Exposing lung cancer as a genetic disease

While lung cancer is not considered an overtly inherited disease, recent studies suggest that genetics may determine whether an individual develops the disease, scientists said last week. Going beyond studies of carcinogen exposure, researchers are trying to redefine the causes of lung cancer on the basis of a complex assortment of genes that either promote or prevent the disease.

Much of the recent lung cancer work stems from an upsurge of interest in tumor suppressor genes. Along with evidence that genetics plays a causative role in many cancers came the idea that the body has so-called tumor suppressor genes responsible for keeping cancer-related genes under control. When suppressor genes are lost through mutation, however, the cancer genes (oncogenes) are free to do their grim deed, say scientists who have been sifting through various cancers seeking tumor suppressor genes. The search, at least in the case of lung cancer, also embraces the relatively new study of self-promoting growth factors made by cells themselves, as well as the concept of multiple deletions.

According to John D. Minna of the Bethesda, Md.-based National Cancer Institute (NCI), new data suggest that an absence of tumor suppressor genes may lead to lung cancer. (Scientists already suspect the oncogenes *myc* and *ras* have a role in the disease.) While Minna says cigarette smoking can cause a loss of tumor suppressor genes and other genetic changes that lead to lung cancer, he feels heredity is partly responsible for a predisposition to the disease. He reported NCI's latest results last week in New Orleans at the American Association for Cancer Research's meeting.

Minna and his co-workers are looking for suppressor genes in a region on chromosome 3 that is "nearly always" missing in cells taken from small-cell lung cancer patients, and is sometimes deleted from other types of lung cancers. Among the 33 cases of small-cell lung cancer studied thus far, NCI scientists have found the abnormality in 31 samples. They also have found deletions on several other chromosomes.

Because each normal cell has two copies of chromosome 3, for example, Minna says there must be a double loss of suppressor genes at some time before lung cancer growth begins. It is likely the losses take place at two different times during years of cigarette smoking or exposure to radon or other chemicals, Minna says, and perhaps one deletion may be inherited from a parent, making a person more susceptible to smoking-caused lung cancer. For example, after statistics are corrected for smoking habits, close relatives of lung cancer patients still have a three-fold risk of developing the disease, he notes.

Genetic damage accelerates, Minna suggests, because normal lung cells apparently produce their own growth factors. This prompts duplication of cells with the initial deletion, thus providing even more targets for the critical second deletion. Included among these growth factors, which are also produced by cancer cells, are insulin-like growth factors and gastrin-releasing peptide.

Looking at the evidence gathered thus far, Minna says "lung [cells] may actually be the repository of virtually all of the chromosome deletions [caused by factors like environmental exposures]." He says this "accumulation" phenomenon, with its multiple genetic damage, may be responsible for recent observations made during an ongoing NCI study — in which half of the patients cured of small-cell lung cancer later developed other types of cancer. *— D.D. Edwards*

Hitting enzymes to kill cancer cells

Going beyond treating the whole tumor, scientists are looking for fine-tuned drugs that attack the inner workings of cancer cells. Among the latest of these efforts is the inhibition of DNA topoisomerases — enzymes needed to alter DNA's structure before synthesis of RNA and new DNA can occur. Scientists at the University of Florida in Gainesville are using a computer modeling system to make unique anti-enzyme drugs. And in doing so, they have resurrected a once-abandoned cancer treatment.

Speaking last week at the American Association for Cancer Research's annual meeting in New Orleans, Warren E. Ross said his group compared the structures of drugs already known to inhibit the enzyme topoisomerase II. Discovered within the last decade, the enzyme helps untangle DNA and may direct DNA arrangement in chromosomes (SN: 2/23/85, p.120). From these studies, Ross says, it became apparent the drugs bind first to DNA and then entrap the enzyme. The Florida researchers found that the higher the enzyme concentration, the more potent the drug, and that adding specific chemical groups onto a drug molecule enhances its inhibitory activity.

The researchers also found that a previously tested drug called camptothecin works by inhibiting topoisomerase I — knowledge that has led to an improved version of the drug. Thus far, Ross says, the new camptothecin has worked well against leukemia and several solid tumors in mice, with "predictable and manageable" toxicities, and without the drug resistance so often developed by cancer cells. *— D. D. Edwards*

Flashbulb memories: The picture fades

Pearl Harbor. President Kennedy's assassination. The space shuttle explosion. According to a recent psychological theory, major events such as these activate a special memory mechanism that creates a detailed, permanent "flashbulb memory" of a person's experience just before, during and after learning of the startling event.

But flashbulb memories are neither always accurate nor immune to forgetting, report psychologist Michael McCloskey and his colleagues at Johns Hopkins University in Baltimore. Indeed, McCloskey suggests, these recollections "fall squarely within the domain of normal memory."

The researchers distributed questionnaires to faculty, support staff and students at the Hopkins psychology department three days after the January 28, 1986 space shuttle explosion. They asked the subjects where and what they were doing when they learned of the tragedy, how they learned about it and what their thoughts were upon hearing the news.

The questionnaire was completed by 45 people within one week of the disaster, and 27 of those subjects returned another questionnaire nine months later.

An average of more than 90 percent of all the subjects provided reports of where they were, what they were doing, how they heard and how they reacted upon learning of the explosion, the researchers report in the June JOURNAL OF EXPERIMENTAL PSYCHOLOGY: GENERAL. Although there is considerable consistency in the responses of the same subjects at one week and nine months, there is also a statistically significant increase in "don't remember" responses at follow-up, as well as a marked shift from specific to general answers. At nine months, seven of the repeated-testing subjects gave a total of nine responses inconsistent with their corresponding one-week responses.

"Flashbulb memories are better than those for mundane events, but they're not perfect," says McCloskey. "They should probably be compared with other important events in our lives."

In the only comparable study, psychologist David Pillemer of Wellesley (Mass.) College questioned subjects one month and seven months after the assassination attempt on President Reagan. He found a high rate of flashbulb memories, but more specific and consistent responses came from subjects who reported the most surprise upon learning of the event.

"This is not an all-or-nothing phenomenon," says Pillemer. "It's still an open question whether these memories are more accurate, vivid or persistent than other memories." *— B. Bower*