paid at the time of the exam. Payment may be made via Visa, Mastercard, check or money order. Cash is not accepted.

To schedule your 30-minute appointment, interested employees may call the OMS Westwood health unit, 496-7638, everyday except Thursday. Space is limited and requests will be handled on a first-come, first-served basis.

In addition to mammography screening, an hour-long general breast health education program will be offered on Wednesday, Sept. 27 at 10:30 a.m. in Bldg. 31, Rm. 2C15.

The screening locations and dates are:
- Monday, Oct. 16 3IC parking lot
- Tuesday, Oct. 17 10C shuttle turn by Convient Drive
- Wednesday, Oct. 18 10C shuttle turn
- Thursday, Oct. 19 Westwood rear parking lot
- Friday, Oct. 20 Executive Plaza parking lot

Take a step toward better health by participating in this breast screening and education program.

Disney on Ice’ Tickets

R&W has tickets to "Walt Disney’s World on Ice" starring Peter Pan and other live Disney characters, Oct. 3-8 at the Washington Convention Center. Ticket prices range from $10 to $13. Call or visit the R&W Activities Desk in Bldg. 31, 496-4600.

Child Health Day Focuses On Prenatal Care, Oct. 2

Each year, 40,000 infants in the United States die before their first birthday. Yet, depending on where they live, their age and their race, up to 18 percent of American women receive little or no prenatal care.

A discussion of the complex and varied reasons behind the mixed success of providing prenatal care in this country will be the focus of a day-long symposium sponsored by a consortium of a dozen federal and private organizations.

The symposium will be held to commemorate Child Health Day, which is celebrated, by Presidential proclamation, on the first Monday in October.

This year’s Child Health Day program, “First Step to the Future: Prenatal Care for All,” will be held Monday, Oct. 2 in the Great Hall of the Hubert H. Humphrey Building, 200 Independence Ave., S.W., Washington, D.C. starting at 9 a.m.

A highlight of the program will be the release of the Public Health Service report, “Content of Prenatal Care.” The report includes a set of recommendations pertaining to the services that should be offered as part of prenatal care and the pattern and schedule of the delivery of these services.

In addition to the report, panel discussions will be held on financial and nonfinancial barriers to prenatal care, provider shortages and quality and delivery of services. Also a videotape presentation illustrating successful programs of prenatal care delivery to hard-to-reach or underserved populations will be premiered.

As part of the program, the Healthy Mothers/Healthy Babies National Achievement Awards will be presented to recognize outstanding projects that have promoted the health of mothers and babies through public education efforts.

The keynote speaker will be Constance Horner, under secretary of health and human services. Other speakers include Dr. James Mason, DHHS assistant secretary for health; Dr. Duane Alexander, director of the National Institute of Child Health and Human Development; Dr. Vince Hutchins, deputy director, Bureau of Maternal and Child Health and Resource Development and Louis Hays, acting administrator of the Health Care Financing Administration.

Admission to the symposium is free and no preregistration is required. For more information, call 496-5133.