Most scientists believe that cancer does not always strike at random, that some people are more susceptible than others. A number of researchers are acting on that belief and are trying to predict who is at risk for cancer, and why. The following two stories examine some of the theories and proposed tests for cancer risk and discuss the social and ethical issues that arise when scientists can tell some people that they are particularly likely to get cancer.

Testing for Cancer Risk

A few years ago, Michael Swift of the University of North Carolina made a dramatic observation which he felt required immediate action. He found that relatives of patients with ataxia telangiectasia (AT), a rare inherited disorder characterized by, among other things, a very high risk of cancer, are five times more likely to die of cancer before age 45 than other people.

Swift was so concerned about these findings that he flew around the country visiting relatives of AT patients, telling them of their cancer risk and urging them to be prompt in having diagnostic tests if they have any symptoms of the cancers to which they may be most susceptible. These include leukemia and cancers of the ovary, breast, gallbladder, and lymph nodes.

What Swift did is highly controversial. It is not absolutely certain that he is right in concluding that relatives of AT patients are especially likely to get cancer. And even if he is right, some people may not want to know of their risk for cancer if they can do nothing to prevent it. Not only is there no known way for the relatives of AT patients to avoid cancer but, with the possible exception of breast cancer, it is debatable whether early diagnosis of the cancers to which these people are susceptible is feasible.

Even more worrisome is Swift's inability to tell the relatives of AT patients whether they carry the AT gene, since there are no good tests to determine who carries the gene and who does not. If they do not, their cancer risk is no greater than normal, so some relatives are being needlessly alarmed. No matter how carefully Swift words his message of cancer risk, it is likely that some AT relatives will misunderstand what he says and be convinced that they will soon die of cancer. Park Gerald of Children's Hospital in Boston says that people who go to genetic counselors to learn whether they are at risk of having children with birth defects very often selectively hear the counselor's advice and selectively read follow-up letters. For example, they may think they are at risk when the counselor specifically said and wrote that they are not.

Swift defends his actions by saying he had made a commitment to the families of AT patients to report his research findings. And he insists he did not coerce them to listen—he asked first if they wanted to know of his results. "Most were eager to see me," he says, "and many still call with questions and problems." Swift says what he hopes to do is encourage these people to be prompt in seeing a doctor when they first have symptoms of cancer. He also hopes to encourage their doctors to promptly test them for cancer if they have symptoms.

Before deciding to visit the relatives of AT patients, Swift says, he did a great deal of soul-searching. "I recall weeks and weeks of discussions here on how to handle this situation," he remarks. He concluded that personal visits would be best, in part because he could then back off if he sensed people did not want to hear what he had to say. "I think people are entitled to know of their genetic makeup," he explains.

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The AT case is illustrative of some problems with using genetic information to predict cancer risk. Even though Swift says he wants to tell people of their genetic makeup, the fact is that he can only tell them of their relatives' genetic makeup. Moreover, it is not certain that he is correct, and if he is not he will have unnecessarily led a number of people to live in fear of cancer. Some people react strongly to the suggestion that they may get cancer. For example, young women have had their breasts removed prophylactically because their mothers and sisters had breast cancer and they feared that they would too.

Another issue is possible misuse by industry of genetic screens for cancer. A number of scientists fear that industries may use screens for cancer risk to bar those most susceptible from employment. In this way, they might avoid taking all the measures needed to make the workplace as safe as possible for all workers.

Of course, as much as physicians may debate whether to tell patients of their cancer risk, in most cases the question never arises. Even though there is a growing consensus among cancer researchers that some people are more susceptible than others, that cancer does not always strike purely at random, there are few tests to decide whose risk is greatest. But indications are that this situation will change. Investigators are beginning to devise tests that may predict who is most susceptible to cancer. The controversy over Swift's actions may portend future arguments over what use to make of the results of these tests.

The tests are still new and as yet unproved, and they vary considerably in the techniques involved. Some are based on genetic makeup. Certainly there are "cancer families" and there are also rare genetic diseases, like AT, that predispose people to cancer. So family histories combined with tests for genetic abnormalities may be useful in deciding who is at risk. Other tests are more biochemical and consist of determining the survival of cultured cells exposed to toxic substances or examining the cells for biochemical indications that they are damaged by these substances.

None of the new tests involve great conceptual breakthroughs. Cancer researchers fully expect their search for reliable tests to be slow, tedious, and to often lead to blind alleys. This view is in sharp contrast to the opinion prevailing 10 years ago, according to Charles Shaw of the M. D. Anderson Tumor Institute in Houston. At that time, scientists trying to determine why certain chem-

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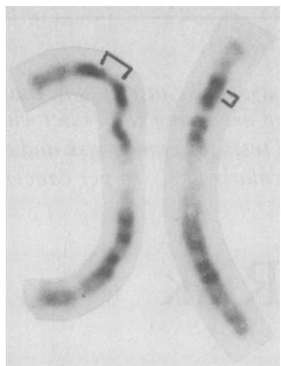
icals cause cancer discovered a clue to why certain people get cancer, or at least why substances like cigarette smoke cause cancer in some people but not in others. They found that animal and human cells contain enzymes that convert a number of chemicals to carcinogens. The enzymes which are usually present in cells but are induced by exposure to the chemicals, are part of the cell's machinery for detoxifying poisons. For example, polycyclic aromatic hydrocarbons, which are among the major carcinogens in cigarette smoke, induce enzymes, called aryl hydrocarbon hydroxylases, and are oxidized by them. Once oxidized, these chemicals can cause cancer.

Seven years ago, Shaw and Harold Gelboin of the National Cancer Institute reported that white blood cells from different people vary enormously in the induction of these enzymes. Cells from lung cancer patients, irrespective of smoking history, tended to make the enzymes readily when exposed to polycyclic aromatic hydrocarbons.

"At that time, we thought a useful test [for cancer susceptibility] was just around the corner," Shaw says. All that seemed necessary was to collect a person's blood cells, expose them to polycyclic aromatic hydrocarbons, and measure the activity of the induced enzymes. Now, Shaw explains, he and others realize that "the work is not as clean as we would like it to be. The results are difficult to interpret and there is a question of whether it will be feasible to use the test to predict cancer susceptibility."

Another complication is that cells make enzymes to convert carcinogens to noncarcinogens as well as the reverse. Alan Poland of the University of Wisconsin points out that the two kinds of enzymes seem to be in some sort of balance. So it may be that people with highly active enzymes for producing carcinogens are not at an increased risk for cancer because they also have enzymes that are effective destroyers of carcinogens.

Since the study of these enzymes has not yet yielded a test for cancer susceptibility, a number of investigators are taking somewhat different tacks. Swift, for example, thinks that a large number of people who are susceptible to cancer may be identifiable through their family histories. "The idea is very simple," he says. "Certain syndromes predispose people to cancer. Perhaps heterozygotes for those syndromes are also predisposed to cancer." The diseases he studies are very rare ones in which homozygotes, who inherit two defective genes, have the disease and also tend to get cancer at an early age, whereas heterozygotes,



One of the few chromosomal abnormalities of cancer. The chromosome on the left is normal. The one on the right has a deletion, marked by a bracket, in the section associated with Wilms tumor. [Source: Jorge Yunis, University of Minnesota Medical School]

who inherit only one gene, seem unaffected. Swift's strategy is to find the medical records of people with these diseases and then see if their relatives' risk of developing cancer is above normal.

So far, Swift has studied three syndromes (*Science*, 5 May 1978, p. 518). His most dramatic results have been with AT. AT patients also are extraordinarily reactive to ionizing radiation—they die from doses normally used to treat cancer patients. Although only one in 40,000 people has AT, Swift estimates that at least 1 percent of the population carries an AT gene as a heterozygote. *If* relatives of AT patients are indeed five times more likely than the rest of the population to die of cancer before age 45, these relatives could account for a significant portion of the early cancer deaths in this country, Swift argues.

Swift also studied the medical records of relatives of patients with xeroderma pigmentosum, a disease in which patients' sensitivity to sunlight causes their skin to blister upon very little exposure. Some patients also have neurological damage, which can range from hearing loss to mental retardation. And patients with xeroderma pigmentosum are extremely likely to get skin cancer.

Relatives of these patients, Swift found, seem more likely than the rest of the population to develop skin cancer. He wrote to these relatives and suggested that they stay out of the sun and avoid unnecessary exposure to ultraviolet radiation, which can precipitate skin cancer. Although this action is not as controversial as the visits to AT relatives (the xeroderma pigmentosum relatives can do something to decrease their cancer risk), it nonetheless gives rise to many of the same questions.

When Swift studied a third syndrome, Fanconi's anemia (a disease characterized by growth retardation, multiple congenital abnormalities, and abnormal skin pigmentation), he found no statistically significant increase in cancer among families of the patients. Patients either are darker than the rest of their families or are marked by "café au lait spots"—brown patches several inches in diameter. Swift suspects that if the heterozygotes for this disorder are at increased risk for any cancer, it may be for a very rare one. If so, he would need to study far more relatives of Fanconi's anemia patients to detect such an excess risk.

Another way to associate inheritance with cancer is to search directly for cancer genes. This is a line of research favored by Alfred Knudson of the Fox Chase Cancer Center in Philadelphia, who thinks researchers should direct their attention to identifying genes that predispose people to develop cancer. "It seems to me that we should have some sort of an objective to shoot for," Knudson says. He believes that there are about 100 human cancers and so there are likely to be only a few hundred "cancer genes," assuming that some cancers are associated with more than one gene.

So far, three kinds of cancers are associated with identifiable genetic abnormalities. The most recently discovered of these is a translocation between chromosomes 3 and 8 that vastly increases peoples' risk of getting a kidney cancer, renal clear cell carcinoma. As Andrew Cohen and his associates at Harvard Medical School showed, carriers of this abnormality have an 87 percent chance of developing this cancer by the time they are 59 years old. In contrast, members of the general population have only a one in 1000 chance of developing such a kidney cancer by that age.

The other cancers associated with chromosomal abnormalities are Wilms tumor, a kidney cancer of children, and retinoblastoma, a tumor of the retina. According to Knudson, it does not seem that these chromosomal abnormalities by themselves are sufficient to cause the cancers. For example, people with a deletion in chromosome 13 tend to get retinoblastoma. But, asks Knudson, if the deletion causes the cancer, why doesn't every cell in the patient's retina become tumorous? He postulates that a second step must occur—a proposal that he calls the two-hit hypothesis. He remarks that "the most intriguing possibility is that the second step affects the same gene in the matched chromosome." In the case of retinoblastoma, a cell would become cancerous when the good copy of chromosome 13 is also damaged and can no longer compensate for the defect in the other chromosome 13.

Knudson is edging toward some sort of biochemical or cytological screen, based on the genetics of cancer patients, that can identify susceptible people. This is also the goal of Malcolm Patterson, Paul J. Smith, and Torben Bech-Hansen of the Chalk River Nuclear Laboratory in Ontario.

Patterson's group began its work by studying AT patients. They found that cultured cells from these patients are killed by low doses of ionizing radiation or by chemicals that produce cellular changes similar to those caused by ionizing radiation. And cells from relatives of AT patients are intermediate in sensitivity—less sensitive than AT cells and more sensitive than cells of nonrelatives. This discovery was also made independently by Chev Kidson of the University of Queensland in Brisbane, Australia. According to Smith, most chemical carcinogens act like either ionizing or ultraviolet radiation, so their test could detect cells sensitive to some chemical carcinogens as well as radiation. He and Patterson hope that they may be able to use their test to decide which members of the general population are unusually sensitive to carcinogens.

One indication that their test may work was obtained by Bech-Hansen and Patterson, who found that cells from patients with acute myeloid leukemia are very sensitive to ionizing radiation. "Although you cannot relate the leukemia to being exposed to radiation, it may be related to chemical carcinogens whose actions are similar to ionizing radiation," Smith explains.

Now Patterson is testing cells from people who are suspected of being at high risk of cancer and is finding that, in many cases, these cells are easily killed by radiation. He gets the cells from Robert Miller of the National Cancer Institute, who is looking for cancer patients and relatives of patients who are unusually susceptible to the harmful effects of certain toxic chemicals or radiation. Combining clinical observations with laboratory test results, Frederick T. Li, who works with Miller, has been able to correctly predict that patients in four different families will get cancer. Each of these families has a different cancer syndrome. "It all fits together eventually," Miller says.

According to Smith, tests of the sensitivity of cells to radiation may be of great practical importance. Optimistically assuming that predictions based on the tests will prove to be well correlated with cancer risk, he says, "This sort of work helps reduce the risk of exposure in nuclear power plants because you can tailor the upper limits of peoples' exposure according to their sensitivities." The problem with the test, however, is that it is too slow. The cells must first be cultured, which can take weeks, and the entire test can take months. Patterson's group is now trying to speed up the test by using blood cells, which need not be cultured. In that way they might be able to do it in a matter of hours.

At the University of Vermont, Richard Albertini reasons that it may be possible to tell who is most susceptible to cancer by seeing whose DNA is most likely to mutate when exposed to toxic substances. He has devised a test in which he looks for an easily detected mutation in a gene on the X chromosome. This is a gene coding for hypoxanthine-guanine phosphoribosyltransferase (HGPRT). Cells with mutant HGPRT genes can grow in media containing certain purine analogs, whereas normal cells cannot. This mutation probably has nothing to do with whether a cell becomes cancerous, but it can serve as an indicator of genetic damage. Since Albertini can use white blood cells to screen for HGPRT mutations, his test is fairly rapid and easy.

The next step is to validate the test—to see whether people whose chromosomes are most prone to damage, as measured by HGPRT mutations, are also most likely to get cancer. Albertini and his associates are now trying to do this by studying breast cancer patients undergoing chemotherapy, a certain fraction of whom later develop leukemia or other cancer. As O. Ross McIntyre of Dartmouth University explains, the chemotherapeutic agents are quite toxic and may be causing these secondary cancers. "As a result of our good intentions of controlling the primary tumor, we may be inducing other tumors or leukemia," he says. He and Albertini are seeing if the patients most likely to have cellular mutations after chemotherapy are those most likely to develop secondary cancers.

Shaw's group is using Albertini's test to monitor workers at a Texas company who are exposed to methylchloroform. "We have told people at the company that we won't know what the test results mean," Shaw says. But he plans to look for an association between mutation rate and cancer in individual workers.

"Of course," says Albertini, "it's possible that all this could be irrelevant." That is, particular tests, like the HGPRT test, could be useless in predicting cancer susceptibility. Or, contrary to the common assumption among cancer specialists, individual susceptibility to cancer could vary little except in rare cases. But even if the current crop of tests do not work, investigators are still hopeful that some future tests will and that particularly susceptible people can be identified.

Investigators foresee that validated tests could be used by industries to screen populations exposed to carcinogens, such as workers at a chemical plant. Those most susceptible to cancer might be denied employment or given jobs only in areas where they would not be exposed to the chemicals. Albertini predicts that some people may resent the tests because they could shut them out of lucrative jobs. Researchers are also concerned that industries could use the results to exclude those most vulnerable to cancer and then fail to protect those they do employ from cancer-causing substances.

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Other abuses of tests of cancer susceptibility are also possible. Dwight Janerich of the New York State Health Department in Albany, for example, foresees the tests being used by insurance companies to raise the rates of those at risk for cancer. He recalls that insurance companies once raised the rates for people who were carriers of sickle cell anemia but who did not have the disease. Yet it is only those who have the disease whose health is affected. He predicts similar abuses of the results of tests of cancer risk.

These potential problems could be resolved, of course, and in the future it may be as routine to screen for cancer risk as it now is to screen for heart attack risk by determining cholesterol levels and screening for high blood pressure. But there is still the question of what to do once you know you are at risk.

—GINA BARI KOLATA