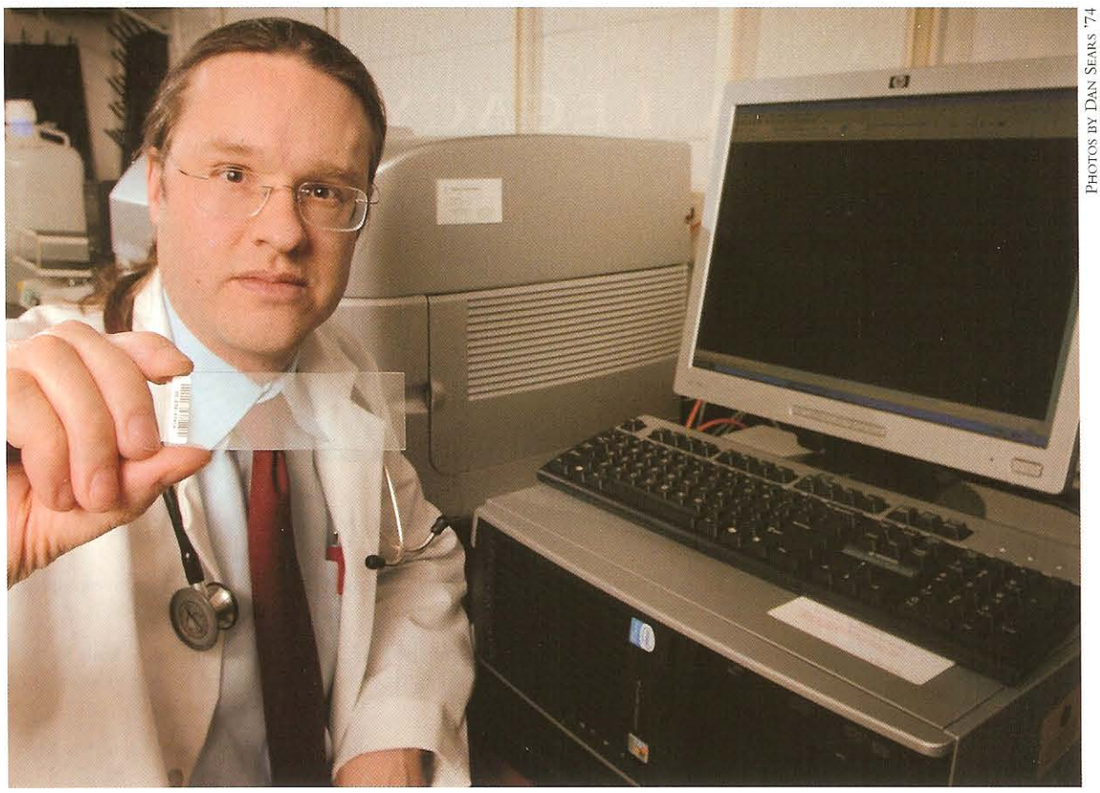

PHOTOS BY DAN SEARS '74

Neil Hayes: Looking at Cancer's Fingerprints

In an age of rapid advancement in medical science, it is easy to forget the basics of diagnosis and cure. Say that you have an ankle injury caused by a slip on a staircase, a fall while skiing or a tumble off a bicycle. Before treating the injury, your doctor might suggest an X-ray. If the bone is broken, it may need to be set. If it's a sprain, you may leave the clinic with an Ace bandage and a box of Epsom salts.

What happens if the physician has no way to look at the details of the injury? Treatment would have to depend on a statistical best guess. That's the situation today in the treatment of lung cancer. An X-ray can show if the disease is present, distinguish small cell lung cancer (the majority of cases) from non-small cell, but the X-ray cannot tell the physician enough to reliably predict the progression of the cancer or the likelihood of response to treatment in a specific patient.

In essence, at the cellular level, we are blind.

If Neil Hayes '96 (MD) is correct, this is about to change. Hayes, an assistant professor of medicine in the division of hematology/oncology in the School of Medicine, has been using a technique called DNA microarray analysis to identify a tumor's genetic pattern.

A tissue or cell sample is placed on a small solid support, usually a glass microscope slide, where the DNA is immobilized or attached at a fixed location. The DNA segments are known as probes. A single DNA microarray, which may contain thousands of probes, then is used to measure the expression levels of large numbers of genes simultaneously.

Hayes explains his work by comparing the microarray to a fingerprint. The *array* or arrangement looks like a sequence of spots — patterns of colored dots that the researcher sees on the computer screen. Studying the patterns is like studying a fingerprint. Looking at large numbers of these microarrays, researchers can identify types of damage caused by lung cancer at the cellular level, the level at which the disease affects the patient.

Neil Hayes '96 (MD) holds a DNA microarray, patterns of colored dots that can been seen on a computer screen, enabling a researcher to identify types of damage caused by lung cancer at the cellular level.

"In the past, we could just look at shadows of these genetic events," Hayes explained. "Now we are looking at the actual broken machinery."

For Hayes, that is a shift equivalent to the introduction of the microscope. It's now a common tool,

but the things the first scientists saw under the microscope were just as mysterious as a DNA fingerprint. "When scientists used the microscope for the first time, they had to figure out what they were looking at. In the same way, we are now examining these DNA microarrays and looking for patterns, looking to see what the associations are between that DNA pattern and the outcome for treatment."

The enthusiasm for a process that may take some time to move from research to clinical practice grows out of Hayes' desire to couple his taste for research with opportunities to work hands-on with people. While completing his medical degree at UNC, Hayes became interested in epidemiology and public health. After receiving his medical degree, he went on to study public health at Harvard.

Looking for a problem that touched a lot of people, Hayes studied the impact of firearms violence.

"Some 40,000 deaths a year are attributable to injuries, and many are firearms-related," Hayes said. "But it was frustrating because the primary population you need to reach for successful intervention — adolescents — do not come for care until it is too late."

So he returned to the field of medicine and took up the challenges of oncology, in particular lung cancer, which kills more people in the U.S. than breast, colon and prostate cancer combined.

"I knew that clinical practice was not going to be enough for me in the long term. I wanted a more diverse experience. I wanted to have interactions with colleagues and to teach, but I also wanted to keep contact and patient care going. In my clinical practice, I can make a huge difference daily to patients in cure, managing symptoms, supporting them and their families. At the same time, in my research I can move the whole field forward. The term I use for this is 'translational clinical research,' where research is designed around patients."

The research tool that tipped the scale came from Hayes' wife, Liza Makowski, a molecular biologist, who first described DNA microarray technology to him. Convinced that cancer was a genetic disease, in 2000 Hayes seized on the DNA microarray as a way to make that assumption visible to the physician and to use it to predict progression of the disease and decide about treatment. Moreover, this research path fit hand in glove with his daily clinical practice.

Hayes is quick to admit that the day when he can produce a DNA microarray in the clinic, look at the image and make a treatment decision may be a long way off. It will not happen this year, but, unlike many long-term research efforts that may take generations to mature, Hayes feels sure he will see his research put into practice.

"The DNA microarrays, our findings, are unlikely to be disputed," Hayes noted. "The fundamental finding that lung cancers can be classified by their DNA fingerprint is solid. These fingerprints are reproducible and reliable. However, the next step is to transfer from a microarray platform, which is difficult to implement for patient care, to something more practical. Right now, frozen tissue is used. We need a test that can be performed on paraffin-imbedded samples similar to a technique now in use for breast cancer."

In other words, there has to be a clinically viable and commercially available way to collect the samples and look at the DNA fingerprint. In a cancer such as lymphoma or leukemia, the clinician can work with a blood sample, so DNA microarrays have been in use for years. Solid tumors, such as lung cancer, are more difficult to sample and test.

Difficult but not impossible. For more than 30 years, the management of lung cancer has changed little. Hayes sees a mood of fatalism around lung cancer that reflects the historic view of the tumor. In many cases, because treatment must be based on a disease category and the prognosis for the patient population as a whole is poor, patients may even be undertreated. Doctors are reluctant to encourage treatment in this environment, and patients are pessimistic about the risk of uncomfortable treatments with unclear outcomes.

If DNA microarray analysis can be made clinically viable, this can change. And, as far as Neil Hayes is concerned, the next question is not if but when.

— *Susan Simone*