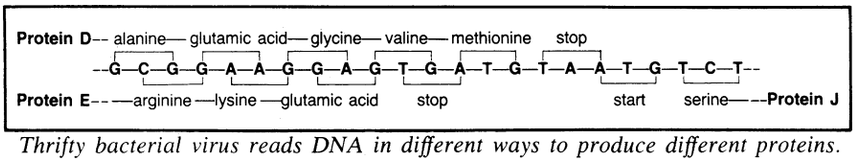
Different ways to read DNA



Thrifty bacterial virus reads DNA in different ways to produce different proteins.

The bacterial virus phiX174 travels lightly. Packed within its tiny polyhedral coat is a chromosome with only nine genes. The virus is so compact that it doesn't even carry the normal double helix of DNA, but only a single DNA strand. Once it infects a bacterial host, phiX174 employs bacterial enzymes to put together the other strand.

This virus must also use other means to lighten its DNA load. For years biologists have been puzzled because phiX174 makes nine different proteins, but it didn't seem to have enough DNA for even those instructions.

Now workers in the laboratory of Fred Sanger at the Medical Research Council in Cambridge, England, have found phiX174's secret. The same stretch of DNA is read in different frames to produce different proteins.

Instructions for making proteins are coded into DNA with three-subunit words. Each word can represent either an amino acid or a stop-or-start signal. Bart Barrell, Gillian Air and Clyde Hutchison III determined the exact sequence of phiX174 DNA in the region of three genes. They compared that sequence to the order of amino acids in the corresponding three proteins.

Usually each subunit in the DNA sequence is read only once. But in the thrifty phiX174 researchers found overlapping instructions for two proteins. One of the proteins, E, somehow participates in the destruction of the bacterial host when hundreds of new viruses are ready to be released. The gene for this protein is coded entirely within another gene, D, whose protein is used in the synthesis of new viruses.

The start of the E gene is in the middle of the D gene, and they end in the same region. But E is not just a shorter piece of D. The two proteins have entirely different amino acid sequences. The trick comes from different groupings of subunits into words in the two readings of the DNA (see diagram of end region of the genes).

Other workers in Sanger's laboratory have found a second example of a shift in reading frame in phiX174. Nigel Brown and Mike Smith discovered that gene B, which codes for a protein that serves in the construction of new viruses, overlaps with gene A, which codes for the protein that nicks the chromosome to begin making DNA copies.

In the early days of work on the genetic code, molecular biologists were uncertain whether the words would overlap. Some thought that every subunit would begin a word. Analysis of the amino acids of actual proteins soon revealed that the code was non-overlapping like written language where each letter is part of only one word. The limitation of a more compressed system can be exemplified by trying to write two sentences of overlapping three-letter words (CANDONEATEELK).

Now, however, it is clear that at least in one tiny virus compactness has won over simplicity and somehow during evolution the same subunits, read in a different frame, came to function in different genes. □

New way to screen for cancer

Animal cells that have been affected by a cancer-causing chemical may wait months or even years before developing into malignant tumors. Yet researchers need simple and rapid tests to screen the thousands of chemicals entering the environment. One recent technique used bacteria as the experimental organisms (SN: 5/1/76, p. 277). Now a new analytical method moves the test back into a mammal.

Dennis Solt and Emmanuel Farber of the University of Toronto report in the Oct. 21 NATURE a method of identifying precancerous liver cells that have been altered by a carcinogen but are not yet cancerous. The researchers provided conditions under which the liver cells will grow and the precancerous cells will have a strong advantage over normal cells.

Among the changes triggered by a carcinogen in liver cells is a resistance to certain poisons and to further exposure to carcinogens. Therefore if a rat liver is exposed to the test chemical, then to a low level of a known carcinogen and cell growth is stimulated, any cells affected by the first chemical will be at an advantage.

Solt and Farber found that when both chemicals were carcinogens, after a few days the number of spots of rapidly dividing cells was proportional to the dose of the first carcinogen. If left for several months, those areas did develop into malignant tumors.

Besides its potential as a screening tool, the new approach will be useful for studying the very early stages of cancer. Farber suggests that the advantage of the altered cells may be an important factor in the usual development of cancer.

This experimental method should be useful to distinguish chemicals that actually inititate cancer from those that facilitate changes made by other chemicals.

"We have to do more experiments, but the method should be able to test hundreds of chemicals in a matter of months," Farber says. "I'm sure it can ultimately be applied also to early detection of cancer." □

How dietary factors combat cancer

Diet can have a dramatic influence on the prevention and treatment of cancer. Spontaneous regression of cancers, for instance, appears to have resulted from a change in the balance of trace elements in the body (SN: 3/16/74, p. 177). Roughage in the diet has been linked with an absence of cancer of the colon (SN: 12/14/74, p. 379). Vitamin A appears capable of preventing lung cancer (SN: 3/13/76, p. 76). And now moderate caloric restriction can prevent breast cancer, at least in laboratory animals, and vitamin C can extend the lives of terminal cancer patients.

The caloric restriction research, by Gabriel Fernandes and Edmond J. Yunis of the University of Minnesota Medical School and by Robert A. Good of the Sloan-Kettering Cancer Institute, is reported in the Oct. 7 NATURE. The vitamin C research, by Ewan Cameron of the Vale of Leven District General Hospital in Loch Lomondside, Scotland and by Linus Pauling of the Linus Pauling Institute of Science and Medicine in Menlo Park, Calif., is reported in the October PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

Past research has shown that caloric restriction prolongs life and the vitality of the immune system in mice and that moderate protein deprivation soups up T cells, those immune fighters that are especially adept at killing cancer cells. So Fernandes and his co-workers attempted to see whether caloric restriction could influence spontaneous tumor development and immunological function.

They fed 17 young female mice a standard rodent diet of 16 calories a day, and 18 young female mice the same diet, but of only 10 calories a day. (Sixteen calories versus 10 calories for the caged mouse would be roughly comparable to a 2,200 calorie diet versus a 1,200 calorie diet for a sedentary human.) The 10-calorie diet completely prevented the development of spontaneous breast cancer, and more than 50 percent of the mice on this diet lived more than 400 days. In contrast, 71 percent of the control mice developed breast cancer by 500 days.

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What's more, the mice on the restricted caloric diet exhibited more vigorous T cells than did the animals on the unrestricted caloric diet, suggesting that the restricted diet prevented cancer by enhancing the functions of T cells.

The researchers will now try to see whether caloric restriction must be maintained throughout life in order to prevent cancer or whether such restriction can achieve the same goal if imposed only after maturity. They also want to better understand the intricate interactions among caloric restriction, the immune system and cancer prevention.

Still another dietary component appears capable of enhancing the immune system—vitamin C. There is evidence—although some of it has been recently refuted—that vitamin C can help the body fight off cold viruses. So Cameron and Pauling wanted to see whether vitamin C might also be capable of rallying the body's immune defenses against cancer.

They gave 10 grams of vitamin C daily to 100 terminal cancer patients, that is, those whom conventional therapies were no longer helping. The patients had stomach, colon, lung, breast, and other kinds of cancers. One-thousand other terminal cancer patients served as controls—were matched with the vitamin C-treated patients for sex, age and type of tumor but did not receive vitamin C. In other words, there were 10 control patients for every vitamin C-treated patient.

The mean survival time was 4.2 times as great for the vitamin C-treated subjects (more than 210 days) as for the controls (50 days), with 18 of the treated patients still alive today and 16 of them clinically well. Analysis of the survival-time curves indicated that deaths occurred for about 90 percent of the vitamin C-treated patients at one-third the rate for the controls and that the other 10 percent had a much greater survival time, averaging more than 20 times that for the controls.

These results, Cameron and Pauling conclude, "cleary indicate that this simple and safe form of medication [vitamin C] is of definite value in the treatment of patients with advanced cancer." They also predict that if vitamin C were given to patients with cancer at an earlier stage of development, it might extend their lives much longer, say from 5 up to 10 or even 20 years. □

More primates listed in danger

Twenty-six types of primates have been listed by the United States as endangered or threatened species in response to the results of a survey by the Fish and Wildlife Service. The United States now lists 54 of the 150 living primate species as endangered.

The Fish and Wildlife Service also proposed to include the squirrel monkey as a threatened species. That decision was postponed after a hearing April 19 where personnel of various organizations with interests in biomedical research presented data indicating that the squirrel monkey may not be threatened. Among those respondents were members of the National Research Council, American Psychological Association and several medical schools and universities.

The rulemaking, published in the Oct. 19 FEDERAL REGISTER, prohibits importation of those Asian, African and Latin American primates for commercial use. Importing primates for the pet trade was banned last year by HEW, so the new ruling will affect primarily circuses and zoos.

Exceptions will be granted by the Federal Wildlife Permit Office for animals used in scientific research and by zoos for propagation. Zoos may also obtain permits to import threatened, but not endangered, species for exhibition purposes.

The prohibitions do not apply to animals now in captivity in the United States, their progeny or the progeny of other animals legally imported after Nov. 18, the effective date of the ruling.

The survey reported that disruption of habitat is the principal reason for the decline of many of the species. Loss of forest to logging and farming was cited as a major factor on all three continents. Military activity, hunting primates for food and collecting them for biomedical research, zoological display and pet trade also have contributed to the threat of extinction, the survey states.

Because habitat loss and hunting play the most important role in the decline, representatives of the American Association of Zoological Parks and Aquariums stated at the hearing that listing these species might actually interfere with propagation efforts, while not alleviating the real problem.

In the last six years there has been a sharp downward trend in the number of primates imported to this country, due to the prohibition for health reasons of primate pet imports. In 1970 90,000 were brought in. Last year only 35,000 primates were imported, according to records kept by the Center for Disease Control. More than 75 percent of those animals were used for scientific research.

Only two of the primate species on the new endangered or threatened lists are now used in scientific studies. The United States imported about 300 stump-tailed macaques and 200 chimpanzees for research last year.

Neither Charles McPherson of the Center for Disease Control or Robert Goy, director of the University of Wisconsin Primate Center, feels that the listing will have much immediate impact on biomedical research, because so few of those animals are used and because it will be possible to obtain permits.

Goy, however, sees a problem with the long-term impact of the policy. "Any animal on the list could become the key species in developing a cure to serious human medical problems, such as finding an anti-hepatitis vaccine. We don't know what species will solve what problems," he says. "The answer to the conservation problem is not restrictions on importation, but large-scale, scientifically managed breeding programs for all the species. That is the only way they'll ever survive." □

Argus hits a billion

The Argus experiment in laser-induced thermonuclear fusion that recently began operations at the Lawrence Livermore Laboratory in Livermore, Calif., (SN: 7/31/76, p. 74) has made a new and significant score in the game. According to a recent LLL announcement Argus has succeeded in inducing a billion fusions in its deuterium-tritium fuel pellet.

The experiment uses laser light to crush and heat the pellet to the point where fusion takes place. Evidence for the fusions is recording of a billion neutrons of 14 million electron-volts energy, the characteristic by-product of deuterium-tritium fusion. Previous achievements along the way were 10,000 fusions in 1974 and 50 million in 1975. About a billion billion (10^{18}) will be required to demonstrate the scientific feasibility of the method. An important point is that the LASNEX computer scheme, used to simulate and design these laser-fusion experiments, correctly predicted this one, giving increased confidence that LASNEX will point the way to future successes. □

Trapezoidal citadel

The ruins of a previously unknown culture are being investigated by archaeologists in Bolivia. Iskanwaya, a citadel discovered in the mountainous jungle 190 miles north of La Paz, covers about 34 acres and is one of the largest pre-Hispanic citadels in South America. Built on the eastern slope of the Andes at about the 5,000 foot level, it was watered by aqueducts up to two miles long and surrounded by terraces 10 to 45 feet wide used for growing grain and supporting houses.

One of the most fascinating and puzzling aspects of the ancient city is its architecture, which is based on the trapezoid. Doors, floors and buildings are predominantly trapezoid-shaped. "We've come across an extremely original form of architecture and we still don't know how it developed," says Carlos Ponce Sanjines, director of Bolivia's National Institute of Archaeology. □