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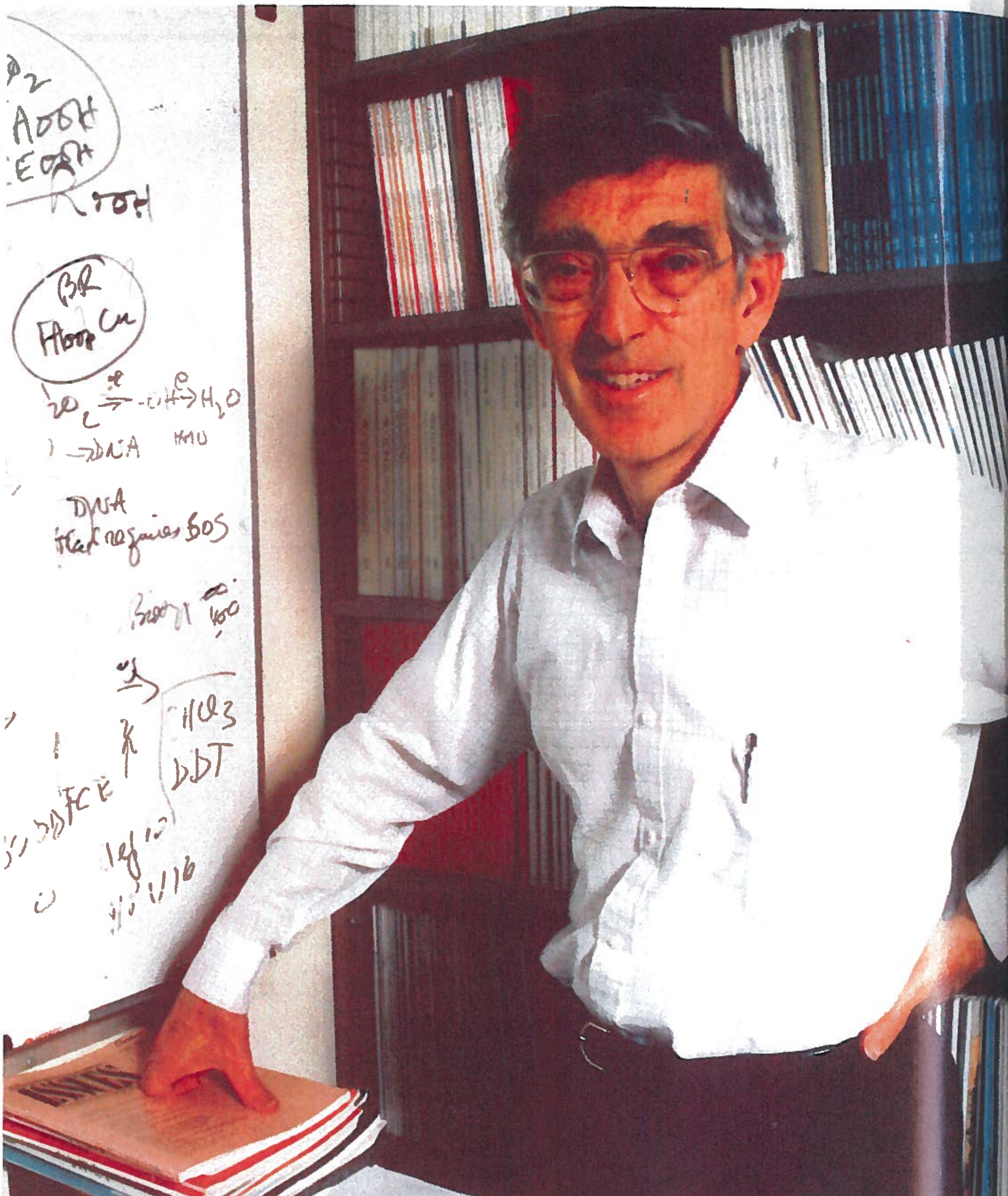

This expert on cancer-causing substances applies his research to products we encounter in our everyday lives.

Bruce N. Ames

BY LUCILLE DAY

One of the first things visitors notice about the office of biochemist Bruce N. Ames is a collection of cartoons taped to a file cabinet. One of his favorites shows a lion cautioning another as they stare at a hunter: "Don't eat one of them. They're loaded with additives and preservatives." Cartoons that satirize the dangers of chemicals added to foods are particularly appreciated by Ames, who developed the world's most widely used test for identifying food additives and other substances likely to cause cancer.

Another cartoon shows an elderly couple grocery shopping. The woman confides to her husband, "I don't trust natural. People die all the time from natural causes." This, too, is an especially appropriate sentiment to find on Ames's file cabinet, because Ames—an expert on diet and cancer—has been instrumental in alerting the public about cancer-causing substances that occur naturally in food.

Ames, chairman of the Biochemistry Department at the University of California at Berkeley, is a multitalented scientist. As a biochemist, he studies the chemistry of living organisms. He is also a geneticist, concerned with the workings of *genes*—the complex chains of *deoxyribonucleic acid* (DNA) that are found in all living cells and that determine all inherited traits.

But Ames's special gift as a scientist is his ability to build bridges between his work in the laboratory and everyday life—to find practical applications for his research. Because of his interest in DNA and the connection between DNA damage and cancer, he invented a test to detect *mutations*—changes in the structure of genes. He then started looking for *mutagens*—agents that cause mutations—in common substances.

And Ames found such mutagens, lots of them, including hair dyes and chemicals used to make children's sleepwear fire-resistant. These substances were subsequently shown to be *carcinogenic*—cancer-causing—as well. Today, Ames's test is an important tool of *genetic toxicology*—the study of substances in the environment that damage genes.

Bruce Ames was born on Dec. 16, 1928, in New York City. Thanks to his father—who was the chairman of a high school chemistry department, and later supervisor of science for all the New York City public schools—Ames and his two younger sisters were always surrounded by science. As a youngster, he was particularly interested in chemistry and biology, eagerly reading the books his father left lying around the house. During the summers, which the Ames family spent at a lakeside cabin in the Adirondack Mountains of New York, he explored the natural world and collected frogs, salamanders, and snakes.

He also had a voracious appetite for books. "I always read enormous amounts," Ames says. "I would come back from the library with a whole stack of books."

As a teen-ager, Ames attended the Bronx High School of Science, where, as the name implies, special attention is given to the study of science (in the People in Science section, see HIGH SCHOOLS OF SCIENCE). There, he conducted experiments to learn how plant hormones affect the growth of tomato root tips grown in laboratory glassware. Propelled by that first taste of the excitement of scientific research, Ames enrolled at Cornell University in Ithaca, N.Y., to study the subjects that had appealed to him since childhood—chemistry and biology.

Ames, a slender, agile-looking man with lively hazel eyes, discovered another talent during his college years—dancing. "It was the first thing I really did well in my life," he declares. He still dances, and his specialties include Scottish country dancing and ballroom dancing. "I'm always happy to waltz all night," he says.

Although Ames was extremely imaginative and adept at problem solving, he was not an "A" student at Cornell. He liked to follow his own interests—which did not always coincide with the assigned reading for his courses. "I just went off my own way in whatever I was doing," he recalls. "For example, I got tremendously excited about Jane Austen when I was in college, and one semester I read all of Jane Austen instead of the books for the courses I was taking."

Nevertheless, Ames managed to do well enough in his courses to be accepted at a prestigious graduate school. He graduated from Cornell in 1950 and headed west to the California Institute of Technology (Caltech) in Pasadena.

Ames found Caltech exhilarating. "Those were marvelous years,"

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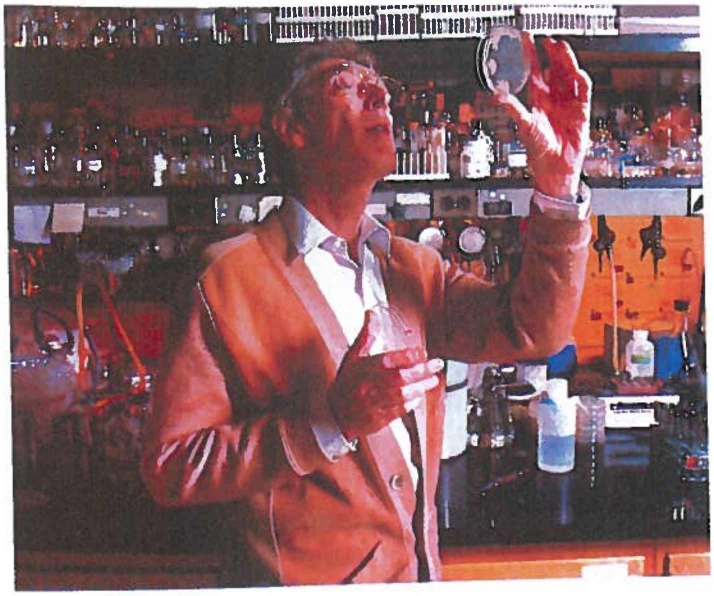
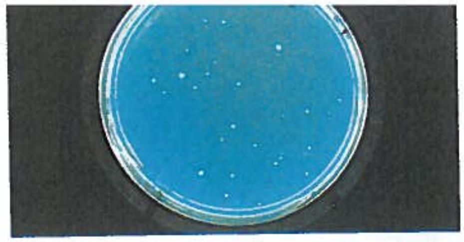
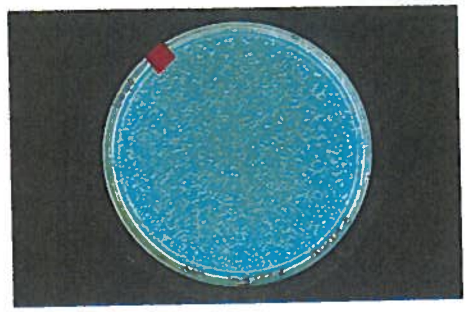






Bruce Ames, *above left,* examines a laboratory dish containing bacteria used in the Ames test to identify *mutagens*—substances that cause *mutations* (changes) in genes. Such mutagens are also likely to be *carcinogens*—cancer-causing substances. In this test, mutagens cause a change in the bacteria that enables the bacteria to grow. Only a few bacteria grow on one dish, *upper right,* indicating it does not contain a mutagen. Many bacteria grow in another dish, *above right,* showing that the substance being tested is a mutagen.

he says. "The students were very high caliber, and many of them are now in the National Academy of Sciences"—a highly distinguished society of accomplished scientists to which Ames himself was elected in 1972.

There were also exceptional professors at Caltech working in Ames's field. During the early 1950's, when Ames was a graduate student, not much was known about how genes worked. Even the molecular structure of DNA was a mystery until American biologist James D. Watson and British biologist Francis H. C. Crick devised their model of DNA in 1953. But some people learned about genes by studying the products of genes—enzymes and other proteins—a field known as *biochemical genetics*. Several of these pioneers in biochemical genetics, including George W. Beadle, Norman H. Horowitz, and Herschel K. Mitchell, were professors at Caltech.

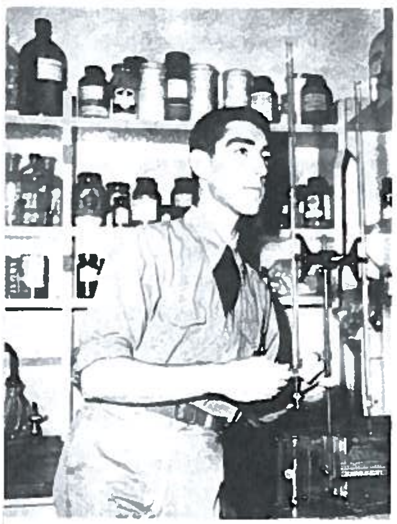
Ames joined Mitchell's laboratory, and decided to tackle the problem of figuring out the step-by-step process used by a cell to make an amino acid called *histidine*. Amino acids are the building blocks of proteins. He chose to study the histidine-making process in *Neurospora crassa*—an orange-colored bread mold often used in genetic research.

A cell of this bread mold contains a set of genes that are needed by the cell to produce histidine. Each gene contains instructions for making an enzyme. When a mutation occurs in one of the genes, the mutant mold cell makes a defective enzyme, and no histidine can be made. Using a number of such mutants, Ames was able to unravel the series of chemical reactions the cell carries out to make histidine—reactions that are controlled by the mold cell's genes and that reflect the ordered activity of those genes.

In 1953, having completed this ambitious research project after only three years at Caltech, Ames received his Ph.D. degree and headed back east to do research at the National Institutes of Health (NIH) in Bethesda, Md. He decided to attack the important question of how the activity of genes is controlled in a cell. This puzzle of gene regulation—how genes are turned "on" and "off" so that enzymes and other proteins are produced at the right time—is crucial to understanding fundamental issues of biology, such as how a single fertilized egg develops into a human being.

Ames continued to work with the bread mold for a while, but soon switched to using a bacterium called *Salmonella typhimurium*, because it is a simpler organism and it grows faster—making it possible to complete experiments more quickly. Even so, it took about 15 years of research before Ames discovered the chemical signals that turn on and off the genes involved in making histidine.

While working at the forefront of research in his field, Ames revealed another side of his creativity—inventiveness. He invented many of the techniques required for his research. One of the most important was a process for separating out certain proteins, which he developed with cell biologist Robert G. Martin. This technique uses a *centrifuge*—a device that holds a ring of test tubes and spins them around at very high speed—to separate certain proteins in a sugar solution from one another. Heavier proteins wind up at the bottom of the test tubes, while lighter ones are suspended higher up. Being able to separate one protein from others makes it possible to study its structure and function. Ames first used this technique to separate the enzymes required by a cell to make histidine. Since then, thousands of researchers have used the method to separate many different kinds of proteins.



As a boy, Ames spent family vacations at a lakeside cabin, exploring the world of nature, *top.* His interest in science eventually led him to the California Institute of Technology in Pasadena, where as a graduate student in the early 1950's, *above,* he did research in genetics and biochemistry.

In 1958, Giovanna Ferro-Luzzi, a young Italian biochemist working at Johns Hopkins University in Baltimore, attended an NIH seminar given by Ames. Shortly after that, the two met at another scientific gathering. Then, Ames says, "I started chasing her—or vice versa." He invited her to help him plant dahlias in his garden, and soon afterward took her to see the celebrated Bolshoi Theater Ballet on tour from the Soviet Union. In 1960, they married.

Ferro-Luzzi, an energetic, enthusiastic woman—and a highly acclaimed scientist in her own right—says that her husband brings the same creativity to his family life as he does to his research. She describes him as "very understanding, persistent, and imaginative—with sort of an artistic flair thrown in."

"He'll come into the kitchen," she explains, "and think how some gadget could be designed a little better—that's very characteristic of him." She adds, good-humoredly, "He's also very dreamy—most of the time he's not listening to what I ask him or tell him to do."

Shortly after they were married, Ames and Ferro-Luzzi spent a year abroad, doing research in the labs of two Nobel laureates—Crick at Cambridge University in England and biologist François Jacob of the Pasteur Institute in Paris. At Cambridge, Ames studied *polyamines*—small molecules that bind to DNA and, he believes, protect it against mutagenic substances. In Paris, he continued his work on the genes involved in making histidine.

Ames returned to the NIH in 1962, and a year later, two important events took place. First, Ames's daughter, Sofia, was born. Then, the day after her birth, the American Chemical Society (ACS) told Ames he had been chosen to receive the Eli Lilly Award for his research—his first major scientific award.

When the editors of *Chemical and Engineering News* magazine asked for a photograph to accompany the announcement of Ames's award, Ferro-Luzzi suggested that he send a picture she had recently taken. It showed Ames, who was recovering from a cold, sitting under an avocado plant looking dejected, unshaven, and in need of a haircut. Amused, he sent it off—and when the magazine appeared, he received an avalanche of fan mail from people delighted to see "a scientist the way he normally looks."

When asked to provide a portrait to accompany a news story about his winning an award, Ames, as a joke, sent a photo taken while he was recovering from a cold—and looking rather disheveled and dejected. Ames received a flood of mail from readers delighted to see a picture of "a scientist the way he normally looks."

The following year was also eventful for Ames. That year, his son, Matteo, was born. Characteristically, Ames brought the same inventiveness that served him in the laboratory to raising his children—especially as they grew into teen-agers. "All his sympathy, understanding, and flexibility came out," says Ferro-Luzzi. "He could really converse with them, I think, much better than I could."

But 1964 turned out to be memorable for another reason besides the birth of Ames's son. During that year, he happened to read the list of ingredients on a package of potato chips. Mulling over the list, he began to think about all the new synthetic chemicals entering the environment and the damage they might cause in human cells. A natural problem-solver, Ames began to wonder if a simple test could be developed to screen these chemicals for their ability to cause mutations in genes. As a hobby, he started looking for mutagens, using the *Salmonella* bacteria strains he had developed for his research on histidine.

In the *Salmonella* test—which everyone but the modest Ames refers to as "the Ames test"—certain strains of *Salmonella* bacteria are placed in laboratory dishes along with some nutrients and the chemical to be tested. Normally, these special bacterial strains will not grow in the laboratory dishes, because they contain a mutation that makes them unable to produce histidine. But when a substance that causes mutations is added, such as cigarette smoke, some of the bacteria will acquire a second mutation. And because some of these newly mutated bacteria are able to make histidine, they grow and form small clumps of cells called colonies. A chemical that causes mutations in the genes of bacteria may cause mutations in human genes, too. So a mutagen identified by the Ames test is well worth further scrutiny.

Ames became convinced that one important property of cancer-causing substances is their ability to damage DNA—in other words, to act as mutagens. "We kept lists of commonly studied carcinogens and kept working to make improvements in the test that could detect them as mutagens," says Ames.

But at first, the *Salmonella* test failed to detect some important

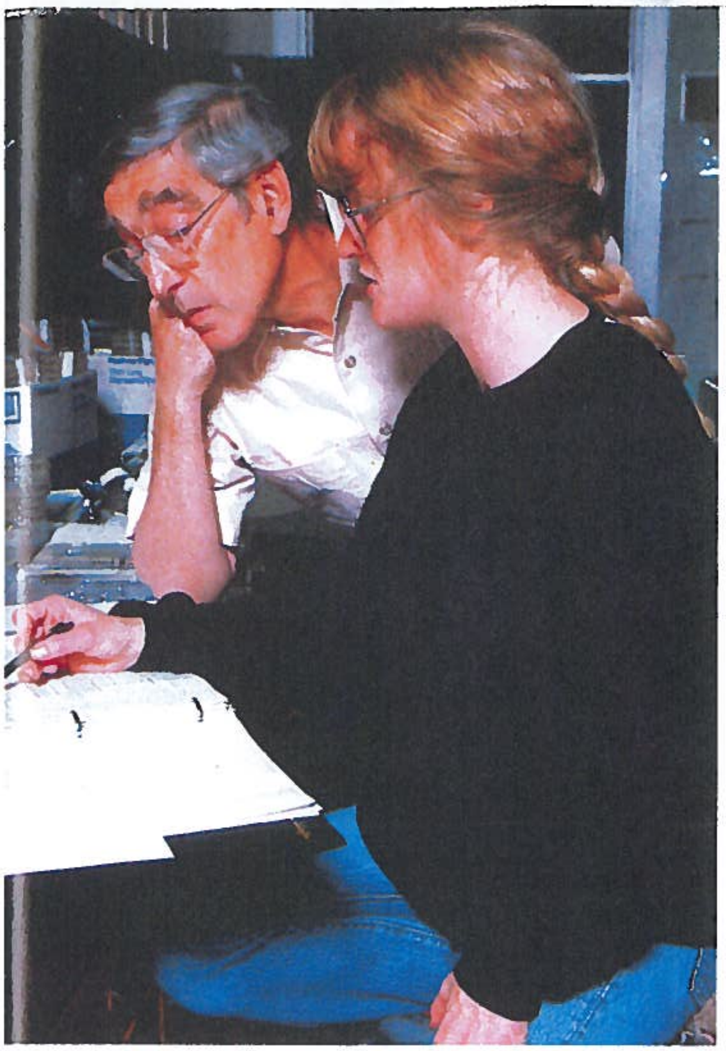
In his kitchen, *above,* Ames brews a morning cup of coffee, even though his research has shown that coffee and other foods contain carcinogens. Ames says the amount of carcinogens in these foods is much too small to worry about if the foods are consumed in moderation. In his laboratory at the University of California at Berkeley, Ames continues to look for links between diet and cancer, *right.*

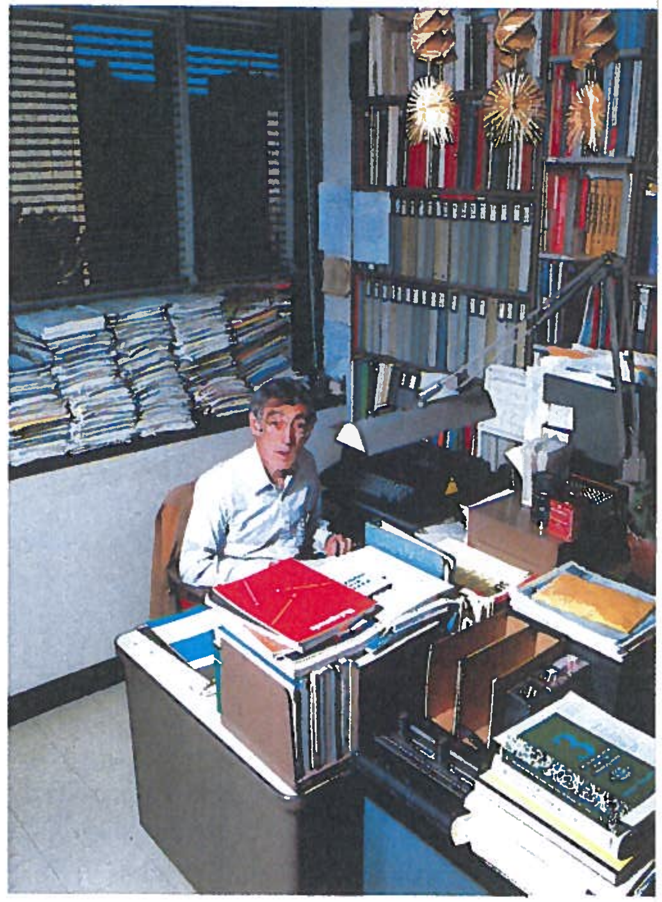
mutagens that had already been identified as carcinogens. So Ames and his colleagues kept tinkering with the test, hoping to improve its sensitivity.

Ames then acted on a hunch. He knew that one of the functions of an animal's liver is to break down *toxic* (poisonous) substances taken into the body. Perhaps, Ames reasoned, the liver converts some substances into mutagens. He added ground-up rat liver to the test dishes in an attempt to imitate what happens to chemicals in a living animal's body.

The hunch paid off. Ames retested powerful carcinogens—such as benzpyrene, a chemical found in cigarette smoke and many other substances—that the test had previously failed to identify as mutagens. "This time," says Ames with satisfaction, "the test worked." With the added rat liver and other improvements, Ames and his group were able to show that more than 80 per cent of carcinogens are also mutagens.

Ames says that his most important talent in science is his imagination. And his hunch about how to improve his test for environmental mutagens is a typical illustration of his creative process. "When I come across a new fact, it's like trying to fit a piece into a jigsaw puzzle. I compare it to all the other facts in my mind to see





Ames has many activities besides his own research. For example, he gives advice and monitors the work of one of his graduate students, *above left,* then spends hours in his office, *above,* reading reports and evaluating research grant proposals for the government and for private foundations.

what connects," he explains. "I'm always making odd connections and asking what they might explain."

Today, the Ames test is used in more than 3,000 laboratories—including those of most major drug and chemical companies. It is widely regarded as an important first step in identifying substances that might cause cancer. After a substance is shown to be mutagenic by the Ames test, it is subjected to animal cancer tests, in which rats or mice are fed the substance over a long period of time to see if they develop cancer. The Ames test is performed first because it is inexpensive, and because it allows a chemical to be screened in a matter of days and at a cost of a few hundred dollars. Animal cancer tests, in contrast, are extremely expensive—about $500,000 per substance tested—and take years to produce results. With hundreds of thousands of new chemicals being developed each year, it would not be feasible for companies to conduct animal tests on all of them.

Ames, who is not particularly motivated by money, never patented his widely used test. "I figured I didn't need the money," he says. Besides, he adds, characteristically, "I was too busy with other things anyhow."

In 1968, Ames left the NIH and headed west again—this time to join the faculty at the University of California, Berkeley, as a full professor. Ferro-Luzzi, an expert on the proteins involved in transporting amino acids into cells, also became a researcher—and later a professor—in the Biochemistry Department. Ames continued to make a number of important improvements in the *Salmonella* test, taking advantage of recent developments in genetic engineering technology. Using genetic engineering techniques, Ames and his co-workers created bacteria with custom-made mutations—that is, they knew both the exact location and the type of chemical changes in the DNA of the mutant strain of bacteria. These customized bacteria became useful tools for learning precisely what physical changes occur in the DNA molecule when it is exposed to a mutagen.

Since 1981, Ames has held an additional post at the Lawrence Berkeley Laboratory (LBL), a national scientific laboratory operated by the University of California for the United States Department of Energy. He is currently collaborating with Lois S. Gold of LBL to develop a computer database—a computerized "library"—designed to help people evaluate the hazards of both artificial and natural cancer-causing substances.

Ames receives the Charles S. Mott Prize for cancer research from General Motors (GM) Chairman Roger B. Smith in 1983. The GM Research Foundation award is one of the many honors that have been bestowed on Ames for his research.

Ames and Gold's database includes the results of thousands of animal cancer tests conducted on hundreds of carcinogens. Using this information—and the estimated amount of each of the substances that a human being will be exposed to during a lifetime—they have created a "possible hazard scale." This scale rates substances according to the strength of the carcinogen and the typical human exposure. Ames hopes the scale will serve as a kind of yardstick to help people estimate the relative risks of different substances—and to pinpoint the most hazardous substances.

But Ames does not consider the hazard scale the final word on these carcinogens. The ratings are based on animal cancer tests, and, as he is quick to point out, "A substance that causes cancer in rats doesn't necessarily cause cancer in mice, let alone people."

Ames is ready to speak up when he sees a genuine hazard to the public's health. He has served on a number of government advisory panels and is frequently asked to testify before government committees concerned with toxic chemicals in the environment. In 1981, for example, concerned about factory workers exposed to the pesticide ethylene dibromide (EDB), he testified before the California Senate Committee on Toxics and Public Safety Management. As a result of the testimony of Ames and others, the standard for EDB exposure in California is now 100 times more stringent than the national standard.

On the other hand, Ames believes that in certain cases, people are unduly concerned about tiny amounts of synthetic chemicals in the environment. For example, in California's "Silicon Valley"—an area where many computer-related industries are located—well water contains small amounts of trichloroethylene (TCE), a carcinogenic industrial chemical. But, says Ames, Silicon Valley well water is ac-

Imitating the figures in American artist Grant Wood's famous painting *American Gothic,* Ames and his wife, biochemist Giovanna Ferro-Luzzi, strike a pose in their garden.

tually safer to drink than a glass of ordinary chlorinated tap water. The tap water contains trace amounts of chloroform, a carcinogen used to sterilize and disinfect drinking water. But neither kind of water, says Ames, poses very much risk to the public.

The money and other resources currently devoted to tracking down and removing tiny amounts of weak carcinogens could be channeled more usefully, Ames believes. "We should try to determine what's really important in causing cancer and zero in on that," he says. Useful efforts, in his opinion, would be studies to identify significant artificial and natural carcinogens, programs geared to help people stop smoking—a major cancer risk—and research into the relationship between diet and cancer.

Ames himself has given a great deal of thought to diet and cancer. In 1983, he wrote an article for *Science* magazine that thrust the issue into the limelight. In the article, Ames discussed common foods that naturally contain mutagens and carcinogens. Since the early 1980's, he and others have used the Ames test to detect naturally occurring mutagens in a variety of foods, including coffee, mushrooms, celery, parsley, peanut butter, black pepper, comfrey herb tea, and mustard.

Many plant foods contain natural toxic chemicals because these chemicals protect the plants from hungry insects, explains Ames. He and others are now showing that many of these substances are both mutagenic and carcinogenic.

"The amount of nature's pesticides we are ingesting is at least 10,000 times the level of artificial pesticides," he explains. That is one reason why foods such as peanut butter and beer, which contain natural carcinogens and which people routinely eat and drink, score much higher on Ames's hazard scale than do artificial pesticides, such as DDT.

Fortunately, Ames points out, human beings and other animals have evolved many defenses against dangerous natural substances in plants, defenses that also help to protect them against artificial

Ames keeps informed about news involving cancer-causing substances and public health by clipping newspaper stories about chemicals present in the environment.

carcinogens. For example, the liver sometimes converts mutagenic substances to harmless ones. Also, the digestive tract has a protective lining and regularly sheds cells that have been exposed to mutagens. And finally, cells throughout the body contain enzymes and other chemicals that help protect against DNA damage.

"But none of these defenses is perfect," Ames cautions. "There are always little bits of harmful chemicals getting by."

Ames is not suggesting that we give up peanut butter and other well-loved foods, however. The hazards are too small to worry about, he says—and besides, there is some good news about diet and cancer. As Ames pointed out in his *Science* article, foods are also full of natural anticarcinogens—chemicals that protect against cancer. These include vitamin E; carotenoids, substances found in green and yellow vegetables; selenium, which abounds in meat and seafood; vitamin C; and uric acid.

Rather than trying to eliminate every carcinogen from our diet—an impossible task—Ames suggests that we should try to identify the more important ones. He also thinks it is useful to eat a balanced diet that includes protective anticarcinogens. Large amounts of some of these substances, however, can cause health problems. High doses of selenium are toxic, for example, and too much uric acid can cause gout. More research is needed before health experts can specify ideal amounts of anticarcinogens in the diet.

An important new area of research in Ames's laboratory that ties in to the diet-cancer connection is the study of damage caused when the element oxygen combines with DNA. Ames and other scientists believe that such damage to DNA could play a major role in both cancer and aging. Many of the mutagens and carcinogens in the diet may act in the same way to damage DNA—by generating oxygen-containing molecules called *free radicals* that combine readily with the DNA and change its chemistry and function. This hypothesis suggests that substances that prevent free radicals from forming should help prevent DNA damage. As it turns out, many of the anticarcinogens in food are chemicals that combine with free radicals before they damage the DNA.

Ames runs a large laboratory at Berkeley, and meets twice a week with his research team to discuss the work. Because of his eminence as a scientist, outstanding researchers and students from all over the world apply for positions with him. On the wall outside Ames's laboratory are pictures of his extended scientific family—all the students and researchers who have ever worked with him. The gallery of Ames's alumni was started, he says, "so that new people can attach faces to the names they read in the research papers." Ames himself has published more than 200 research papers.

Ames also teaches a laboratory course for biochemistry students at Berkeley, which brings him into contact with another 100 or so students every year. His enthusiasm and sense of humor, as well as his scientific reputation, make him a popular teacher and a sought-after speaker for universities, government agencies, companies, and the general public.

In addition to overseeing the work in his laboratory, Ames does a lot of reading. Besides keeping up with new research in his field, he is often asked to evaluate papers for publication in various scientific journals. Government agencies and private foundations also seek his advice on funding research projects—which means reading and evaluating lengthy proposals.

But in spite of these demands on his time, Ames's research continues to thrive, as his dozen or so major scientific awards testify. These include the Charles S. Mott Prize of the General Motors Cancer Research Foundation and the John and Alice Tyler Ecology Award. The fact that Ames has won the highest awards for both cancer research and environmental achievement reveals his unusual versatility as a scientist.

Recently, Ames again applied his practical mind to his favorite theoretical issue—the role of DNA damage in aging and in such illnesses as heart disease and cancer. He developed a test to measure chemicals in the urine that indicate DNA damage associated with aging and these ills. The test will help determine what factors are related to DNA damage.

"The more we can understand about what's really damaging DNA, the more we can study defenses that might prevent the damage," says Ames. So, for example, the test will help show differences in DNA damage between smokers and nonsmokers and will help determine whether such anticarcinogens as vitamin E and selenium reduce the amount of DNA damage.

Ames is also developing a blood test that uses levels of oxidized fat—fat molecules that have combined with oxygen to form chemicals called *peroxides*—as a measure of abnormal processes in the body that could cause heart disease and DNA damage. He hopes that both these new tests—or similar ones—will ultimately prove useful as diagnostic tools in medicine.

Daniel E. Koshland, Jr., a biochemistry professor and the editor of *Science* magazine, says that Ames is that rare individual who can come up with new theories about a basic scientific problem and then put his ideas to practical use. "A lot of people are very good theorists but can't translate theory into what it means for industry or people or the environment," says Koshland. Ames, he says, is one of the few theorists who can develop practical applications for his ideas.

Although Bruce Ames's reputation as an innovative scientist is firmly established, he has no intention of resting on his accomplishments. He intends to continue his lifelong commitment to unraveling the secrets of DNA, and applying that knowledge to our everyday lives.