

each agent with the control. The ability to test multiple therapies in a smaller population will become more important as disease subcategories are increasingly defined by specific phenotypic, biologic, and genetic markers, and the available number of patients in a given category becomes a limiting factor in conducting relevant studies. The collaborative trial approach permits direct evaluations of multiple new therapies, as well as comparisons between new and old therapies. The many variables limiting comparison across studies are eliminated, since therapies are tested in a single, defined population, with a common end point and a uniform study protocol and analytic plan.

Of course, there are also limitations of collaborative studies. Such studies are possible only when several similar or relevant therapies are available for testing at the same time. New regu-

lations might be required from the Food and Drug Administration to impose a clinical trial structure on companies with competing products, since companies are often in a race to get to market first. In addition, there are antitrust and patent issues associated with such collaborative trials that will require negotiation and possibly new legislation.

Conflicts of interest must be avoided when conducting any clinical trial, and especially when conducting collaborative trials with corporate sponsors. It is essential to establish a firewall between the supporting corporations and the independent investigative group that designs the trial and manages and analyzes the data. We encourage discussion of these issues as part of the preparation for more frequent use of collaborative clinical trials, which will ensure that safe and effective therapies become avail-

able more quickly and at lower cost than they do today.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Combating Environmental Causes of Cancer

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In April 2010, the President's Cancer Panel — an advisory committee comprising physicians and scientists appointed by President George W. Bush in 2006 — released a report emphasizing the need for stronger regulations to control Americans' exposure to toxins.¹ Between September 2008 and January 2009, the panel had convened four meetings to assess the status of environmental cancer research, policy, and programs addressing known and potential effects of environmental exposures on cancer risk. The group heard testimony from 45 representatives of academia, government, industry, the environ-

mental and cancer advocacy communities, and the general public.

The panel, originally established by the National Cancer Act of 1971, delivered a forceful message about underestimation of the burden of environmentally induced cancers and the lack of testing data on many chemicals in use or in products on the U.S. market. For example, there is potentially widespread exposure to some compounds and chemicals with unknown health effects, such as bisphenol A (BPA), found in hard plastics made from polycarbonate and often contained in soft plastic beverage bottles, intravenous bags, and toys, and

2-methylnaphthalene, which has been found as a contaminant in cereal packaging. Other widely used chemicals, including benzene, asbestos, and formaldehyde, are known or suspected carcinogens. As the panel's recommendations are contemplated, some important facts should be considered.

Despite decreases in the incidence of some cancers and associated mortality, cancer remains highly lethal and very common. About 41% of Americans will develop some form of cancer (including nonmelanoma skin cancer) in their lifetime. One fifth of Americans will die from

cancer. During the past three decades, increases in the incidence of some childhood cancers, such as leukemia and brain tumors, may implicate prenatal exposure to environmental carcinogens — and more than 300 industrial chemicals have been detected in umbilical-cord blood.

The knowledge that environmental factors play a role in carcinogenesis dates back centuries. Dr. Percival Pott described scrotal tumors in young chimney sweeps of 18th-century London, demonstrating that cancer could be caused by environmental factors. This discovery led to the passage of public health legislation regarding disease prevention.

More recently, research has focused on mechanisms of carcinogenesis, the genetics of cancer initiation and progression, and the epidemiology of cancer as a complex chronic disease. Researchers have aimed to identify avoidable causes of cancer, increase early detection, and develop treatments to improve outcomes in patients with cancer. The relative contributions of genetic and nongenetic factors to the development of common cancers have been studied and debated for decades. Relative contributions are expressed in terms of the “population attributable risk” — the percentage of disease incidence that would be eliminated if a given risk factor were removed. Epidemiologists have long known that for most cancers, environmental factors have high attributable risks (as high as 85 to 95% in Western populations), even when the specific carcinogenic agent or agents in a particular exposure are unclear² — as they remain, for example, in paint manufacture and use, carbon electrode production,

and rubber product manufacturing. The incidence of major cancers can vary by a factor of 5 to 100 among populations, and when groups migrate from low-risk to high-risk regions, their cancer rates usually shift to match those of their new environment.³ Observations of such differences among populations have contrib-



uted important knowledge about environmental causes of cancer such as tobacco use, dietary factors, and viral infections.

Despite the contributions of genomics to unraveling the interplay among genetic variants, environmental exposures, and cancer risk, the incidence and mortality associated with cancer have not declined as sharply as those associated with other major causes of death. We will always need more effective therapies and better early detection and screening methods. However, the most valuable approaches to reducing cancer morbidity and mortality lie in primary prevention — avoiding the introduction of carcinogenic agents into the environment and eliminating exposure to carcinogenic agents that are already there. The first approach

would be most effective if carcinogenic substances were identified before they could be introduced, although it's impossible to quantify the success of this approach.⁴ The value of the second approach has been shown by the disappearance or reduced incidence of particular types of tumors after the elimination of specific occupational exposures. For example, the incidence of angiosarcoma of the liver decreased dramatically after exposure to vinyl chloride monomer was eliminated; occupationally related small-cell lung cancer was eliminated after exposure to bis-chloromethyl ether (used in producing bulletproof glass) was reduced; and bladder-cancer incidence decreased after aromatic amines were eliminated from dyes. Furthermore, risk has been reduced through greater regulatory control over compounds that remain in use — for instance, through Occupational Safety and Health Administration restrictions on exposure to asbestos fibers and coke-oven emissions. The President's Cancer Panel detailed the importance of reducing unacceptably high exposures among people pursuing particular occupations, given the prevention opportunities these cases present.

The population exposed to carcinogens outside of high-risk occupations is a much larger group with a wider age distribution, though carcinogen concentrations in their environment are lower than those in occupational exposures. Although we must continue reducing exposure to known cancer-causing agents, such as tobacco, asbestos, radon, and dietary carcinogens, much more information is needed about the effects of other environmen-

tal carcinogens. The sparseness of relevant research suggests that a previous estimate of a 6% attributable risk of cancer from environmental and occupational chemical exposures understates the true hazard and represents a missed opportunity for risk reduction. The cancer panel argued for expanded research on the relationships between cancer and environmental materials such as the hormonally active BPA and manufactured nanomaterials.

Of the 80,000 chemicals in products on the U.S. market — many of which are imported — only 200 have been adequately tested for carcinogenicity. In addition, since 1971, the International Agency for Research on Cancer has evaluated the literature on the cancer-causing potential of more than 900 agents and processes and identified 165 as carcinogenic or probably carcinogenic to humans and another 249 as possibly carcinogenic.⁵ The current regulatory approach calls for safety testing only when evidence of possible danger arises. Since most cancers are long-latency diseases, waiting for population-based evidence of a problem allows avoidable cancer epidemics to occur. Recent reports of sometimes fatal effects from imported products contain-

ing toxic chemicals and contaminated medications (such as heparin, toys containing lead, and pet food tainted with melamine) have raised concern about the safety of the U.S. food and pharmaceutical supply.

Cancer is the number-two killer in the United States, with 1.5 million new cases and 560,000 deaths each year. I believe that the Obama administration, while not redirecting cancer-prevention efforts away from major known causes of cancer, should expand the resources of the National Institutes of Health for investigating environmental causes — particularly new compounds and those to which Americans are already being exposed. Moreover, researchers should evaluate the effects of low-level exposures to combinations of potential carcinogens, as well as exposures that may begin in utero and extend through a lifetime.

Finally, we need stronger environmental laws and regulations to require premarketing safety testing, reduce industry influence on regulation, and control the importation of toxic chemicals and products. The panel suggested a regulatory approach closer to the European Union's — a scientifically based, prevention-oriented approach to replace our

current postmarketing reaction to environmental contaminants. Though the panel noted that it is not always possible to take precautionary action, this approach should be the cornerstone of a new national cancer-prevention strategy emphasizing primary prevention that redirects both research and policy agendas and sets tangible goals for reducing or eliminating environmental exposures implicated in cancer causation.

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Clearing Out the Underbrush in Constitutional Challenges to Health Insurance Reform

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This week's decision by federal district Judge Roger Vinson in Pensacola, Florida, declaring the Affordable Care Act (ACA) unconstitutional is far and away the most prominent decision is-

sued to date in this ongoing litigation. Because this lawsuit involves about half the states, it has received the most attention. But it is only one of about two dozen legal challenges across the coun-

try. Two other federal judges (in Detroit and in Lynchburg, Virginia) have upheld the law, and one other (in Richmond, Virginia) sided with Judge Vinson on the unconstitutionality of the individual