Cancer in the Family

Special tools and techniques are being developed to detect and defeat cancers that may be inherited

BY JOAN AREHART-TREICHEL

Do people sometimes inherit genetic quirks that predispose them to cancer? Physicians have accepted this notion for years because certain types of cancers seem to cluster in families and even to segregate according to Mendelian genetic laws (occur in families according to statistical patterns that suggest they have been passed from one generation to the next). Only now, though, do scientists have tools sophisticated enough to *physically* demonstrate that some human cancers are due to inherited genetic mixups.

One line of evidence was reported recently by genetic epidemiologist Mary-Claire King of the University of California School of Public Health at Berkeley. "We have what appears to be the first real evidence for an inherited gene increasing susceptibility to breast cancer in some families," she announced in New York at the 1980 International Symposium on Cancer. This finding, King explains, was made possible by advances that other investigators made during the past decade in the identification of 26 gene products in the blood that are clinically harmless but that appear in different forms in different persons. These 26 gene products provided King and her colleagues with potential markers — searchlights if you will — for suspected inherited cancer genes.

King and her team, which includes Henry T. Lynch of Creighton University in Omaha, Robert C. Elston of Louisiana State University in New Orleans and Nicholas L. Petrakis of the University of California at San Francisco, studied 21 large families (100 to 300 members) that suffer a high incidence of breast cancer. Blood samples showed that in 14 of the families most breast cancer victims, but not their healthy relatives, contained the same form of one of the 26 known gene products, the enzyme glutamate-pyruvate transaminase (GPT). Because breast cancer was so consistently associated with the same form of GPT in each family, King and her team concluded that breast cancer in these 14 families was inherited and possibly due to a gene closely associated with that coding for GPT. And because the gene that makes GPT is known to be on chromosome number 10, the researchers concluded that the inherited breast cancer gene in these families must also be on number 10.

Following another line of research, A. J. Cohen of the University of Massachusetts Medical Center in Worcester and Frederick P. Li of the Sidney Farber Cancer Institute in Boston and their colleagues found that kidney cancer can be inherited. Their success was made possible by better preparations of chromosomes for visualization under the microscope. When Cohen, Li and their colleagues encountered a family with an extraordinarily large incidence of kidney cancer — 10 victims over three consecutive generations — they performed chromosomal analyses on as many members of the family as possible. And as they reported in the Sept. 13, 1979, NEW ENGLAND JOURNAL OF MEDICINE, all eight cancer victims studied had a translocation between chromosome number three and number eight.

Jorge J. Yunis of the University of Minnesota Medical School in Minneapolis and his colleagues have found that two childhood cancers can be inherited. Their finding was made possible by advances in chromosomal visualization under the light microscope. They found that if they examined chromosomes during the phase of chromosome division called prophase, they could see far more bands (sections) on the chromosomes than if they examined them at other times. When they looked at chromosomes during prophase from families that had a large clustering of Wilms' tumor (a childhood kidney tumor) they found a chromosomal error peculiar to victims of the tumor that was not found in other family members — deletion of a particular band on chromosome number 11. "So loss of a particular gene on this band may be responsible for the development of Wilms' tumor," Yunis concluded at the 1980 international cancer symposium. Using the same tools, he and his coworkers also found that inheritance of a tiny deletion in the long arm of chromosome number 13 could cause retinoblastoma, a childhood eye tumor suspected of being inherited on the basis of family clustering and Mendelian genetic analysis.

Still more inherited cancers will probably be documented during the next few years due to the techniques now available, King, Cohen, and Li concur. But biochemical and chromosomal documentation for inherited human cancers is still not as strong evidence for such cancers as identification, isolation and transcription of an inherited cancer gene product would be, so some scientists are working in this direction. For instance, efforts are underway in a number of laboratories to isolate the gene or genes missing in patients with retinoblastoma, Louise G. Strong of the M.D. Anderson Hospital and Tumor Institute in Houston reported at the American Cancer Society's 1980 National Conference on Cancer Prevention and Detection in Chicago. At present, she explains, the chromosomal deletion identified in patients with this cancer is "so large that there must be hundreds or thousands of genes involved, and identifying the specific gene or gene product related to tumor predisposition seems a distant hope. However, as more small deletions are detected, and the critical regions more precisely identified, I think the technology exists to isolate the chromosomal segments, and, using a bacterial system, to translate those genes into identifiable gene products."

If such cancer genes or gene products are eventually isolated and produced, they might provide an effective treatment for patients whose retinoblastoma is due to the deletion of such genes, Alfred G. Knudson of the Institute for Cancer Research in Philadelphia speculates. And once enzyme markers have been consistently identified with certain types of inherited cancers, King predicts, they might be used for screening large families for inherited cancers. Individuals found to be at high risk for an inherited cancer could be counseled about avoiding environmental carcinogens or other factors that might be involved in activating the cancer to which they are genetically predisposed. The patients could be closely followed so that any developing cancers would be diagnosed and treated early. They could also be counseled about their chances of passing cancer genes on to their offspring. In fact, where inherited cancer susceptibility approaches 100 percent, Knudson contends, individuals might be counseled to have a susceptible organ removed before cancer actually appears in that organ.

These practical spinoffs, of course, are a few years in the future. Meanwhile, some health benefits are already accruing from demonstrations of inherited cancers. For instance, Li points out that when he and his colleagues identified eight kidney cancer patients on the basis of a chromosomal translocation, three of the eight patients were asymptomatic and did not know they had kidney cancer. The early diagnosis led to early treatment, and the prognosis is good. Also, six more family members were found to have the translocation but have not yet developed kidney cancer, probably because five of the six were under 35 years of age. These six individuals are being carefully monitored for signs of kidney cancer so that if they get it they can be treated early, when their chances of a cure are much better.

What are the larger ramifications of all this research? "Genetic susceptibility to cancer may be a more important factor than we have appreciated in the past," Paul Marks of Memorial Sloan-Kettering Cancer Center says. And as Li emphasizes: "There is some secret locked up in hereditary cancers that condemns someone to the development of cancer. Assuming we understand these genes, they will greatly advance our understanding of cancer in general." □