Scientific American, December 2003 (Innovations, pages 26-28)

Breath Takers

A quixotic career-long quest to diagnose disease simply by exhaling

By Gary Stix

In 1971 Linus Pauling published a paper in which he analyzed the constituents of human breath. His study showed that an exhalation contained about 200 different compounds, many more than had been previously suspected. In the mid-1970s Michael Phillips, at the time a thirtysomething physician from Western Australia working on his fellowship at the University of California at San Francisco, read the paper with fascination. Phillips was looking for a field of research to which he could devote himself. "Pauling opened up a new area of science," he says. "I thought: if all of these compounds are there, they must be signaling something. This grabbed my attention, and I've pursued it since."

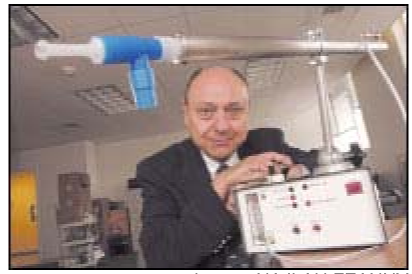

Image: NAJLAH FEANNY

DIAGNOSTIC PUFF MACHINE: Menssana Research chief executive Michael Phillips poses with an apparatus that collects breath that is then analyzed for the presence of a condition such as lung cancer or heart transplant rejection.

About a quarter of a century later, Phillips received preliminary approval from the U.S. Food and Drug Administration for a device that samples the breath of heart transplant patients for organ rejection in the first year after the operation, a supplement to regular biopsies. He hopes that last year's assent will soon be followed by endorsement from the agency to charge for the procedure. Checking breath would be potentially faster, simpler, cheaper and less invasive than biopsies or other procedures used to detect disease. Phillips's tiny company, Menssana Research, is considering development of breath analyses for ailments ranging from lung cancer to markers of biological aging. At the same time, he continues to battle deep-seated skepticism in the scientific community about the validity of Menssana's approach to creating a diagnostic breath sniffer.

The idea of making a diagnosis by examining breath is as old as medicine. Hippocrates observed that the aroma of a patient's exhalation could provide clues to disease. Today testing is done routinely to discern a compound such as alcohol or the breakdown product of a substance fed to a patient, which can confirm the presence of, say, the bacterium *Helicobacter pylori*, implicated in ulcers and other diseases.

In contrast, Phillips, like Pauling, attempts to measure more than a single compound. Formed in the 1990s, Fort Lee, N.J.–based Menssana looks at an entire spectrum of organic chemicals, elevated or diminished levels of which could serve as an indicator of disease. Early work proceeded by first freezing these volatile organic compounds using liquid nitrogen and then identifying the individual components with a gas chromatograph. But the collection device could be used only once, because an ice plug formed in the tube into which the subject blew.

When Phillips set up a laboratory at Bayley Seton Hospital on Staten Island in the late 1980s, he received a small grant that allowed him to adopt a different technical approach. He used an activated-charcoal adsorbent trap to capture volatile organics and a thermal desorber to bake off and concentrate the breath constituents—all equipment that was developed for conducting environmental tests. The chemicals are separated by a gas chromatograph and identified using a mass spectrometer. A statistical analysis then searches for a particular "fingerprint" of volatile organics that differs from that of a healthy individual and characterizes, for example, heart transplant rejection or the presence of a lung tumor. The theoretical basis for the breath tests stems from the increase in molecules with unpaired electrons called free radicals that are present in many disease conditions. Free radicals cause damage to certain lipid tissues, which results in higher production of a number of volatile organics.

Image: NAJLAH FEANNY

JUST BLOW: Michael Phillips demonstrates the use of Menssana's breath trap.

Phillips, also a clinical professor of medicine at New York Medical College, is widely credited for bringing some recognition to the nascent field of breath testing in a Scientific American article that is still cited today, even by detractors [see "Breath Tests in Medicine," by Michael Phillips; *Scientific American*, July 1992]. But he has at times taken an especially risk-laden approach to developing such diagnostics. One of the initial experiments performed during the early 1990s attempted to assess whether a breath analysis machine could diagnose schizophrenia by detecting high levels of pentane and another organic molecule, a finding that seemed to confirm the work of Russian researchers, who had seen a rise in the hydrocarbon pentane during the course of the disease. Phillips acknowledges that schizophrenia, whose biology is not well understood, was a poor first choice. "Looking back on it, it was not a smart move," he says. The 1993 paper based on the research was eventually published in the *Journal of Clinical Pathology* after numerous rejections and criticism.

"It's been a long slog," Phillips comments, adding, "I could paper the walls with the number of my grant applications turned down." One of the main objections from investigators in the small breath-testing community has to do with the organic molecules, called alkanes, measured by the company's assays. Critics contend that a particular fingerprint of alkanes—and alkane derivatives—may not be a product of a sick person's metabolism but rather turns up because of exposure to hydrocarbons from environmental sources, perhaps absorbed from passing vehicles. Phillips and his Menssana colleagues Joel Greenberg, Renee N. Cataneo and Irfan Munawar have tried to compensate for this problem. Samples are drawn from both the patient's breath and the room air. Then the measurements of substances found in the room's air are subtracted. What is left, they contend, should be constituents that result from metabolic processes.

But even this step does not satisfy doubters. Residues of hydrocarbons may persist in body fat for days. So merely taking room air out of the calculation may not suffice. Moreover, the amount of the specified alkanes being detected is so vanishingly small that other researchers question whether the disparity between the breath profile of a diseased and a healthy individual may be nothing more than a statistical fluke. "I don't want someone to come out with a test only to have it be measuring artifacts. That would hurt the field," says Terence H. Risby, a professor of environmental sciences at Johns Hopkins University who is developing breath tests using another method. Sydney Gordon of Battelle Memorial Institute in Columbus, Ohio, believes that if detection issues can be overcome, a more fruitful approach would be to look for nitrogen-, sulfur- or oxygen-based compounds, which might give a clearer signal. In addition, skeptics contend that Menssana's work has yet to be replicated by other laboratories.

Phillips remains a diehard optimist. And he has a response for any debating point. Clinical trials for heart transplant rejection and lung cancer tests show a statistically significant difference in alkane-related levels in the breath of patients with and without the conditions, he emphasizes. Both groups, he argues, have an equal likelihood of being exposed to car exhaust and other environmental contaminants, so the influence of external pollutants should not be a confounding factor.

No matter where these academic discussions go, the company will have to move quickly. It has survived for years on small-business grants from the National Institutes of Health. It has no venture capital. And the transplant rejection tests will probably not produce much revenue. Physicians are comfortable doing standard biopsies and, unless a biopsy is extremely difficult to perform, may be reluctant to utilize the novel breath exams.

Menssana has a clinical trial under way for lung cancer detection, and it has done a pilot study on breast cancer, research inspired by Phillips's wife, a breast-cancer survivor. In the longer term, Phillips contemplates tests for angina and environmental toxins. But it could be a while, if ever, before his vision for the future of this technology is realized: a Tricorder-like device reminiscent of *Star Trek* that lets a patient exhale into it before diagnosing any of a range of diseases.