Zeroing in on Individual Cancer Risk

Researchers are identifying a set of specific biochemical markers that they hope will enable them to pick out which people are most likely to get cancer

OVER THE YEARS THE CLASSIC METHODS OF epidemiology have worked well enough in identifying groups of people who have a high risk of developing cancer. The linkage of lung cancer to cigarette smoking is but one of many examples in which those methods have succeeded, even causing some people to change their habits. But when it comes to predicting individual risk, classical epidemiology doesn't help. The problem: Individuals vary dramatically in their responses to carcinogens. For example, only one in ten cigarette smokers actually comes down with lung cancer, which is why classical epidemiology is helpless when asked the question every individual most wants answered: What's *my* risk of cancer?

Now, aided by advances in understanding cancer at the molecular level, researchers may be on the verge of being able to make such predictions. Indeed, for one group—people with certain rare, hereditary cancer susceptibilities—they already can. Last year's discovery of the gene for Li-Fraumeni syndrome, for example, made screening possible for this condition, which predisposes its carriers to several kinds of cancer. And screening may soon be available for people with a hereditary susceptibility to colon cancer. In this week's issue (see pages 661, 665, and 616), a group led by Bert Vogelstein of Johns Hopkins University School of Medicine and Yusuke Nakamura of the Tokyo Cancer Institute announce that they have just identified a previously unknown gene as the probable cause. (Ray White's group from the Howard Hughes Medical Institute at the University of Utah announces similar findings in the 9 August *Cell*.)

But these inherited syndromes are only a small part of the problem. Most cancers are caused not by inheritance of specific susceptibility genes but by exposure to environmental carcinogens, including the personally imposed one of smoking. Attempts to find molecular markers that can, like the cancer susceptibility genes, help detect the individuals at highest risk from environmental exposures are still in the early stages. But as Frederica Perera of Columbia University School of Public Health in New York City, one of the pioneers in developing the new molecular methods, says: "The field is moving very fast. We're not yet at the point of predicting individual risk, but there's cautious optimism that we may eventually be able to do that."

Molecular screening for cancer will cause some thorny ethical quandaries—particularly if no treatments are available (see box on page 614). But at the same time, there's hope that it may be possible to develop ways to prevent cancer in people at risk. As carcinogenesis expert I. Bernard Weinstein of Columbia University's College of Physicians and Surgeons puts it: "What I find exciting is that as we put these markers into play we may have the opportunity to intercede." Interceding might simply mean minimizing a high-risk person's exposures to carcinogenic insults. But the ultimate goal would be "chemoprevention"—using drugs or dietary changes to ward off cancer development, a prospect that some groups are already pursuing (also see opposite page).

The new molecular methods, which are usually categorized under the rubric "molecular epidemiology," aim to identify the actual biochemical effects that carcinogens produce in different people and then relate those effects to the chances of getting cancer. There's a need for such methods because each individual will respond differently, according to his or her own metabolic capabilities.

One place that the molecular epidemiologists are looking for carcinogen effects is in the large number of cancer-causing oncogenes and tumor suppressor genes that cancer researchers have identified in the past several years. Indeed, earlier this year, independent work by the groups of Curt Harris at the National Cancer Institute and Mehmet Ozturk at Harvard's Massachusetts General Hospital pinpointed a specific mutation that may help explain how the potent environmental carcinogen aflatoxin contributes to liver cancer development. The researchers discovered the mutation in the p53 gene—the same tumor suppressor gene found to underlie Li-Fraumeni syndrome —in liver cancers obtained from patients in Qidong, China, and southern Africa, two areas where that cancer is very common.

Blazing a molecular trail. *The pioneers in the new field of molecular epidemiology include Curt Harris* (left)*, Frederica Perera* (center)*, and Steven Tannenbaum* (right).

Why have the researchers fingered aflatoxin as the culprit? Partly because of the unusual specificity of the mutation. Between them, the Harris and Ozturk groups found that 13 of the 26 liver cancers they examined had p53 gene mutations—and 11 of the 13 had the mutation in the same codon, amino acid 249 in the p53 protein. That's very different, Harris says, from what's found in other cancers, in which p53 mutations are usually spread throughout the gene. This specificity indicates that the p53 mutations were caused by a single carcinogen, and aflatoxin is the best candidate. Not only have animal and classical epidemiological studies linked it to liver cancer, but it is a major food contaminant in the regions where the cancer patients live. What's more, lab work has shown that aflatoxin induces precisely the same kind of mutation, the conversion of guanine bases in DNA to thymines, seen in the p53 genes from the liver cancers.

But while studies such as those conducted

Efforts to Prevent Cancer Are on the Increase

As molecular epidemiologists close in on ways of identifying individuals who have a high risk of getting cancer, their work raises another question: What kind of preventive measures can clinicians offer to people identified as being at high risk? Their physicians could, of course, monitor them closely to catch telltale signs of cancer at its earliest stages. But what if researchers could develop agents for "chemoprevention" that would prevent cancers from developing in the first place? Indeed, chemoprevention research, though still in its early days, is a hot pursuit at many labs.

Perhaps the best measure of the excitement that chemoprevention is generating is the number of clinical trials that are planned or already under way. The National Cancer Institute is currently sponsoring more than 40 clinical chemoprevention trials, expected to include a total of about 77,000 people if they all reach their full enrollment. The cancers under study include the major killers—lung, breast, and colon cancer—as well as tumors of the skin, head, and neck. A wide variety of agents, more than 20 in all, are being tested. And that may be just the beginning, because, as Marjorie Perloff of NCI's Chemoprevention Branch says: "The number of trials is certainly going up."

SELECTED AGENTS IN CHEMOPREVENTION TRIALS

Drug	Cancer	Mechanism of Action
Retinoids	skin, lung, breast, cervix	Induces cell maturation and inhibits proliferation
B-carotene	lung, cervix, skin	? Similar to retinoids
Calcium carbonate/ calcium lactate	colon	Binds bile acids; decreases their proliferative effects
DFMO	colon	Anti-proliferative; blocks polyamine synthesis
Ibuprofen	colon	Anti-inflammatory
α-Tocopherol	colon	Anti-oxidant
Tamoxifen	breast	Anti-inflammatory, anti-estrogen

Most of these trials will test known quantities that are expected to have minimal side effects. Either they are familiar substances—vitamins, high-fiber materials such as wheat bran, and other dietary components, for example; or they are drugs that have been widely used for many years, such as over-the-counter painkillers. That's because the agents will generally be used by healthy people and for many years, perhaps a lifetime. "They have to be much safer than drugs used in the treatment area," says David Alberts, who heads a large chemoprevention program at the University of Arizona in Phoenix.

Safety concerns have, for example, slowed at least temporarily a trial planned by NCI officials aimed at testing whether the drug tamoxifen can prevent breast cancer in high-risk women. Tamoxifen is widely used for breast cancer chemotherapy, and its side effects, including blood-clotting problems and a possibly increased risk of uterine and liver cancers, are acceptable under those life-threatening conditions. But before it goes into the chemoprevention trial, the Food and Drug Administration wants further assurance that the healthy women who would receive it have a risk of breast cancer high enough to justify their taking the drug.

The major types of agents for which clinical chemoprevention trials are moving ahead include the following:

■ **The retinoids.** The rationale for testing members of this group, which includes naturally occurring vitamin A as well as synthetic compounds such as 13-*cis* retinoic acid, is based partly on epidemiological studies showing that foods rich in vitamin A and its precursor, β-carotene, may protect against cancer. The retinoids also induce cell maturation and, as a result, inhibit cell proliferation.

And a retinoid has already proved its mettle in one trial. Last year, Waun Ki Hong and Scott Lippman of the University of Texas M.D. Anderson Cancer Center and their colleagues reported that daily treatment with high doses of 13-*cis* retinoic acid prevented patients who had had one head or neck cancer from getting a second primary tumor, although the drug did not reduce the recurrence or spread of the original tumor.

One of the largest of the current chemoprevention trials, the aptly named CARET study, will also put a retinoid to test. This trial, which will be conducted at several medical centers, will include 17,000 men at high risk of lung cancer from smoking or asbestos exposure. Treatment will consist of daily doses of β-carotene and retinol (vitamin A). Retinoids are also being tested for chemoprevention of skin, breast, and cervical cancers. Current retinoids have side effects, including skin problems such as rashes and peeling, that may limit their use, and researchers are developing new ones that they hope will avoid the problems without sacrificing efficacy.

■ **Anti-oxidants.** This class of substances, including vitamin E, may protect against potentially carcinogenic gene mutations induced by free radicals. A very large trial, to include 19,000 subjects, will test whether vitamin E, given with β-carotene, can prevent lung cancer in women who smoke.

■ **Nonsteroidal anti-inflammatory agents.** Aspirin and ibuprofen (the active ingredient in pain killers such as Advil and Nuprin) are two well-known members of this group, which may suppress cancer by inhibiting cell proliferation and also by reducing free radical formation. Clinical trials have shown that in some people anti-inflammatory agents can cause the disappearance of polyps, precancerous growths that progress to colon cancer if not removed.

■ **Calcium.** Calcium carbonate and calcium lactate, which are thought to work by binding to bile acids and thereby helping to suppress the proliferative effects of the acids on the cells of the intestinal lining, are in trials to see if they prevent colon cancer in people who are known to be at high risk because they have previously had colon polyps removed.

■ **Dark horses.** In addition to the familiar agents mentioned above, there are other less well known drugs moving along in the chemoprevention pipeline. Among the more promising: DFMO (difluoromethylornithine), which suppresses cell proliferation by inhibiting the synthesis of growth-stimulatory polyamine compounds, and Oltipraz, a drug used for treating schistosomiasis that also stimulates carcinogen detoxification. Clinicians hope that some of these many contenders will prove to be the chemoprevention agents they want. Noting the continuing lack of success in finding treatments for the major cancers, Alberts says, "The only thing I can think to do is early diagnosis—or prevention." ■ **J.M.**

by the Harris and Ozturk groups can provide valuable information about carcinogen action, the mutation they found can't, for some very practical reasons, be used directly as a means of screening for exposure to the carcinogen. For one thing, the mutation is present only in tumor cell DNA, not in normal liver, so it wouldn't provide an early warning of cancer risk. For another, it's not feasible to use carcinogen target tissue, such as liver or lung, for screening purposes. As Steven Tannenbaum, a molecular epidemiologist at the Massachusetts Institute of Technology points out, "You just can't go up to people and say, 'give me a piece of lung.'"

But according to Gerald Wogan of MIT, John Groopman of Johns Hopkins University School of Medicine, and their colleagues, it is possible to screen for aflatoxin exposures with much more readily obtainable blood and urine samples. Instead of looking for the actual carcinogenic mutation itself, these researchers take a tack used by many other molecular epidemiologists and look for "surrogates"—indicators that can show aflatoxin has been wreaking its mischief in an individual, but don't require sampling of target tissues.

Like most other carcinogens, aflatoxin has to be activated by enzymes in the body to unleash its cancer-causing power. Only the activated form of aflatoxin can attack the DNA, which it does by forming chemically bound "adducts" that can lead to carcinogenic mutations if they are not repaired. The reactive aflatoxin molecules can also form adducts with proteins, such as blood albumin. In their study, Wogan and his colleagues have compared the aflatoxin adduct concentrations in blood and urine samples from people living in Guangxi Province in China and The Gambia, West Africa, with the aflatoxin concentrations in the people's diets. The result? "In both populations the study is working very well," Wogan says. "We see a relation between the adducts and exposures."

> ***"What I find exciting is that as we put these markers into play we may have the opportunity to intercede."***
>
> —I. Bernard Weinstein

Adduct measurement is also proving to be an effective indicator of exposures to other carcinogens that require activation. For example, Perera, Regina Santella, who is also at Columbia University School of Public Health, and their colleagues have shown that adduct formation by the DNA of white blood cells reflects the occupational exposures of iron foundry workers in Finland and coke oven workers in Poland to the powerful carcinogens known as the polycyclic aromatic hydrocarbons (PAHs). What's more, the researchers have also found significant increases in the PAH-DNA adducts in people living in a highly polluted region of Poland, the first time such a link has been found to environmental pollution.

And the Tannenbaum group found that adduct formation between the blood pigment hemoglobin and 4-aminobiphenyl, a chemical in cigarette smoke that has been linked to bladder cancer, is highest in people who smoke black tobacco, next highest in people who smoke blond tobacco, and lowest in nonsmokers. That exactly parallels the carcinogen exposures of the three groups—and their risks of getting cancer. "We feel we've really closed the loop," Tannenbaum

Testing for Cancer Risk: Tough Questions Ahead

With the recent discoveries of a few genes involved in rare inherited cancers, screening healthy individuals for cancer susceptibility has at last become possible. Such genetic tests have been eagerly awaited, as they open up the possibility of early detection, intervention, and perhaps even prevention. While expectations are still high, the pioneers in this field are finding that the tests raise some thorny questions as well.

The problem, in a nutshell, is that cancer often involves changes in several genes, unlike the "classic" genetic diseases. In Huntington's, for instance, inheritance of the faulty gene means an individual will get the disease. But inheriting a cancer susceptibility gene does not necessarily lead to cancer, though the risk is high—sometimes extraordinarily so. Given that uncertainty, do the benefits of knowing about cancer susceptibility outweigh the risks of anxiety, depression, and potential job or insurance discrimination? Should patients undergo preventive treatments, and if so, how radical?

If early experience is any indication, the answers to such questions will vary widely with each new susceptibility gene discovered. At one end of the spectrum is the retinoblastoma gene. Although it was the first inherited cancer gene to be identified (in 1986), the benefits of screening were clear and screening began almost immediately. Explains geneticist Louise Strong of the M.D. Anderson Cancer Center at the University of Texas, Houston: "With the retinoblastoma gene, the outcome is predictable [about 95% of those who carry the gene will develop eye cancer by age 5], and there is something specific you can do. You can examine the infant from the time it is born every 4 to 6 weeks. And if you detect lesions, they can be treated very successfully without doing anything invasive, without losing the eye. And there is almost 100% survival."

But then there's the gene involved in the Li-Fraumeni cancer syndrome, discovered just last November. Extremely rare—so far only 100 families worldwide are known to be affected, though the number could be far higher—the syndrome is nevertheless a good test case because it raises some of the toughest issues of any cancer susceptibility gene that is likely to be discovered over the coming decades.

The syndrome was first identified in 1969 by Fred Li and Joseph Fraumeni of the National Cancer Institute, who described individuals extremely susceptible to not just one type of cancer but to at least six: breast cancer, soft tissue sarcomas, brain tumors, bone cancer, leukemia, and adrenocortical carcinoma. Li-Fraumeni patients tend to develop cancer as children or young adults, and those who survive their first cancer sometimes go on to develop a second, especially if they've been given radiation therapy.

Last November, Stephen Friend of the Massachusetts General Hospital Cancer Center, along with Li, Fraumeni, and Strong, found that at least some of these patients have a germline mutation in a tumor suppressor gene, p53, that has been implicated in several types of cancer. Finding the gene meant a new DNA test was possible to detect those who carry the Li-Fraumeni defect—but should such a test be offered? The difficulty is that once the mutation has been found, the physician doesn't know what, precisely, that finding means, other than that the individual has a

says. "We can say unquestionably that there's a set of compounds in cigarette smoke that causes bladder cancer."

Other researchers are assaying for carcinogen exposures by looking for the increased mutation rates they cause, although again the mutations are usually in surrogate genes. Richard Albertini and his colleagues at the University of Vermont in Burlington developed one widely used assay of this type. It involves determining what percentage of T cells in the blood have undergone mutations that have caused them to lose an enzyme known as HPRT (for hypoxanthine-quanine phosphoribosyltransferase), an enzyme the researchers chose mainly because there is an easy way of determining whether cells have it. In addition, William Bigbee, Ronald Jensen, and their colleagues at Lawrence Livermore National Laboratory in Livermore, California, have developed a similar assay that looks for mutations that have caused red blood cells to lose certain surface proteins, called glycophorins.

The adduct and mutational assays have somewhat different strengths and weaknesses. The adduct assays, for example, aren't much use in detecting exposures that occurred many years in the past, because the adducts will be lost within days to weeks after the exposures cease. The mutations, however, may last a long time—even a lifetime. Both the HPRT and glycophorin assays have detected increased mutations in survivors of the Hiroshima and Nagasaki nuclear bomb blasts more than 40 years after the radiation exposures.

The very shortness of the adducts' lifetimes may give them an advantage in another regard, however. They might be used to monitor the effectiveness of intervention trials aimed at preventing cancer development. Groopman and his colleagues are already planning such a trial in the areas of China and Africa that have high liver cancer incidences. Their motivation to undertake it was, Groopman says, heightened by the Harris and Ozturk groups' results linking aflatoxin to the p53 gene mutation.

The plan is to treat the people with the schistosomiasis drug Oltipraz, which has been shown to block aflatoxin-induced liver cancer in rats. "There's virtually no way we are going to prevent these people from getting aflatoxin in the diet," Groopman says. "The economic resources aren't there." And since Oltipraz apparently blocks aflatoxin's carcinogenic effects by preventing its metabolic activation, it should be possible to get an idea of whether the drug is having an effect in humans by measuring their aflatoxin adduct concentrations. As mentioned previously, only the activated carcinogen can form the adducts.

But while molecular epidemiologists are confident that the biomarkers they are studying provide accurate indicators of exposures to environmental carcinogens, even they have to concede that they there is a key step still to come: proving that the markers will actually predict individual cancer risks. "I'd like to tell you that we know that," Albertini says, "but the relationship to health is dangling and this has to be nailed down."

Still, there is some rationale for the "cautious optimism" Perera described in discussing these markers. "What's been really intriguing," she notes, "is that we all see a large inter-individual variability." Even the control groups, who were not supposed to have any unusual carcinogen exposures, have their "outliers"—people with much higher biomarker concentrations than others. The individual variability suggests that the biomarkers can be used to find the people who are most sensitive to carcinogen action and therefore most likely to get cancer.

The next step is to do the prospective studies needed to find out whether that is

Syndrome discoverers: *Joseph Fraumeni* (left), *Fred Li.*

50% chance of developing cancer by age 30.

"We don't know what to recommend if someone has an asymptomatic young child," says Strong. "That child may develop cancers anywhere. And it is very difficult to screen for soft tissue sarcoma, bone cancer, and brain cancer. There is nothing you can recommend, other than common-sense things like being alert to lumps and bumps that don't go away."

And even if these cancers can be detected early, investigators are uncertain about whether that is always an advantage. "For some diseases, like breast cancer, early detection is a way to cure it," says Li, now at the Dana Farber Cancer Center. "But what is the benefit of early diagnosis of leukemia? That is a question mark. So does early diagnosis benefit these patients or are you just giving them the bad news earlier and prolonging stress and anxiety?"

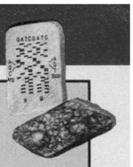
These questions are complex and stubborn enough that Li convened a workshop earlier this summer at the National Institutes of Health (NIH) to examine them. At the workshop, participants agreed that the first task is to untangle the relations among Li-Fraumeni syndrome, the p53 germline mutation, and other cancers. So far, Friend's group and others have found the germline mutation in dozens of Li-Fraumeni families; they are in the process of evaluating more. At this early stage, it is still unclear whether an individual can have the mutation but not the syndrome, or vice versa.

To complicate the picture further, Friend and others suspect that the same germline p53 mutation may be more widely involved in human cancer—in people without a history of Li-Fraumeni syndrome—which raises questions about screening other cancer patients or perhaps the general population. To find out, dozens of researchers are scouring tissue banks, looking for the mutation in a variety of cancers. At Massachusetts General, Friend has been evaluating women with early-onset breast cancer as well as children with multiple primary malignancies.

For now, participants at the NIH workshop agreed, testing for the germline p53 mutation should be offered only to Li-Fraumeni families and other high-risk groups, perhaps including women with early-onset breast cancer or individuals with radiogenic tumors. The group will meet again in November to take a second stab at crafting guidelines for screening, looking at who to test, what sorts of education and counseling are needed, and how best to monitor and care for those who test positive.

One reason that investigators would like to sort out such issues quickly is that discoveries of other susceptibility genes are expected to follow closely on the heels of Li-Fraumeni. With any luck, those new genes will prove to be more like retinoblastoma than Li-Fraumeni—but no one is banking on it.

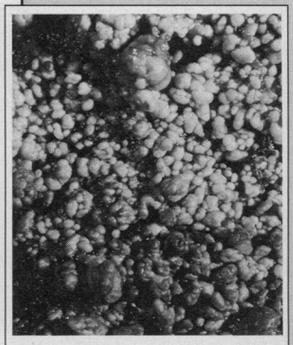
■ LESLIE ROBERTS



Gene Identified for Inherited Cancer Susceptibility

Molecular epidemiologists may still be struggling to find ways to identify people who have a high cancer risk because of environmental exposures. But their molecular geneticist colleagues have just opened the door to screening for people who have one of the most common inherited cancer susceptibilities—familial adenomatous polyposis (FAP), which affects about one person in every 5000 in the United States and carries a very high risk of colon cancer. Two teams of researchers, one led by Bert Vogelstein and Kenneth Kinzler of Johns Hopkins University School of Medicine and Yusuke Nakamura of the Tokyo Cancer Institute and the other by Ray White of the Howard Hughes Medical Institute at the University of Utah, have isolated a new gene that appears to be the one responsible for FAP. And in a spirit of cooperation not always seen in the highly competitive field of disease gene isolation, the two groups agreed to publish the papers describing their work simultaneously.

Bert Vogelstein



Danger sign. *Field of polyps from FAP patient.*

The Vogelstein-Nakamura group's reports are on pages 661 and 665 of this issue of *Science*, and the White group's appear in the 9 August issue of *Cell*. Reports Vogelstein: "There was a lot of interaction—exchanging reagents and information—and it's worked out very well." Indeed, the work "is a beautiful example of what modern molecular biology is able to do," says Stephen Friend of Harvard's Massachusetts General Hospital, the leader of the group that last year identified the gene underlying another hereditary cancer susceptibility, Li-Fraumeni syndrome (see box on page 614).

From the clinical view, says Friend, the FAP gene discovery is important since a genetic screening test for the gene carriers would be a boon to families affected by the condition. FAP is characterized by development of numerous colon polyps, small growths that begin developing in childhood and progress to cancer if not removed. Usually the entire colon has to be removed, a drastic—but life-saving—measure. As Vogelstein notes, "Death is mostly preventable in this disease if you know who's got it."

Currently, however, all family members have to undergo frequent, uncomfortable colonoscopy exams to look for the polyps. So a genetic test could be a relief to family members who don't have the gene. What's more, there is also the possibility of developing chemoprevention treatments that might prevent polyp development in those who are affected (also see page 613). And, of course, the discovery is also important to cancer researchers because it should help them learn more about the basic biology of colon cancer in general.

The two groups knew where to look for the FAP gene because about 4 years ago Walter Bodmer's group at the Imperial Cancer Research Fund in London and White's Utah group independently mapped the disease locus to segment q21 on chromosome 5. That region was interesting to colon cancer researchers for another reason as well. Several groups, including Vogelstein's, had found that it is missing in about 40% of nonhereditary colon cancers. And the loss usually occurred very early, possibly helping to initiate tumor growth. Those findings suggested that 5q21 contains a tumor suppressor gene, the loss or inactivation of which may contribute to cancer development by essentially releasing the brakes that keep cell growth in check. Could the putative suppressor gene and the FAP gene be one and the same? The answer, the new results show, is not a simple yes or no.

Earlier this year, the researchers thought they might have the FAP gene when they isolated a gene designated MCC (for "mutated in colon cancer") from the 5q21 region. But subsequent work showed that while about 15% of nonhereditary colon cancers have MCC mutations, no mutations in the gene have been found so far in people with FAP—making it unlikely that it causes FAP, although that possibility has not been ruled out for all families. Fine-scale mapping of the 5q21 region also suggested that MCC was not the FAP gene, but that another gene nearby might be.

The MCC gene was thus used to pull out clones for three other genes in the area—and the work now being reported says that one of them fits the bill of indictment for the FAP gene. For example, the Vogelstein-Nakamura and White groups have found mutations in the gene, which they have designated APC (for adenomatous polyposis coli), in nine FAP families. The gene is also mutated in some nonhereditary colon cancers. So the 5q21 region contains two possible tumor suppressor genes: the APC gene, which may play a role in both hereditary and nonhereditary cancers, and the MCC gene, which is apparently involved only in the nonhereditary type.

The next big question is what these genes do. So far, there are few clues. Neither MCC nor the APC gene show significant resemblances to any other genes now in the databases. "As far as we know, it [the APC gene] is a new kind of gene," White says. "That's good news and bad news." Good, because finding a novel gene may give researchers some fresh insight into both cancer development and normal cell activities; bad, because in the absence of significant similarities to known genes, a great deal more work will be needed to figure out what the genes' functions are.

In addition, more work will be needed because APC gene mutations have been found in a small minority of patients, and until all, or at least most, of the mutations are identified, screening will be limited to just the families with the known mutations. But Nakamura says, "We are optimistic that in the near future we will find the mutations in most families with FAP." ■ **J.M.**

indeed the case. And just about all of the molecular epidemiologists are either planning, or have begun, such studies. Groopman and his colleagues will, for example, examine the link between aflatoxin adduct concentrations and liver cancer, and Albertini plans to use his HPRT method in a study of the Chernobyl nuclear disaster. The general idea is to preserve frozen blood or urine samples, and then, as people come down with cancer over the years, compare their biomarker concentrations with those of healthy, matched controls. Albertini would like to see a central repository set up for such samples, and he says that the appropriate funding agencies have expressed interest in the idea.

And Perera sees another reason for optimism as well. "What's really struck me," she says, "is the feeling of sharing and cooperation in the field. There's a lot of collaboration." And with any luck, that cooperation may help researchers take their biomarkers into the next era, where they can be used to predict your risk of cancer. ■ **JEAN MARX**