

Uncovering New Clues to Cancer Risk

A growing discipline called molecular epidemiology is attempting to find early biological signposts for heightened risk of cancer. The research should enhance prevention of the disease

by Frederica P. Perera

Imagine that well before tumors arose in people, a laboratory could detect biological clues, or biomarkers, indicating that tissues had been assaulted by specific cancer-causing agents or, worse, were beginning to undergo precancerous changes. And suppose it were possible to identify biomarkers of special vulnerability to the effects of carcinogens in the environment. (These agents can include tobacco smoke, radiation, certain microbes, and natural and synthetic chemicals in our food, water and air.) Discovery of such markers could help affected individuals to prevent cancer, in part because they would know which carcinogens they most needed to avoid. Use of markers to demonstrate heightened risk in certain groups, such as children, might also spur public health officials to take new measures to reduce exposures that are beyond an individual's control.

With such aims in mind, researchers in a burgeoning discipline called molecular epidemiology have begun looking for biomarkers that can signal enhanced risk for cancer. The field is still young. Scientists cannot yet screen for a panel of markers in an individual and then offer a meaningful assessment of the person's likelihood of acquiring cancer. Nevertheless, such testing should one day be feasible. (The delay is not all bad. People who undergo screening will need to be carefully protected from discrimination by insurance companies and employers, but the needed safeguards are not yet in place.)

In the meantime, the available data are proving to be informative in other ways. In particular, they are lending support to the view that current methods for determining "acceptable" levels of

exposure to environmental carcinogens may seriously underestimate the danger faced by some segments of society. Biomarkers may also soon be useful to researchers interested in developing new approaches to preventing cancer. Instead of waiting years or decades to learn whether exposure to some chemical increases cancer rates in humans or whether an experimental intervention reduces incidence, investigators may be able to attain relatively quick answers by monitoring selected signs of precancerous damage in the body.

Epidemiology with a Difference

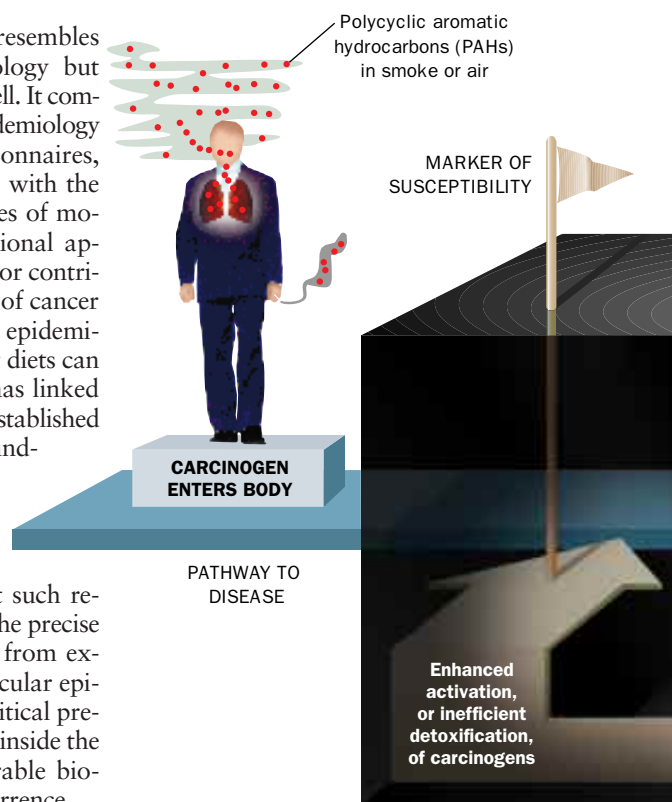
Molecular epidemiology resembles conventional epidemiology but differs in important ways as well. It combines the tools of standard epidemiology (such as case histories, questionnaires, and monitoring of exposure) with the sensitive laboratory techniques of molecular biology. The conventional approach by itself has made major contributions to the understanding of cancer risk. For instance, traditional epidemiology has shown that high-fat diets can play a part in colon cancer, has linked benzene to leukemia and has established that cigarette smoking profoundly increases the chance of acquiring lung cancer. It has even quantified risks: one in 10 heavy smokers is likely to get lung cancer. But such research reveals nothing about the precise continuum of events leading from exposure to overt disease. Molecular epidemiology aims to uncover critical precancerous events taking place inside the body and to identify measurable biologic flags signaling their occurrence.

CLASSICAL EPIDEMIOLOGY



POPULATION EXPOSED TO TOBACCO SMOKE OR AIR POLLUTION

MOLECULAR EPIDEMIOLOGY



This work is informed by, and is contributing to, a growing understanding of how cancer develops. It now seems clear that malignancies generally arise through the serial accumulation of damage to genes in a single cell. When the collected defects finally free the cell from normal restraints on growth, tumors develop and, all too often, invade near-

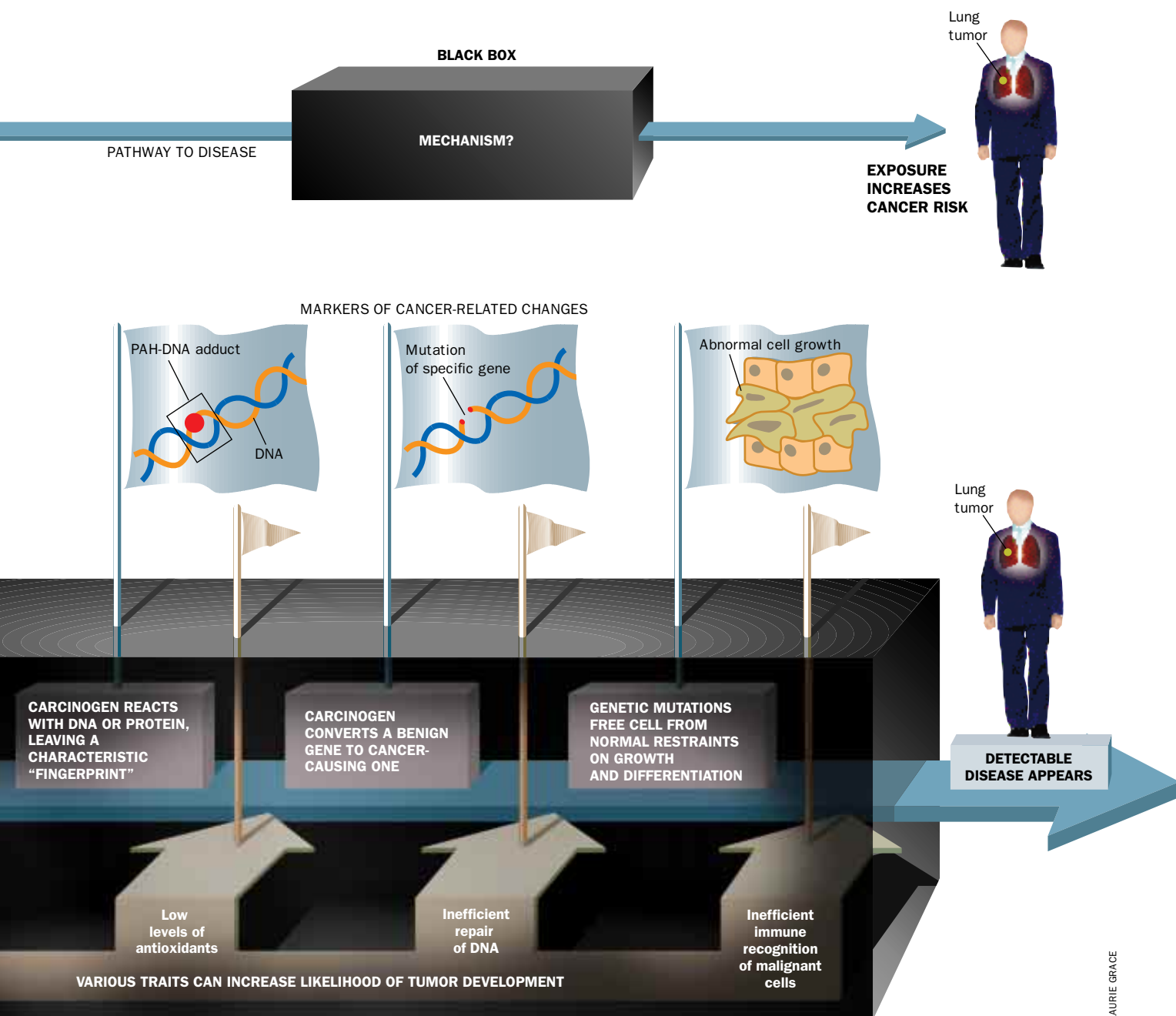
by tissue and establish lethal satellites (metastases) elsewhere in the body.

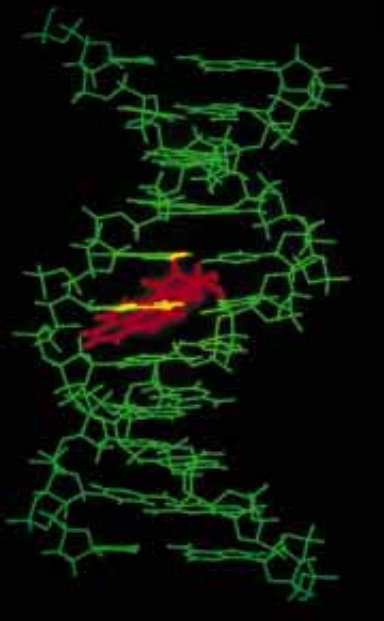
The discovery that genetic damage lies at the root of cancer does not mean most malignancies stem from the inheritance of seriously flawed genes. In fact, such inheritance probably explains no more than 5 percent of all cancers in the U.S. The genetic disruptions that transform

a normal cell into a malignant one typically arise in the course of living—via complex interactions between carcinogens and the body's systems for contending with them. (The offending carcinogens include those in the environment and those, called oxidants, that our bodies generate during normal metabolism.) Indeed, whether any agent

MOLECULAR EPIDEMIOLOGY supplies information that classical epidemiology cannot, as is illustrated here by the example of lung cancer. Classical epidemiology (*top*) identifies factors that increase risk for cancer (such as inhalation of polluted air or tobacco smoke), but it does not address how the disease arises. Molecular epidemiology (*bottom*) looks into the black box to uncover important steps leading from carcinogenic exposures to

disease. It also identifies biological signs, or biomarkers, that may indicate increased risk. Some markers (*rectangular flags*) reflect exposure or advancement along the pathway to cancer. Others reflect innate or acquired susceptibility to the effects of carcinogens (*small banners*). By detecting such markers, researchers may one day be able to pinpoint groups or individuals who most need preventive interventions.





A. M. JEFFREY AND I. B. WEINSTEIN ET AL. Columbia University



FOUNDRY WORKERS (*photograph*), smokers and people who live in highly industrial regions often breathe in high levels of combustion products, including carcinogens known as polycyclic aromatic hydrocarbons (PAHs). “Fingerprints” of this exposure can be detected in lung and blood cells, in the form of PAH-DNA adducts: DNA-damaging complexes arising when such hydrocarbons (*red in computer-generated image at left*) bind to DNA (*green*). Adducts in white blood cells of one exposed individual appear as green fluorescence in the micrograph at the right.



REGINA M. SANTELLA Columbia University

contributes to cancer depends not only on the extent of an individual’s exposure but also on the effectiveness of the body’s defensive responses—responses now known to vary from one individual to another, sometimes profoundly.

In the early 1980s my colleagues and I at Columbia University laid out the basic conceptual framework for molecular epidemiological investigations of cancer after we detected a new molecular marker indicating that a specific carcinogen had damaged DNA in human tissue. Simply put, molecular epidemiologists probe samples of human tissue for biologic markers that reflect exposure to a carcinogen, cancer-inducing damage to cells or tissue, or special vulnerability to carcinogens. Through a series of steps, these markers are “validated,” tested to show that they indicate an increased risk for cancer well before clinical signs appear. Valid markers (those that pass many such tests) can then be measured in selected groups and can signal a need for intervention.

The steps by which we found a new marker and established its potential value as a warning of increased risk for lung cancer serve to exemplify the overall approach. In 1982, working with I. Bernard Weinstein of Columbia and Miriam C. Poirier of the National Cancer Institute, I noted that a well-known class of carcinogens—polycyclic aromatic hy-

drocarbons (PAHs)—left a unique “fingerprint” in human lung and blood cells. These hydrocarbons are among the approximately 400 chemicals that have been shown to be carcinogenic in studies of animals or humans; they are combustion products found mainly in tobacco smoke, polluted air, and barbecued, grilled or smoked foods. The fingerprint took the form of an adduct, a complex that results when a chemical attaches to a biological molecule, usually to DNA or a protein in a cell.

Intrigued by the presence of PAH-DNA adducts in blood—which would be easy to obtain for use in widespread screening—we set out to determine whether these fingerprints could serve as early markers of an increased propensity for lung cancer. My colleagues and I, including Regina M. Santella of Columbia and Kari Hemminki of the Karolinska Institute in Stockholm, demonstrated that people known to have been exposed to high levels of PAHs in tobacco smoke, in polluted air and at certain work sites displayed markedly higher levels of PAH-DNA adducts in their blood than did people whose exposure was lower.

These findings could not by themselves tell us whether the adducts signified a heightened likelihood that lung cancer would develop, but subsequent studies supported that idea. Subjects who har-

bored high levels of PAH-DNA complexes and related adducts in the blood also suffered greater than normal levels of genetic mutations and other chromosomal disturbances in blood cells. Because such changes are common in malignant cells, the results were consistent with the notion that increased quantities of the adducts could reflect added liability for cancer.

Further circumstantial evidence came from our finding that blood samples from patients with lung cancer contain markedly higher amounts of PAH-DNA adducts than do samples drawn from cancer-free individuals who have been exposed to similar doses of lung carcinogens. We are now analyzing stored blood samples from volunteers enrolled in a long-term study to determine whether PAH-DNA adducts and other markers are able to predict lung cancer years before diagnosis.

Markers of Exposure and Damage

A number of other biomarkers show promise for detecting heightened risk of cancer, including that of the liver and the bladder. For instance, it is well known that a natural substance called aflatoxin B1 (common in moldy corn

and peanuts) can play a part in liver cancer. Molecular epidemiological studies by John D. Groopman and his colleagues at Johns Hopkins University and elsewhere have established that this carcinogen, too, leaves fingerprints in the form of adducts on DNA. Furthermore, Chinese subjects with detectable aflatoxin B1-DNA complexes or aflatoxin derivatives in their urine proved three to four times more likely to fall ill with liver cancer than were people whose urine contained no such substances. If the subjects were also infected with the hepatitis B virus, another known carcinogen, they were 60 times more likely to acquire the cancer.

Like adducts, mutations in cancer-related genes can constitute biomarkers of incipient tumor formation, but these signposts reflect later occurrences in the chain of events that culminates in cancer. If a gene disrupted in many cancers is found to be damaged, the information may say little about the causative agent. But the precise type of mutation may well be revealing, as seems to be the case with the *p53* gene, one of the most frequently mutated in cancer. In its healthy state, *p53* is a tumor suppressor; it blocks the growth and division of cells harboring damaged genes. When the *p53* gene itself is mutated, disturbed cells are allowed to transmit potentially carcinogenic genetic rearrangements to their progeny.

Evidence compiled by Curtis C. Harris and his co-workers at the National Cancer Institute suggests that some patterns of mutation in *p53* reflect exposure to specific substances. Lung tumors in smokers commonly display a *p53* mutation that is characteristic of exposure to PAHs or to oxidants and occurs at many sites in the gene. In contrast, a single, "hot spot" mutation in *p53* appears in lung tumors of radon-exposed uranium miners. In geographical areas where aflatoxin B1 and hepatitis B virus yield high rates of liver cancer, *p53* mutations in liver tumors tend to congregate at yet another, single site on the gene.

Distinct *p53* mutations are also seen in a rare liver tumor (angiosarcoma) induced by occupational exposure to vinyl chloride, in colon cancer presumably caused by carcinogens in food, and in skin tumors that result from exposure to ultraviolet light. As is true of carcinogen-DNA adducts, mutational patterns do not conclusively reveal the identity of the agent that caused them. But when combined with other data, such patterns

can help spotlight the carcinogens at fault and send a warning that exposure must be reduced.

Biomarkers of Susceptibility

Of course, an individual's own traits can also influence cancer development, and these characteristics undoubtedly help to explain why a given "dose" of carcinogen will cause only some people to get cancer, whereas others escape the disease. Consequently, in addition to searching for biomarkers of exposure and of early damage from carcinogenic agents, molecular epidemiologists try to

uncover biomarkers of heightened in-born and acquired susceptibility.

Certain rare inherited mutations in genes seriously elevate a person's risk for cancer. A child normally inherits two versions, or alleles, of a gene—one from each parent. Occasionally, a youngster may be born with one defective allele of a tumor suppressor known as the *retinoblastoma* gene and subsequently sustain a mutation in the normal allele. This unlucky series of events almost single-handedly releases the brakes on cell growth and accounts for a sight-robbing childhood cancer called retinoblastoma (hence, the name of the gene). And wom-

Some Biomarkers under Study

	Tissue or Fluid Usually Examined	What Marker Indicates
Markers of exposure to or damage by a carcinogen		
Aflatoxin B1-DNA adduct*	Urine, liver	Genetic damage from aflatoxin in moldy peanuts or corn; increased risk for liver cancer
PAH-DNA adduct	Blood, lung, placenta	Genetic damage from polycyclic aromatic hydrocarbons (PAHs) in polluted air, in workplace or in cigarette smoke (being assessed as marker of lung cancer risk)
4-Aminobiphenyl-hemoglobin adduct	Blood	Active or passive exposure to cigarette smoke (being assessed as marker of increased risk for bladder cancer)
Thymine glycol (oxidized DNA base)	Urine	Genetic damage from oxidizing agents (being assessed as marker of increased risk for various cancers)
Mutation in <i>p53</i> tumor suppressor gene	Breast, liver, lung, among others	Increased risk for various cancers; pattern of mutation may help reveal carcinogen that caused the damage
Markers of inherited susceptibility to cancer		
Certain (fairly common) variations in <i>cytochrome p4501A1</i> gene or its activity	Blood	(Being assessed as marker of increased risk for lung cancer)
Absence of <i>glutathione-S-transferase M1</i> gene (absence very common; occurs in almost half of whites, 35 percent of African-Americans)	Blood	Increased risk for lung and bladder cancer
<i>H-ras-VTR</i> variant of <i>H-ras</i> gene (common in African-Americans)	Blood	Increased risk for breast and other cancers
Mutation in <i>BRCA1</i> gene (mutation rare; occurs in fewer than 1 percent of people)	Blood	Greatly increased risk for breast and ovarian cancer
Markers of acquired susceptibility to cancer		
Low blood levels of antioxidants or vitamins	Blood	(Being assessed as marker of increased risk for lung, esophageal, cervical, breast and other cancers)
Immunosuppression	Blood	Increased risk for various cancers

*An adduct is a complex formed when a carcinogen combines with DNA or a protein.

en born with a mutated *breast cancer 1* (*BRCA1*) gene face a very high (greater than 70 percent) lifetime risk for breast cancer. Inheritance of the damaged gene can be devastating to the individual but probably accounts for only about 5 percent of all breast cancers.

Yet the inherited traits that most often predispose people to cancer act more subtly and indirectly, generally by modulating the body's reaction to carcinogens. (The characteristics may therefore be harmless if exposure to the offending agents is limited.) These traits may lead to rapid conversion of fairly quiescent carcinogens into active forms, or they may render a person relatively ineffective at detoxifying carcinogens or repairing the damage they do. Any of these attributes could facilitate cancer development by increasing adduct formation and subsequent genetic mutations. People differ in their responses to carcinogens because our gene pool contains multiple forms of certain genes that control these responses; the forms one person inherits may be more or less helpful than those another person receives.

Variations in genes that encode, or carry the instructions for manufacturing, a family of enzymes known as cytochrome p450 have been linked to a propensity for cancer. As a group, cytochrome p450 molecules generally render harmless a wide range of internally produced and foreign chemicals. Unfortunately, in the process they can sometimes generate intermediate products capable of damaging DNA and other cellular components. It is these "activated" intermediates that are the true carcinogens; left unprocessed, many so-called carcinogens would be innocuous.

One cytochrome p450 enzyme—CYP1A1—acts on polycyclic aromatic hydrocarbons. Molecular epidemiological studies suggest that smokers who harbor certain forms of the *CYP1A1* gene have an increased chance of ending up with lung cancer. Presumably the risk is elevated because the gene variants lead to enhanced activation of PAHs by CYP1A1 proteins. Small differences in genes coding for other cytochrome p450 enzymes appear to influence the extent to which additional carcinogens, such as aflatoxins, benzene and carbon tetrachloride, can contribute to tumors. These differences, too, might thus serve as markers of susceptibility to cancer.

Certain classes of detoxifying enzymes are more consistently beneficial than the cytochrome p450 family. Among

Anatomy of a Molecular Epidemiological Study

Airborne carcinogens have long been suspected of contributing to the increased rates of lung cancer in heavily industrial regions. This suspicion has been bolstered by the finding that certain products of combustion in polluted air—such as polycyclic aromatic hydrocarbons (PAHs)—can cause lung cancer in test animals and in people exposed to high amounts of those substances in the workplace.

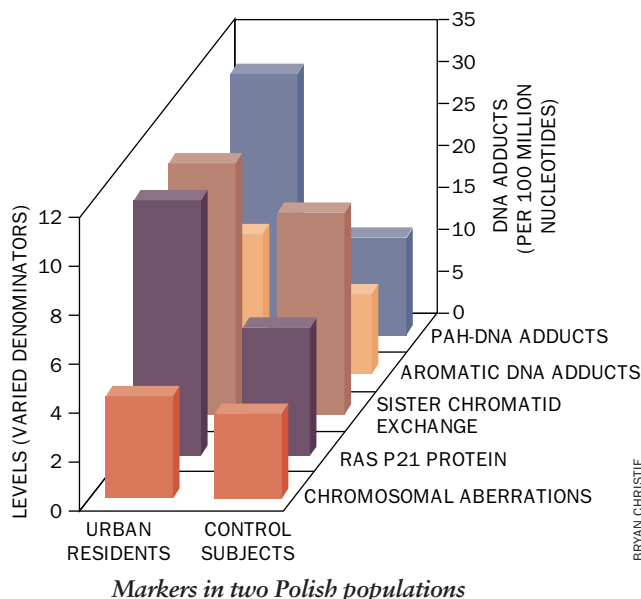
Yet the link between air pollution and cancer in the general population has been difficult to demonstrate, in part because residents in polluted environments, usually urban, tend to follow living patterns that differ from those of their counterparts in cleaner, more rural areas. Ruling out the importance of those differences has proved extremely difficult.

In 1990 my colleagues and I at Columbia University, Mieczyslaw Chorazy of the Institute of Oncology in Gliwice, Poland, and others carried out a molecular epidemiological

study that attempted to trace the influence of polluted air on lung cancer. We showed for the first time that contaminants inhaled in extremely dirty air leave their "fingerprints" on DNA.

Moreover, elevations in these fingerprints accompany rises in irreversible damage to chromosomes. Because such damage enhances the probability that cancer will develop, these findings strongly suggested that severe air pollution could indeed help induce lung cancer.

To conduct this study, we examined two populations. One set of subjects



BRYAN CHRISTIE

these are the glutathione-S-transferases (GSTs), one variant of which, named GSTM1, efficiently detoxifies PAHs, ethylene oxide and styrene (all found in tobacco smoke, in certain workplaces and in urban air). Roughly half of all whites entirely lack the gene for GSTM1. This deficiency has been consistently associated with an increased tendency to bladder and lung cancer, and so the absence of this gene might reasonably be monitored as a biomarker of innate susceptibility.

Another enzyme, NAT2 (*N*-acetyltransferase), deactivates carcinogenic aromatic amines—chemicals present in air pollution, tobacco smoke and certain cooked foods. Various findings suggest that a slow-acting form of NAT2 contributes to bladder cancer. Patients with this cancer are more likely than their healthier counterparts to have the gene encoding the slow enzyme. And Paolo Vineis of the University of Turin in Italy and Steven R. Tannenbaum of the Massachusetts Institute of Technology have

demonstrated that blood of individuals possessing the slow NAT2 enzyme contains elevated levels of protein bound by aromatic amines.

Beyond genetic signposts of vulnerability, scientists are searching for markers of acquired vulnerability to carcinogenic agents. The likelihood of tumor development is increased by impairment of the immune system and by such disorders as hormonal imbalances, hepatitis and chronic lung disease. Convincing evidence also indicates that a diet low in fruits and vegetables containing antioxidants and other nutrients (such as vitamins A, C and E) increases the probability of acquiring diverse cancers, including lung, esophageal, oral, laryngeal, cervical and breast. Through a variety of mechanisms, antioxidants can block oxygen radicals, PAHs and other chemicals from damaging DNA.

Molecular epidemiology promises to refine greatly estimates of cancer risk by considering variations in innate and acquired susceptibility within a popula-

lived in Gliwice in the Silesia region, which is one of the most polluted areas of the world and has a high death rate from cancer. The other subjects lived in Biala Podlaska, a rural province in northeastern Poland, where the air is much cleaner and the cancer incidence is lower.

We measured the levels in the blood of biomarkers reflecting exposure to PAHs and other aromatic compounds. We also measured cellular changes more directly indicative of enhanced cancer risk. The markers of exposure, which also reflected the biologically effective dose of carcinogen, were PAH-DNA and related aromatic adducts. The other markers included chromosomal aberrations, a specific chromosomal disturbance known as sister chromatid exchange, and excess production of a protein (called ras p21) encoded by the gene *H-ras*.

The results (*graph*) showed that compared with the rural residents, those of Gliwice had much higher levels of PAH-DNA and aromatic adducts, chromosomal aberrations, sister chromatid exchanges, and *ras* activity. In other words, it appeared that carcinogens in dirty air could contribute to lung cancer, and their cancer-inducing effects were heralded by the formation of adducts on DNA. Since then, other studies have linked high levels of PAH-DNA adducts to an elevated risk for lung cancer.

—F.P.P.

*A street in the highly polluted
Silesia region of Poland*



CHRISTOPHER PILLITZ *Matrix*

tion. I would emphasize, however, that in most cases, calculations of risk based on single genetic characteristics will be incomplete and could even be misleading. The effect of any one, subtly acting gene can be modulated by environmental influences, by other genes, by health and nutritional status, and by an array of other host characteristics. To add to the complexity, certain genetic traits may protect against one type of cancer but may predispose to another. (NAT2, for example, both detoxifies bladder carcinogens and activates colon carcinogens.) But assessment of multiple traits, combined with biological assessments of exposure and early damage, should eventually yield meaningful estimates of risk.

Risks in Special Populations

Molecular epidemiologists may not yet be poised to assess precisely the odds for cancer in any given individual, but the research is already helping to clarify some of the variation in cancer

risk seen across races and ages. For instance, classical epidemiology has shown that cancer incidence and death rates are often higher for black Americans than for whites. The U.S. incidence for a form of esophageal cancer (squamous cell cancer) is more than three times higher among black men than white men; lung cancer incidence is about 50 percent higher in black males. Black women younger than 40 years experience more breast cancer than white women of the same age do, although the situation is reversed in women older than 40.

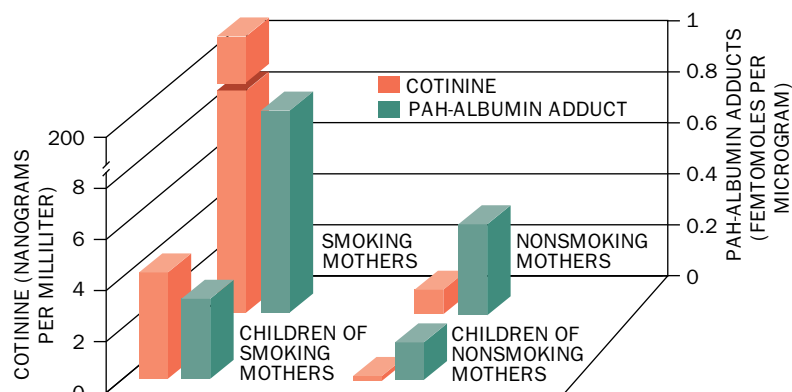
A review of many studies provides compelling evidence that at least some of the excess risk in blacks and other minorities may stem from increased exposure to carcinogens. People of color and of lower incomes in the U.S. are disproportionately exposed to certain environmental toxic substances, including lead, air pollution and hazardous waste. Moreover, individuals who live in poverty often eat foods low in vitamins and other protective nutrients.

Molecular epidemiology suggests that the effects of environmental exposure and of poor nutrition can be exacerbated in these groups by inborn differences in internal processing of carcinogens. For example, a variant of the carcinogen-activating *CYP1A1* gene found only in African-Americans has been linked in one study to an increased risk for a form of lung cancer (adenocarcinoma): black smokers with this variant were two to three times more likely to have lung cancer than were black smokers who lacked the variant. DNA damage from PAHs also appears to be greater in African-Americans than in Mexican-Americans. Another genetic variant, this time affecting a gene called *H-ras*, is found more frequently in blacks than in whites; this variant is associated with increased risk of leukemia as well as cancers of the lung, breast, colon and bladder, through mechanisms not yet understood.

No racial or ethnic group appears to be consistently more susceptible to cancer as a whole than any other group. But each population seems to display a relatively high frequency of certain genetic traits thought to increase their propensity for one malignancy or another.

Investigators have long known that, as is true of ethnicity, a person's age at the time of exposure to a carcinogenic agent can influence the probability that cancer will result. Data from studies of both animals and humans suggest that fetuses, infants and children may be at greater risk than adults from a variety of environmental carcinogens. Studies of air pollution, tobacco smoke, PAHs, pesticides, nitrosamines, aflatoxin B1 and radiation all show that the lifetime risk of cancer can be heightened if exposure begins in utero or in childhood rather than in adulthood. A longer incubation time and higher rates of cell proliferation during early development presumably play a part in this outcome (proliferating cells are more prone to genetic damage than resting cells are). Molecular epidemiological studies indicate that young children are also less efficient than adults at detoxifying certain carcinogens and repairing molecular injury. Moreover, children frequently absorb higher amounts of some carcinogens relative to body weight than adults do.

As evidence of these last points, nursing infants are estimated to ingest 10 to 20 times more dioxin for their weight than adults do in the course of a day. My colleagues and I have recently found that



SECONDHAND SMOKE in the home may raise the odds that youngsters will acquire lung cancer later in life. A study by the author and her colleagues has contributed to this understanding. Blood levels of cotinine (a derivative of nicotine and a marker of smoke inhalation) and of an adduct called PAH-albumin (an in-

direct marker of DNA damage) were higher not only in mothers who smoked than in nonsmoking mothers but also in children of smokers than in children of nonsmokers (*graph*). Because all the women smoked less than a pack a day, the findings suggest that even light use of cigarettes by parents can harm children.

levels of PAH-DNA adducts in the blood of newborns in a polluted area of eastern Europe exceeded those of their mothers, even though a fetus is thought to be exposed to only a tenth of the PAH dose absorbed by its mother. We have also shown that young children whose mothers were fairly light smokers (smoking an average of 10 cigarettes a day) had markedly higher PAH-protein adducts in their blood than children of non-smoking mothers did.

Implications for Policy

Two general themes emerging from molecular epidemiological research on cancer have strong implications for public health policy. First, the work confirms an already impressive body of evidence indicating that most cancer has an environmental component and thus can be prevented by the dual approach of modifying hazardous behaviors and, at the governmental level, reducing involuntary exposure to carcinogenic substances in the air, water, food supply and workplace. Indeed, it has been estimat-

ed that in the absence of environmental exposures, cancer incidence would be reduced by up to 90 percent.

Second, the collected data reinforce other convincing evidence that carcinogenic agents in the environment are more harmful to certain members of society than to others who are similarly exposed. It follows, therefore, that significant gains in cancer prevention will come only from ensuring—through regulation, education and other measures—that these more vulnerable people are protected.

At the moment, the government is not paying adequate attention to the fact that people can differ markedly in their susceptibility to carcinogens. Governmental agencies use a tool called risk assessment to determine the levels of carcinogenic exposures that would cause an “unacceptable” number of future cancers. That goal is reasonable, but most of the current approaches rest on the mistaken assumption that all individuals in a population have an identical response to a cancer-causing agent. Hence, the results can seriously underestimate risk for certain groups. Dale B. Hattis

and his colleagues at Clark University have calculated that possession of only a few susceptibility factors could increase a group’s risk of cancer by an order of magnitude or more over that predicted for the mythical “standard” population.

To remedy this problem, policy makers should determine, and present to the public, the estimated risks to specific groups thought to be most sensitive to the carcinogenic agent in question (such as particular ethnic groups, women, children, the elderly). Failure of regulatory decisions to account for individual variability could lead to environmental standards and public health policies that cause the most susceptible subsets of the population to bear the greatest risks.

Prevention of cancer is the best “treatment.” Avoiding even 20 percent of cases in the U.S. would translate into more than 270,000 people spared from the disease every year. Molecular epidemiology can help guide the development of preventive strategies, and it is already providing new scientific impetus for protecting the most vulnerable members of society. SA

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Further Reading

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