

MEDICINE

IN THE LAB

Inhale, exhale, wait for results

A billion times more sensitive than police breathalyzers, breath sensors may one day be used to routinely detect cancers, tuberculosis and diabetes.

By LINDA MARSA
Special to The Times

AFTER receiving a heart transplant in March, Michael Sinno endured painful monthly biopsies to make sure his body wasn't rejecting his new organ. In August, instead of going under the knife again, his doctor surprised him — by asking him to just breathe into a tube.

The device sampled his breath, then a lab checked it for key chemicals that would indicate rejection.

"It was such a relief... this was fast and I wasn't sore afterward," says Sinno, 56, of East Stroudsburg, Penn.

The tool, known as the Hearts-breath test, won't completely replace painful biopsies, but it can be a good adjunct and patients prefer it, says Dr. Mark Zucker, director of the Heart Failure Treatment and Transplant Center at Newark Beth Israel Medical Center, N.J.

It is one of a number of new diagnostic tests that stand to make detecting disease as simple as exhaling.

A billion times more sensitive than the breathalyzers police use on traffic stops, these breath sensors can already spot a diverse array of medical conditions: asthma, ulcers, trouble with a heart transplant. Trials are underway on breath tests for tuberculosis and the early detection of lung cancer.

Someday soon, some scientists predict, hand-held devices similar to a Palm Pilot may be routinely used for the early detection of breast, colon and other cancers, tuberculosis, diabetes and pre-eclampsia, the dangerous hypertension that sometimes occurs during pregnancy.

"All we need to know is the chemical fingerprint of a disease and we can devise a test for it," says Dr. Michael Phillips, an internist at the New York Medical College in Valhalla.

Phillips invented one of these devices, which is made by Menssana Research in Fort Lee, N.J. Small enough to sit on a tabletop, it consists of a powerful pump that sucks a patient's breath through a long steel tube. Carbon lining the tube absorbs the volatile organic compounds excreted in the breath, and a small carbon cartridge about the size of a pen is then analyzed in the laboratory.

First, a lab machine known as a gas chromatographer separates all the different molecules in the breath, then another, a mass spectrometer, identifies these chemicals.

The procedure itself is painless: The patient simply breathes into the tube for two minutes.

Recent tests of the Menssana device have been encouraging. In a 2003 pilot study of 201 women, some of whom had diagnosed breast cancers, the breath test identified 88% of those cancers. The test's accuracy is comparable to a mammogram.

And in a 2004 clinical trial that involved 407 volunteers, including 195 patients with untreated lung cancer, the breath test picked up nearly 91% of the tumors.

Researchers are now gearing up for a larger study of the device for detecting lung cancer in preparation for applying for FDA approval. If all goes well, the breath test could become the first effective screening tool for this disease — which could, doctors say, save thousands of lives.

Currently, there is no FDA approved method of lung cancer screening. As a result, only 21% of lung cancers are diagnosed early, at their most treatable stage.

What's more, "the screening tools we do use for lung cancer, such as chest X-rays or CT scans, have serious drawbacks — they're expensive, and they expose patients to small doses of radiation," says Dr. Robert Cameron, a thoracic surgeon at UCLA's Geffen School of Medicine, who helped conduct the lung cancer study.

The Menssana breath test is also being used in a clinical trial for tuberculosis, funded by the National Institutes of Health, which eventually will involve 3,000 patients in the United States, Mexico, Britain and the Philippines who are suspected of having TB.

Current TB tests are costly, time consuming and unreliable, says Dr. Antonino Catanzaro, a TB expert at UC San Diego who is conducting this research. So there is an urgent need for a quick and definitive diagnostic.

"The idea of a breath test is appeal-



EASY AND PAINLESS: Sensors detect disease by checking for key chemicals in the breath. The device developed by Dr. Michael Phillips of New York Medical College could become the first FDA-approved method of lung cancer screening.

Breath tests

Only six breath tests are currently used for medical diagnostics. In the last two years, the FDA approved Menssana's Heartsbreath — which identifies methylated alkanes, chemicals that are produced when the body is rejecting a newly transplanted heart — and a breath test for asthma that measures nitric oxide, a marker of airway inflammation.

Breath tests are also used to detect extra carbon dioxide and thus to diagnose jaundice in newborns, and to detect urea, a chemical that signals the presence of the ulcer-causing bacterium *Helicobacter pylori*.

ing because it is inexpensive and taking a sample is simple," Catanzaro says.

Before breath tests can be routinely used in a doctor's office, some technical hurdles need to be overcome.

Right now, a gas chromatographer and mass spectrometer are required to analyze breath samples — instruments that are "too big, too expensive and too slow," says Phillips. Faster and less expensive methods, such as ones using laser spectroscopy, are under development.

In addition, several research teams are busy devising miniaturized tools, so that breath samples could be analyzed on the spot instead of being dispatched to a lab.

"Everything should be the size of a shoe box," says Janusz Pawliszyn, an analytical chemist at the University of Waterloo in Ontario, Canada, who is testing a prototype of a portable sampling device.

Scientists are also in the early stages of crafting a hand-held breath monitor that patients can use at home, in the same way diabetics do blood tests. Within the next year or two, asthma sufferers may be able to avert an attack by using a portable device that alerts them to lung deterioration.

Someday, maybe we'll all tote around personalized breathalyzers to spot disease.

"This would be a cheap device... that you can just hand to every patient and tell them to call when they get a negative read," says Terence H. Risby, an environmental scientist at the Johns Hopkins Bloomberg School of Public Health who is developing such a portable appliance. "That's the future."



GIVING A SAMPLE: A demonstrator blows into a sensor that absorbs volatile organic compounds in the breath for later measurement.

In every breath, myriad chemical clues to illness

By LINDA MARSA
Special to The Times

Scientists have long known that when you get sick, it can sometimes show in your breath — if only you know what to look for. But only recently have they had the tools to detect trace chemicals produced by cells whose chemistry is going awry.

That discovery is feeding the next generation of breath tests.

Crucial to the test is not the shallow breath from the upper part of our lungs but the breath derived from alveoli, the tiny chambers at the tips of the bronchial air passages, deep inside. Alveoli are lined with membranes loaded with tiny blood vessels. The chemicals in the blood easily cross this membrane so that the alveolar breath "mirrors the composition of the blood," says Dr. Michael Phillips, inventor of one of these breath tests and an internist at the New York Medical College in Valhalla.

In one test under development, a combination of nine different volatile organic chemicals, including a principal one named nonane, and others known as octanes and propanes, have been found to be present in the breath of women who have breast cancer.

A combination of volatile chemicals, including ones named alkanes, are di-

agnostic of early lung cancer.

In both cases, the tests don't rely upon chemicals that are unique to these diseases, but rather to combinations of chemicals.

Although these new tests go further than ever before, smelling the breath to diagnose illness is not a new idea. Doctors dating back to Hippocrates have paid attention to patients' breath. Breath that smells of ammonia warns of kidney failure. A sweet sickly smell reminiscent of rotting apples can indicate uncontrolled diabetes. It's caused by the chemical acetone.

(Plain old stinky breath means our teeth may be rotten.)

In 1971, Nobel Laureate Linus Pauling ushered in the modern era of breath analysis when his research revealed that human breath contained more than 200 different organic compounds.

Because the technology wasn't yet available, he couldn't identify those chemical constituents with any degree of certainty.

Since then, armed with modern analytical equipment, scientists have identified hundreds of breath compounds. They also discovered that illnesses such as cancer, diabetes and heart disease trigger the excess production of volatile chemicals that leave their fingerprints in the air we exhale.