gene found that actually would retard the development of breast tumors—and it seems to do that," said Anne Bowcock, a breast cancer researcher and associate professor of pediatrics at the University of Texas Southwestern Medical Center in Dallas. "I think it's a significant step toward the treatment of at least some breast cancers." Most of the 184,000 new breast cancer cases diagnosed annually are not the inherited type. But the new research suggests that the protein produced by normal *BRCA1* genes may be effective against the more common noninherited forms of breast cancer.

Researchers led by Jeffrey Holt of Vanderbilt first implanted normal *BRCA1* genes into human breast and ovarian cancer cells and found that cell growth was inhibited *in vitro*. Next, the researchers stably transferred either normal or mutant *BRCA1* genes into breast cancer cells and injected the cells into mice. Tumors developed in all 15 mice given mutant *BRCA1*, but in none of the 20 mice given normal *BRCA1*. Finally, the researchers injected viruses carrying the *BRCA1* gene into the abdomens of 10 mice with established breast cancer tumors; half the mice got normal *BRCA1*, the others got mutated *BRCA1*. The mice with mutant *BRCA1* all died of cancer within two weeks. Those with normal *BRCA1* survived 15 to 41 days, and their tumors either shrank or disappeared.

All the experiments used a cell line derived from noninherited breast cancer, suggesting that the treatment might work against the more common types of the disease. Against hereditary breast and ovarian cancer, "presumably it would have an even more dramatic effect—at least that's what we hope," said Roy Jensen, an assistant professor of pathology and cell biology at Vanderbilt.

Translating the results into treatments for human cancers will take time. "It's going to be a long time before this is taken to the bedside," said Bowcock. "The problem is actually getting *BRCA1* into breast cells—it's not going to be easy."

It's easier to get *BRCA1* into ovarian tumor cells, and Vanderbilt researchers recently began clinical trials using *BRCA1* on about 20 ovarian cancer patients, a move that concerns some of their colleagues. While he finds the results of the mouse and cell culture experiments "intriguing" and "encouraging," Roger Wiseman, head of the Comparative Carcinogenesis Group of the NIEHS Laboratory of Molecular Carcinogenesis (part of the team that identified *BRCA1*) feels the human gene therapy trials are "premature, based on the data that have been presented so far." Wiseman would like to see more animal studies performed before *BRCA1* is used in patients.

A related study led by Jensen found evidence that the BRCA1 protein may be secreted and do its work outside the cell. If this is true, it would be much easier to design and deliver drugs that mimic the protein's effects. However, this finding is controverted, and other research groups are convinced that the BRCA1 protein works from inside cells.

"What we need to do to confirm our theory is purify recombinant *BRCA1* and put it onto cells and see if it actually has a growth inhibitory action," said Jensen. If it does, and if it works only on breast and ovarian cancer cells and not other cells, "then that's pretty good evidence that there are specific receptors for this protein. Our efforts then would be focusing on trying to find those receptors."

EHPnet

Genetics and Biosafety

With the pounding pace at which research in genetics and biotechnology is progressing, it has become increasingly difficult for scientists to stay abreast of all the advances and ensure that the new technology is being used in a safe and cautious manner. In an effort to improve communications among scientists and promote the safe use of biotechnology, the United Nations established the International Centre for Genetic Engineering and Biotechnology (ICGEB).

The center maintains two main research laboratories, one in Trieste, Italy, and another in New Delhi, India, with several other smaller labs scattered around the world. These laboratories distribute their findings along with other biology-related information over the Internet via the ICGEB home page and ICGEBnet, an information resource network for molecular biologists.

The ICGEB home page, located at **http://base.icgeb.trieste.it/**, provides information on ICGEB-sponsored meetings and symposia, access to biology-related databases and newsgroups, and information on accessing ICGEBnet. A second biology-related network available from the home page called BIN21 is still being developed by the ICGEB and will focus on issues of biodiversity.

Among the databases accessible from the ICGEB's home page is one relating to P450 proteins and P450-containing systems, an on-line directory of biologists around the world, and SBASE (a sequence database of protein domains). An extensive library of biosafety-related rules and regulations from various nations, organizations, and research institutions is also available, along with lists of experts and databases that can be contacted to help researchers in dealing with biology-related legal issues. For further assistance on biosafety and legal questions, a link is provided to the Stockholm Environment Institute's Biotechnology Advisory Board home page. This international board of scientists will answer questions and give advice on any issue relating to ecology, biochemistry, genetics, biotechnology, pathology, environmental law, or economics.

Access to ICGEBnet and BIN21 will be free of charge but generally limited to scientists and policymakers with a pertinent interest in biology. Currently, ICGEBnet gives scientists around the world access to a variety of databases and provides a computer environment that allows molecular biologists to analyze nucleotide and protein sequences. Analysis software, including three major program packages, is distributed over ICGEBnet. In addition, information services such as electronic mail and bulletin boards are also available. The center's goal is to distribute these services to areas of the developing world where they are not yet widely available.

Fueling the Gas Debate

New findings continue to fuel the debate over the safety and effectiveness of gasoline additives, such as methyl tertiary butyl ether (MTBE) and ethanol, being used to reduce air pollution. The Clean Air Act Amendments of 1990 required that, beginning in 1992, areas that fail to meet air quality standards must use oxygenated fuels. Not only has the effectiveness of the oxygenates in reducing carbon monoxide (CO) emissions been questioned, the additives have also been accused of causing health problems including headaches, dizziness, nausea, and rashes. However, a recent study has found that the additives are successful in reducing CO emissions and do not appear likely to substantially increase health risks when compared to normal gasoline. The report

emphasizes that further research is needed, but recommends that the use of the additives should not be abandoned at this time.

The Potential Health Effects of Oxygenates Added to Gasoline: A Review of the Current Literature was released in April by the Cambridge, Massachusetts-based Health Effects Institute, a cooperative effort of the EPA and the auto industry created to examine the health effects of motor vehicle emissions. HEI conducted a review of existing research, public complaints, and occupational exposures concerning gasoline additives.

According to the report, potential health effects from exposure to gasoline containing MTBE include headaches, nausea, and sensory irritation; acute, reversible neurotoxic effects (based on studies with rats at high exposure levels); and cancer (based on increased frequency of tumors in rats and mice at high exposure levels). Exposure to ethanol by ingestion of moderate to large quantities has been found to increase the risk of cancer, adversely affect embryos, and produce neurotoxicity. However, the report points out that these effects are unlikely to occur at low levels of inhalation.

The report concludes that possible short-term and cancer-causing effects of exposure to gasoline without oxygenates are similar to those from exposure to gasoline with oxygenates. Adding oxygenates to gasoline reduces the emission of carbon monoxide and benzene from motor vehicles, which may lower health risks for some people, the report stated. However, the process may increase exposure to oxygenates and aldehydes, which may have other health risks. The report concluded that an immediate reduction in oxygenate use is not warranted at this time because adding oxygenates is unlikely to significantly increase health risks associated with fuel use.

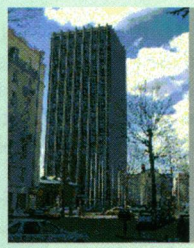
The report recommends that further research be conducted and outlines several priorities, including comprehensive assessments of personal exposure to oxygenates, human environmental chamber studies to evaluate the health effects of MTBE and MTBE-gasoline mixtures, epidemiologic and animal studies to evaluate cancer risks of MTBE, and comprehensive assessments of other oxygenates.

The study was commissioned by the EPA and the Centers for Disease Control and Prevention (CDC) as part of a broad review of oxygenated fuels being conducted by the White House Office of Science and Technology Policy, which will examine air quality benefits, engine performance, fuel economy, and costs of the fuels. The HEI study's conclusions are similar to those of a recent National Science and Technology Council report conducted by an interagency

IARC on Tamoxifen

Tamoxifen, an antiestrogenic compound that has been recognized by the World Health Organization as an essential drug for the treatment of breast cancer, is itself carcinogenic, according to the International Agency for Research on Cancer. IARC researchers, who met in February in Lyon, France, reviewed evidence on the potential carcinogenicity of 13 pharmaceuticals. Though they found evidence that tamoxifen increases a woman's risk of developing endometrial cancer, they emphasized that this does not abate the drug's benefits.

"No woman being treated for breast cancer should have [her] treatment stopped because of the conclusions of the [IARC] working group," the researchers concluded. "The risk of endometrial cancer is far lower than the benefits women with breast cancer receive from tamoxifen."



International Agency for Research on Cancer

Tamoxifen has been prescribed to women with metastatic breast cancer for over 20 years and it is registered for use in nearly 100 countries. It has been used as both a curative agent and a secondary cancer-preventive agent, and it is also being evaluated for use as a primary preventive agent for healthy women at an increased risk of developing breast cancer, IARC director Paul Kleihues said in a 17 February 1996 article in *The Lancet*.

The IARC group, which consisted of 19 scientists from 8 countries, reviewed all the published scientific data on second primary tumors reported in patients who were given tamoxifen as treatment for breast cancer. In a draft of the study results, the group concluded that there was "sufficient evidence in humans for the carcinogenicity of tamoxifen in increasing the risk of endometrial cancer." However, the group also recognized that "there is conclusive evidence that tamoxifen reduces the risk of contralateral breast cancers" (second cancers in the other breast), and that "there is inadequate evidence tamoxifen affects the risk of other cancers." The results of the study will be published in volume 66 of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Though statements on a drug's benefits are not normally included in the *Monographs* series, Kleihues told *The Lancet* that the working group would probably make an exception for tamoxifen. Such a statement may help quell the concerns of those worried that an overzealous reaction to IARC's findings could stop the use of a very beneficial medication. Criticism of the agency's decision to evaluate the carcinogenicity of tamoxifen began late last year when the state of California, in response, considered listing tamoxifen as a carcinogen under its Proposition 65. Critics point out that IARC's report could cause tamoxifen to be quickly replaced by any of a number of new antiestrogens currently being introduced. With comparatively little human data available on the new drugs, the danger exists that tamoxifen will be uncritically replaced by a less effective or more toxic medicine.

Kleihues said that IARC received many letters concerning its study on tamoxifen, but that the agency did not cancel or reschedule the evaluation as a matter of principle. "It is important that women have access to scientific opinion on the low risks of endometrial cancer," Kleihues and working group chairman George Lucier stated in a press release, "so that they can make informed decisions on the treatment they will accept."

Tamoxifen is one of three triphenylethylene antiestrogenic compounds that will be reviewed in volume 66. The other two, droloxifene, a drug also used in the treatment of breast cancer, and toremifene, which is just being introduced, were found to be "not classifiable" as to their carcinogenicity to humans due to inadequate data.

Similar results were found for six of a group of seven benzodiazepines and benzodiazepine analogues that are used in the treatment of insomnia, anxiety disorders, and alcohol withdrawal. One, oxazepam, was found to be "possibly carcinogenic to humans."

Two cholesterol-lowering drugs, clofibrate and gemfibrozil, were also found to be "not classifiable" as to their carcinogenicity to humans. Phenytoin, which is used to treat epilepsy and certain cardiac arrhythmias, was found to be "possibly carcinogenic to humans."

IARC has evaluated the carcinogenicity of more than 800 agents. Of these, 70 have been deemed human carcinogens and about a half dozen of these are still in use.

panel, says Mary White, an epidemiologist with the CDC. "Both reports clearly state that the information available on the additives is very limited." White emphasized the need for additional research. "There are some troubling and unanswered questions about the acute health effects [of the oxygenates]. These are a real concern, which no one dismisses, but we're talking about acute headaches, not acute mortality," White said.

Representatives of the oil industry who support the use of oxygenates were satisfied with the report's conclusions. "HEI did a good job of reviewing the information. I found the report to be favorable, although it overemphasized the carcinogenesis [of the oxygenates]," said Robert Drew, director of health and environmental research for the American Petroleum Institute. "Even though the results highlighted the carcinogenic and neurotoxic endpoints, [HEI] was not concerned enough for the materials to be taken off the market in the short term," he said.

However, the HEI report findings have angered opponents of oxygenate use, including Myron Mehlman, a staff scientist at the Environmental and Occupational Health Sciences Institute at Rutgers University. Mehlman, who feels that the additives should be immediately removed from the market, says the HEI report does not accurately address the acute effects of the oxygenates, and he criticized the studies cited in the report. "I don't know of any studies that have been conducted [on oxygenates] that are adequate," he said. Mehlman also says there are not sufficient data to show that the additives reduce carbon monoxide emissions; therefore, using the oxygenates is causing unnecessary health risks. Drew counters, "MTBE at this point is a thoroughly studied chemical. We concur with the conclusion that MTBE is certainly no more harmful than gasoline itself."

Although HEI acknowledges that it is not possible to have complete information about a substance before it is used, the report said that, in the future, more research—including a comprehensive testing program, rigorous exposure assessment, and epidemiologic studies—should be conducted before introducing a substance into widespread use.

PECORA thirteen

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