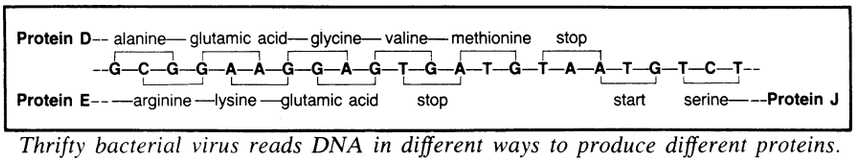
Different ways to read DNA



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.