Chemical difference in cancer cell genes

Scientists looking for the molecular basis of cancer have turned up another possibility. Genes in tumor cells are decorated with fewer chemical clusters called methyl groups than are the same genes in normal cells of a patient. Previous reports from various laboratories have suggested that active genes have fewer methyl groups than genes that are silent in a given cell (SN: 12/18/82, p. 388). Therefore, it has been suggested, this chemical difference may underlie the abnormal activity of cancer cells.

Andrew P. Feinberg and Bert Vogelstein of Johns Hopkins School of Medicine have looked at cancer cells and normal cells from five patients — four with colon cancer and one with lung cancer that had spread to the liver. These patients had not received radiation treatment or chemotherapy. The investigators examined three genes — one for growth hormone and two for components of the blood protein hemoglobin. These genes, each located on a different chromosome, are silent in normal colon, lung and liver cells.

To determine how many methyl groups are present, the scientists used an enzyme that cleaves DNA molecules at specific sites. The enzyme does not make its cut when a methyl group is present. In cells of four of the five patients, the enzyme made more cuts in genes of the cancer cells than in those of the normal cells. This result indicates the presence of fewer methyl groups.

"Further studies are required, using other tumours and different probes, to determine the prevalence of this form of genomic alteration in neoplasia [cancer]," the scientists say in the Jan. 6 NATURE. "However, this study clearly shows that such DNA alterations exist in at least some human cancers."

The pattern of methyl groups reflected some special properties of cancer cells. Cells in the same tumor can have a variety of properties (SN: 2/27/82, p. 135). Feinberg and Vogelstein found heterogeneity in the methyl group pattern among the cancer cells of a patient but not among normal cells. Therefore, different genes may be turned on in different cells within a tumor.

The scientists also report that in the patient whose cancer had spread, there were fewer methyl groups in the genes of the liver cancer cells than in those at the primary site of disease. They suggest this finding may explain why cancer can become worse as it spreads.

Neither the cause nor the consequence of this gene alteration is yet clear. Vogelstein suggests the low number of methyl groups might be due to a specific enzyme that removes methyl groups. It also might be the result of a deficiency in the process that attaches methyl groups to DNA during repair or replication.

One property of some cancer cells is that they produce normally inappropriate hormones when they become cancerous. Loss of methyl groups may help to switch on hormone-producing genes. Vogelstein says, however, in their recent experiments there is no evidence that the cancer cells are expressing growth hormone or globin genes. He is looking into that possibility now. "If these genes were expressed, it would indicate these cancer cells are really profoundly defective in gene regulation," he says.

The critical question remains whether loss of methyl groups is a direct cause of cancer or whether it is only a side effect. "There are lots of changes in DNA. We don't know which is most important," Vogelstein says. Recent work in many other laboratories has demonstrated mutations and rearrangements of DNA associated with cancer (SN: 11/13/82, p. 316; 11/20/82, p. 326). Because cancer development is a process that involves many steps, any or all of these genetic changes may turn out to be important.

—J. A. Miller

Man-made growth factors works in volunteers

Release of growth hormone in normal subjects has been stimulated by injection of a chemically synthesized factor, an international team of scientists reports. This factor may eventually provide a treatment for children with growth disorders and for elderly people and other patients with tissue-wasting conditions.

Two months ago two groups of scientists at the Salk Institute in La Jolla, Calif., reported independently that they had isolated and then synthesized a molecule that acts to release growth hormone from the pituitary gland. Roger Guillemin led one group (SN: 11/6/82, p. 292) and Wylie Vale led the other. The sources of natural material for the groups were different human pancreatic tumors that secrete abnormally large amounts of the factor. It is a peptide, a chain of 40 amino acids, called GRF, which stands for growth hormone releasing factor.

Michael O. Thorner of the University of Virginia, who provided the tumor material to Vale's group, began clinical studies last month with the factor synthesized by those scientists. Six normal male adults were injected with the peptide.

"Within five minutes after the male volunteers received the synthetic peptide, their own growth hormone was released," Thorner says. Their growth hormone levels detected in the blood reached a peak after 30 to 60 minutes, and no side effects were observed. The factor did not affect other hormones of the pituitary, pancreas or gut, the scientists say. The work is reported by Thorner, Vale, Steven Bloom of the Royal Postgraduate Medical School in London and 10 colleagues in the Jan. 7 LANCET.

The next step in the clinical research will be to give GRF to adults, and then finally to children, lacking normal growth hormone production.

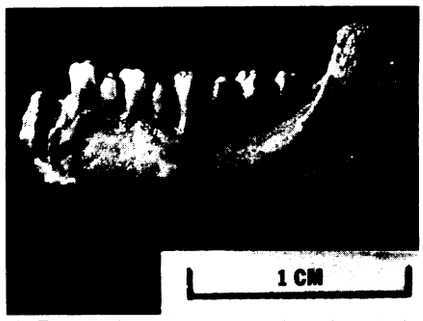
The factor eventually may be used instead of injections of growth hormone to treat children with growth deficiencies. Because the releasing factor is less than half the size of growth hormone, it can be synthesized chemically, so there should be no problem with supply, Thorner says. He suggests also that it may be medically preferable to induce the pituitary to release its own growth hormone. This approach may prevent problems of overtreatment.

Growth hormone releasing factor also may be able to stimulate release of growth hormone to reverse thinning bones in aging and to treat tissue-wasting conditions that occur in old age and also after burns, trauma or major surgery. Thorner suggests in addition that GRF may be useful to regulate growth and size of livestock.

Although it fulfills all the biological criteria, the scientists do not yet know whether the synthetic GRF modeled after pancreatic tumor material is identical to the natural substance released by the brain. Thorner says, "We are being cautious, but there is a lot of evidence of great similarity."

—J. A. Miller

Fossil marsupial unearthed



Cynthia Lindquist/Natl. Geographic Soc.

A French-American team has found the fossilized remains — including this left lower jaw bone — of the oldest land mammals yet discovered in South America. The bones are those of marsupials, mammals whose young develop in pouches, and all are believed to be from 70 million to 75 million years old. This suggests that the placental mammals, whose young develop in wombs, did not arrive in South America until the late Cretaceous period, according to Larry G. Marshall of the Department of Geosciences at the University of Arizona. The team has planned further expeditions to the site of the discovery in southwestern Bolivia.