A NEW KIND OF SLEUTH

AT THE CUTTING EDGE OF A NEW FIELD THAT COMBINES GENETICS, ENVIRONMENTAL MEDICINE, AND EPIDEMIOLOGY, DR. RICHARD HAYES IS FINDING LINKS BETWEEN GENES AND DISEASE IN UNEXPECTED REGIONS OF THE GENOME. HIS RESULTS ARE PROVIDING NEW INSIGHTS INTO WHY CANCER DEVELOPS.

BY ERIC GOLDSCHEIDER
ILLUSTRATION BY NOMA BAR

WHEN ASKED ABOUT HIS EARLY professional career, Richard B. Hayes, DDS, PhD, gestures toward the window of his Manhattan office. The window faces the Empire State Building, symbolic center of the city where his career began almost four decades ago, serving the dental needs of patients in the Williamsburg section of Brooklyn on the other side of the swift-flowing East River. Now, like that river's shifting currents, his work life has circled back to New York City.

In fact, Dr. Hayes, 64, uses the sometimes mercurial movement of water as a metaphor for his path from dentist to high-level epidemiologist—a path that passes through Holland, Maryland, and China. "The river flows, and you go one way and then veer off in another," he muses. Last February, in the river's latest turn, Hayes assumed dual appointments as associate director for population sciences at The Cancer Institute of NYU Langone Medical Center and director of the Division of Epidemiology within the Department of Environmental Medicine at NYU School of Medicine, where he'll be helping to guide NYU's research programs in cancer detection and prevention.

This fresh turn is a natural extension of where he's been: A two-year career in dentistry for the underserved led to an interest in public health, inspired by fluoridation campaigns that showed the promise of systemic approaches to keeping teeth whole. While pursuing a master's degree in public health and a PhD in epidemiology at Johns Hopkins University, Dr. Hayes found a completely new direction, joining in the hunt for carcinogens in the environment and the workplace. Relishing the classic role of epidemiologist as medical detective, he used his doctoral dissertation to examine measures to limit exposure to chromium in a Baltimore factory. His findings uncovered continuing excesses of chromium-related lung cancer, leading to the plant's closure and designation as a superfund site.

Dr. Hayes ventured to Holland, where he worked for the Queen Wilhelmina Cancer Foundation, studying chemicals like formaldehyde and their connections to various cancers. He had great leeway to pursue ideas that interested him, but little in the way of infrastructure. "I really had to develop studies from scratch," says Hayes, who speaks Dutch fluently, "so I became accustomed to making things happen on my own and not relying on others to do things for me."

The foundation retrenched during the recession of the early 1980s, and Dr. Hayes found himself in the job market. An opportunity at the National Cancer Institute (NCI) in Bethesda, Maryland, captured his imagination. The opening of China following President Nixon's trip there a decade earlier had created interesting new avenues for epidemiology, since China's large population and centralized control of employment and healthcare allowed the assembly of large cohorts supported by extensive records. Dr. Hayes started going to China first to negotiate and then to conduct studies. The largest of these looked at connections between leukemia incidence and occupational exposure to benzene among 100,000 industrial workers in 12 cities. The results clearly showed that leukemia risk rose as exposure increased, and that prolonged exposure to benzene was linked to the development of myelodysplastic syndrome, a group of conditions affecting the production of blood cells in the bone marrow.

"Richard's work has been really seminal in formulating public health policy with respect to benzene," said his longtime colleague Robert N. Hoover, MD, ScD, director of the Epidemiology and Biostatistics Program at the NCI. Findings from that study resulted in recent regulatory decisions at the U.S. Environmental Protection Agency on how much benzene to allow in gasoline.

While carrying out a smaller-cohort project in China, it occurred to Dr. Hayes that he could learn things about the participants' genetic makeup by testing for phenotype characteristics relating to the rate at which they metabolized substances like caffeine. He then compared that information to disease incidence, yielding some of the earliest data on the connection between common genetic traits and bladder cancer. With novel ideas like these, Dr. Hayes found himself at the forefront of a new approach to cancer, which used these

PHOTOGRAPH BY FIONA ABOUD

kinds of associations to understand how genes combine with environmental factors to influence disease risks.

Dr. Hoover calls his colleague "a synthesizer" whose imagination is remarkably unrestricted and who is nimble in applying new ideas. "He has the ability to walk into something he didn't know," says Dr. Hoover, "and very quickly become an expert."

Today, this quality has made Dr. Hayes a leader in cutting-edge genetic research on a variety of tumors. From the early 1990s until he left the NCI last year, Dr. Hayes was the institute's principal investigator for follow-up studies that grew out of a project to measure the benefits of screening for prostate, lung, colorectal, and ovarian cancers in some 150,000 Americans.

Seeing the opportunity to study additional variables by collecting data on things like diet and chemical exposure, he and his colleagues drew blood from each participant, even though it wasn't fully apparent at the time what could come of it. When the genetics revolution occurred years later, this effort proved prescient: the information became the basis for one of the largest and most significant databases for studying cancer. Dr. Hayes is still making new discoveries based on this project.

"In the informed consent document, we didn't mention genetics at all—we just said, 'for future research and so forth,' " Dr. Hayes recalls. "Around 1998, when it became obvious that there was tremendous interest in these kinds of data collections, we had to go back and reconsent all these people." It's one of those war stories that, in retrospect, draws a grin.

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One major finding has been that variations in regions of the genome with no suspected connections to cancer are in fact linked to the disease. Dr. Hayes' background positioned him to be a leader in the genomewide association studies that have proliferated in the last five years as new technology has made it possible to quickly identify up to a million variants in the DNA of a single subject. (*See sidebar.*)

His latest move into academia offers Dr. Hayes an opportunity to fulfill his lifelong passion for addressing human needs on a broad scale. "At the NCI, I was doing research," he observes. "Now, I'm being asked to be a leader in developing NYU's capacities in population sciences." His mandate extends to organizational challenges, like building outreach and screening programs, and to setting and shaping priorities for new initiatives in the kinds of high-level science he is known for. "I'm trying to develop large-scale projects in genetic discovery in colon cancer and am also working on projects on air pollution and disease risk," he says. If there is an overarching theme to his career, adds Dr. Hayes, it involves a focus "not on treating individual patients, but on protecting the health of entire populations."

A Long Island native who attended Manhattan College in the Bronx and received his degree in dentistry from Columbia University, Dr. Hayes is glad to be back in New York. He loves to walk the streets of the city and people-watch as a way of relaxing. During these rambles, he says, he's reminded not only of why he got interested in public health, but also of how, in life, circles are often completed. "The great wheel turns," he says, smiling—and with each revolution, the scope of his understanding deepens and broadens. ●

The Pace of Discovery

IN ORDER TO APPRECIATE the looming potential of genomewide association studies, Dr. Richard Hayes asks us to consider that the Human Genome Project took hundreds of scientists the better part of a decade and more than $1 billion to sequence the nucleotide base pairs that form the genetic map of one human being. Now, it is possible to accomplish this task for less than $40,000, and the technology for driving the cost down even more is on the horizon.

This means that the prodigious data being produced by geneticists and epidemiologists studying inherited susceptibilities to cancer is about to grow by orders of magnitude. In the process, our understanding of how naturally occurring variations in the way the adenine, guanine, cytosine, and thymine nucleotides—the basic chemical components of DNA—are ordered is undergoing a qualitative transformation.

The collaborative pooling of genomic data worldwide means that an increasingly robust picture of highly subtle variations within humans is coming into view. Finding patterns and correlations between these variants, called single nucleotide polymorphisms (SNPs, pronounced "snips"), and other kinds of common genetic variants and disease incidence is giving biologists new tools and insights to guide research.

Dr. Hayes' most significant contributions have been in prostate cancer research. In the last three years, he has had a hand in identifying multiple genetic variants connected to the development of prostate tumors. Amazingly, none of these variants were previously on anybody's list of potentially fruitful areas for research.

"I don't know if you can appreciate how extraordinary that is," says Dr. Hayes. "In one region of the genome, for example, where there would have been absolutely no reason whatsoever for anybody to ask questions, it turns out we and others found associations with not only prostate cancer, but also cancers of the breast, colon, and bladder."

He emphasizes that looking at the nucleotide sequence of any single person doesn't yield much useful information about his or her susceptibility to cancer. Even if a man has, say, 10 SNPs shown to be associated with prostate cancer, the chance that he will be afflicted goes up only very slightly.

The real value of these studies, at least in the intermediate term, is to alert biologists to which regions of the genome may be associated with a particular disease. Then they can go to work to figure out why. ●