developed by Nikolai Lisitsyn, Ph.D., and Michael H. Wigler, Ph.D., at Cold Spring Harbor Laboratory, N.Y., and colleagues. Called representational difference analysis, the method yields “difference products”—bits of DNA that are either amplified or have both copies deleted in a tumor. These are used as probes to obtain subsequent gene map information.

So far, in studying biopsy tissue from sporadic breast cancers, the group has found about a dozen areas where genes are amplified and even more that have both copies of genes deleted. “We’re trying to identify the genes involved,” said Wigler, “and find out how frequently these areas are amplified or deleted.

We’re also trying to assemble a complete panel to detect genomic instability in any gene at the earliest stage. In addition, we want to study the involvement of these areas in other cancers.” A few groups are using the technique to study other solid tumors such as pancreatic cancer.

Other new genetic approaches to cancer scrutinize tumor tissue for variations in gene expression, gene re-arrangements, DNA sequence mutations, or viral genes. For example, Pat Brown, M.D., Ph.D., associate professor of biochemistry at Stanford University, Stanford, Calif., and the Howard Hughes Medical Institute, and colleagues are exploring variations in gene expression using their own DNA microarrays, or chips, produced in the laboratory by high-speed robotic printing. The assay gives information on both the number of genes and the level of gene expression. The group has studied yeast and human cells and plans to focus on cancer cell genes.

Other methods of looking at gene expression include serial analysis of gene expression (SAGE), developed by Kenneth Kinzler, Ph.D., and Bert Vogelstein, M.D., of Johns Hopkins University in Baltimore, and the differential display method, developed by Arthur Pardee, Ph.D., and colleagues at Harvard University and the Dana-Farber Cancer Center, Boston.

A Possible Winner?

Will one technique win out over another? Maybe, but “I see all these new techniques as working in complementary fashion in the future,” said Brown.

Said Wigler, who thinks gene expression differences alone are hard to interpret, “If you find a difference in expression of a gene that maps to an area that is amplified or deleted, then you’re probably onto something.”

These techniques may eventually be able to give a read-out of the relative levels of all genes.

At a cancer genetics seminar in Boston last spring, Eric Lander, Ph.D., of Massachusetts Institute of Technology, Cambridge, said, “Someday you may be able to say to a computer, ‘Here are 100 tumors; here are the expressions of 100,000 genes. Cluster them for me [and find a pattern].’ You may find that some tumors respond well or poorly to certain drugs, and this may correlate with all the tumors that have expression of certain genes.”

— Gail McBride

Details Seen as Critical to Long Island Study

There may be many ways to vacuum a room, but in the Long Island Breast Cancer Study Project, there is only one way to do it right.

Before heading out to women’s homes to collect carpet dust samples for this study, which is designed to establish a potential environmental link to breast cancer, field workers undergo a day-long training session on how to operate a special vacuum cleaner called the Small High-Volume Surface Sampler. If needed, they can also consult the special vacuum’s usage manual.

The Small High-Volume Surface Sampler used to collect carpet dust samples.
from the American Society for Testing and Materials.

"Select a sampling area according to the established protocol for your sampling campaign," the manual reads. "Begin with strip 1. Move the sampler at approximately 0.5 meters per second. Move the sampler a total of eight passes per strip. Then gradually move to strip 2 and repeat."

Although this may seem out of place in the search for causes of breast cancer, managing such minutiae is now the main challenge for this study’s lead researchers.

Scientists and women in areas where breast cancer incidence is high have long speculated over whether environmental toxins in the soil, water, and air contribute to the development of breast cancer. Many studies have been done on this topic, but the $19-million Long Island study is the first federally mandated effort to try to answer these questions in a large population, said Marilie Gammon, Ph.D., an assistant professor at the Columbia University School of Public Health, New York, and lead investigator on the project.

A companion study, led by Cristina Leske, a professor at the State University of New York at Stony Brook, will try to determine if there is a link between the electromagnetic fields given off by power lines and household appliances, and breast cancer.

On August 1, investigators began seeking 1,600 breast cancer patients to participate in the study and began identifying 1,600 controls — women without breast cancer — by dialing randomly selected phone numbers throughout Long Island. This recruitment phase of the study will last through July 1997.

Field workers have begun trekking out to women’s homes to conduct interviews and collect samples, which are already being sent back to the labs for analysis. Researchers hope to finish collecting data by the middle of 1998 and to issue a final report by mid-1999.

Regina M. Santella, Ph.D., a professor of public health at the Columbia University School of Public Health, who is analyzing some of the blood samples, said that as each sample comes in, it has to be labeled with a bar code and a control number.

"It’s been an enormous amount of work," Santella said.

The two main things scientists are concerned about are organochlorines — chemical pollutants from pesticides such as DDT — and polycyclic aromatic hydrocarbons — compounds found in car exhaust, cigarette smoke, and foods that have been charcoal-broiled. Scientists are analyzing participants’ blood and urine, as well as the soil, tap water, and carpet dust from their homes.

Mary Wolff, Ph.D., a professor of community medicine at the Mount Sinai School of Medicine in New York, is studying the link between breast cancer and organochlorine levels in the blood. Researchers think organochlorines are stored in fatty tissue such as the breasts, and may mimic the female hormone estrogen, which is thought to play a crucial role.

Old Tools Find New Shed in Long Island Breast Cancer Study

Researchers in the Long Island Breast Cancer Study Project have adapted several existing technologies to work for breast cancer research. Here are some examples:

- The Small High-Volume Surface Sampler is a modified commercial vacuum cleaner, said David Camann, a staff scientist at the Southwest Research Institute in San Antonio, Texas. It has a special attachment called a cyclone that filters out all dust particles less than 5 micrometers in diameter. What’s left behind goes into a catch bottle that gets sent back to the lab for analysis.

- The water sampling kit is a standard portable lunch cooler filled with glass and plastic bottles coded by size and cap color. Field workers go to the kitchen faucet, turn on the cold water, fill up the bottles, and put them back into the lunch cooler for transportation back to the lab, said Martin Trent, principal public health sanitarian at Suffolk County’s Office of Water Resources in Hauppauge, N.Y.

- A computerized mapping system called a geographic information system (GIS) will be able to store, display, and analyze data on breast cancer patients by geographic area. This concept is borrowed from a technology already in use by city and county governments. The National Cancer Institute committee that is in charge of soliciting bids for the system held a series of public workshops Nov. 13-14 to gather input from Long Islanders on what the GIS should be able to do. The official request for proposals should be announced by mid-1997, said Linda Anderson, an NCI spokeswoman for the Long Island study.

— Brad Keoun
in the development of breast cancer. Gammon emphasized that this part of her study — testing blood samples for organochlorines — is the most important scientifically because a lot of studies have shown that there is a precedent for this kind of work. Looking at the link between breast cancer and traces of chemicals in environmental samples is still somewhat “exploratory,” she said.

As to the long standing debate about whether EMFs can cause cancer, researchers hope this study will add to the already substantial body of evidence. The most extensive study to date, released in late October by the National Resource Council, found no conclusive evidence that EMFs cause cancer.

A team of EMF specialists will use a special meter to take spot measurements on electromagnetic fields in the home, said Geoffrey Kabat, Ph.D., an associate professor at SUNY-Stony Brook, and a co-investigator on the EMF study.

After that, the specialists will leave behind two additional meters, which will be programmed to check EMF levels every 15 seconds for a 24-hour period. Another team of EMF specialists will measure how far the house is from the nearest transmission lines.

The project’s field workers — about 20 so far — take a week-long training course before they make their first house calls, Gammon said. All are trained nurses, phlebotomists, or medical technicians, and they must learn how to take soil and water samples and to operate the special vacuum. Gammon said this kind of extensive training is important so the field workers will seem competent and trustworthy.

“We try not to have people show up at the front door with a huge duffel bag full of stuff,” Gammon said. “We leave the vacuum cleaner in the trunk of the car until later.”

— Brad Keoun

New Criteria Established for Assessing Human Carcinogens

This year, government programs for identifying and performing risk assessment on known and suspected carcinogens are being modernized to accommodate recent advances. Additionally, a formal procedure has been added for the first time to “de-list” chemicals no longer considered hazardous to human health.

The National Toxicology Program of the National Institute of Environmental Health Sciences has established new criteria for identifying known and suspected carcinogens to which humans are exposed. The lists NTP publishes biennially are used in the United States by the Environmental Protection Agency, the Food and Drug Administration, the Occupational Safety and Health Administration, and the Consumer Product Safety Commission, as well as by states and localities.

For example, California’s Proposition 65, which requires warning labels for human carcinogens wherever they occur, is closely linked to NTP’s listing process, said C.W. “Bill” Jameson, Ph.D., coordinator for the NTP’s biennial report.

“The regulatory agencies help the NTP select about 20 to 25 chemicals for lifetime testing in rodents each year,” said Gilbert S. Omenn, M.D., Ph.D., chairman of the Presidential Commission on Risk Assessment and Risk Management at the National Academy of Sciences, adding that the number of chemicals tested is “a drop in the bucket compared to all the chemicals out there.” Therefore, the chemicals are chosen to represent important classes and key scientific issues.

Under both old and new NTP criteria, human studies must first establish whether these chemicals are “known human carcinogens.” Another category, for compounds “reasonably anticipated to be carcinogens,” which was formerly based only on rodent data, now allows evidence from dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive subpopulations, genetic effects, or other data relating to mechanism of action.

Concurrently with NTP’s revisions, the Environmental Protection Agency has proposed changes to its own risk assessment guidelines, including changes in the categories of evidence that may be invoked to suggest that a chemical poses a carcinogenic risk to humans.

“My view,” said Omenn, “is that both the NTP and the EPA revisions very appropriately use all available evidence about structural, cellular, mechanistic, and pharmacokinetic properties of these agents.” But Omenn, dean of Public Health at the University of Washington, Seattle, cautioned against too much reliance on data from in vitro studies.