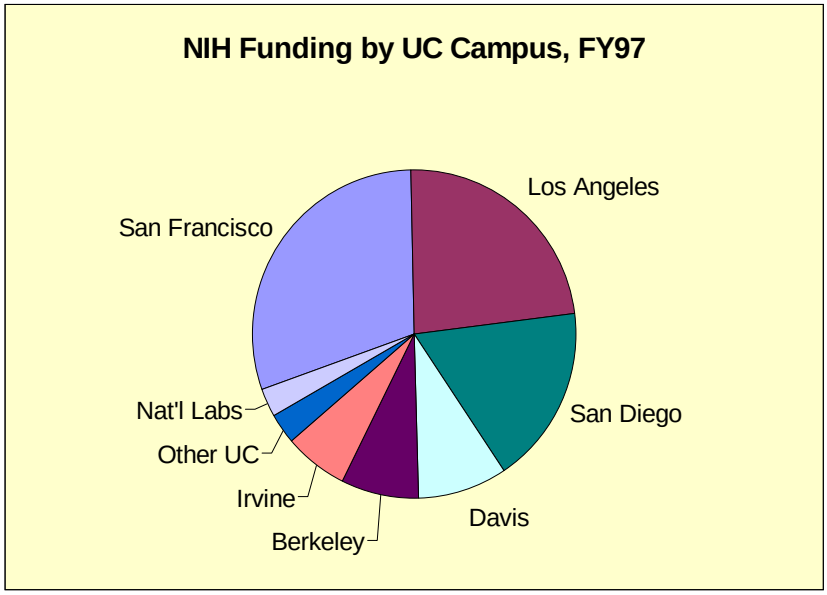
NIH at UC

OFFICE OF RESEARCH, UC OFFICE OF THE PRESIDENT SPRING, 1998

The National Institutes of Health at the University of California

The National Institutes of Health awarded 2,731 grants to UC during Fiscal Year 1997, for a total of $733 million. The bulk of this money flowed to the five UC campuses with medical schools--San Francisco, Los Angeles, San Diego, Davis and Irvine. Berkeley was the only nonmedical campus to receive substantial funding.



San Francisco, the only UC campus dedicated to the Health Sciences, alone captured 30% of the award funding. Fifty percent of the total pie was shared by the campuses of Los Angeles, San Diego, and Davis.

The remaining 20% was split among Berkeley and Irvine (14%) , with smaller amounts flowing to the campuses of Santa Cruz, Santa Barbara, and Riverside (3%). The three National Laboratories administered by UC (Lawrence Berkeley, Lawrence Livermore, and Los Alamos) got the final 3%.

(continued on page 8)

NIH funding facts in brief

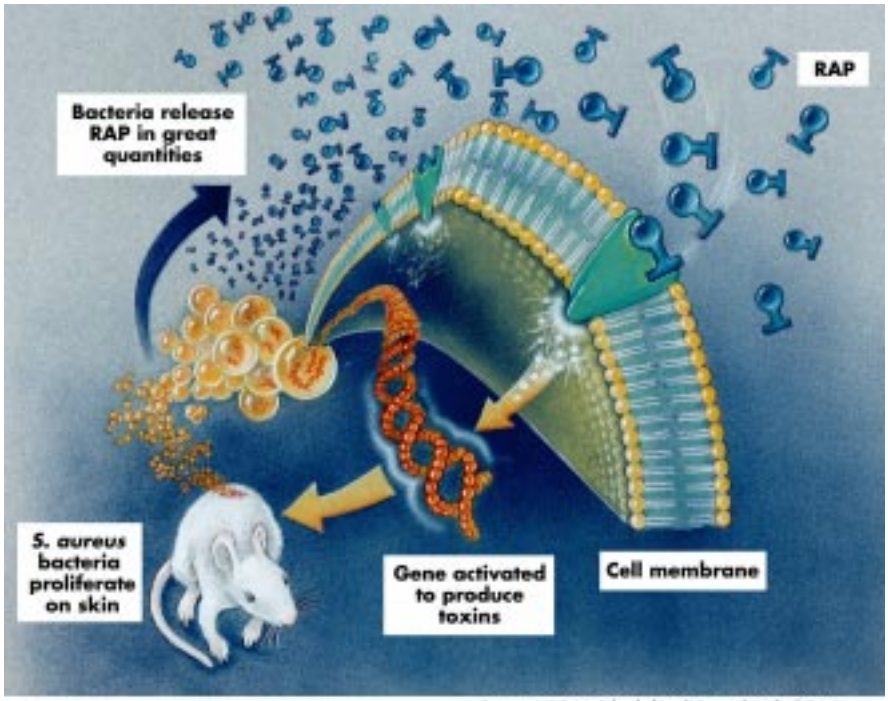
- UC received 2,731 NIH awards in FY97, worth over $733 million.
- Berkeley was the only nonmedical campus to receive sizeable NIH funding–$58 million.
- San Francisco alone garnered about 30% of all NIH funding to UC–over $222 million.
- The three national labs administered by UC do a small amount of NIH-funded research–worth about $20 million.
- UC alone gets more NIH funding than every state except Massachusetts and New York.
- San Diego has been awarded a $13.3 million NIH grant to study diet and breast cancer (pages 4-5).
- At Davis, researchers have discovered a novel way to fight antibiotic-resistant Staph bacteria (page 2).
- San Francisco's Stanley Prusiner was awarded the 1997 Nobel Prize for his NIH-supported research on prions (page 7).

Defanging *Staphylococcus aureus*

In one food poisoning outbreak in the early 1990s, 1,364 children in 16 elementary schools in Texas became ill from eating improperly prepared chicken salad. The culprit was Staphylococcus aureus, or "Staph," a common bacteria present on the skin of most healthy individuals.

Usually benign, Staph can become harmful when triggered to release a deadly toxin. This toxin can cause symptoms of food poisoning in doses as small as one millionth of a gram. Staph also causes many other diseases including impetigo, toxic shock syndrome, pneumonia and septicemia.

Worldwide, many strains of Staph are resistant to every known antibiotic except vancomycin. In 1997, vancomycin failed to knock out Staph infections reported in three different cases in the United States.



Source: UC Davis School of Medicine and Medical Center
Artwork by Nelva B. Richardson

We may be on the verge of a public health nightmare, when many infectious diseases will no longer be treatable with antibiotics. Ironically, the success of antibiotics is leading to their failure. Often overprescribed, dumped into animal feed, or sold without prescription in developing countries, the pervasiveness of antibiotics have led to mutated forms of bacteria immune to them.

At UC Davis, with the help of an NIH grant, Dr. Naomi Balaban has discovered a novel way to fight Staph. "Standard antibiotics kill bacteria," says Dr. Balaban. "Our approach disarms the bacteria by blocking the chain of events that triggers toxin production at the genetic level. Without toxins, Staph has no weapons and is rendered harmless."

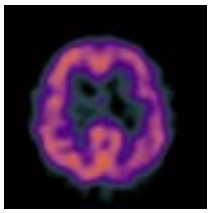
Staph bacteria are constantly secreting RAP (RNAIII activating protein). If RAP builds to a critical level, it triggers the production of toxins that destroy surrounding tissue and make room for the expanding Staph colony.

Dr. Balaban developed a technique to purify RAP and used it to vaccinate mice. The vaccinated animals were far more resistant to Staph infections than unvaccinated mice.

Dr. Balaban developed the vaccine in conjunction with colleagues at Panorama Research, Inc., in Mountain View, California. The NIH supported this research with a grant from its Small Business Innovation Research program.

The Emerging Epidemic: Alzheimer's Disease in an Aging Population

As the Baby Boom generation ages, fighting the diseases of aging will become even more important. Alzheimer's disease, strokes, and other forms of dementia are already the fourth leading cause of death among adults, and their impact is growing.



Examples of brain scans

Estimates predict that 12% of people over 65 and 45% of those over 85 will develop dementia. About half of those dementia cases will be caused by Alzheimer's disease. Dementia costs society an estimated $100 billion annually in health care costs and lost wages.

The NIH's Institute on Aging funds several Alzheimer's disease research centers. UC Irvine has been designated as such a site in partnership with the University of Southern California.

UC Irvine's Institute for Brain Aging and Dementia also receives funding from the State of California and from private donations. In addition to an assessment and treatment clinic, the Institute operates an extensive basic research program. The brain images on this page were created at the Institute's brain imaging analysis unit.

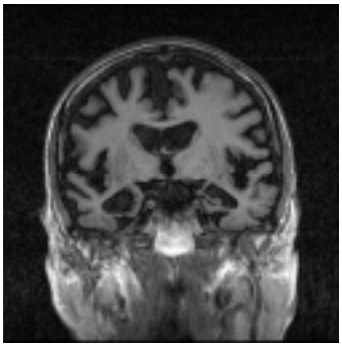
Alzheimer's Disease (AD) is caused by a massive degeneration of specific parts of the brain (see images on the right). In AD, neurons degenerate and aberrant structures called senile plaques and neurofibrillary tangles form in the brain.

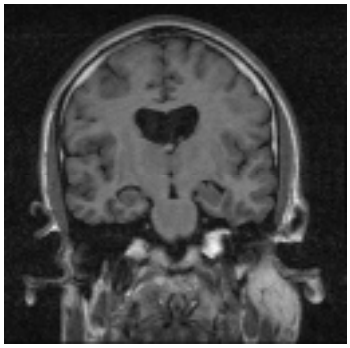
A recent study shows that vitamin E, an antioxidant, can reduce the symptoms of AD. It was UC Irvine's Carl Cotman, Ph.D., director of the Institute of Brain Aging and Dementia, who suggested vitamin E be included in the large clinical trial of anti-AD drugs.

The study was funded by the National Institute on Aging, and appeared in the New England Journal of Medicine in April, 1997. "It's thrilling to see that something predicted as a real possibility through basic research showed such positive results in clinical trials and really helped people with dementia," says Cotman. He adds that the study reinforces the idea that oxidative damage plays a role in AD.

Although there is no cure for AD, early diagnosis and treatment can slow the loss of function and increase the quality of life for both AD patients and their care givers.

Dementia remains an extremely complex illness that demands a multidisciplinary approach and sophisticated tools. At UC Irvine, the Institute for Brain Aging and Dementia draws on the resources of several different departments from both within and outside the medical school.





These two scans shows the difference between a normally aged brain (right), and a brain with Alzheimer's Disease (left).

Cancer and Nutrition: UC

Sometimes it takes years of research at a leading medical center to reveal that our parents were right after all--we should eat our vegetables. At UC San Diego's medical school, researchers are beginning a massive study to learn how fruits and vegetables can fight cancer.

The National Cancer Institute of the NIH has awarded $13.3 million to the UCSD Cancer Center to determine how diet can help prevent the recurrence of breast cancer. Over the course of eight years, the Women's Healthy Eating and Living (WHEL) study will trace the effects of high-vegetable diets on the health of 3,000 women with a previous occurrence of breast cancer.

Cancer-Fighting Compounds in Vegetables and Fruit

Broccoli–Vitamin C, Folates, Beta-carotene, Lutein, Dithiolthiones, Isothiocynates

Blueberries–Lignans (Phytoestrogens)

Cabbage–Vitamin C, Indoles, Dithiolthiones, Isothiocynates

Carrots–Alpha- and Beta-carotenes

Onions–Diallyl Sulfide, Allyl Methyl Trisulfide

Oranges–Vitamin C, Folate, Limonene, Beta-cryptoxanthin

Peaches–Beta-carotene, Beta-cryptoxanthin

Spinach–Folate, Beta-carotene, Lutein

Tomatoes–Vitamin C, Lycopene

Each year in the United States, 180,000 women are diagnosed with breast cancer, and 44,000 die from a recurrence. In many respects, breast cancer is a disease of affluence. Cross-cultural studies have found a much lower rate of breast cancer in low-income countries with high-vegetable and low-fat diets.

Yet cancer researchers have been stymied when they have looked for a single factor to explain these differences. Higher fiber, lower fat and higher carotenoid intake all have been found to be effective by some researchers, but not by others.

For Cheryl Rock, Ph.D., these results are not surprising. Dr. Rock is a nutritionist and is one of the primary investigators on the WHEL study. According to her, Americans tend to place too much emphasis on a single "dietary magic bullet," whether it's carotenoids or fiber, protein powders, bee pollen or broccoli sprouts.

The single-factor studies overlook the thousands of possible synergistic interactions between the various ch
Rock adds, "There are many chemi
known in the laboratory to prevent
ing as it's the first large scale study
diet."

Dr. Cheryl Rock in her lab. The carot
The analysis of patient's plasma sam
similar to those used in photographic

The NIH also awarded $1.5 million
Cancer Prevention for Women (CAP
CAPRE study was the reversal of ce
results show a strong relationship b
blood plasma and cervical tissue. In
presence of carotenoids was found t
cell death) in cervical cancer cells.

San Diego's WHEL Study

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cals in vegetables and fruits that are
cancer. The WHEL study is excit-
to investigate the role of the overall

tenoids oxidize easily under UV light.
mples takes place under safe lights
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for an early project at UCSD, the
PRE) study. The focus of the
rvical cancer through diet. Early
etween diet and carotenoids in
n laboratory tissue cultures, the
to induce apoptosis (programmed

The WHEL study is coordinated by John Pierce, Ph.D., director of the Cancer Prevention and Control Program of the UCSD Cancer Center. The program will be carried out at seven sites in California, Oregon, Arizona and Texas.

The medical director for the whole study, and the principal investigator for the UCSD site, is Vicky Jones, M.D., a medical oncologist. Dr. Jones treats women with breast cancer at the UCSD Cancer Center. In her words, the WHEL study "answers a need that patients have. They want to know, 'should I be eating something special?' It's an area that has not been paid a wealth of attention in the past."

The WHEL diet does not require consuming massive quantities of carrots and brussel sprouts. It adds several small daily servings of fruits and vegetables to a typical healthy dietary plan.

The WHEL researchers integrate their recommendations into the daily lives of their often busy patients. They avoid stringent diets that would require working women to spend an unrealistic amount of time in the kitchen. Instead of vetoing trips to the local fast food outlet, the WHEL researchers ask their patients to bring a menu, and together they work to find items that meet the study's requirements.

In the words of WHEL director Dr. Pierce, "We set about to prove that women could and would make a major change in their diet in the interest of their own long-term health. The awarding of this grant to UCSD is a strong message for the federal government and our peers that we are investigating one of the most important hypotheses in cancer prevention."

How the Cancer-Fighting Compounds Help

Dithiolthiones and Isothiocynates–Have been shown to increase the activity of enzymes that detoxify carcinogens.

Carotenoids (Carotenes, Lutein, Beta-cryptoxanthin and Lycopene)–Inhibit the production of cancer and protect cells against oxidative stress.

Folate–Protects and normalizes gene expression, and prevents the accumulation of metabolites.

Indoles–Promote the production of a less potent form of estrogen.

Limonene–Increases the activity of detoxifying enzymes.

Vitamin C–Reduces the formation of nitrosamines, and protects against genetic damage to cells

Hunting the Slow Killer of Yangzhong

One hundred and fifty-five miles up the Yangtze River from Shanghai lies Yangzhong County. An island of 88 square miles with a population of 270,000, Yangzhong has one of the highest rates of stomach cancer in the world.

Each year, about 600 people die from stomach and esophageal cancer in a region with a

The Yangtze River from Yangzhong.

population roughly the same size as Louisville, Kentucky. The death rate due to these cancers among elderly men in Yangzhong is approximately seven times as high as the United States. These two cancers alone account for two-thirds of all cancer deaths in Yangzhong.

Why? That is the epidemiological puzzle UCLA's Dr. Zuo-Feng Zhang is trying to solve, with help from a grant from the National Cancer Institute. Working with collaborators at Shanghai Medical University, Dr. Zhang will attempt to discover what makes the people of Yangzhong so vulnerable.

A list of possible culprits includes genetic factors, highly salted food, smoking, green tea, and Helicobacter pylori, the bacteria implicated in stomach ulcers.

Dr. Zhang suspects that malnutrition in early life prevents the proper development of the

The entrance to the Yangzhong County Hospital.

stomach and its mucous lining. Later in life Yangzhong's residents may become more susceptible to highly salted foods and other carcinogens.

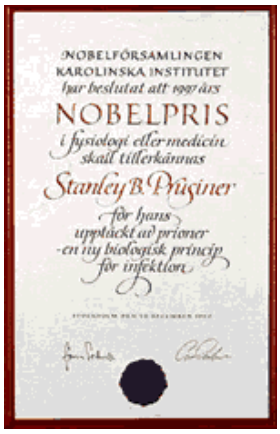
By studying this epidemiological "hot spot," the investigators hope to learn more about the role of H. pylori in stomach cancer, not only in China, but in the rest of the world as well.

Team of Investigators in China. 2nd from left: Dr. Shun-Zhang Yu, Dean of School of Public Health, Shanghai Medical University. 4th from left, Dr. Guo-Pei Yu, Associate Chairman of the Department of Epidemiology, Shanghai Medical University.

Prions, Prusiner and a Nobel Prize

In 1972, Stanley Prusiner, a neurology resident at UC San Francisco, lost a patient to the unusual Creutzfeldt-Jakob disease. Intrigued, Prusiner set up a laboratory at UCSF in 1974 and began intensively studying this puzzling neurological ailment.

Prusiner and his colleagues came to a startling conclusion--the infectious agent that caused Creutzfeldt-Jakob disease and other related diseases in animals contained no nucleic acids. They were simple proteins, dubbed "prions" (pree-ons), for "proteinaceous infectious particles."

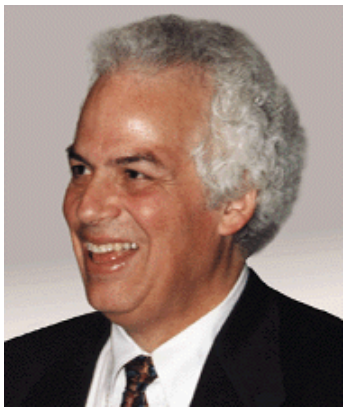


Like many scientific breakthroughs, Prusiner's theories were greeted with strong opposition. Undaunted, Prusiner returned to his laboratory and produced finding after finding over the course of more than two decades. This work paved the way for the acceptance of his once heretical ideas.

On December 10, 1997, dressed in black tails, Stanley Prusiner stood at the ceremony in Stockholm, Sweden, and received the Nobel Prize for Medicine.

This was not the first Nobel awarded for the study of degenerative brain diseases. In 1976, D. Carleton Gajdusek and Baruch S. Blumberg won the Nobel prize for their research on Kuru, a brain disease that afflicted cannibalistic tribes in Papua New Guinea.

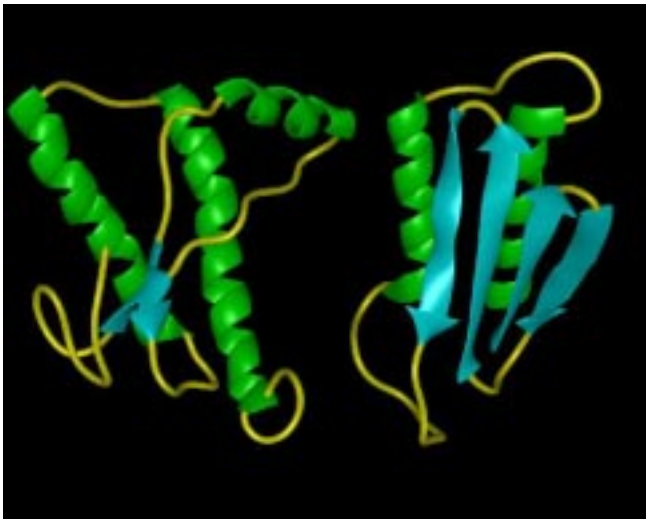
Kuru, at first considered to be caused by a slow-acting virus, is now thought to be a prion disease, along with Scrapie in sheep, Bovine Spongiform Encephalopathy (mad cow disease) in cattle, and Creutzfeldt-Jakob disease in humans.



Throughout the years of diligent research that led to the Nobel prize, Dr. Prusiner and his colleagues were aided by a silent partner–the NIH.

According to Dr. Prusiner, "the discovery of prions was the culmination of years of work by many dedicated researchers. The grants we've received from the NIH have played an extremely significant role in funding this research, and without them our findings might have taken many more years to come to fruition."

Many researchers suspect prions will eventually be implicated in Alzheimer's disease. Far more research needs to be done to identify the exact mechanisms of the prion diseases. There may be more Nobel prizes to come.



This illustration compares a normal prion protein (left) to a disease-causing form (right). The infectious form arises when regions in the normal protein unfold, enabling the protein molecules to clump together and react in ways that contribute to disease.

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When compared to its peers, the University of California does very well. UC San Francisco is the fourth-ranked university in terms of NIH funding awarded. UC Los Angeles is ranked 10th, and UC San Diego 15th.

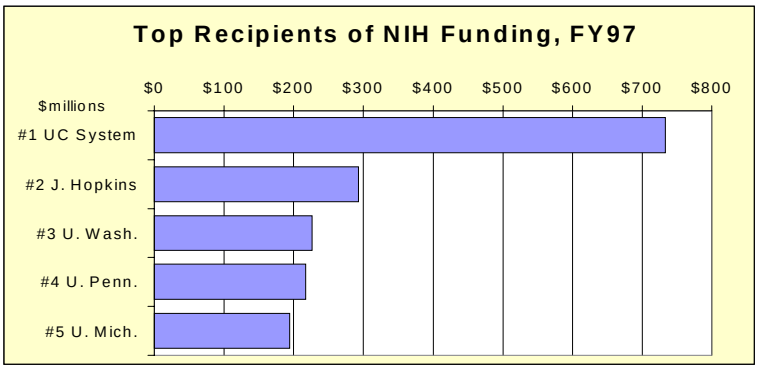
This comparison slights UC San Francisco, because it lacks the nonmedical life sciences departments of other major universities. If the comparison is based upon NIH grants awarded to medical schools only, then UCSF ranks second only to Johns Hopkins.

The National Institutes of Health divide their research among several different institutes. Some institutes, such as the National Cancer Institute (NCI), direct research funding to fight specific diseases. Other institutes support basic medical research.

NIH Funding to UC by Institute, FY97

National Institute of:	$mil.
Cancer	$97.3
General Med. Science	$82.6
Infectious Diseases	$82.1
Heart, Lung and Blood	$75.5
Mental Health	$66.7
Stroke & Neuro.	$50.6
Diabetes	$41.6
Child Health	$38.0
Research Resources	$36.8
Aging	$30.9
All Others	$131.4
Total	$733.4

UC captured $97.3 million in FY97 from the National Cancer Institute, the largest contributor to UC among the NIH institutes. The second largest NIH contributor was the Institute of General Medical Science. This Institute granted UC $82.6 million in FY97 to conduct basic research.



There is broad bipartisan support in Washington, D.C. to dramatically increase the NIH budget. Most plans call for increases in the range of 8%-9% for FY99, bringing the NIH budget to over $14 billion.

However, this support is linked to controversial changes in funding of other programs, so it remains to be seen just how big the increases will be for the NIH. In general, the prospects for NIH funding look very good.

For more information about NIH awards at UC, please contact:

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