CANCER GENETICS

Test Could Yield Improved Colon Cancer Detection

During the past 10 years, cancer researchers have put a great deal of time, to say nothing of money, into working out the molecular and genetic events that cause cells to become cancerous. And their efforts have been scientifically very successful. They've identified a large number of genes whose malfunction contributes to cancer development. But, unfortunately, the work has so far had little impact on cancer patient survival. Now comes a new study from Bert Vogelstein of Johns Hopkins University School of Medicine and his colleagues suggesting that it may be possible to put some of that molecular genetic information to good use—in cancer detection.

"Very significant." The Vogelstein team (itself one of the leaders in the molecular genetic work), reports on page 17 that it can identify some people with colon cancer by screening stool samples to see if they contain certain mutant forms of the *ras* gene, one of several that are often defective in colon cancers. Sheila Taube, chief of the cancer diagnosis branch at the National Cancer Institute, calls the work "very significant in the sense that [Vogelstein] has begun to go in an important direction, applying some of the information about molecular genetic changes to patient diagnosis."

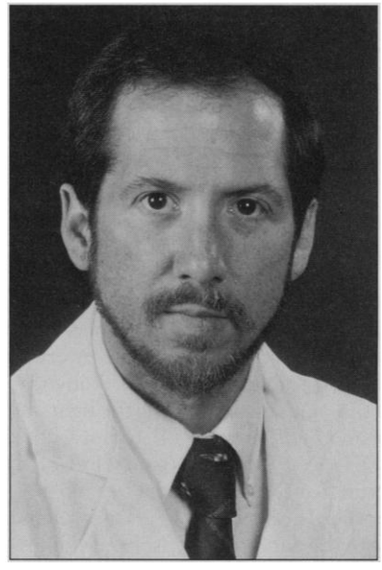
Indeed, because the Vogelstein group's method detects gene changes known to be associated with colon cancer development, it may lead to a more specific test for the disease. Now physicians usually screen for colon tumors by checking stool for "occult blood." But, says gastroenterologist Bernard Levin of M.D. Anderson Hospital in Houston, a collaborator in the Vogelstein work, many people who test positive don't actually have cancer, but have instead some benign condition, such as hemorrhoids, that can also cause bleeding, while many colon cancers are missed because they don't bleed.

The Vogelstein group's results also suggest that their new method has the potential to pick up colon cancers early, when they are most curable, although it's not yet capable of detecting all cases of what is the third most common cancer in the United States. This is because only about 40% have the *ras* gene changes. But it might be possible to extend the method to catch many more of the cancers by including screens for one or more of the other gene defects they are known to contain. The same general approach might also be applied to early detection of some other common cancers, including lung and bladder cancer.

While mutations in some half-dozen genes contribute to colon cancer development, Vogelstein says he chose the Kirsten variant of the *ras* gene for the current study partly because it generally mutates early in the course of the disease. In addition, the mutations primarily affect amino acids 12 or 13 of the protein encoded by the gene, and that makes it easier to screen for them than if they were spread out over the entire gene.

Still, there was no guarantee that the researchers would be able to detect the mutations in stool samples, even though they were expected to contain both normal and tumor cells shed by the colon lining, and thus the cells' genetic material. Not only is stool a very complex mixture, containing, among other things, bacteria, undigested food residues, and mucous, as well as shed cells, it is also loaded with enzymes that can break down nucleic acids and other biological materials. "So it wasn't at all obvious that stool would contain any human genes intact enough to analyze," Vogelstein says.

Despite these concerns, the researchers embarked on the study by obtaining stool samples from 24 patients scheduled to undergo surgery or colonoscope exams for suspected colon cancer. Analysis of tumor tissues removed from the patients showed that nine of them had *ras* gene mutations. The researchers then analyzed the stool samples of those patients, aided by polymerase chain reaction (PCR) techniques that enabled them to amplify the *ras* gene segments. The result: They detected *ras* mutations in eight of the nine, but not in any control stool samples.



Cancer gene detective.
Johns Hopkins' Bert Vogelstein.

And much to the team's gratification, the analysis proved easier than expected. "When David [Sidransky] and Takashi [Tokino] did the analysis, the mutant genes were present in the stool in a higher fraction than we anticipated," Vogelstein says. Also encouraging was the discovery that the mutations could be detected in stool samples from two patients with early lesions that had not yet become cancerous.

That finding suggests that screening for mutated *ras* or other genes in stool samples could ultimately be a good test for early colon cancer. That's important because colon cancer can be cured about 90% of the time when the tumor is still localized to the inner lining of the colon, but that figure plummets to less than 10% by the time it's metastasized to distant sites in the body.

What's more, says molecular biologist Jeffrey Trent of the University of Michigan School of Medicine, it might be possible to extend the gene-based detection method to screen for other tumors, including bladder cancers, which shed cells into the urine, and lung cancers, which shed them into sputum. "I'm very enthusiastic. You're going to see this used over the years," Trent remarks.

In fact, Vogelstein, his John Hopkins coworker Sidransky, and their colleagues demonstrated the feasibility of the approach with bladder cancer about a year ago by showing that they could identify p53 gene mutations in cells from the urine of bladder cancer patients. But a p53 screen won't help with early detection for bladder cancer, Vogelstein says, because the mutations don't crop up until the tumors begin invading surrounding tissue.

In spite of the apparent promise offered by the new cancer detection technique, a great deal more work will be needed before it can be used for widespread colon cancer screening—if it ever is. "In a screening modality you would have to go beyond *ras* and look at all possible mutations," says Taube. And then there is the issue of cost. PCR screening probably wouldn't come cheap, although it's too early to say just how expensive it's likely to be. Still, Taube says, at the very least the method would be "very appealing" for following people who are at high risk, either because they have a genetic predisposition to colon cancer or have already had a tumor removed.

And Vogelstein argues that even an expensive cancer test might be a bargain in the long run if it's very specific and doesn't pick up a lot of people who have to undergo further medical exams to find out that they don't actually have cancer after all, as is the case with the occult blood test. "If these mutations really are driving the neoplastic process, then they have to be among the best markers one could think of for detecting specific tumors," he concludes.

–Jean Marx