Cancer View: Roughing Up the Chromosomes

Massive rearrangements of genetic material, rather than local subunit changes, are the underlying cause of most cancer, says John Cairns of the Imperial Cancer Research Fund in London. This view reflects the new era in understanding of genetic information, he told the International Symposium on Aging and Cancer held recently in Washington. Previous work focused primarily on tiny changes in the genetic information, the equivalent of typographic errors in an encyclopedia, which gradually set the finely tuned cell mechanisms awry. Now Cairns suggests that the cell's own proofreading system can identify and correct such small mistakes. But it is the "chopping and switching" of larger pieces of the chromosomes, whole pages of the encyclopedia deleted or inserted in the wrong volume, that initiates malignancies. "Agents that drive such changes are causing cancers," Cairns says.

Movement of large segments of DNA is now in vogue in several areas of biology. Recent techniques for analyzing extensive areas of genetic material have revealed that genes rearrange during development (SN: 12/11/76, p. 372) and during evolution (SN: 7/7/79, p. 13).

Cairns was persuaded that massive rearrangements and not small changes are the basis of cancers by the study of persons with a genetic disorder called Xeroderma pigmentosa. The cells of those persons are defective in the ability to repair small changes in DNA, such as those caused by ultraviolet radiation from the sun. Such persons are unusually susceptible to skin cancer. But when Cairns examined the records of 114 patients with the genetic defect he found no excess of other types of cancer. If small changes in DNA are responsible for cancer, those patients should have far more such local lesions than the average person. Since they do not develop more than the average number of internal cancers, Cairns concludes that the instigation of cancer is not, on the whole, due to local changes in the DNA.

In contrast to the Xeroderma pigmentosa patients, Cairns considered, as a "pseudocontrol," people with another inherited disease. Patients with Bloom's syndrome develop cancer 100 times more frequently than does the general population. The syndrome is characterized by unrepaired chromosome breakage, and a high incidence of chromosome rearrangements and deletions. "The main causes of human cancer must be the things Bloom's syndrome patients make a mess of," Cairns reasons. Another clinical association of high cancer incidence and chromosome rearrangements turns up in Werner's syndrome, a rare disease of accelerated aging, discussed by George M. Martin of the University of Washington (see p. 216).

Another speaker at the meeting raised the possibility of chromosome changes underlying particular cancers. Janet D. Rowley of the University of Chicago reports that certain chromosome changes are seen repeatedly in leukemic cells of patients with various types of acute leukemia. Particular chromosome rearrangements are associated with specific subtypes of leukemia, she says. In addition, both the incidence of acute leukemia and the frequency of certain chromosome changes increase with age.

A genetic element, such as one found in yeast, could be responsible for the large genetic changes required to commit a cell to the cancerous state, says Gerald R. Fink of Cornell University. In yeast, pieces of DNA called transposons insert into a chromosome in many places. Fink reports that a transposon can subvert normal control by causing a high frequency of gene mutation and by rearranging genes to cause dramatic changes in chromosome structure.

When the arrangement of genes on a chromosome is changed, the cell's characteristics are likely to be altered. James A. Shapiro of the University of Chicago reviewed several examples of rearrangements that provide control of gene expression. In the world of microorganisms, inversion of specific sequences determines which of two types of flagella appear on a Salmonella bacterium (SN: 3/12/77, p. 164) and which group of bacteria a virus known as Mu can infect. The mating type of yeast is determined by insertion at a specific location of an extra copy of one of two stretches of DNA (SN: 3/12/77, p. 164). Similarly, the protozoan parasite trypanosome adds an extra copy of a gene to alter its surface molecules to avoid its host's immune system. Shapiro suggests that moving genes to different positions on a chromosome can change their expression. More obviously adding or subtracting copies of a gene, thereby changing the gene dose, can alter a cell's characteristics.

Massive changes of genetic material also occur in development in higher animals. Robert T. Schimke of Stanford University reports that cells achieve drug resistance by attaching to their chromosomes multiple copies of an appropriate gene (see p. 216). Susumu Tonegawa described his most recent work in plotting rearrangements of the DNA sequence during normal differentiation of the cells responsible for producing antibodies. Earlier work showed that genetic material coding for one region of the light chain of an antibody molecule comes together with the genetic material for the other region during maturation from embryonic to adult cells (SN: 12/11/76, p. 372). Now Tonegawa has shown the same phenomenon for the antibody heavy chain and has mapped out more details of the rearrangement.

In the search for the agents responsible for human cancer, Cairns predicts scientists will need to change their strategy. Instead of looking primarily for substances that make small changes in DNA, such as those detected with the Ames bacterial test, they need to detect chemicals and viruses that promote extensive chromosomal changes. □

Politics: Making something of space

"We are taking the space constituency as a real part of the political constituency," says Michael Fulda, a professor of political science at Fairmont State College in West Virginia. And apparently as a significant part. Working with the campaign of independent presidential candidate John Anderson, Fulda wrote the policy statement (and helped with the resultant platform plank) in which Anderson calls for an expanded space program, at a time when such proposals are less than universally supported.

Except as it is sometimes related to national defense, space development is not one of the more visible issues in the campaign. Fulda, however, is now the Anderson campaign's "Coordinator for the Space Constituency," and by the end of this week

NASA

The space shuttle, being transported between its launch pad and assembly facility.