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To: Jeannie Nappo
From: Randy Black, UC Irvine

Jeannie,

Please find attached several articles and press releases relevant to the research at UCI we discussed this morning.

Although some of the material may seem dated, the nature of science dictates that current work is quite similar--these researchers continue to refine and improve their work rather than shifting focus completely.

Please feel free to contact me if you would like more information or if I can be of help in any way.

(714) 856-7912

Text of Brochure
for Call Center's
Alzheimer's Research



Research strategies
for tomorrow

SUCCESSFUL AGING

U CAL IRVINE CAMPUS FAX
THE NUMBER OF PEOPLE
OVER 65, THE FASTEST GROW-
ING GROUP OF AMERICANS, IS
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MILLION OR 20 PERCENT OF
THE POPULATION BY THE
YEAR 2020."

Mrs. Florence Dysinger is 90 years old but she still swims in the ocean before climbing the steps back to her home in Dana Point. Sometimes, she takes it a little easier and plays tennis with her friends, including a 76-year-old youngster. Clinical tests show she has the sensory acuity, including the sense of smell, equivalent to that of a 40-year-old.

"Florence has a handshake that could crush a Volkswagen," says Dr. Rodman Shankle, a clinician in the Alzheimer's Disease Diagnosis and Treatment Center at the University of California, Irvine. Despite her years, Florence enjoys a life still rich with new experiences, both physical and intellectual.

Lucas Fafara is 74 and may be showing the first signs of a form of dementia known as Alzheimer's disease (AD). At the urging of his daughter, he came to the Center for information, more extensive diagnostic testing and treatment. He and his wife of 50 years still enjoy life and maintain a positive outlook but, along with many older people, his memory is not what it used to be. Lucas will tell you with pride that he has acted in movies, including a small part in "From Here to Eternity". In the course of an hour, he will tell this story over and over.

TEL: 714-856-5451

He has trouble remembering recent events. Still independent, although their daughter drives the couple where they need to go, the Fafaras say their lives have been "wonderful." "At least so far," adds Lucas.

"John," a typical Alzheimer's patient, is 65 years old and has advanced AD. He has difficulty remembering even simple information. Incapable of caring for himself, he has become a burden on his family and requires full time care in an institution. Typical of many diagnosed with Alzheimer's, John has great difficulty distinguishing and remembering smells. His intellectual incapacity has affected his physical well-being and he rarely goes out or exercises. Although he has many years left in his life, his relatives wonder how much life he has left in his years.

Jan 31, 90 10:00 No.010 P.04



At 90 Florence Dysinger still enjoys a game of tennis. "What's my secret? Three things: stay active physically, stay active mentally and don't go to doctors--they can always find something wrong with you."



"It took a lot of doing to get Lucas to come down here. He can be pretty stubborn." They met at the 1939 World's Fair. "My first words to her were, 'Hello honey, how was heaven when you left?'"



Images of the human brain provide continuous history of neuronal circuitry in normal aging and AD. New approaches are being developed to enhance resolution and visualize specific molecules. (Dr. Richard Bridges, Assistant Professor, Neurology; Dr. Jim Geddes, Assistant Professor, Division of Neurosurgery)

THE AGING OF AMERICA: THE BABY BOOM REACHES SENIORITY

In the U.S. today there are about 29 million people over 65; about 12 percent of the population. The number of people over 65, the fastest growing group of Americans, is expected to increase to 54 million or 20 percent of the population by the year 2020.

Due to improvements in medical care, the life expectancy of Americans has increased dramatically in this century. However, a major concern for the elderly is not just living longer but maintaining their quality of life. "Successful aging" is more than a catch phrase, it represents an increasingly important goal of a growing number of Americans whose happiness and the nation's vitality will depend on their retaining health and independence.

SUCCESSFUL AGING: AN ATTAINABLE GOAL

Why do some people age more successfully than others? One reason, contrary to popular belief, is that "senility," "second childhood" and loss of mental acuity are not an inevitable consequence of aging. Few neurons are lost with age, though some do become smaller, perhaps due to disuse. In fact, the brain has natural repair mechanisms that compensate for minor cell loss and other damage. The brain's inherent resilience, resistance to disease and capacity for self-repair, are hopeful signs that successful aging is not only possible but a goal consistent with the brain's own design. Research to date indicates that mental impairment during aging is not a

normal process, but the result of undetected disease of the brain, primarily AD and related disorders.

ALZHEIMER'S DISEASE: CHALLENGE TO SUCCESSFUL AGING

Described first in 1907 by Dr. Alois Alzheimer, AD is a progressive, irreversible disease characterized by gradual memory loss, disorientation, impaired judgement and finally, loss of control over body functions. AD crosses all social and economic boundaries and affects both men and women.

AD victims suffer progressive impairments of memory. Initially the problems appear as forgetfulness,

The peculiar tragedy of AD and related dementias is that over their course of as long as 20 years and averaging 8-10 years, they dissolve the mind and steal the humanity of the victim leaving a body from which the person has largely been removed.

poor judgement, difficulty in making calculations and handling money. Cognitive losses ultimately leave the person confused, disoriented and incapable of communicating normally. Affected individuals undergo personality changes that range from social withdrawal to belligerence and agitation. Other symptoms include

disturbed sleep and a tendency to wander aimlessly. Over time these individuals lose their ability to care for themselves and may be unable to control their elementary body functions such as bladder and bowel control.

According to a report to Congress by the Advisory Panel on AD (February 1989), "The peculiar tragedy of AD and related dementias is that over their course of as long as 20 years and averaging 8-10 years, they dissolve the mind and steal the humanity of the victim, leaving a body from which the person has largely been removed."

Approximately 15 percent of people over 65 now have AD, which accounts for from 2.5 to well over 3 million cases in the U.S. According to the Office of Technology Assessment of the U.S. Congress, the prevalence of AD could more than triple within 50 years. It is estimated that at least 25 percent of people now in their 30s and 40s will become victims of AD before they die.

Medical research offers the only hope for understanding and eventually eliminating AD and age-related dementias. Scientists have not yet discovered what causes AD. At present no effective therapeutics exist and the development of treatment is handicapped by the absence of basic knowledge. However, major advances have been made in the area of early diagnosis and therapeutic options that hold great promise for the management of the degeneration process.

SUCCESSFUL AGING VS. AD



The increase of dementia sharply increases with age



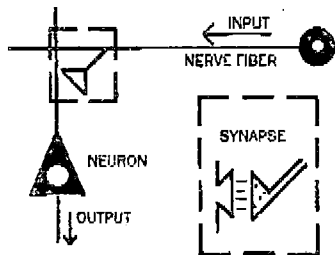
Increase in number of people over 65 years as a percentage of the population

Some people like Florence age successfully whereas others fall victim to age-related dementias. Research on aging has emphasized losses while neglecting the successful side. Efforts must be made to discover the scientific basis for why the aged brain in some people possesses such resilience and vitality.

AD victims suffer progressive impairments of memory. Initially the problems appear as forgetfulness and poor judgement. Over time these individuals lose their ability to look out for their own well being in AD.

Memory is lost progressively
Body health is preserved
Plaques and tangles accumulate in the brain
Neurons are lost in selected brain areas

BRAIN FUNCTION IN A SIMPLE NETWORK



The brain contains several billion neurons of different sizes and shapes as unique as people. Each neuron has over 10,000 synapses on its surface. Small electrical signals (nerve impulses) travel along a nerve fiber (axon) at speeds of up to 90 m.p.h. When these impulses reach synapses, chemicals (neurotransmitters) are released into the dendritic surface of target neurons. Activity of synapses excites, inhibits or modulates ongoing signalling in the network. Most drugs which alter brain function affect various aspects of synaptic activity.

Drugs are currently being developed which may improve cognitive function. Generally these drugs mimic the natural neurotransmitters and selectively enhance key network functions. Many drugs act on specific receptors located at synapses. Neurotransmitters act like keys fitting specific receptors. Each unique neurotransmitter "key" fits like opening tiny doors in the neuronal membrane. Research at UCI has pioneered the development of innovative approaches to study N-methyl-D-aspartic acid (NMDA) receptors.

Currently the best receptor candidate for mediating the storage of memories in the brain. Modulators for this receptor are currently being developed and tested. Normal brain function requires a fine balance of NMDA function much like a finely tuned violin. Ironically, brain damage causes overactivation of NMDA receptors due to a surge of the neurotransmitter glutamate. Blockers of NMDA receptors appear to protect against traumatic brain injury while activators appear to enhance information storage. (For further reading see Cotman and Iverson, The NMDA Receptor, Trends in Neuroscience, 1987)

COMBATING ALZHEIMER'S REQUIRES A SPECIAL RESEARCH ENVIRONMENT

To understand and eventually treat a disease as complex as Alzheimer's, a broad range of questions must be answered and discoveries pursued on many levels. The scope of the research must range from the molecular level to the highest levels of cognitive behavior and memory. The findings from these multidisciplinary projects must be compared, contrasted and integrated into a picture of Alzheimer's disease that not only provides understanding of causes and damage, but identifies new therapeutic approaches.

To properly address these challenges, scientists require a fertile research environment that allows techniques and results from

Current research expenditures on AD are less than \$30 per patient compared to an estimated average of \$10,000 to \$20,000 spent last year on the AD patient.

several disciplines to be shared and integrated into novel approaches to investigate the brain. UCI is unique in its ability to provide such an environment, which encourages creative and cooperative interdisciplinary exchange. In no academic area has this collaborative focus been more apparent or successful than in

Irvine's internationally recognized program in the neurosciences. Irvine's brain research program has evolved into a network of specialized, interactive research units. Among these is the internationally recognized program in aging and age related mental disorders headed by Dr. Carl Cotman, professor of psychobiology and neurology.

BRIDGING THE GAP BETWEEN THE LABORATORY AND CLINIC

Following several years of basic research on Alzheimer's disease and related neurological disorders, Cotman recognized the potential of bringing research strategies and discoveries from the laboratory into clinical application. Early in 1989, the state of California designated UCI as the location for a state sponsored Alzheimer's Disease Diagnostic and Treatment Center. The Center opened in April of 1989 and promises not only to provide the most modern diagnosis and treatment to patients but also accelerate Alzheimer's research through the gathering of extensive clinical data. The Alzheimer's Center is a critical component of the overall program on aging and a vital conduit for potential therapies, delivering the latest research discoveries to AD patients. Orange County is an ideal environment also because of the number of people who are aging successfully and serve as a "gold standard" for following the progression of dementia.

Consistent with a multidisciplinary strategy for research in

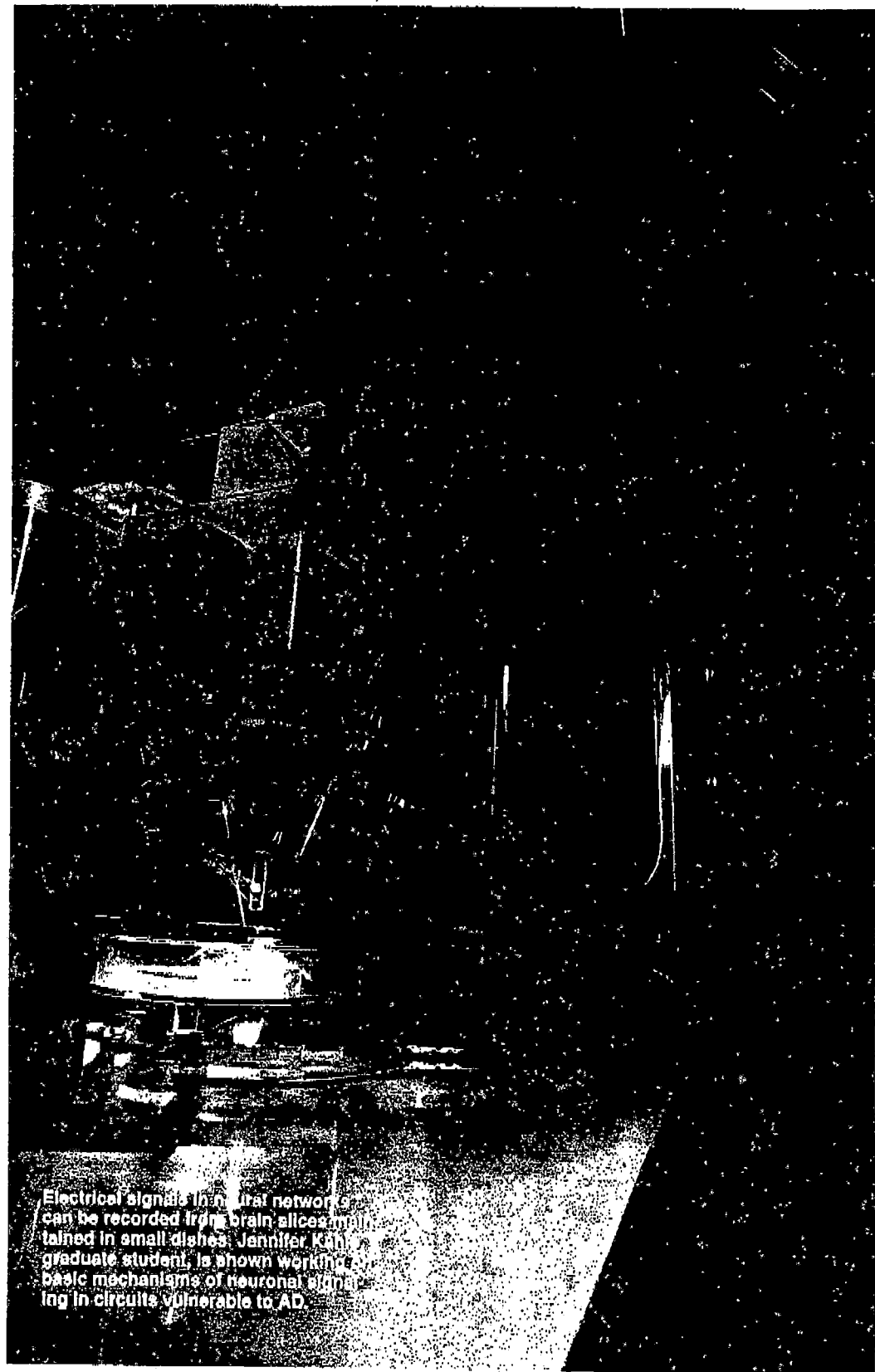
successful aging, the Alzheimer's Center has begun to serve as an indispensable new source of data for comparative studies of the normal and degenerative brain. This continued interaction between laboratory and clinic sets the program apart and provides an invaluable source of new insights, ideas and discoveries.

BASIC RESEARCH AND THE AGED BRAIN

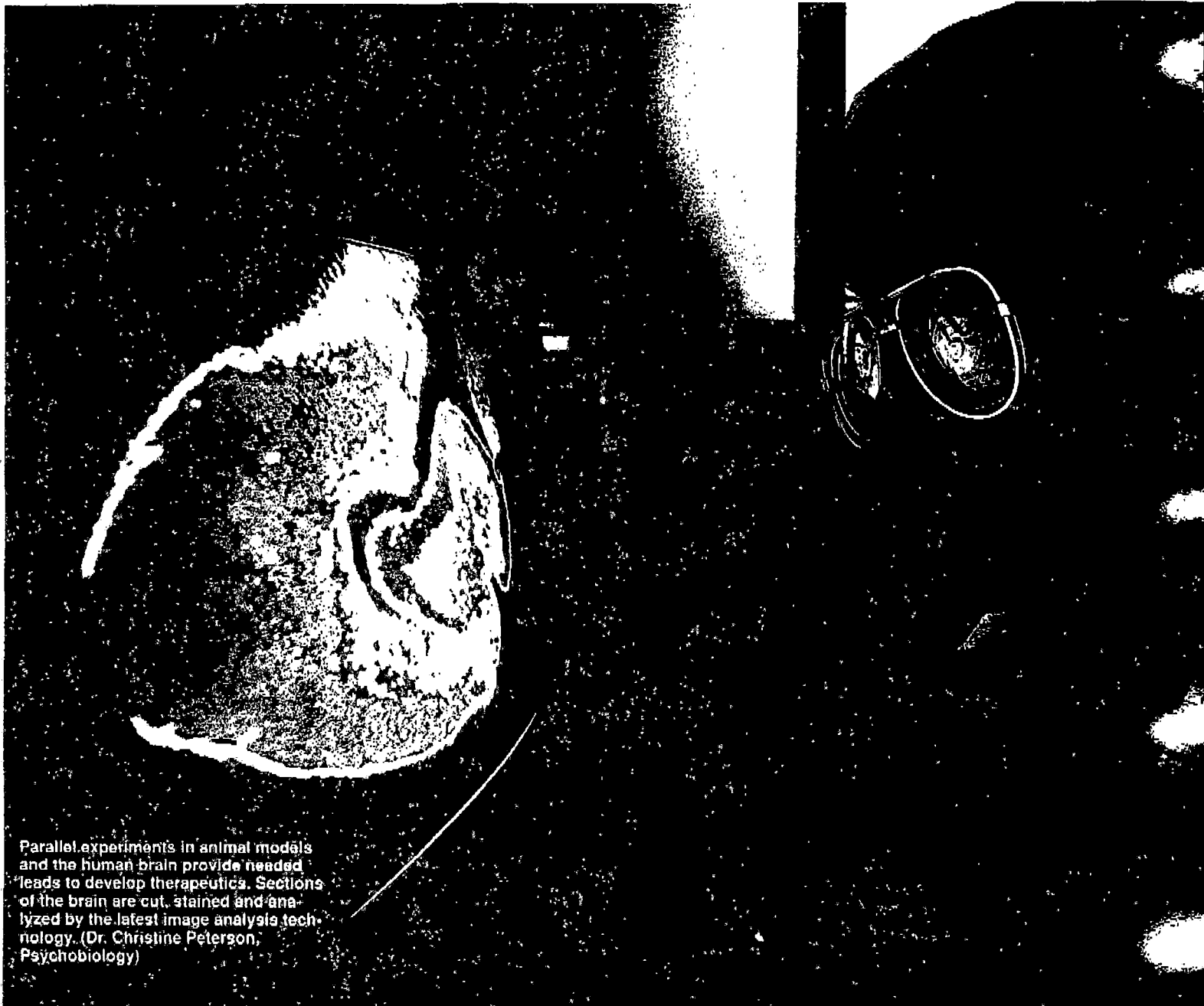
Less than 20 years ago, accepted scientific theory maintained that damage to the brain was permanent and irreversible because cells of the central nervous system were believed incapable of regeneration. This perspective was elucidated by the Noble laureate Ramon y Cajal, in his book *Degeneration and Regeneration in the Nervous System*, published in 1928.

"In adult centers the nerve paths are something fixed, ended, immutable. Everything may die, nothing may regenerate," he wrote.

In recent years this concept of fixity has been replaced by a recognition of the brain's capacity to grow and regenerate. Cotman and collaborators demonstrated that the brain possesses a natural regenerative capacity that is triggered by loss of neurons during aging, disease or injury. Although brain and nerve cells cannot divide to replace losses as do other types of cells, Cotman found that the brain has a unique



Electrical signals in neural networks can be recorded from brain slices maintained in small dishes. Jennifer Kahn, graduate student, is shown working on basic mechanisms of neuronal signaling in circuits vulnerable to AD.



Parallel experiments in animal models and the human brain provide needed leads to develop therapeutics. Sections of the brain are cut, stained and analyzed by the latest image analysis technology. (Dr. Christine Peterson, Psychobiology)

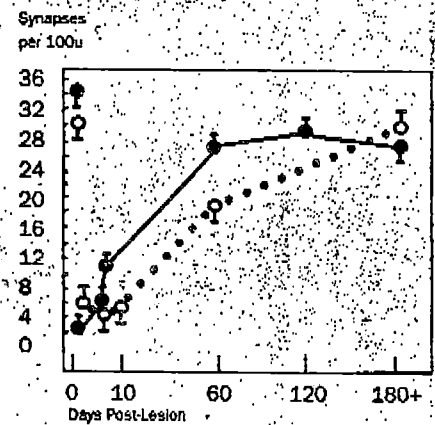
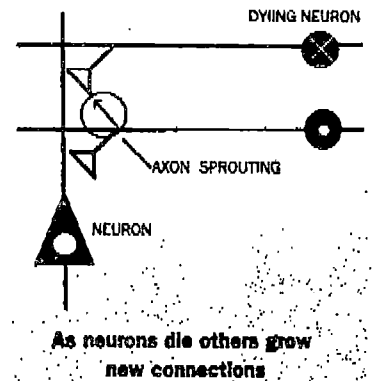


method of compensating for cell death. He dubbed the brain's healing process "reactive synaptogenesis," the capacity to regrow new synaptic connections between brain cells in reaction to disease and injury.

In early work on rodents, Cotman discovered that when neurons were damaged or died, neighboring neurons compensated for the loss by sprouting new branches in an effort to restore the circuit. Thus, as cells are lost, new connections made by healthy cells can assume parallel functions and fibers from converging pathways can boost weakened signals. In much the same way that trees in a forest will extend their branches to fill in an opening left by a fallen comrade, neurons will sprout new axon connections to maintain brain function.

Key to the concept of recovery of function is a built-in redundancy in the brain's information processing and storage network that postpones the clinical threshold at which function disappears completely. However, once circuits degenerate beyond a certain point, function declines quite rapidly, indicating that if the brain's compensation mechanism is stretched too far, even further sprouting cannot prevent final collapse.

Reactive sprouting may be a natural mechanism of successful aging and may also function in the course of some degenerative disorders to temporarily protect the brain. This compensation for neuron loss appears to be triggered automatically in response to brain injury or other insult to neural tissue.

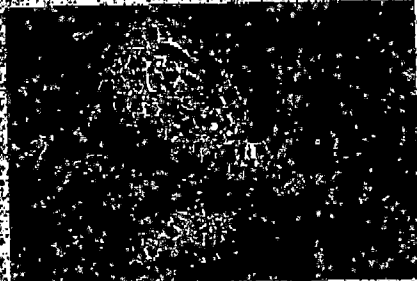


A PROMISING THERAPEUTIC APPROACH: NEURONAL GROWTH FACTORS

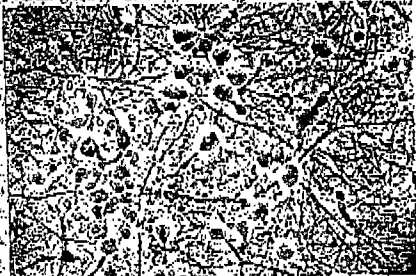
Current pharmacological approaches for neurodegenerative conditions are palliative. That is, they make the system work better without actually stopping or even slowing down degenerative processes. Recent work shows that neuronal growth factors may counteract degeneration directly, giving them unprecedented therapeutic potential.

Neuronal growth factors are small chains of different amino acids linked in specific sequences. It has been known for some time these factors play a critical role in the development of the brain and in its long term maintenance. Recent research pioneered at UCI has demonstrated that classes of growth factors participate in the natural healing processes of the brain after injury. Their concentrations increase after injury and enhance axon sprouting. These factors also will improve the survival of neurons transplanted into the brain and immediate behavioral recovery after injury. When infused into the brain after injury, they can save damaged neurons from dying and also can reverse neuronal shrinkage, a characteristic feature of the normal aged brain in many elderly.

Neurons in Culture with no Growth Factor Die



Neurons with Factor Thrive



GROWTH FACTORS AND BRAIN SELF-REPAIR OPEN UP NEW LEADS IN AGING RESEARCH

Cotman's group observed that one or two weeks following injury, the brain exhibited an increased ability to grow sprouts and accept other neurons transplanted into it. They also knew that a special class of small proteins called growth factors can control differentiation and growth of a variety of cell types. Might the brain's response to injury be an increased production of growth factors?

Extracts from injured brain tissue improved the survival and growth of neurons growing in culture, indicating that the sprouting mechanism relied on one or more molecules produced by the brain following injury. The scientists were excited to learn that the healing

It is estimated that at least 25 percent of people now in their 30's and 40's will become victims of AD before they die.

molecules were in fact a class of naturally occurring growth factors that act on neural tissue.

Following injury, these growth factors appear to participate in the natural healing process, although many neurons still die. In part this is due to a delay of several days before growth factor concentrations rise naturally in the brain. Would

supplying growth factors immediately after injury improve neuronal survival? Indeed, Cotman and other investigators have shown that particular molecules, such as fibroblast growth factor, when infused directly into the brain, are able to save damaged neurons.

This and related discoveries open up new avenues for therapeutic interventions that are now being explored at UCI and elsewhere around the world. The goal is to take advantage of the brain's own strategies for healing itself and apply them to Alzheimer's disease and related disorders.

THE REGENERATIVE RESPONSE APPEARS TO BACKFIRE IN AD

The finding that cell loss during injury promotes a growth response by the remaining healthy neurons provided exciting new insight into how the brain protects itself during neurodegenerative disease. Further investigation of the phenomenon in the AD brain led to a surprising discovery.

In a key paper published in *Science*, Cotman's team reported that axon sprouting similar to that predicted does indeed occur in the Alzheimer's disease brain.

However, as Alzheimer's disease progresses, a strange and unexpected consequence of sprouting appears to occur. Examination of brain tissue of Alzheimer's patients following death shows excessive accumulation of nerve fiber tangles and extra-cellular deposits of material called senile plaques.

Refuting the earlier notion that



*Jan Whitson
Graduate
Student, Senior
author of a
recent Science
paper on AD
"Alzheimer's dis-
ease has been a
maze of ques-
tions for 80
years. Now, at
last, we're start-
ing to find the
answers."*



*Jeanette Shelly
R.N., Clinical
Nurse
Alzheimer's
Disease
Diagnostic and
Treatment
Center, UCI
"I enjoy working
with AD patients
and their fami-
lies. It is particu-
larly satisfying
now to be able to
offer something
to help them."*



The AD Clinic of
ment and new in

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The Cotman lab is internationally well represented. Dr. Jolanta Czeh, working here with Dr. Cotman, came from the Nencki Institute in Poland. They investigate NMDA receptors and plasticity.

senile plaques are merely accumulated debris, a junkyard of the brain, Cotman and collaborators suggest that plaques are the result of aberrant uncontrolled axon sprouting. They observe that sprouts from reactive neurons are attracted into the plaque as if it acts like a magnet for growth.

It is ironic indeed that the brain's plasticity mechanisms may ultimately contribute to pathology. The exquisitely subtle mechanism of the brain, despite its capacity for complex thought and understanding, appears to be tricked into aberrant growth by a simple molecular trap. This does not happen to any significant degree in successful aging and new approaches are being developed to intervene at a molecular level to prevent aberrant sprouting in AD patients.

Basic research offers great hope for the future. The knowledge gained from studying Alzheimer's disease will provide insight into the secrets of successful aging. Says Cotman, "If we can harness the capacity for regeneration and control the onset of neurological decline, the idea of 'successful aging,' prolonging the quality as well as the length of life, becomes a viable goal."

THE COLLABORATIVE NETWORK

The interdisciplinary program developed by Cotman extends far beyond the first floor of the Biological Sciences Building to include collaborative contacts on the main campus, medical school and UCIMC, including faculty in

Neurology, Psychiatry, Radiology, Developmental and Cell Biology and Chemistry. For several years, Cotman has been a participant and adviser in the multi-campus Harvard/MacArthur Foundation Program on Successful Aging. He also maintains both formal and informal research relationships with leading scientists and clinicians from USC, Harvard and Duke University. Frequent international meetings and workshops keep Cotman in close contact with scientists in Germany, Denmark, Japan, Sweden, France, Spain, England and Finland. He has regularly interacted with a number of firms interested in keeping abreast of developments in basic research, including Cortex Pharmaceuticals, Bristol Myers, Searle Pharmaceuticals, and Merck, Sharp & Dome.

FUTURE DIRECTIONS

Despite significant advances, support must be increased if science is to meet the needs of the afflicted, the family and society at large. Current research expenditures on AD are less than \$30 per patient compared to an estimated average of \$10,000 to \$20,000 spent last year on the AD patient. Senior citizens, as the major recipients of health care, accounted for over \$145 billion, about one third of the nation's health care costs. One quarter to one third of this went to AD related health care. Without a significant investment in treatment for the disease, the increasing number of patients threatens to place our future health care system in fiscal jeopardy.



Pat Kesslak
Behavioral
Neuroscientist
"I believe that the promise of the future is the interface of basic research and clinical medicine."



Pam Leeper
Administrative
Analyst
"This approach to research requires a new mode of thinking in terms of administration. The challenge is to provide enough structure to keep the projects on target without killing them with procedural requirements."



Dan Monaghan
Assistant
Professor,
Neurosurgery
"It is quite satisfying to see basic research in my field of work begin to have a positive influence on clinical research and its applications."

WITH SCENTS

Computer simulation of neural circuitry recognizes and categorizes the electronic equivalent of smells.

BY RANDALL BLACK

Despite their power to perform seemingly impossible intellectual tasks, computers are, in biological terms, less intelligent than insects. It's the little things that elude them, the mental activities people perform almost effortlessly.

Biological brains, for example, quickly understand when two things are similar; presented with a novel experience, a person immediately notices if it resembles something experienced before.

Computers, on the other hand, must be provided with exhaustive rules to classify information and have great difficulty identifying patterns or other data when portions are altered or missing. Change a single bit in a group of data and a computer will classify it as "different" from the original.

At UCI, scientists are attempting to electronically duplicate some of the things brains do by simulating their circuitry on a computer. In collaboration with the Department of Information and Computer Science, researchers at the Bonney Center for the Neurobiology of Learning and Memory have created a computer program that simulates the operation of about 100 brain cells. Modeled on the neural network found in the olfactory cortex, the program stores and recognizes the computer equivalent of smells.

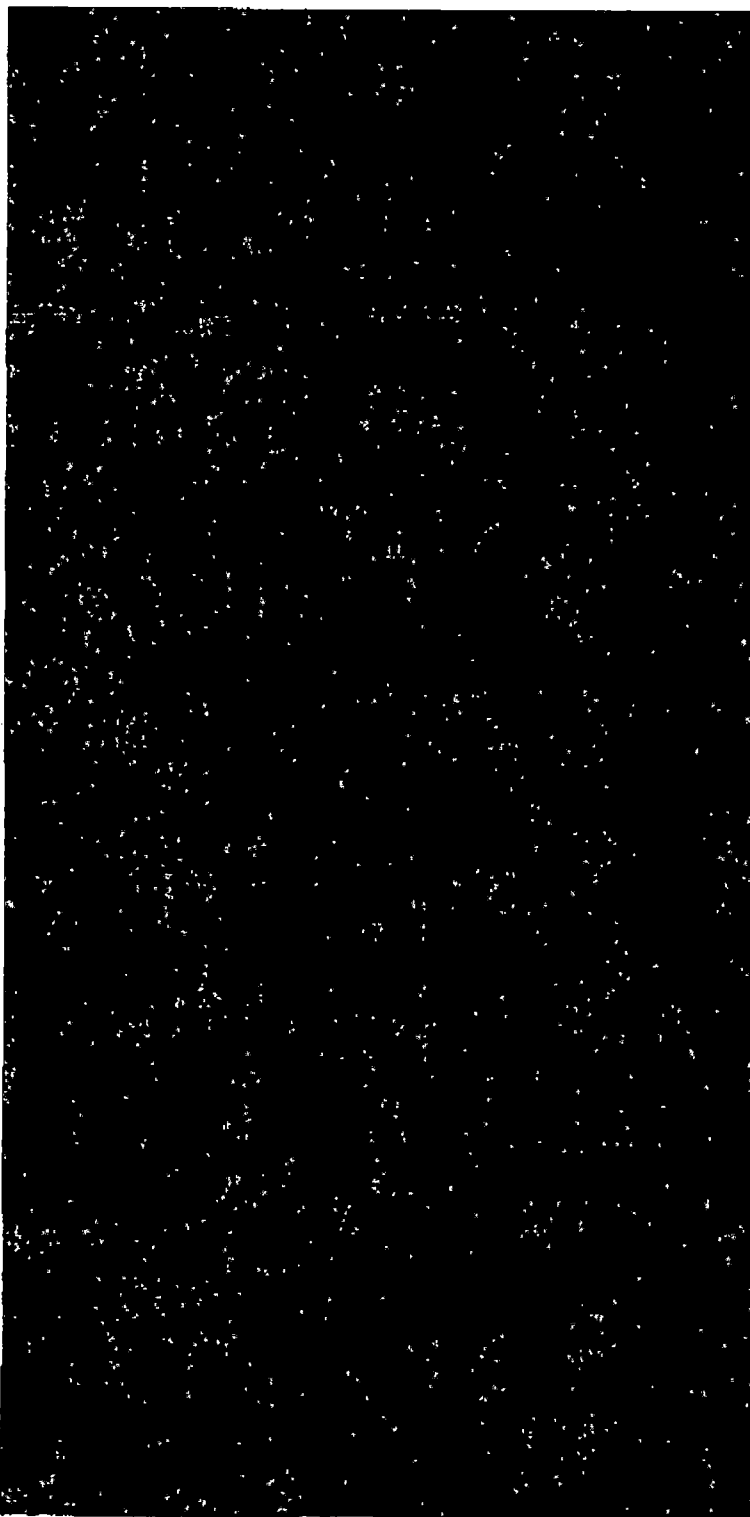
Evolution spent an enormous amount of effort in developing the mammalian olfactory cortex.

According to Gary Lynch, professor of psychobiology and leader of the brain network computer project, the olfactory cortex was chosen for study because it represents one of the shortest pathways between the outside world and memory.

"There are only three connections between your nose and the hippocampus, the part of your brain you use to store any new information," says Lynch.

Most complicated brain functions seem to occur in the large neocortex, but it is extremely difficult to study. Much of the activity in the neocortex appears to depend on information processed in other areas of the brain. Lynch says that understanding olfactory memory is the first step toward describing what occurs in higher-order learning.

While Lynch and his co-researcher, Michel Baudry, chose the olfactory cor-



The pattern on this page is a representation of one of Lynch's computer simulations of brain cells in the olfactory cortex. An actual simulation is shown in vivid color on Page 9.

tex purely for its simplicity, the link between smell and mammalian intelligence appears to run much deeper.

"Human beings are almost unique among terrestrial mammals in their reduced sense of smell but, when you think about it, smell is the sense mammals have made their specialty," says Lynch.

"Birds can hardly smell at all and reptiles are lousy at odor discrimination. Evolution spent an enormous amount of effort in developing the mammalian olfactory cortex."

Comparative anatomy hints that the more primitive cortex. Evolution tends to modify existing structures rather than produce qualitative leaps in design. Just as the human foot still bears resemblance to the grasping appendages of our tree-dwelling ancestors, the neocortex shares structural similarities with the cortex.

"The basic features of the olfactory cortex are found throughout the neocortex; the same design principles are repeated over and over again," says Lynch.

He believes it is no coincidence that amnesia and Alzheimer's disease greatly affect patients' sense of smell, the very network he is studying.

"If you understand the olfactory cortex, it should serve as a Rosetta stone for understanding the neocortex."

The work of Lynch and fellow researchers in the past several years has focused on the cellular mechanisms of memory storage. Among other discoveries, Lynch found that an enzyme, calpain, is responsible for strengthening electrical connections between nerve cells during learning.

When a particular nerve path is stimulated by an electrical impulse, calpain is released and activates additional nerve receptors by dissolving a molecular coating that has kept them dormant.

In a way, calpain is like acid that is used to etch circuit boards from copper plates, irrevocably altering the structure of the brain cells to fit an organism's experiences. In certain diseases, especially those associated with aging, the powerful enzyme becomes a double-edged sword, damaging brain cells instead of molding them into receptacles of memories.

With a working knowledge of the components of neural circuitry, Lynch was ready to begin finding out how the various enzymes, synapses, transmitters and receptors fit together to make memory. But unlike manmade transistors, resistors and capacitors, the brain's

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RESEARCH

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Computer

parts are not easily assembled on a laboratory bench. Instead, Lynch relied on another member of the Bonney Center, computer science professor Richard Granger, and graduate students Howard Henry and Mark Rentmeesters to simulate the operation of neural components on a computer.

"I can't program my name," says Lynch, grinning as he turns on his computer. "The extent of my knowledge of computers is I can turn on this switch in back and run the simulation."

In the simulation are 100 synthetic neurons and 20 smells. The electronically reproduced fragment of olfactory cortex is given smells in the form of data representing chemical components that make up each particular aroma. Pictorially represented, each smell looks something like a bar code that is read by a supermarket scanner.

Images they remembered. The researchers finally gave up when ordinary students were able to remember the same percentage correctly after 10,000 pictures—two days of viewing them at five seconds apiece.

He concluded that the memory capacity of the human brain is virtually infinite. Ten thousand pictures corresponds to about a trillion bits, the capacity of the largest supercomputer.

"Here's the incredible part," says Lynch. "When you show one of these students a picture three days later, he is no slower recognizing it whether he's seen 100 or 10,000 of them and he can do it if you take pieces out of it."

Lynch can perform the same sort of degradation on the smells for the simulation and it still recognizes them. And, like natural memory, the program operates just as quickly no matter how much information it has stored.

The biggest surprise from the simulation is that it automatically sorts the

Blood filtered in experimental cancer therapy

Cancer patients at the UCI Medical Center are being treated with a new blood filtering technique that removes a portion of the blood associated with failure of the immune system.

"The most common cause of death in cancer patients is infection caused by a loss of function of the immune system," said Alan Wile, associate professor of surgery and associate director of the medical center's cancer program.

Although drugs such as interferon and interleukins have been used in an attempt to reverse immunosuppression, Wile says they have been largely unsuccessful, prompting him to investigate the underlying mechanisms of why the phenomenon occurs.

Previous experiments by Wile established that serum, a blood component, from cancer-bearing animals had the effect of suppressing a normal immune system. However, Wile found that, when separated into high and low molecular weight, only the low molecular weight blood component suppressed the immune system.

He concluded that if the low molecular weight component could be removed, the effects of its molecular immunosuppressants might be reversed.

The experimental treatment was begun recently on patients for whom conventional cancer therapy failed. Use of a similar technique, plasma exchange,

resulted in tumor regression in about one-fourth of the cases treated. However, the need for large quantities of human plasma, potential risks of infection and the time expended on such treatments make them less feasible and much more expensive.

The new technique separates the larger molecules in the blood from the low molecular weight components using a device consisting of a customized blood pump loaned by Cobe Laboratories of Colorado and ultrafine filters contributed by Amicon Co. of Massachusetts.

Although a large volume of fluid is removed during the procedure, approximately 12 percent of the patient's weight, the fluid is replaced with safe and inexpensive salt water.

According to Wile, drugs such as interferon or interleukins later may be administered in conjunction with the treatments.

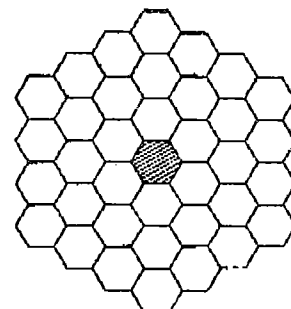
"We are hoping that if we get rid of the suppressor molecules some of the things that have been tried in the past and failed may work," said Wile.

Participating in the study are Gale A. Granger, professor of molecular biology and biochemistry; Nouratola D. Vaziri, chief of nephrology at UCI-MC; and Steven A. Armentrout, professor of hematology.

Camera will bring stars into focus

Gary Chanan, associate professor of physics, has been awarded a \$25,000 contract to design a sophisticated camera to align what will be the world's largest telescope mirror.

Now under construction atop the dormant volcano, Mauna Kea in Hawaii, the Keck Telescope is a joint effort of more than 100 scientists and engineers from the University of California and California Institute of Technology.



Pattern of Keck Telescope's mirror.

When the telescope begins operations in 1990, it will have nearly three times the light gathering power of the six-meter Soviet Large Altazimuth telescope.

The telescope's mirror consists of 36 hexagonal segments, individually positioned to form a continuous surface some 33 feet in diameter. Constructing a conventional mirror the same size from a single block of glass would be prohibitively expensive, said Chanan.

A control system employing 108 individual motors can adjust the shape of the mirror to an accuracy of about 30 nanometers, one thousandth the thickness of a piece of paper, but requires Chanan's alignment camera to tell it how to bring the 36 reflected images into a single focus.

The W.M. Keck Foundation in Los Angeles donated \$70 million for the observatory. Chanan's camera is funded as part of the project.

The summit of Mauna Kea, literally "White Mountain" in Hawaiian, extends nearly 14,000 feet above sea level, making it the highest point in the Pacific. At this altitude, many of the blurring effects of the earth's atmosphere are eliminated.

Low levels of atmospheric water vapor will allow excellent viewing in the infrared region of the spectrum, a frequency of light that passes through interstellar dust and could reveal the existence of a black hole at the center of our galaxy.

In a sense, the telescope is a powerful time machine. Because light travels at a finite speed, the farther one looks into space, the longer the light has taken to reach earth. Existing telescopes can observe galaxies 10 billion light years away and provide astronomers with a tantalizing glimpse of how the universe appeared half the way back to the Big Bang.

The Keck Telescope should show a far younger universe and answer fundamental questions about its creation, evolution and ultimate fate.



Gary Lynch runs program simulating the neural pathways of the olfactory cortex.

Currently, the neural network's electrical responses to aromas are reproduced by a program written in a standard computer language. Someday, the researchers believe, the brain's circuitry may be directly incorporated into the wiring of computer chips.

"If you had a computer based on one of these neural networks, you would have to teach it before it would work," says Lynch. The payoff would be a "computer brain" that would really deserve the name.

In spite of high expectations following the invention of the first electronic computers, making them truly smart has proven difficult. Proponents of artificial intelligence traditionally have approached the problem of machine learning from two directions. The "top-down" school attempts to use existing computer hardware to imitate the way people think. But Lynch points out that ordinary computers are designed to process information sequentially, as a computerized series of commands.

"The problem is when you deal with most problems encountered in the everyday world, those sequences become unbelievably long," says Lynch. "It is quite clear that human beings are not doing things sequentially; you are not driving down the freeway doing 200 sequential steps per millisecond."

Biological organisms instead process information in parallel. The "bottom-up" school of artificial intelligence hopes to imitate the brain's activity by duplicating the underlying structure of its hardware, or "wetware" as it is sometimes called. In trying to reconstruct a segment of olfactory cortex, the UCI scientists fall squarely into the "bottom-up" camp.

The potential for memory storage and retrieval alone are startling.

In an experiment to test the total memory capacity of the human brain, college students were shown pictures and tested three days later to see how many

smells into categories, something biological memory also does.

"If you had never smelled a cheese in your life and, over the course of a day, you smelled four cheeses, you would develop a category without being told," says Lynch. "If you smelled a fifth cheese that you had never smelled, you would say 'I don't know what it is but it's like those other things.'"

The simulation does the same thing, even though the programmers didn't intend to give it that ability, a sign that their understanding of memory circuitry is on track.

"We are beginning to approach a moment which will be in some senses unique to Irvine," says Lynch.

Lynch foresees a day when the development of artificial brain networks will be accelerated by both physiologists comparing them to real brain tissue and behaviorists matching their reactions to those of real animals.

The researchers already have simulated symptoms of memory loss experienced during Alzheimer's disease by removing certain "cells" in the network, he says.

And brain network computers someday may be able to take their turn watching radar screens for enemy aircraft, part of the reason why the Navy has funded Lynch's research. The art of identifying aircraft by their radar signatures now involves recognizing subtle distinctions currently beyond the capability of ordinary computers. Were the electronic smells now classified by Lynch's network replaced with radar signals, a tireless electronic crewmember might stand watch, sniffing out friend from foe.

Other applications could include computer voice recognition, ultrafast information retrieval or automatic data sorting.

"We will be able to use these brain network simulations for some phenomenal purposes," says Lynch.

132-RB-89

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or Janet Ruprecht, (714) 856-8403

Nov. 22, 1989

REMOVING CHILDREN'S BIRTHMARKS WITH LASERS

Although many babies are born with wine-red or pink marks on their skins, most fade before the child turns 7. But birthmarks known to physicians as "port-wine stains" grow larger and darker with time.

Not only physically disfiguring, port-wine stains also can cause psychological scars. Children with birthmarks are teased and taunted. Sometimes their disfigurement is mistaken for contagious disease.

"To prevent psychological scarring and remove vessels while they are small and respond better to treatment, we recommend that children be treated for port-wine stains before they reach school age," says Dr. Bruce Achauer, associate professor of surgery and chief of plastic surgery at UCI's Beckman Laser Institute and Medical Clinic.

Until the development of the pulsed dye laser two years ago, ordinary lasers could not be used to treat the fine skin of children because they caused excessive scarring.

"In the past, even an adult patient had to choose between living with a birthmark and living with a scar," says Dr. Jay Applebaum, assistant clinical professor of dermatology. "Now we can remove a child's birthmark so precisely and gently that, when the skin heals, it appears completely normal. It is smooth and supple and it tans in the sunshine," says Applebaum.

Port-wine stains commonly appear on the face, head and neck and are

BIRTHMARKS

Page Two

caused by the abnormal growth of blood vessels under the skin. These vessels enlarge with age, turning from pink to red to purple. If the condition goes untreated, the vessels may elevate the skin in a smooth or cobbled lesion and in some cases they develop nodules that bleed easily.

The key to removing port-wine stains and other vascular lesions has been the development of a pulsed dye laser that selectively destroys the unwanted blood vessels without harming the overlying skin. The yellow light of the pulsed dye laser passes harmlessly through the translucent layers of skin and heats the red blood cells in the targeted vessels.

Because the laser beam is emitted in microsecond-long pulses, the heat produced in the blood pigment diffuses instead of accumulating and producing damage in the surrounding tissue. Once the heated blood congeals, the vessels degenerate and fade away.

Young children are treated under general anesthesia because it is essential that they be perfectly still. The laser treatment stings; adult patients treated without anesthesia compare the feeling to being snapped repeatedly with a rubber band.

"Anesthesia isn't necessary for adults but makes the treatment far less traumatic for children," says Joyce Zeiler, institute director of nursing.

The first step in the treatment is to expose a test spot to the laser and study the skin's response. If it heals satisfactorily, the entire port-wine stain is treated. At first, the treated area turns blue-grey, like a bruise. This discoloration clears in a few weeks and the birthmark begins to fade. A second treatment may be necessary after three or four months. The port-wine stain will continue to fade slowly for a year, leaving behind only a faint pink blush.

BIRTHMARK
Page Three

Opened in 1986, the Beckman Laser Institute is one of the few places in the world that has a pulsed dye laser, continuous wave lasers to treat larger vessels and the general anesthesia facilities necessary to treat children successfully.

"Parents have brought children from as far away as Ecuador and Australia, and therapy has been proposed for children from Thailand and Poland," says a visiting assistant professor from Australia, Dr. Adrianna Scheibner.

Dr. J. Stuart Nelson, associate director of research, has just returned from the Soviet Union and is developing a program to treat Soviet children who will come to the U.S. as part of an official exchange program.

The institute also is establishing a program that will provide funds to help the families of children in need pay for the laser treatment of skin disorders.

"Because this is one of the few facilities in the world where children can be treated, we feel a special responsibility to make treatment available to patients in need," said institute director Dr. Michael Berns.

The institute plans to use private donations to reduce or offset the cost of therapy and, for special cases, to match sponsors with specific children.

Physicians from the UCI College of Medicine performing laser surgery at the institute include Drs. Achauer, Applebaum, Scheibner, Nelson, Patricia Brenn, Matthew Goodman and Nancy Silverberg.

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Editor's Note: Color and black and white photographs of children before and after laser birthmark removal are available upon request.

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134-RB-89

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April 26, 1989

FDA APPROVES ULTRAVIOLET LASER FOR BLOCKED ARTERIES

Researchers at the Beckman Laser Institute and Medical Clinic at UCI have received approval from the Food and Drug Administration to begin clinical trials of a new excimer laser system to open clogged arteries using ultraviolet laser light.

The procedures will be performed either at the UCI Medical Center or the Long Beach Veterans Administration Hospital and will complement previous experience using a laser-heated metal tip to open blockages in the legs and coronary system.

Unlike the previous procedures, which used laser light passed through an optic fiber to heat a metal catheter, the excimer laser light will be applied directly to arterial obstructions. Ultraviolet light is uniquely capable of removing stone-hard calcified plaque resistant to other conventional angioplasty techniques.

Because the laser light can be passed through an optical fiber directed through internal body arteries to the point of blockage, the excimer laser provides a precise and non-invasive method to open clogged arteries. Prior to the development of this and other types of angioplasty, the removal of arterial blockage required extensive surgery.

The clinical trials of excimer laser angioplasty will be performed by Dr. Jonathan Tobis, associate professor of cardiology at the UCI College of Medicine, and other UCI faculty in the departments of cardiology and radiology.

#

Cancer Research

Last year, 500,000 Americans received a death sentence. They had committed no crime. In some cases, the verdict was carried out within a few months. For others, death would come with agonizing slowness. The death sentences were spoken not by a judge but by physicians. They usually began, "You have a cancer"

The American Cancer Society estimates there will be 1.1 million new cases of cancer next year. Approximately 50 percent of them will die. That's nearly 10,000 people who will die each week. That's one cancer death per minute.

The battle against cancer is being fought in laboratories on the UCI campus. Basic researchers labor to understand the underlying causes of the uncontrolled cellular growth called cancer. At the UCI Medical Center, doctors on the front line treat patients. They use standard cancer therapies and attempt to discover new ones. There are small victories, flashes of scientific brilliance and dedicated investigation that continues after decades of hard work.

However, until recently many of the basic researchers and clinicians were fighting separate battles against cancer. What was needed was a commitment to join ranks and create a universitywide cancer program.

In early 1989, Dr. Frank Meyskens became director of the UCIMC Cancer Center. He came from the University of Arizona Cancer Center in Tucson where he spent 12 years helping to put together a cancer center now recognized as one of the best in the country.

"We started with five of us in a room," says Meyskens. "When I left in 1989 there were 200 people working there."

Meyskens envisions a similar transformation taking place at UCI except that this time around he'll be starting with significant resources already in place, including the Interim Cancer Center at UCIMC and the Cancer Research Institute on campus.

"My plans are to develop a comprehensive cancer program that deals with all aspects of cancer, including treatment, education and prevention," says Meyskens.

A fifth-generation Californian, Meyskens spent the first 28 years of his life in San Francisco where he attended UCSF and took a degree in medicine. Following his residency, he spent three years at the National Cancer Institute in Bethesda, Maryland, where he worked with Robert Gallo, a brilliant scientist who went on to discover the AIDS virus.

In 1977 Meyskens travelled to the Arizona desert to join the small Tucson cancer center where he built a scientific reputation in the study of melanoma and chemical prevention of cancer. In the meantime, the U of A center grew like the cancer its scientists studied, with research grants increasing 1,000 percent during Meyskens' tenure.

Meyskens doesn't mince words when he gives his assessment of UCI's strengths and weaknesses and what he plans for the future. There is a polite impatience about the man, almost as though he has a clock ticking somewhere in the back of his mind. Perhaps because a minute means another cancer death somewhere in the U.S.

"There is much cancer research going on here at UCI but it is not projected that way outside this institution so it is not very well known," says Meyskens. "The clinical program here has some

strengths but is also not well known because it has not been integrated. Right now, we are sort of unranked. I see the potential to get into the second tier of cancer centers rather rapidly. To get into the first tier will take another five years after we enter the game. We are not in the ball park yet." Meyskens smiles. "I don't know how you can put that in a nice way but I'm trying to be honest about it."

What was their secret in Arizona?

"We worked hard and we worked together and we had a common goal," says Meyskens, "the cure of cancer."

Getting people to work together is a top priority for Meyskens who says that interdisciplinary research is a prerequisite to receive a National Cancer Institute core grant, vital for putting the UCI cancer program on the map.

"One of the things that attracted me here is the enormously strong Cancer Research Institute, which is a group of about 30 investigators headed by Dr. Hung Fan who are working in diverse areas of cancer research," says Meyskens. "I hope to work with them to translate their basic research into clinical application."

According to Meyskens there are two major research efforts in the CRI now ripe for clinical trials.

One project, led by professor of molecular biology and biochemistry Dr. Gale "Morrie" Granger, focuses on fighting cancer by modifying the body's immune system, a complex array of defenses that distinguish between "self" and "not self" and attack the latter. Granger has been refining techniques to "educate" white blood cells using proteins such as interleukins to turn them into cancer killers. The killer cells are produced by the billions and placed directly into the body where a tumor has been surgically removed.

Although Granger says it's too early to gauge the technique's success, preliminary trials in brain cancer patients show that the modified cells can extend life.

"Normally these patients with recurrent brain tumors have a 22 week life expectancy," says Granger. "We have lost about 30 percent of our patients but none before 8 months and some well beyond. The quality of their lives is good--these people are playing golf, scuba diving--within a few days they are back on their feet and running around."

Dr. Lewis Slater, professor of medicine and pathology, recently began clinical trials of cyclosporin to decrease the sensitivity of tumors to standard chemotherapy. Cyclosporin, an immunosuppressive drug approved by the FDA to prevent rejection of organ and tissue transplants, significantly improved the effectiveness of treatment in chemotherapy resistant cancers during laboratory experiments in mice. The effect of chemotherapy also was increased in non-resistant cancers by the addition of cyclosporin.

"In certain types of mouse leukemias that ordinarily are always fatal, we observed long-term survival 30 to 40 percent of the time," says Slater.

The chemical combination now is being tested in human patients with two kinds of lung cancer: small cell and the intrinsically resistant non-small cell lung cancer.

"Morrie"
Gale Granger

Slater

Paradoxically, cyclosporin, most chemotherapy drugs and cancer itself all suppress the immune system's ability to protect the body from foreign invaders. However, when cyclosporin is administered at the three-week intervals used during the new chemotherapy regimen, the immune system can recover in between doses rather than being suppressed.

Granger and Slater are only two of many scientists at UCI that Meyskens has begun recruiting into his burgeoning army of cancer fighters.

"We have tremendous resources here," says Meyskens, "the goal is to get them together." He says he faces several challenges to developing the kind of cooperative program that will make a great cancer center. "The UC system promotes a high level of individualism among the faculty and therefore getting them together to work toward an altruistic common goal is difficult. Secondly there has not been a tradition of this kind of interdisciplinary activity at UCI. Thirdly, the bureaucracy here is extremely complex and it seems to take an awful lot of time to accomplish simple administrative goals."

His strategy to overcome reluctance to cooperate relies on a subtle mix of salesmanship, keen judgement and administrative carrots.

"The way you get people together is to create environments in which they want to participate. You talk to people individually a lot before you put them in a room together. You present them with projects they find too good to refuse. And you make people aware of things that are going on--it always surprises me how people don't know what's going on in their own institution."

One thing that's going on: space for cancer research at UCI is expanding. Along with planning the existing space--including 5,000 square feet of laboratory space on campus, 10,000 square feet clinical space in the Interim Cancer Center and dedicated inpatient wards at UCIMC--Meyskens is looking forward to moving into a 52,000 square foot clinical cancer research facility opening at UCIMC in two years.

"That building will set the tone for the next 20 years of how clinical cancer research goes on at this institution," says Meyskens. "That was one of the things that attracted me here."

Frank Meyskens candid approach to solving problems and reaching goals can be a little startling to the uninitiated. He takes a hard look at the matter at hand and speaks his mind. About UCI he's frankly enthusiastic.

"Having been a creature of a cancer center, I know what they can do for a discipline like cancer and I know what it can do for a university. UCI has the potential to be one of the finest medical schools in the country."

014-RB-89

CONTACT: Randall Black (714) 856-7912

Aug. 2, 1989

HUMAN TRIALS OF CYCLOSPORIN/CHEMOTHERAPY BEGIN

A combination of chemotherapy and cyclosporin, shown to enhance the success of cancer therapy in laboratory experiments, will be tested in patients with two kinds of lung cancer by researchers at the UCI College of Medicine and the UCI Medical Center.

According to Dr. Lewis Slater, professor of medicine, experiments in mice showed that cyclosporin, an immunosuppressive drug approved by the FDA to prevent rejection of organ and tissue transplants, significantly improved the effectiveness of treatment in chemotherapy resistant cancers. The effect of chemotherapy also was increased in non-resistant cancers by the addition of cyclosporin.

"In certain types of mouse leukemias that ordinarily are always fatal, we observed long-term survival 30 to 40 percent of the time," said Slater.

Although the researchers do not fully understand the effects of cyclosporin, Slater said that evidence indicates there is greater retention of chemotherapy drugs in tumor tissue. He intends to begin the human trials with small amounts of cyclosporin and slowly escalate the dosage. If patients show signs of excessive side effects, the amount of cyclosporin will be reduced.

Paradoxically, cyclosporin, most chemotherapy drugs and cancer itself all suppress the immune system's ability to protect the body from foreign invaders. However, when cyclosporin is administered at the three-week intervals used during the new chemotherapy regimen, the immune system can recover in between doses rather than being suppressed.

- more -

CYCLOSPORIN/CHEMOTHERAPY TRIALS

Page Two

According to Slater, the human trials will include two types of lung cancer: small cell and the intrinsically resistant non-small cell lung cancer. Patients accepted for the small cell trial may or may not have had prior chemotherapy; those accepted for the non-small cell trial also should have inoperable or metastatic cancer.

Slater's co-researchers are Dr. Sudhir Gupta, professor and chief of basic and clinical immunology; Dr. Siu-fun Wong, staff pharmacist; and Dr. Jonathan Cho, clinical instructor in hematology/oncology.

Persons interested in further information on the drug trials may call nurse coordinator Nancy Downey-Hurtado at (714) 634-5152.

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013-RB-88

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INTELLIGENCE TEST PERFORMANCE CORRELATES WITH BRAIN SCAN

The brains of people who perform well on intelligence tests expend less energy than poor performers and may have more efficient neural circuitry, according to University of California, Irvine researchers.

Speaking today (Sunday, Feb. 14) at the national meeting of the American Association for the Advancement of Science in Boston, Dr. Richard Haier, associate professor in residence of psychiatry and human behavior at UC Irvine, presented data that indicate an inverse correlation between the rate of metabolism in the brain's cortical areas and performance on the Raven's Advanced Progressive Matrices (RAPM), a test of abstract reasoning. Positron Emission Tomography (PET) scan images revealed that the level of brain activity, measured by the uptake of glucose, was lower in subjects who scored well on the test than poor performers.

"Although one might assume that a good performer's brain would 'work harder' than that of a subject who did poorly, our data suggest that the opposite is true," said Haier, speaking at a special symposium on the neurobiological bases of personality.

The PET scan allows direct measurement of brain function based on the quantity of a harmless, positron-emitting tracer absorbed by active cells.

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TEST PERFORMANCE
PAGE TWO

The tracer, fluorodeoxyglucose (FDG), is injected into a volunteer's bloodstream during a mental task and is taken up in greater quantities by areas of the brain with higher rates of activity. Unlike ordinary glucose, which is completely metabolized or "burned" as it fuels mental activity, FDG remains for a time in the brain cells that absorb it. As the radioactive FDG decays, it emits gamma rays, which are recorded by the PET scanner as color images of the brain in cross section.

According to Haier, the Raven's Advanced Progressive Matrices are a difficult, non-verbal test of abstract reasoning that have been well correlated with other tests of general intelligence. The test requires that the subject recognize a pattern within a matrix of abstract designs and select a design that completes the pattern.

Eight subjects took the test and their PET scans were compared with a group of 13 who took a visual vigilance test and a group of nine that simply viewed flashing visual stimuli.

Haier and collaborators found few correlations between performance on the visual vigilance task and cortical metabolic rates, in contrast to the strong inverse correlation with the abstract reasoning performance.

Haier suggests that the lower metabolic rates in good performers on the RAPM may be due to differences in the efficiency or density of neural circuits in individuals with higher cognitive ability. He cautioned that the results are tentative pending replication of the experiment with a larger sample size.

-more-

INTELLIGENCE TEST
PAGE THREE

Haier and his associates have helped pioneer the use of PET scanning in the study of personality, intelligence and psychopathology at the UCI Department of Psychiatry and Human Behavior, the only such department to have its own PET scanner.

The researchers' findings are scheduled to appear in the journal Intelligence this summer.

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EDITOR'S NOTE: Color PET photographs that graphically illustrate the differences in brain metabolism between good and poor performers of the RAPM are available upon request.

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025-RB-89

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Aug. 10, 1989

BRAIN IMAGING CENTER CYCLOTRON UP AND RUNNING

Technicians have used a cyclotron at the UCI Brain Imaging Center for the first time to produce isotope for use with the center's positron emission tomography (PET) scanner.

The \$1.8 million, 22-ton cyclotron was delivered last fall and will allow researchers to conduct sophisticated brain studies without reliance on outside isotope sources.

Cyclotron director Dr. Paul Jerabek processed the isotope working with a robotic "one-armed chemist" to manipulate vials inside the shielded cyclotron room. Performing a feat of modern day alchemy, the cyclotron transformed atoms of an isotope of oxygen into a different element: fluorine 18.

Following binding to a special glucose, the fluorine isotope was used in the PET scan of a head injury patient to detect brain damage hidden from other examinations. "The cyclotron gives us a chance not only to expand our basic science research but to be a clinical resource for patients in Orange County with head injuries, epilepsy, brain tumors and Alzheimer's disease," said Dr. Monte Buchsbaum, Brain Imaging Center director and professor of psychiatry and human behavior.

Purchase of the cyclotron was made possible by a \$575,000 grant from the Irvine Health Foundation. Previously, the researchers used isotopes flown in from UC Davis at significant expense. According to Buchsbaum the in-house supply of isotope will double PET research.

- more -

CYCLOTRON

Page Two

Part of the UCI department of psychiatry and human behavior, the Brain Imaging Center is the only facility in the world with a PET scanner devoted exclusively to brain research.

The PET scanner, unlike other imaging techniques that reveal only brain anatomy, allows the scientists to record brain function. Areas of the brain that are more active take up more of a sugar that is chemically bound to the isotope tracer. Particles of antimatter called positrons are released by the isotope and collide with electrons to produce gamma rays. The PET scanner records the gamma ray emissions and produces color images that map mental activity. The images reveal hidden injury, disease and details of intellectual activity during performance of various tasks or under the influence of drugs.

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UCSF NEWS

University of California, San Francisco

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UCSF NEWS

University of California, San Francisco

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January 31, 1990

TO: Jeanne Nappe
FROM: Carol Fox

In addition to what Bob Sanders sent you yesterday and in connection to the work on genetic disease, I thought you might be interested in the quote from our new Dean of the School of Medicine, Joseph B. Martin.

"For the first time in history we can now actually identify the cause of diseases, particularly genetic diseases, that were simply not approachable by any known scientific strategy even five years ago. That will expand at geometric ratios over the next while."

MR-- I think the doctors would be very interested in your ideas on that.

I gave her a long interview on the telephone, she obviously took the little bit that she wanted.

MR -- You mean this was an interview

No, that one.

MR -- Oh that.

I must have spoken for 20-minutes on the phone and I gave three general ^{arena} ~~points~~ as in which I think there will be a major ~~impact~~ of the changing medical school activities on the public in the next two or three decades. I can't remember what the three points were now. It was focused on opportunities ~~and~~ / in science. Finding genes for diseases. For the first time in history we can now actually identify the cause of diseases, particularly genetic diseases that were simply not approachable by any known scientific strategy even five years ago. That will expand at geometric ratios over the next while. The second point I made was related to what ~~she~~ quoted me on. The opportunities brought by science to the patient for treatment will exceed our ability to provide that treatment for everyone who wants it.

MR -- There will be more treatment than patients?

There will be more treatments available than patients can pay for than the new system can pay for. We already make choices of ration. It really the issue of ration. The state of Oregon decided they're not going to do certain kinds of medical procedures, they've decided they won't pay for it. And those patients are already invading our community here and we're being asked to pay for it. So, the issues of rationing, how it relates to the first point is that science produces treatment opportunities that are expensive and which will require health policy decisions about who gets them and who doesn't. Say people over a certain age don't get them because they lived their life. Dick Littlejohn, we went to his bone marrow transplant was taken outside the usual criterion. He was the oldest patient they ever done..... So, we end up with all kinds of problems emerging from the development of new methods of treatment which spring out of the science but we can't do everything. Third point I made there was that the science arena have more opportunities to do work to solve diseases when you get people to do that work for age fundings to support. And so, one can imagine for genetic disease for example, you can put all of our science to work right now on specific diseases that you know how to solve and just say everybody work on that set of problems to the exclusion of other problems like cancer or AIDS. Obviously we can't do that nor enough dollars to support it and people to do the work. So the constraint on progress in medical science is actually a manpower, womenpower, personpower and national resource issue. One can imagine science at a pace that will far outstrip the available resources of people and that the future.....So imagination is not the issue any more it's really these factors. And I don't know really if that sort of think is how you can link that in with what the school needs to do with Laurel Heights.

MR - What I'm asking is do have to go into Laurel Heights in this letter?

- UCAL San Francisco
vaccine devel
- Cal State ~~ant~~ LA
DNA research
- Berkeley
micromotors
chem catalysts
- Cal Poly at Pomona
aerospace design
- Stanford
- Irvine

Competitiveness

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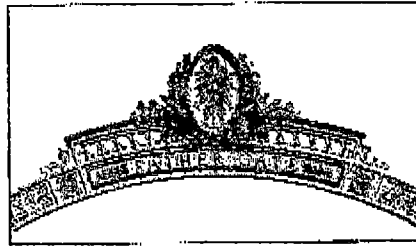
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3/8/88--Ravven--File #10728

FOR RELEASE AFTER 10 A.M. PST, THURSDAY 3/10/88 -- TIME OF PRESENTATION AT INDUSTRIAL LIAISON PROGRAM CONFERENCE, UNIVERSITY OF CALIFORNIA AT BERKELEY

Berkeley -- The technology that launched the microelectronics revolution is about to take on the everyday world of machines.

The goal: flea-sized machines and microscopic sensors, mass produced on a chip using semiconductor manufacturing technology and materials.

Such micromachines, integrated with microelectronic devices, could be employed as miniature assembly line workhorses or as vital new instruments for intricate surgery and delicate laboratory manipulation, capable of tasks unimaginable with today's mechanical equipment.

Last year, engineers and computer scientists at the University of California at Berkeley reported their success using semiconductor manufacturing technology to make the first microscopic movable mechanical parts, including cranks, gears and springs.

Now, Berkeley mechanical and electrical engineers are working hard to produce the first silicon micromotor -- a functional machine with dimensions the width of a human hair.

Pioneering efforts now under way at Berkeley to fabricate such devices and sensors were reported today (March 10) at Berkeley's annual Industrial Liaison Program Conference, sponsored by the College of Engineering.

"Today's microprocessors provide silicon 'brainpower.' The coming revolution will couple these with silicon 'muscle' -- and silicon 'eyes, noses and ears,' at the same scale," said Richard S. Muller, professor of electrical engineering and computer science at Berkeley.

Muller is co-director, with Professor Richard M. White, of the Berkeley Sensor and Actuator Center, begun 18 months ago with support from the National Science Foundation and now largely funded by a dozen major industrial corporations.

-more-

-2-

"Billions of dollars have been invested in the research, technology and machinery to make silicon-based microelectronics," Muller explained. "Now, by modifying slightly these materials and the fabrication process we can make useful mechanical devices on a microscopic scale.

"Polysilicon, a key material in integrated circuitry, for example, is comparable in strength to some steels and more resistant to deformation. At Berkeley we are studying the basic properties of these materials and at the same time using them to develop microscopic sensors and actuators (machines)."

On the sensor front, Muller and his colleagues last year developed a tiny silicon microphone, an acoustic sensor small enough to fit on a silicon computer chip, with potential for hearing aids as well as computerized speech-recognition and robotics systems.

The latest developments in thin-membrane microsensors for a wide variety of applications in industry will be presented at the Thursday meeting, as will recent successes on microscopic movable mechanical devices.

Researchers will discuss their progress in establishing a range of mechanical properties for polysilicon and developing the means to protect electronic components while sensors and actuators are at work.

In fabricating the microscopic gears, cranks and other mechanical parts, the Berkeley researchers use polycrystalline silicon prepared under slightly different conditions from those used to manufacture microelectronic devices on a chip.

To make the micromechanical parts, the polysilicon is deposited and patterned on layers of silicon dioxide. The polysilicon parts are assembled in layers and held in place during processing in a matrix of silicon dioxide.

After enough layers have been deposited to produce the complete assembly of movable parts, the silicon dioxide is chemically etched away, leaving the assembled "micromechanism" on a chip.

The dimensions of the entire assembled unit are about the thickness of human hair.

Like the microelectronics assembly process it mimics, fabrication of the mechanical devices is essentially two-dimensional, producing thin structures that impose some design constraints, Muller said. Nonetheless, he says, many useful mechanical parts can be built.

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"Building mechanisms on a microscopic scale provides some unexpected benefits," observes Roger Howe, assistant professor of electrical engineering and computer science and associate director of the Berkeley Center.

Virtually all conventional motors use magnetic fields to convert electrical energy to mechanical force, but it has long been known that the force between two objects at different voltages -- the electrostatic force -- can also be used to run machines.

Unfortunately, electrostatic force falls quickly at increasing distances, so that impractically high voltages would be necessary to make use of this force in conventional motors.

At a microscopic scale these problems are easily avoided, making miniature motors driven by electrostatic force a practical option. In addition, the electrostatic drive interfaces with conventional microchip circuitry efficiently, Howe said.

The Berkeley researchers are exploring other materials and other properties to be exploited in the new microdevice effort. They expect that as in any emerging technology, alternate materials may eventually prove superior to the ones being tested and proven in today's pioneering research.

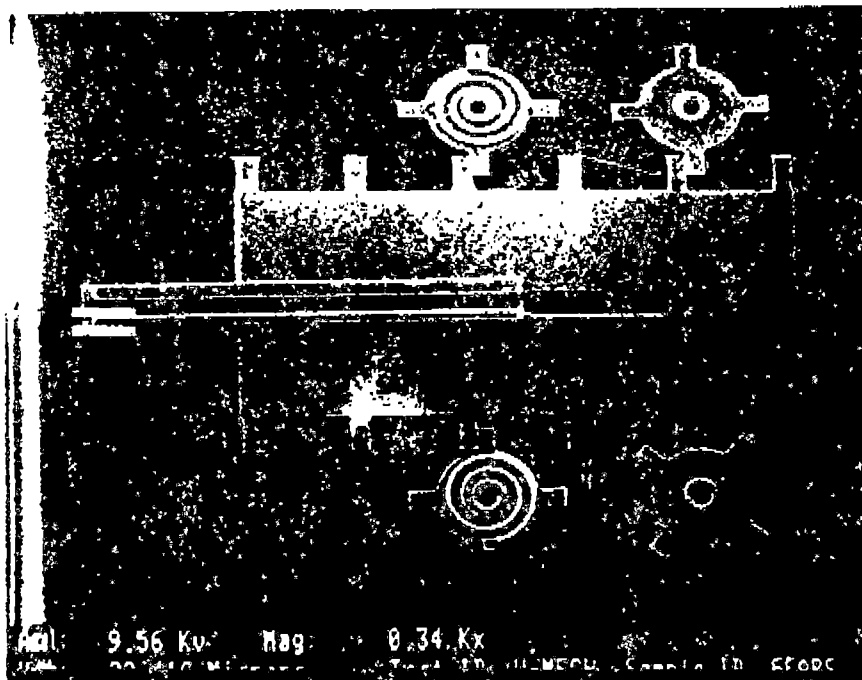
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NOTE: On March 9 and 10 (Wed. and Thurs.) most of the Berkeley faculty scientists and engineers as well top graduate students in this field will be presenting reports of their recent progress at the annual Industrial Liaison Program Conference held at Berkeley. During and after the meeting, **CONTACT: Professor Richard S. Muller, Electrical Engineering and Computer Science: (415) 642-0614.** Or, Wallace Ravven, Public Information (415) 643-7843. After the meeting, contact Karen Holtermann: 642-5857.

Caption #10728.1

MICROSCOPIC MECHANICAL DEVICES -- "Micromechanisms" -- devices with movable parts and overall dimensions about the width of a human hair -- have been produced by a team of scientists and engineers at the University of California at Berkeley. They used slight modifications of the widespread microelectronics manufacturing technology developed for the semiconductor industry. This application of microelectronic manufacturing to produce the smallest mechanical devices ever made promises to open a new field, with miniature machines and sensors mass produced for use in industry, robotics, intricate research and surgical techniques. The electron-microscope photograph here shows a device only a few thousandths of an inch on each side, with movable parts (horizontal strip in center) and functional springs (circular objects).

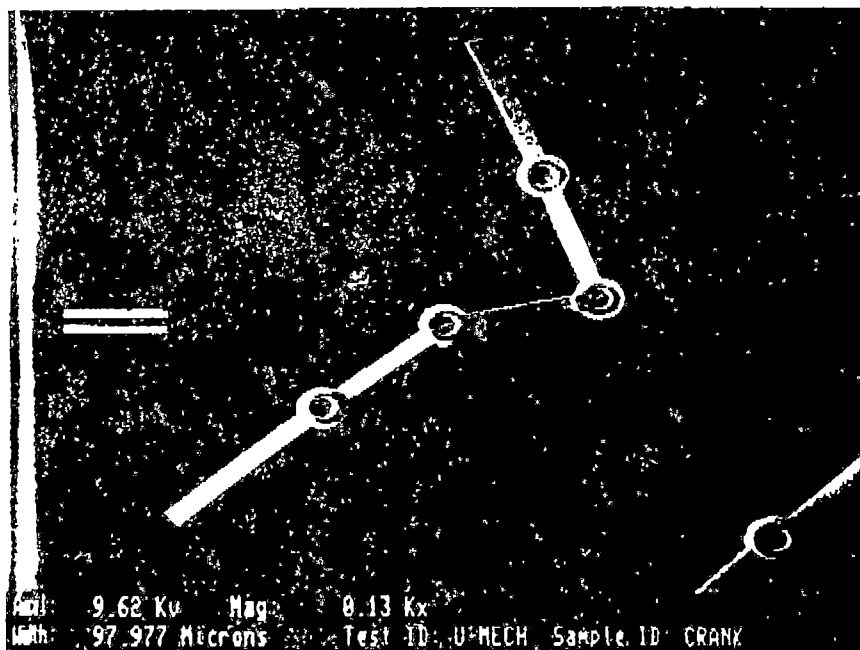
CREDIT: Berkeley Sensor and Actuator Center, University of California at Berkeley.

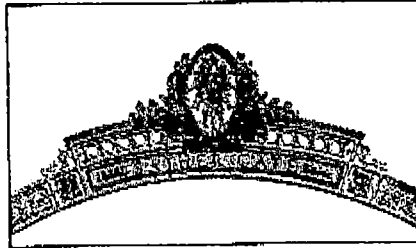


Caption #10728.2

MICROSCOPIC CRANK -- Movable mechanical devices with overall dimensions about the width of a human hair have been produced by a team of scientists and engineers at the University of California at Berkeley. The team uses slight modifications of the widespread microelectronics manufacturing technology utilized in the semiconductor industry. This application of microelectronic manufacturing to fabricate the smallest mechanical devices ever made promises to open a new field, with miniature machines and sensors mass produced for use in industry, robotics, intricate research and surgical techniques. The electron-microscope photograph here shows a crank, only a few thousandths of an inch in overall length, with two fixed joints (one at each end) and two rotating joints.

CREDIT: Berkeley Sensor and Actuator Center, University of California at Berkeley.



File: Gareth Thomas

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11/22/88--Mena--File #11076

FOR IMMEDIATE RELEASE

Berkeley -- By unraveling some of the mysteries surrounding the breakdown of structural ceramics at high temperatures, Berkeley researchers have discovered a new ceramic processing method that has tremendous commercial potential.

Engineers have long sought ceramics that can survive extremely high temperatures for use in building more fuel-efficient diesel engines and turbines for power generators and jet engines. But the most heat-resistant ceramics currently available show significant breakdown at 1,000 degrees C.

Berkeley scientists recently announced that they have developed a silicon nitride ceramic that shows no loss of strength at 1,000 degrees C. The ceramic retained 71 percent of its strength at 1,300 degrees C, withstanding pressures of 55,000 pounds per square inch.

"This is a world record for silicon nitride ceramics," said Gareth Thomas, professor of mineral sciences and engineering at Berkeley.

Thomas -- who worked in close collaboration with Sylvia Johnson, ceramics program manager at the Stanford Research Institute -- reported the new development recently at the Pacific Coast regional meeting of the American Ceramic Society.

The theoretical research that led to the formulation of the ceramic is an important stepping stone to major advances in the field, he said.

The super heat-resistant material was the product of eight years of analyzing ceramics with electron microscopes. By studying the materials at the atomic level, Thomas and his colleagues developed a comprehensive theory outlining key aspects of the stability of ceramics at high temperatures. This theory allowed them to scientifically formulate the new ceramic, instead of concocting it by trial and error.

"Japan has held a lead in the race to develop practical ceramic turbines but their

-more-

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methods for producing ceramic materials have been largely trial and error," said Thomas.

"Our work gives the U.S. an edge in the race. By eliminating the need to try out costly and time-consuming 'recipes' for new materials, our approach is much more cost effective."

The Japanese auto firm Isuzu has already built a ceramic diesel engine. But the materials used to construct it are prohibitively expensive.

Ceramics are attractive as materials for internal combustion engines and turbines because they do not oxidize readily and they weigh much less than the metals currently used. If ceramic engines could run at very high temperatures, they could burn very low quality fuel with minimal pollution.

"They could be particularly useful in the construction of diesel trucks," said Thomas.

"There are also potential advanced aerodynamic applications."

Ceramics are made up of grains that are bonded together by an oxide "cement." Ideally, the "cement" should form a stable crystalline bond between the grains.

However, the "cement" in most ceramics contains pockets of "glassy phase" between the grains that are the weak links in the materials. At high temperatures, these weak links soften, the grains shift and the material deforms.

Thomas said the process his team developed eliminates those weak links, providing a more uniform crystalline bond between the grains. The process is being patented.

The research into the theoretical facets of ceramic stability will help formulate even stronger ceramics in the near future, he said.

"This kind of long-term fundamental research is necessary for answering the question 'why'," said Thomas. "Once we know why, the 'how' is not far off."

Berkeley graduate student Mike Cinibulk is conducting the current research for his masters thesis. The research is sponsored by the National Science Foundation.

In addition to his faculty appointment at Berkeley, Thomas is scientific director of the National Center for Electron Microscopy at Lawrence Berkeley Laboratory.

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Note: Professor Gareth Thomas can be reached at (415) 642-3813 or (415) 486-5656.

Antibodies as "Designer" Catalysts

Exploiting the extremely specific "fit" between antibodies and their target molecules, chemistry professor Peter Schultz and his colleagues in the department and at Lawrence Berkeley Laboratory are developing novel ways to tailor-make chemical catalysts vital to medicine, biotechnology and industry.

The new technology is expected to enable researchers to "cut and paste" proteins and other large biological molecules as precisely as modern biotechnology can now modify DNA. Selective protein-cutting catalysts, for example, could cut up the protein coat of viruses or dissolve blood clots.

A colleague has said the research represents the foundation of a new biotechnology.

In recognition of his pioneering achievements Schultz received the Alan T. Waterman

Award in 1988, the highest honor given by the National Science Foundation to a young scientist.

Until this development, most efforts to bioengineer new catalysts have focused on altering the structure of existing enzymes to change the reactions they can catalyze. But changing enzyme structure in just the right way has proved difficult.

The Schultz group has taken a different tack. Rather than trying to change an enzyme to bind to a different compound, the scientists custom-make antibodies that they know will

bind to the desired molecule. The trick is then to introduce the ability of this "abzyme" to catalyze the desired reaction.

Schultz reported his group's first major success in this area in 1986. At that time he designed antibodies as catalysts to boost by thousands of times the rate of a basic chemical reaction known as hydrolysis.

The rate of the reaction was enhanced, or catalyzed, by producing an antibody that could fit like lock and key the highly unstable intermediate structure in the reaction.

The catalyst provided a custom-made "pocket" in which the reaction could proceed.

Since then, the Schultz research group has developed several other approaches. Taken together, they open a field of vast promise to achieve efficient chemical reactions for a wide range of applications.

A custom-made antibody molecule binds to its target molecule, greatly speeding the chemical reaction.

How Nerves Make the Right Connection

Discoveries at the cellular and molecular level are beginning to reveal how nerves find their way to the right target in the developing embryo and how flaws in this vital process can lead to severe behavioral disorders.

Much of the new evidence on the early "wiring" of the nervous system comes from research on fruit flies. But the discoveries appear to have strong parallels in many organisms including humans.

"Humans and flies are using the same proteins in their nervous systems, so we may gain insight into the causes of human nervous disorders by studying mutations in the simple nervous system of the fruit fly," explains Corey Goodman, professor of genetics and a Howard Hughes Medical Institute investigator at Berkeley.

Early in the life of the embryo, individual nerve cells produce a series of glue-like proteins that enable them to stick to their targets within the maze of developing nerves. In the picture that is emerging, proteins produced at the advancing end of a nerve cell recognize complementary proteins along their pathway

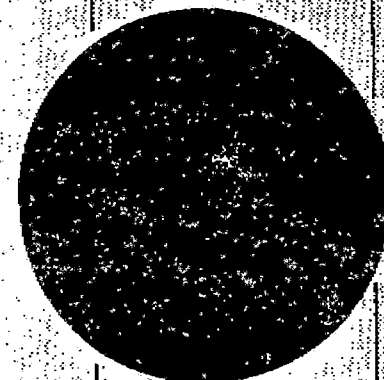
and stick to them. The rest of the nerve cell is then drawn in that direction. The nerve cell apparently changes course by switching to production of different proteins that draw the cell in a different direction.

"Different nerve cells arriving at the same point will move in different directions and pick different targets based on the unique combinations of proteins on their surfaces," says Goodman.

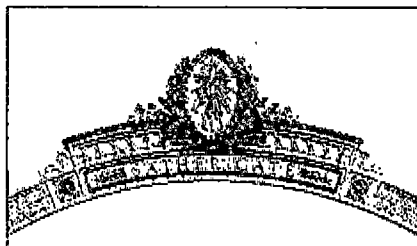
If the gene for just one of these proteins in the embryo is defective, Goodman's has found, motor coordination is disrupted in the adult.

In the last four years, his Berkeley research group has identified and purified a half dozen of the recognition proteins and has used recombinant DNA technology to identify which of the fruit fly's 20,000 genes instruct the nerve cell to produce each of the proteins.

In central branching region, where nerve growth is advancing, nerve cells produce glue-like proteins to stick to their targets.



AAAS Annual Meeting-Boston
Presented at session #7
"Protein Design: What Can
We Get Away With?"--part of
symposium #22--"PROTEIN
FOLDING PROBLEMS"
(Sun. 2/14 p.m.)



File: Peter Schultz
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2/8/88--Ravven--File #10679

**FOR RELEASE SUNDAY P.M. 2/14/88 -- TIME OF PRESENTATION AT THE
ANNUAL AAAS MEETING IN BOSTON**

Berkeley -- Exploiting the extremely specific "fit" between antibodies and their target molecules, scientists are beginning to develop novel ways to tailor-make chemical catalysts vital to medicine, biotechnology and industry.

The new developments provide a sort of primer to rationally design chemical agents of great potential impact to drug manufacturing, molecular biology and materials chemistry.

Very recent research successes in this interplay of molecular biology and chemistry were described today (Sunday, Feb. 14) at the annual meeting of the American Association for the Advancement of Science (AAAS), in Boston.

Peter Schultz, associate professor of chemistry at the University of California at Berkeley, described how researchers in his laboratory have begun to exploit nature's chemical binding machinery to design a range of new catalysts.

One of the leaders in this new field, Schultz reported his group's first major success in the journal SCIENCE in December, 1986. At that time, he had succeeded in designing antibodies as catalysts to boost by thousands of times the rate of a basic chemical reaction, known as hydrolysis.

Modern techniques allow researchers to make a pure antibody to virtually any molecule by injecting quantities of the molecule into a mouse, selecting cells from the immune system that make antibodies to it, and fusing these with modified tumor cells that grow indefinitely. The result is known as a monoclonal antibody.

The rate of the hydrolysis reaction in Schultz's laboratory was enhanced, or catalyzed, by producing an antibody that could fit like lock-and-key the highly unstable intermediate

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molecular structure in the reaction. The catalyst provided a custom-made "pocket" in which the reaction could proceed more swiftly.

At today's AAAS meeting, Schultz reported on several other approaches, as well as new progress with this first type of catalysis, known as "transition state stabilization."

Advances in the stabilization efforts have led to antibody catalysts to assist a reaction that makes and breaks carbon-carbon as well as carbon-oxygen bonds, Schultz reported. These bonds are ubiquitous in organic and biological molecules, and such improved catalysis could be important in synthesizing drugs and other useful new materials.

A second catalysis success, he reported, may have boosted the reaction rate by better orienting the two reacting groups within a molecule. This increased reaction rate due to greater "proximity" of the reactants within a molecule is seen as a preliminary step toward increasing rates of reactions involving two "partners" -- the textbook $A + B \rightarrow C$ chemical reaction. This type of reaction plays a vital role in both industrial and biological reactions, including protein or polypeptide formation, Schultz pointed out.

Another reported success involves antibody catalysts made to cleave the kind of bond formed when the body's genetic material, DNA, is damaged by exposure to ultraviolet light.

Schultz also reported initial progress in using genetic as well as chemical techniques to introduce "synthetic catalytic groups," possibly the most powerful approach for engineering catalysts.

Taken together, Schultz said, the new approaches to design highly selective catalysts help open a field of vast promise to achieve efficient chemical reactions for a wide range of applications.

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NOTE: Schultz will be at his Berkeley office Tues. Feb. 9: (415) 642-9277. He will then be unavailable until he arrives at the AAAS meeting Fri. Feb. 12. Messages Feb. 12-14: At AAAS message center board near the general registration area, or through AAAS newsroom (617) 236-6160.

NEWS FROM U.C.-BERKELEY'S

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1/10/90--File #11577

**The Sloan Foundation has given
\$3 million to five universities for
a study of U.S. competitiveness**

FOR IMMEDIATE RELEASE

Berkeley -- Scholars at five leading American universities will tackle a research and teaching agenda on international competitiveness and declining relative U.S. performance in the international economy.

Several large American companies will cooperate.

Ralph E. Gomory, president of the Alfred P. Sloan Foundation, announced Wednesday (Jan 10) a \$2.97 million grant to fund the work.

It is the Sloan Foundation's largest university grant in 25 years.

A consortium of faculty at the University of California at Berkeley, Columbia, Harvard, MIT, and Stanford will do research on the competitiveness and economic performance of the U.S. vis-a-vis other industrialized nations. The consortium has assembled leading scholars from a variety of disciplines--especially economics, management, and engineering.

The funds will be channeled through and managed by the Consortium on Competitiveness and Cooperation at Berkeley's Walter A. Haas School of Business.

"The problem of competitiveness needs both the objective and continuing research of scholars and the realism that can come only from contact with industry. For this reason, we have asked a few leading American companies to cooperate with this outstanding group of scholars," Gomory said.

Gomory said the CEOs of General Electric, General Motors, Hewlett-Packard, IBM and Xerox have already agreed to cooperate with the consortium's research. "They share my conviction that this a worthwhile enterprise," he said.

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Gomory said the Sloan Foundation is deeply committed to the support of research on all factors -- production, manufacturing, economics, technology -- related to U.S. competitiveness problems.

The Consortium on Competitiveness and Cooperation is headed by Professor David J. Teece at Berkeley's Haas School.

"We are trying to incorporate the study of technology and institutions and organizations into economic science," Teece said. "Economists everywhere must pay close attention to what is really taking place in the global economy, especially how organizations and management affect and are affected by technological progress. Business, government, and academia all need much better understanding of this process. The Sloan Foundation is endorsing an important experiment in American higher education."

Professor Richard R. Nelson of Columbia, a member of the consortium's executive committee, said the Sloan grant will support fundamental research on such issues as the factors influencing productivity growth at the level of the firm, the industry, and the nation, and the relationships between science and technology.

"These are inherently interdisciplinary topics and need to be tackled as such. We want the next generation of scholars to be confident and competent about crossing disciplinary lines when this enables research to be better and deeper. This grant will help us provide such training to our future faculty, who must have early exposure to the multidisciplinary connections inherent in unruly reality."

The Sloan grant will be expended over a three to five year period and managed by the executive committee of the Consortium on Competitiveness and Cooperation.

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Note: Ralph E. Gomory can be reached for interviews at the Sloan Foundation at (212) 649-1649. David J. Teece is available at the Haas School of Business, U.C.-Berkeley, (415) 642-1075. Names of the consortium's executive committee members with affiliations and phone numbers are attached.

**Consortium on Competitiveness and Cooperation
in the U.S. and Global Economies**

Center for Research in Management
University of California at Berkeley
554 Barrows Hall
Berkeley, CA 94720

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Releasing the Might of Mites

Three-fourths of the world's almonds grow in California's Central Valley. Some 400,000 acres yield a harvest worth about \$600 million a year. But each year, before the nuts are harvested, growers must contend with millions of unwelcome visitors trying to lay claim to the crop.

Navel orangeworm larvae and peach twig borers eat their way into the nuts, creating wormy almonds at harvest time. The peach twig borers also attack twigs, while colonies of spider mites can weaken trees by sucking almond leaves dry in a matter of days.

The good news is that the orangeworms and twig borers can be kept in check with two insecticides. The bad news is that these chemicals can also knock out a beneficial bug that eats spider mites, so growers resort to a third pesticide to control the spider mites.

But in the last five years many Central Valley almond growers have turned to a new strategy that cuts down on the spider mite pesticide without cutting down on the harvest. The new approach saves money and reduces chemicals in the environment.

The strategy was developed by entomology

professor Marjorie Hoy, and it relies on the beneficial bug—a mite no larger than a grain of sand. The tiny creature, known by the daunting name *Metaseiulus occidentalis*, is native to the Central Valley and feasts on spider mites, not on almond leaves.

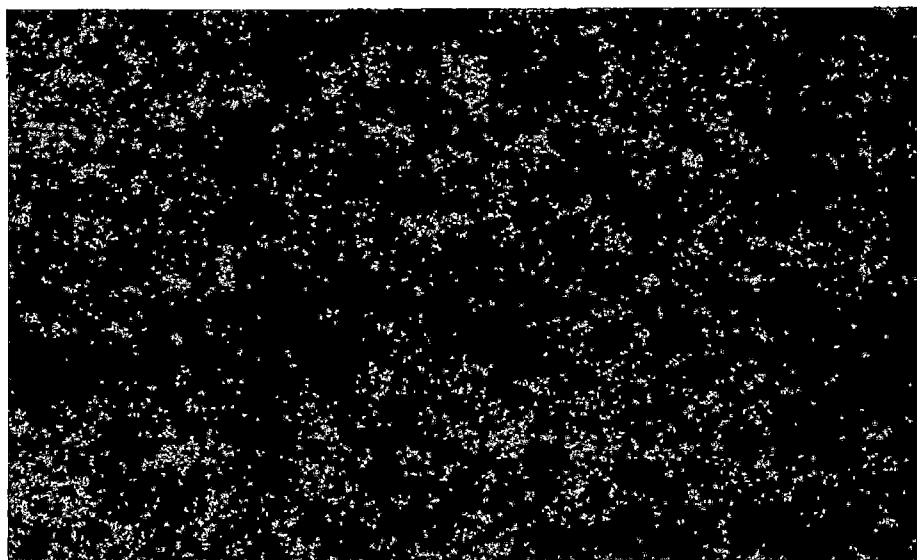
Hoy knew that a healthy predator mite population could keep the spider mites in check, but she also knew that the growers would continue using insecticides to control orangeworms and twig borers even though the practice killed the helpful mites at the same time.

The only practical way to bring the predator mite population back to full fighting strength, she figured, was to breed into the mites a resistance to the two insecticides.

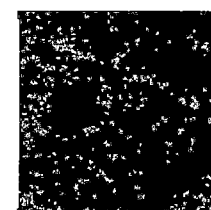
Working in Berkeley's insectary on Oxford Street, across from the campus, Hoy and her graduate students sprayed a variety of pesticides on predator mites and then bred the survivors over many generations.

After two years, Hoy's research team developed an insecticide-resistant strain of predator mites able to thrive over winter. After three more years of tests—this time in commercial orchards

With the population of voracious spider mites kept in check by the predator mites, trees on the left side of the orchard are thriving. Those on the opposite side, without the beneficial mites, have lost most of their leaves.



The good mite and the bad: predator mite attacks its natural enemy, an immature two-spotted spider mite. As a result, orchards are protected and pesticides use can be cut.



Marjorie Hoy, Professor of Entomology and Parasitology

"In the long run, we may be able to breed beneficial insects as we now breed crops.

"We hope to increase the use of natural predators and parasites to reduce the use of pesticides in agriculture. That would be safer for the environment, and provide long-term economical pest control."

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predator mites earned a good reputation by bringing spider mite populations to levels as low as pesticides could achieve.

"There is no doubt that Marjorie Hoy's research has had a great impact on pest management in almond orchards," says William Barnett, an integrated pest management advisor for UC Cooperative Extension. Integrated pest management, or IPM, is the strategy of combining natural enemies, chemicals and cultivation practices to control crop pests.

"She really deserves praise for going beyond research and working with farm advisors and growers to get those predator mites into commercial orchards," Barnett says.

"All the publicity stemming from her talks at meetings really got growers thinking more about predator mites already in their orchards. Many of them have been able to cut way down on the amounts of miticide they use (against spider mites)."

J.C. Headley, an agricultural economist from the University of Missouri, estimated that almond growers are able to save about \$44 per acre per year after introducing the insecticide-resistant predator mites and cutting back on miticides. About 65 percent of almond growers now using some form of the predator mite strategy. Savings can run more than \$20 million annually, according to his economic impact study.

Two companies are now in business marketing insecticide-resistant predatory mites for use in almonds, strawberries and grapes. Apple growers are beginning to employ insecticide-resistant predator mites in orchards in Canada, Chile and Israel.

Hoy is now trying to apply such a biological control approach to California's walnut crop. She released an insecticide-resistant wasp that is a natural parasite of walnut aphids. Field tests are under way, and another crop pest may soon meet a similar natural fate.



A parasitic wasp lays its eggs in a walnut aphid.

Computers: The RISC Chip Pays Off

In 1980, computer chip designers were on a steep path that was getting steeper. For two decades, more and more transistors had been crammed onto thumb-nail-sized microprocessor chips—the brains of personal computers. In high-performance computer systems, such as those used by engineers, the complexity and the sheer number of transistors were now actually limiting computation speed.

David Patterson, then an assistant professor of computer science, and a few other colleagues in the country saw a simple but revolutionary solution.

"I thought that a microprocessor could be designed that was both simpler and faster," Patterson says.

He believed that performance could be boosted by streamlining the microprocessor chip, eliminating many of its built-in instructions. Less common, specialized tasks could be shifted to the software, and frequent tasks could be processed on the chip by repeating simplified steps at faster speeds rather than performing more complex computations.

In addition to their speed, simpler high-performance chips would be easier to produce and would bring down the computer price. And, with chips easier to manufacture, more companies could enter the chip market, Patterson reasoned.

To demonstrate the potential of the simpler-is-better approach, he and Carlos Sequin, also a Berkeley computer science professor, launched a four-quarter graduate course in 1981 to design and send to manufacturers for production a "blueprint" for a simpler, faster high-performance computer chip.

When the chip was produced, the results surprised even Patterson: "This was the first time any of us had ever designed a computer chip. In our first attempt, we built a chip that worked faster than any comparable microprocessor on the market."

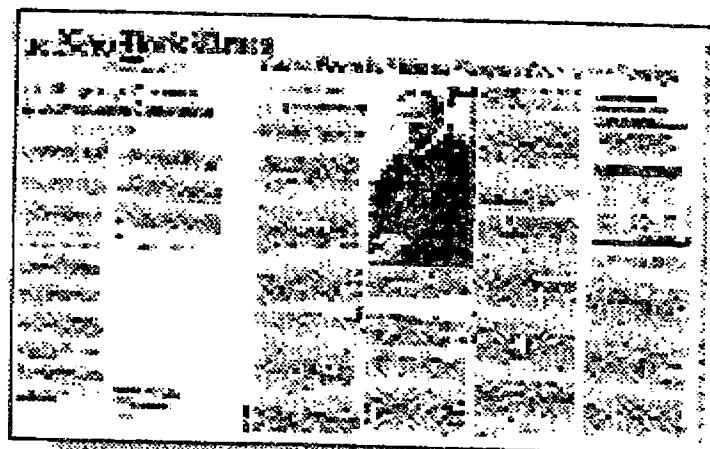
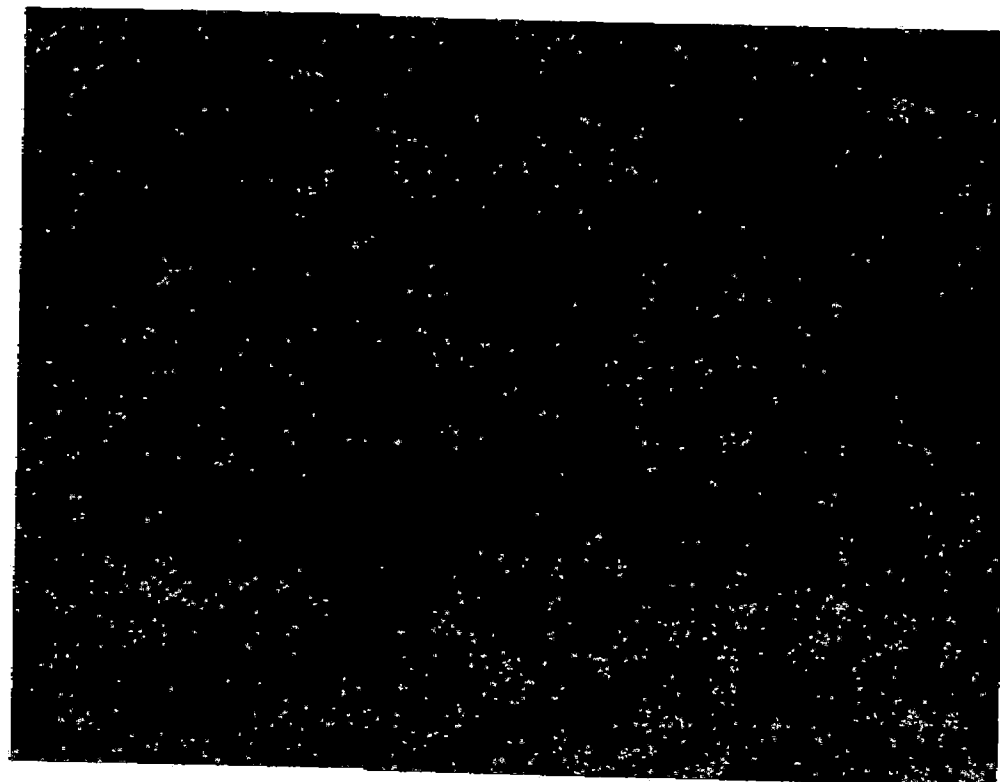
Patterson and his graduate students designed two more generations of simplified chips in 1984 and 1987. Patterson and Sequin called them RISC chips, for reduced instruction set computer, an



Commercial RISC chip: solution to an industry problem, on a fingertip

"RISC designs cut in half the time needed to develop a new computer.

In an industry where technological change is so rapid, a shorter design and production time means you can incorporate the latest technology into your chip before you are locked into production."



So pleased were Patterson and the graduate students with the first Berkeley RISC chip (a portion enlarged above) that they each inscribed the chip in dummy circuitry with their initials and a sand-grain sized image of a Porsche to symbolize their powerful, efficient chip design approach.

Left: Patterson, professor of electrical engineering and computer sciences, was featured in an article about RISC chip design in *The New York Times*, April 16, 1988.

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gym that has since become the industry term
streamlined chip designs.

Meanwhile, Patterson and other early RISC
ments were consulting with industry to pro-
the streamlined chip design. And by 1989,
major U.S. computer manufacturer had ei-
adopted a RISC chip design for some of their
performance computers or was developing a
type. An article in *The New York Times*
labeled the computer industry as "rapidly em-

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Forty-one students and several
faculty members helped develop
Berkeley's first RISC chip.
Patterson is seated front and
center. To his immediate left is
Carlos Sequin.

ISC designs
half the time needed to develop a new com-
Patterson says,

an industry where technological change is
d, a shorter design and production time
you can incorporate the latest technology
or chip before you are locked into produc-
Patterson explains.

for the speed of computation. Dataquest,
computer market research firm, noted in
ing of 1989 that RISC chips can run at least
ion instructions per second, essentially
ing the performance of the more complex
they are replacing.

International Datacorp, another industry mar-
lyst firm, projected that RISC chips would
t for more than two-thirds of the high-
performance computer market by 1992.

says a great deal about the pace of the com-
industry that a chip design considered utterly
t the beginning of the 1980s will be the
d during the early 1990s.

oday it is unusual to produce a high-
performance chip without a RISC design," Patter-
son. "In just eight years it has become the
active thing to do!"

It's what
can put
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Ice-Minus Equals a Big Plus for Agriculture

Steven Lindow was curious, and in science, curiosity often leads to discovery. While a graduate student, Lindow found that plants grown in a greenhouse suffered no frost damage even if the temperature inside dropped below what we call freezing—32 degrees Fahrenheit or 0 degrees Centigrade. But greenhouse plants did become susceptible to frost damage at that same indoor temperature if other plants that had been grown outdoors were brought into the greenhouse and came in contact with them.

Lindow discovered that frost doesn't form on leaves just because the thermometer drops to 32 degrees. It takes a common bacterium, found out-of-doors around the world, to turn water into ice crystals. Greenhouse plants not exposed to the bacterium can withstand a drop of another five or six degrees before dust or other material triggers the water molecules to form into ice.

"This bacterium is just about everywhere," says Lindow, now professor of plant pathology. "Except for causing frost, it's harmless to people and animals. You probably swallow millions of them every time you eat a salad or bite into an apple."

If plants in the field could be protected from the bacterium, known as *Pseudomonas syringae*, Lindow reasoned, they would be safe from the mild frosts that ruin many a crop early in the growing season.

"I grew up on a farm in Oregon and I saw what a drop of a few degrees below freezing could do," he says.

In the United States alone, farmers lose about \$1.5 billion worth of crops to frost each year. Current frost protection methods—sprinklers and wind machines—are effective over only a narrow temperature range, and they are costly.

In Lindow's laboratory, graduate student Cindy Orser made another startling discovery: just one gene out of the 3,000 in the bacterium accounts for its ability to promote deadly ice crystal formation on plants' leaves.

Lindow and his Berkeley colleague Nickolas Panopoulos, professor of plant pathology, then used the modern tools of genetic engineering to turn these discoveries into a strategy to protect the potato crop from frost damage.

"Basically, we developed a strain of the bacterium that lacks part of the gene that causes frost to



Protected (top) and frost-damaged potato plants. Coating the young plants with the modified bacteria prevents naturally occurring bacteria from gaining a foothold and triggering frost damage.

form. We call it 'ice-minus.' It is frost-promoting bacterium in every doesn't nucleate ice crystals," Lindow says.

Lindow's strategy was to coat pieces with a solution of ice-minus planting, and then spray the seedlings when they came up.

"We expected that if the ice-minus could get on the plants' leaves first, frost-promoting form couldn't hold, and the plants would be protected," he explains.

Greenhouse tests showed that it worked, and in 1983 the government small-scale field test near Mt. Shasta's Agricultural Field Station.

But because this was the first engineering experiment ready to move and into the field, it came under fire. Environmentalists questioned the experiment. Others called for a better federal plan for this and future experiments. It was delayed for more than three years.

During the delay, the government procedures to assess the safety of engineering field tests. And the University's 700-page environmental impact report further studies by Lindow and Panopoulos affirmed the safety of the ice-minus.

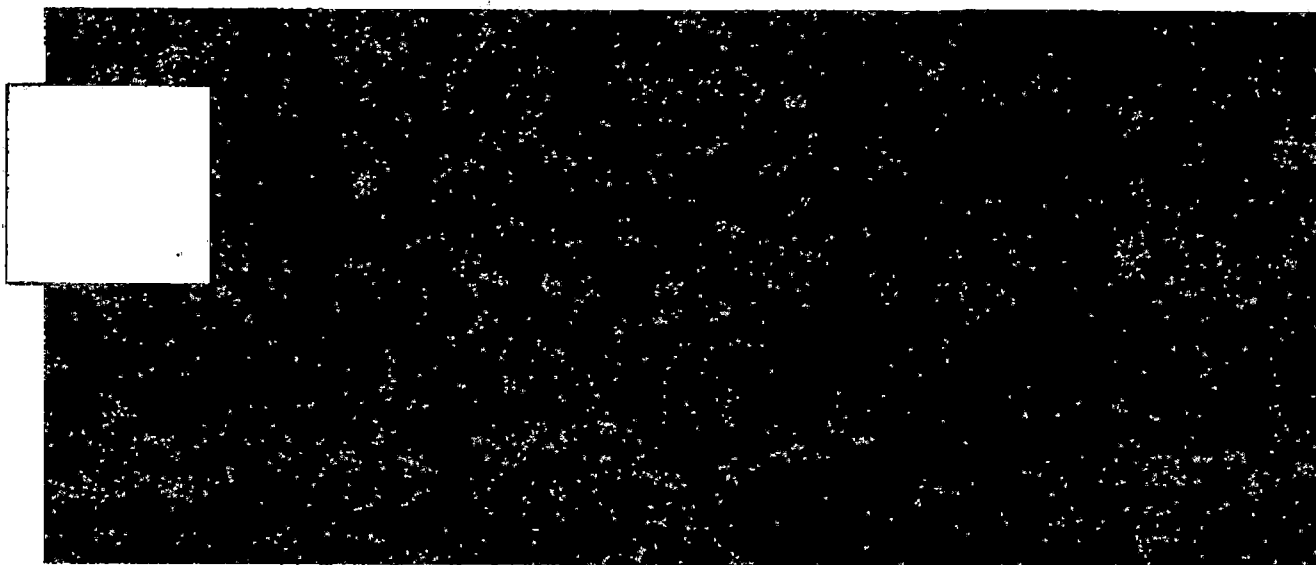
In April 1987, Lindow and Panopoulos had their field day. The potato seedlings were coated with ice-minus and planted. Later, the seedlings were sprayed with the bacteria. The Environmental Protection Agency's intensive monitoring equipment to see if the bacteria remained within the site.

The experiment proved safe after two years of field tests. In 1988, Lindow and Panopoulos found that potato seedlings protected with the bacteria received, on average, only one-fifth the frost damage as the unprotected plants.

The University licensed its patent protection strategy to Advanced Genetic Technology Corporation in Oakland, since acquired by the firm. This company will develop ice-minus under the name "Ice-minus." The first strains will be targeted to protect almonds, pears, peaches, and

Inset: In April, 1987, when Lindow launched his pioneering field test, dozens of reporters followed him to the remote Tulelake site.

Right: Lindow and assistant spray potato seedlings with protective ice-minus bacteria. Although the bacteria poses no health threat, EPA regulations require wearing protective suits and respirators when spraying in high concentrations.



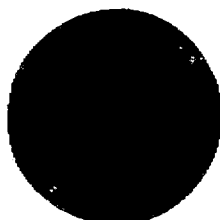
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*Steven Lindow,
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Info you requested on university based technology R&D related to American competitiveness.

swimming, tennis, track and field, and volleyball; and coeducational badminton, archery, and fencing. The Library has more than 740,000 volumes and several special collections. The university is accredited by the Western Association of Schools and Colleges. Stephen Horn has been president since 1970.

REFERENCES: Mary Ann DeAngelis, California State University, Long Beach; Sawyer E. Wiley, ed., "The First Decade of Long Beach State College, 1949-1959" (Ms., Long Beach State College, 1960).

213-343-3000
 California State University, Los Angeles. 5151 State University Drive, Los Angeles, California 90032 (213) 224-0111. Los Angeles State College was established by the California legislature on September 19, 1947, with P. Victor Peterson as first president (1947-1949). Seven transfer students comprised the first graduating class in June 1948. The college was located on the Los Angeles City College campus on Vermont Avenue near Hollywood from 1947 to 1956 when it was moved to a 100-acre site that had been part of Rancho Rosa Castilla. Howard S. McDonald became president in 1949; he served until 1962. In 1949 the curriculum was extended to include professional programs, and the name was changed to Los Angeles State College of Applied Arts and Sciences. The first master's degrees were awarded to thirteen graduate students in 1952. In 1956 the college occupied twenty-four temporary buildings on the new campus. Eight new buildings were occupied in the fall of 1958. The name was changed to California State College at Los Angeles on January 4, 1964. John A. Greenlee was president from 1965 to 1979. On June 1, 1972, the college became California State College, Los Angeles. On the 175-acre campus are eighteen buildings, including the Administration Building, Biological Sciences Building, Fine Arts Building, John F. Kennedy Memorial Library, Music Building, Physical Education/Gymnasium building, Physical Sciences building, University Student Union, and Theatre. Among graduates were tennis player Billie Jean King and actor Robert Vaughn.

California State University, Los Angeles, is a public, coeducational, commuter university operating on the quarter academic calendar with a summer session. In the 1980s there were about 22,180 students with a full-time faculty of 650 and a part-time faculty of about 650. The university is organized into schools of Business and Economics, Education, Engineering, Fine and Applied Arts, and Letters and Science. Degrees offered are bachelor of arts, science, music, and vocational education; master of arts, science, and business administration; and doctor of philosophy. The university conducts the Bureau of Business and Economic Research and centers for the Study of Armament and Disarmament, Study of Business in Society, Japanese Studies, Korean-American and Korean Studies, Mental Retardation, Child Abuse and Neglect, Latin American Studies, Transportation Educational Information, and World Trade Education. The university participates in the California Desert Studies Consortium and Southern California Ocean Studies Consortium. Also maintained by the university are the institutes of Entrepreneurship and Retail Management, Institute for Governmental

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Union, Administration Building, Student Service Center, Education Building, Music Building, Science Building, and five student residence halls.

California State University, Sacramento, is a public, coeducational, commuter and residential university operating on the semester academic calendar with a summer session. In the 1980s there were about 14,700 full-time and 7,960 part-time students with a faculty of 900 full-time and 400 part-time members. The university is organized into schools of Arts and Sciences, Business and Public Administration, Education, Engineering, and Social Work and divisions of Health and Physical Education and Nursing. Degrees offered are bachelor of arts, science, music, and vocational education and master of arts, science, public administration, and social work. The Continuing Education Office conducts six external degree programs, provides on- and off-campus courses and programs, and administers domestic and foreign travel study courses.

Students may enroll in the Army Reserve Officers' Training Corps program. There are about ninety student organizations, including the Student Senate, professional associations, nine honor societies, six social fraternities, and three social sororities. Students publish the *Hornet* newspaper and *Enquirer* yearbook. The university is a member of the Northern California Athletic Conference and participates in men's football, soccer, and wrestling; women's softball and volleyball; men's and women's cross-country, basketball, swimming, track and field, tennis, golf, and gymnastics; and coeducational fencing. The University Library has more than 733,000 volumes. The university is accredited by the Western Association of Schools and Colleges. Donald R. Gerth became president in 1984.

REFERENCES: Patricia Hebert, California State University, Sacramento; D. E. Moore, *The History of Sacramento State College: Twenty Years of Higher Education* (Sacramento: Associated Students of Sacramento State College, 1967).

California State University, San Bernardino. 5500 University Parkway, San Bernardino, California 92407 (714) 887-7301. The California legislature provided in 1962 for the establishment of a state college in the Riverside and San Bernardino, California, area. A 590-acre site north of San Bernardino was selected, and John M. Pfau was chosen as the first president in 1962; he served until 1982. A faculty was recruited, and construction of three buildings was begun in 1965. A class of 293 junior and freshmen students was admitted to California State College, San Bernardino, at the opening of classes in the fall of 1965. The Physical Sciences and Biological Sciences buildings were constructed in 1967, the physical education facility in 1968, and the library-classroom building in 1969. Graduate instruction was introduced in 1972. On July 23, 1984, the name was changed to California State University, San Bernardino. On the 430-acre campus are eighteen buildings, including the Administration, Visual Arts, Biological Sciences, Creative Arts, and Physical Education buildings; John M. Pfau Library; Student Union; and nine-building Serrano Village student residence halls.

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California, Berkeley, University of. Berkeley, California 94720 (415) 642-6000. California gold-field missionaries from the American Home Mission Society of New York established Contra Costa Academy in Oakland, California, in 1853 with three students and Henry Durant (BDAE) as principal. On April 13, 1855, the legislature passed a bill establishing the academy as the College of California, and a charter was granted on the same day. On March 1, 1858, a site in nearby Berkeley was selected as a new campus for the school where regular college classes were opened in Oakland in September 1860. The first class was graduated on June 1, 1864. On October 9, 1867, the college board agreed to a merger with a proposed state university that was to be organized under the Morrill Act of 1862. The college continued until June 1869, and the University of California, chartered by the legislature on March 23, 1868, was opened in the fall of 1869 with thirty-eight students, ten faculty members, and John Le Conte as acting president. Durant was named president on August 16, 1870; he served until 1872. The university moved classes into North and South halls on the Berkeley campus in 1873, although students commuted from Oakland to Berkeley until dormitory facilities were made available.

A series of short-term presidents, including John Le Conte and Daniel Coit Gilman (BDAE), served until 1890 when Martin Kellogg was appointed. James Lick donated the Lick Observatory to the University, and in 1873 Hugh H. Toland (BDAE) gave the Toland Medical College in San Francisco to the university. Benjamin Ide Wheeler (BDAE) succeeded Kellogg in 1899; he served until 1919. Under Wheeler the University Farm, Citrus Experiment Station, Scripps Institution for Biological Research, and Hooper Foundation for Medical Research were established. In May 1917 the university was among the first six institutions in the nation to establish a United States School of Military Aeronautics; by the end of the program in 1920 more than 2,000 cadets had been graduated from the program. In 1920 the university was one of four to establish the first Air Service Reserve Officers' Training Corps programs; it was discontinued in 1932. Los Angeles State Normal School became the Southern Branch of the University of California in 1919. Additional branch campuses were established at Santa Barbara (1944), Davis (1951), Riverside (1954), San Diego (1960), Irvine (1964), and Santa Cruz (1964). The branch campuses were established as separate units under the statewide University of California administration. Robert Gordon Sproul was president (1930-1958).

Schools established at the Berkeley campus included Law (1912), Education (1914), Librarianship (1926), Business Administration (1936), Optometry (1941), Public Health (1944), Social Welfare (1944), and Forestry (1946). Ernest O. Lawrence invented the cyclotron in 1930. Clark Kerr (BDAE) was named first chancellor in 1952; in 1958 he succeeded Sproul as president of the university. The School of Criminology (1950), College of Architecture (1953), and College of Environmental Design (1959) were established. The Berkeley campus became a center of student unrest in the 1960s. Albert Hosmer Bowker served as chancellor from 1971 to 1980.

calendar. In the 1980s there were about 1,500 students with a full-time faculty of about 55 and a part-time faculty of more than 30. The college confers the juris doctor degree. There are joint juris doctor/master's degrees programs with graduate departments of the University of California. The college is a member of the Bay Area Public Interest Law Consortium with Golden Gate University,† University of San Francisco,† and the University of Santa Clara.† Among student organizations are the Associated Students of Hastings College of the Law, athletic clubs, and Order of the Coif and one other honor society. Students publish the *Hastings Law Journal* and *Hastings Constitutional Law Quarterly*. Other school publications are the *Hastings International and Comparative Law Review* and *COMMENT: A Journal of Communications and Entertainment Law*. The library contains 220,000 volumes. The school is accredited by the American Bar Association and the Association of American Law Schools. Bert S. Prunty became president in 1980.

REFERENCES: Herbert Hovenkamp and Roni Crochton, Hastings College of the Law; Thomas G. Barnes, *Hastings College of the Law, The First Century* (San Francisco: University of California, Hastings College of the Law Press, 1978).

➤ **California, Irvine, University of.** Irvine, California 92717 (714) 833-5011. In March 1959 the regents of the University of California selected a site on the Irving Ranch near Newport Beach, California, for a branch of the university. One thousand acres was given as a gift for the university on January 20, 1961; an additional 510 acres was purchased in January 1964. Daniel Gaskill Aldrich, Jr., became the first chancellor on January 19, 1962; he served until 1984. The staff moved into the Irving Ranch house in 1962; the campus was opened on September 26, 1965, with a faculty of 114 and an initial enrollment of 1,589. Among buildings on the campus are the Administration Building, Crawford Hall physical education building, Fine Arts Village, Humanities Hall, Library, Science Lecture Hall, Commons, Social Science Hall, Student Center, University Center, and student dormitories and apartments. The Medical Center is located in Orange, California.

University of California, Irvine, is a public, coeducational, commuter and residential university operating on the quarter academic calendar with two summer sessions. In the 1980s there were more than 11,000 students and a faculty of 1,000. The university is organized into schools of Biological Sciences, Fine Arts, Humanities, Physical Sciences, Social Sciences, and Engineering; Graduate School of Management; and College of Medicine. The School of Biological Sciences offers bachelor of science, master of arts in teaching, master of science, and doctor of philosophy degrees. Student activities include the Biological Sciences Student Association and a national honor society. The school publishes the *Journal of Undergraduate Research in the Biological Sciences*. It conducts the Laser Microbeam Program, Biohazard Facility, Museum of Systematic Biology, Development Biology Center, San Joaquin Freshwater Marsh Reserve, and Burns Pinon Ridge Reserve. There is a cooperative bachelor's/master's degrees program with the Graduate School of Management.

The University of California provides the Intercampus Graduate Student Exchange Program and foreign study opportunities through the Education Abroad Program. The university is a member of the West Coast Regional Consortium of Universities in the Neurosciences with eleven other institutions.

Among 164 student organizations are the Associated Students of the University of California, San Diego; Graduate Student Council; Phi Beta Kappa (1977); 3 social fraternities; and 3 social sororities. Students publish the *Guardian* student newspaper and *Trident* yearbook and operate KSDT radio station. The university participates in intercollegiate athletics in men's baseball, golf, and rugby; women's softball; and men's and women's water polo, tennis, soccer, volleyball, swimming and diving, basketball, track and field, cross-country, crew, and fencing. The Central University Library and five branch libraries (Science and Engineering, Biomedical, Medical Center, Scripps Institution of Oceanography, and Cluster Undergraduates) have more than 1.4 million volumes. The university is accredited by the Western Association of Schools and Colleges. Richard Chatham Atkinson has been president since 1980.

Bob Sender
California, San Francisco, University of. Third Avenue and Parnassus Avenue, San Francisco, California 93143 (415) 666-9000. Hugh Huger Toland (BDAE) established Toland Medical College in San Francisco, California, in 1864; he served as dean until 1870 and as professor of surgery until his death in 1880. The college occupied a new building shortly after it was established. Toland turned the school over to the University of California in 1873, and it was continued at its location as the Medical Department of the University of California. Richard Beverly Cole was dean of the Toland Medical College from 1870 to 1873 and of the Medical Department of the University of California from 1873 to 1875 and 1878 to 1882. The California College of Pharmacy, organized in 1872, also was affiliated with the University of California in 1873. The pharmacy program was housed in the Toland Medical College building; it later was located in the California Academy of Sciences building and in 1883 was moved into a building of its own. In the fall of 1881 the Board of Regents authorized the establishment of a dental school; it began operations on June 5, 1882, in the medical school building. In 1892 it acquired separate clinical facilities although instruction continued at the medical department.

In the 1890s the city of San Francisco donated a site on which buildings were constructed for the medical and dental schools and Hastings College of the Law.* The law school chose not to occupy the site, but the medical, dental, and pharmacy schools were moved into the buildings. After the San Francisco earthquake and fire of 1906 the heavy destruction of hospitals led to transfer of the first two years of the medical curriculum to the Berkeley campus, and part of the medical school building became the first University of California Hospital. In 1907 a training school for nurses was established, and in 1917 a second hospital was constructed. The Medical Department became the College of Medicine in 1912, Medical School in 1915, and School of Medicine in 1949. The