# Cancer Genes, Growth Factors and the Multi-Step Process

The genes implicated in cancer development are genes from normal cells that have somehow gone astray. About 20 such genes have been identified, but scientists have not known the role these genes play in the operations of a normal cell (SN: 11/13/82, p. 316). Now convergent work from several laboratories indicates the normal function of at least one cancer gene. It codes for a growth factor that participates in the body's response to tissue injury, scientists report.

"This is the first time we know the cellular role for an oncogene [cancer-causing gene]," biochemist Leroy Hood told SCIENCE NEWS. "It makes you wonder all sorts of things, such as, 'are many of the oncogenes growth factors?'"

Hood described the linking of a growth factor and an oncogene at the meeting in San Francisco of the American Society of Biological Chemists. Other scientists presented new ways of identifying genes involved in cancer development and a laboratory procedure for demonstrating a multiplicity of steps required to convert a normal cell to a malignant one.

The current findings relating a growth factor and an oncogene stem from a similarity in amino acid chains determined by unrelated research in different laboratories. Hood, Michael Hunkapillar and colleagues at California Institute of Technology and Harry Antoniades at Harvard University were studying the major growth factor, called platelet derived growth factor, in human blood serum. They found the factor to be composed of two distinct chains coded by related genes.

In independent work at the National Cancer Institute, Stuart Aaronson and colleagues determined the amino acid sequence of a cancer-causing gene, called *v-sis,* isolated from woolly monkeys. Russel Doolittle of the University of California at San Diego noticed that the *v-sis* sequence is almost identical to that of one of the platelet derived growth factor's polypeptide chains. Thus it seems the virus contains and employs the platelet derived growth factor gene to make cells cancerous. Hood says expression of that gene has also been recently detected in human connective tissue tumors. He speculates that this discovery has therapeutic implications; perhaps antibodies to specific growth factors can halt some types of tumor.

A means to discover more cancer-causing genes has been developed by Harold Varmus of the University of California at San Francisco. He uses RNA viruses not carrying an oncogene. Such viruses induce tumors only occasionally and after a long time lag. They appear to work by inserting control sequences into DNA regions flanking cellular genes. Varmus has worked out a method to identify cellular genes that, when influenced by the viral sequences, transform normal cells into cancerous ones.

Varmus used this method to determine such a gene, which he named *int-1* (for integration site 1), using mouse mammary tumor virus. This gene is found in all vertebrates examined, and even in fruit flies, but had not been previously detected in any cancer virus. This technique is being used now with other viruses, including human T-cell leukemia virus.

Oncogenes in human tumors have also been identified by Varmus and colleagues through observation of extra copies of cellular genes, either as expanded regions of chromosomes or as characteristic, extra pieces of DNA. Varmus says, "We are now beginning to finger genes involved in cancer by looking for gross rearrangements of DNA."

Another development in cancer research, as studied by molecular biologists, is a procedure to demonstrate multiple steps in tumor initiation. "Cancer is a multi-step process" has become a litany of cancer biologists, the phrase repeated religiously in talk after talk. But now Robert A. Weinberg of Massachusetts Institute of Technology reports that he and Hartmut Land have discovered sets of cooperating genes that together, but not independently, will change normal cells into tumor cells.

Much of the work on cancer-causing genes uses a line of cells called NIH/3T3, which have been reproduced in laboratory culture for many years. These cells are considered abnormal in that it is unusually easy to make them cancerous. Weinberg now reports that more normal cells, fibroblasts taken from rat embryos, can be transformed by pairs of oncogenes. For example, the gene called *ras* will not itself change the cells but *ras* and another oncogene called *myc* will transform them. "The two oncogenes in the same cells are helping one another out," Weinberg says.

The scientists are now sorting other oncogenes into functional groups on the basis of whether they collaborate with *myc* or with *ras* in making the rat cells malignant. One gene appears to supply a protein to the nucleus and the other to supply a protein to the cytoplasm. Weinberg concludes, "The multi-step aspects of cancer may be discrete molecular events."

—*J. A. Miller*

## Brain peptides in a chemistry of anxiety

Antianxiety drugs, such as Valium, bind to specific receptor sites in the brain. But the natural compound that occupies those sites has eluded scientists (SN: 2/9/80, p. 94), despite concentrated efforts and intriguing drug possibilities. Now pharmacologists at Saint Elizabeths Hospital in Washington, D.C., report purification of such a substance from rat brains. It is a 104-amino acid chain that not only blocks the binding action of such antianxiety drugs as benzodiazepine but appears to *induce* anxiety in rats — suggesting the long-sought substance is not a natural tranquilizer, but just the opposite.

The newly identified compound, called diazepam binding inhibitor (DBI) peptide, was described by Alessandro Guidotti, M. G. Corda and Erminio Costa at the meeting in San Francisco of the American Society of Biological Chemists. They have determined the amino acid sequence of half the chain and report it is extremely basic (non-acidic) and does not resemble any of the other known brain peptides. "This is a new type of peptide in the brain," Guidotti says. The scientists have cut DBI into three fragments and find one is active by itself.

Behavioral effects of the DBI were examined in a test of the amount of water thirsty rats consume when they receive a mild electric shock through the drinking tube. Benzodiazepine increases the amount of water the animals drink, as if they are less sensitive to the shock. But if DBI is injected into the brain, the drinking decreases. Guidotti and colleagues suggest naturally occurring DBI acts to trigger behavior associated with anxiety. —*J. A. Miller*

## $Z^0$ found at CERN

It's official. Physicists at the European international laboratory CERN in Geneva claim to have found the particle called $Z^0$. The $Z^0$, along with the two W particles whose discovery was announced by CERN in January (SN: 2/5/83, p. 84), form a triad of so-called intermediate bosons. These particles embody the forces of the weak interaction, a class of force that governs many radioactive decays of particles and atomic nuclei. Their existence and properties are an important confirmation of the Glashow-Weinberg-Salam theory, which unites a significant part of physics in a single unified description. Carlo Rubbia of CERN and Harvard University, leader of the group of physicists called UA1, had hinted about the discovery in several places. At a recent symposium held at CERN. the claim was made officially. □