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Impaired lung function, as measured by breathing apparatus, is a sign of COPD, but researchers are looking for easier and more reliable ways to diagnose disease.

DIAGNOSIS

To catch a killer

The first symptoms of COPD can be subtle, so the disease often goes undiagnosed. Researchers are searching for ways to detect the disease and to identify those most at risk.

BY CASSANDRA WILLYARD

In 1985, John Walsh began having trouble breathing. His doctor diagnosed him with asthma, but asthma medications didn't seem to help. John's non-identical twin brother, Fred, began having similar problems at about the same time. He too was told he had asthma, but asthma treatments didn't work for him either.

For years, the two men struggled to find a way to alleviate their symptoms. Then, in 1989, John got a phone call from his brother. "He said, 'I got good news and bad news,'" John Walsh recalls. The good news was that the brothers, who were 40 at the time, finally had a correct diagnosis. The bad news was that they had a genetic form of chronic obstructive pulmonary disease (COPD) — the same disorder that had killed their mother when they were 13 years old.

The Walsh brothers have a rare mutation in the gene *SERPINA1* (present in 5% of people with COPD) that causes them to produce an abnormal version of a protein called $\alpha 1$ -antitrypsin, which usually protects lung function. But the disease is common, killing millions of people each year, mainly as a result of exposure to tobacco smoke or airborne pollutants.

According to the World Health Organization, 65 million people worldwide have COPD, but the exact number is hard to pin down because many cases are not diagnosed. Data from the third National Health and Nutrition Examination Survey in 2000 showed that 24 million people in the United States had impaired lung function that might indicate COPD, but less than half had received a diagnosis of COPD.

Lack of awareness is part of the problem. COPD hasn't garnered the recognition that other chronic illnesses such as cardiovascular disease and cancer have, says Bartolome Celli, a doctor who specializes in lung diseases at Brigham and Women's Hospital in Boston, Massachusetts.

John Walsh — who is now president of the COPD Foundation, a non-profit organization based in Washington DC that advocates research and education — and health officials around the world are working to change that by launching massive awareness campaigns. Meanwhile, researchers are searching for new ways to identify individuals with COPD.

A SILENT EPIDEMIC

COPD comes on slowly, typically in individuals over the age of 50. The disease "sneaks up on

you", says James Kiley, director of the division of lung diseases at the National Heart, Lung, and Blood Institute (NHLBI) in Bethesda, Maryland. People often attribute their symptoms to normal ageing or to being out of shape, and thus they fail to seek medical care. For smokers, there may also be a sense of "I did it to myself", says Roger Goldstein, a doctor who specializes in respiratory medicine at the University of Toronto in Canada.

Because COPD symptoms resemble those of other conditions such as asthma, even patients who visit the doctor's office might be incorrectly diagnosed. In the early stages of the disease, people complain of "vague and minor symptoms that the doctor doesn't always associate with COPD", says Leonard Fromer, a family doctor who specializes in lung diseases at the University of California, Los Angeles. "It could be something like 'I can't play three sets of tennis anymore. I get tired too quickly.'" In some cultures, the doctor might not even ask about patients' smoking habits for fear that this might be "digging too much into people's private habits," says Anne Frølich, a doctor who studies chronic diseases at the University of Copenhagen.

Even a textbook case of the disease may be missed if the patient doesn't fit the stereotypical

COPD profile. Doctors have long been trained that COPD is a disease of elderly men who smoke, says Fromer. In 2001, for example, a team of researchers presented 192 general practitioners in the United States and Canada with a hypothetical case description that was indicative of COPD (Chapman, K. *et al. Chest* 119, 1691–1695; 2001). When the researchers said that the patient was a man, 58% of the doctors gave COPD as the most probable diagnosis. That dropped to 42% when the researchers said the patient was a woman. Yet, in the United States at least, more women than men are being diagnosed now, and more women have died from COPD each year since 2000 — perhaps because women are biologically more susceptible to developing the disease than men or perhaps because, as a group, they started smoking later than men.

Among men and women, awareness of COPD is on the rise. In 2007, the NHLBI launched the Learn More Breathe Better campaign. And, in February 2010, an awareness campaign called DRIVE4COPD was launched by the German pharmaceutical company Boehringer Ingelheim, which markets the widely used COPD medication Spiriva (tiotropium bromide) together with pharmaceutical giant Pfizer. Boehringer Ingelheim selected stock-car racer Danica Patrick as its celebrity spokesperson, and the DRIVE4COPD campaign, now led by the COPD Foundation, has screened nearly 2.5 million people via an online questionnaire. Participants are encouraged to share the completed questionnaire with their doctor or other health-care professionals. These campaigns may be paying off. A 2011 web-based survey by the NHLBI found that 71% of US adults say that they're aware of the disease, up from 65% in 2008.

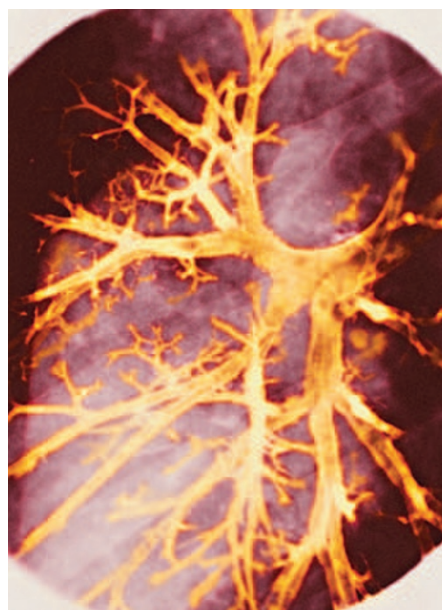
SEEKING THE SICK

In addition to lack of awareness, another factor that contributes to underdiagnosis is the diagnostic test itself. General practitioners and pulmonary specialists diagnose COPD based on a patient's medical history, symptoms and a lung function test called spirometry. The test requires the patient to blow into a tube as hard and fast as possible. A device then measures the total amount of air exhaled and the amount of air exhaled in 1 second.

Spirometry is simple, but it is not flawless. If the patient accidentally fails to blow hard enough, the results may mean little. "Thirty to forty per cent [of the test results are] pretty much uninterpretable," says David Mannino, an epidemiologist at the University of Kentucky in Lexington. Mannino is interested in devising alternative tests, such as one "where you see what happens to a person's blood oxygen as they hold their breath." But this research is still in the earliest stages: Mannino is currently putting together grant proposals. Other researchers are beginning to look for diagnostic biomarkers in the blood, urine and sputum. A peptide called *N*-acetyl-proline-glycine-proline, a by-product of the breakdown of collagen, has been found

in the sputum of COPD patients but not in the sputum of people without the disease. In addition, the protein fibrinogen, a marker of inflammation, appears to be elevated in the blood of people who have COPD, but it may be more useful for predicting future risk of exacerbations than as a diagnostic tool. One NHLBI initiative, the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS), aims to identify molecular markers of disease progression. Such markers may enable doctors to "find [pulmonary] lesions extremely early," Kiley says.

Besides developing better tools for diagnosing COPD, researchers are also trying to find ways to target screening efforts. Mass spirometry screening doesn't seem to be a good option. In 2008, the US Preventive Services Task Force found that health workers would need to screen roughly 450 adults between the ages of 60 and 69 to pick out a single person who might later



Damaged bronchi lead to a build-up of mucus and swollen bronchioles (orange).

develop symptoms of COPD severe enough to require a trip to the emergency department.

Mannino and Fernando Martinez, a lung specialist at the University of Michigan in Ann Arbor, were recently awarded a multimillion dollar grant by the National Institutes of Health to develop a more targeted method of diagnosis that could be used for screening programmes. They plan to combine a series of five simple questions on COPD risk factors — for example smoking status, wheezing and a chronic cough — with an easy-to-use, hand-held device that costs about US\$30 and measures peak flow (the fastest speed at which an individual can breathe out). Spirometers, by comparison, generally cost several thousand dollars each, and health workers need special training to learn how to use them correctly. Both factors may have led to the underuse of spirometers in developing nations (see "Where there's smoke," page S18). Patients with a

normal peak flow are unlikely to have clinically significant COPD. Patients who fare poorly on peak-flow tests could undergo a more thorough assessment, including spirometry testing.

COPD occurs when the tiny sacs inside the lungs, called alveoli, become damaged or chronically inflamed. This damage or inflammation leads to breathing troubles. Spirometers and other airflow-sensing devices give doctors information about airway obstruction, but such tests cannot directly assess damage to lung tissue, says Jan-Willem Lammers, head of the respiratory medicine department at the University Medical Centre Utrecht in the Netherlands. This damage can be seen in computed tomography (CT) scans. In fact, research conducted as part of the COPDGene study, which aims to identify common genetic factors that may subtly predispose people to the disease, found that CT imaging can identify lung deterioration in an individual before considerable airway obstruction occurs. The guidelines don't recommend treating individuals who are asymptomatic, but Walsh and others hope that therapies might one day be able to prevent symptoms in those who are found to have early stages of COPD-like lung damage.

CT scans aren't likely to become a screening tool just for COPD though. "That's going to be way too expensive, and people are going to be worried about the exposure to radiation," Walsh says. However, joint guidelines issued in May 2012 by the American College of Chest Physicians and the American Society of Clinical Oncology recommend that former and current heavy smokers of 55 to 74 years of age have a CT scan each year to screen for lung cancer. Those same images could also reveal signs of COPD.

Clearly, a diagnosis isn't a cure. It is unclear whether detecting the disease early will actually benefit many patients. Will it help them live longer or improve the quality of their lives over the long term? Research addressing these questions is surprisingly scarce, says Mannino.

But an earlier diagnosis might have changed things for the Walsh brothers. Today, John Walsh is hooked up to an oxygen tank when he sleeps. His lung function is one-third of what it should be for a man his age. His brother Fred Walsh needs oxygen around the clock, and he is waiting for a lung transplant. John can't help but wonder how their lives might have been different had they been correctly diagnosed sooner. If the men had known that their mother died of COPD — which they didn't fully realize until they themselves were diagnosed — would Fred have taken up smoking? Did Fred's lifestyle choices make his disease more severe than that of his brother, who has never smoked?

The Walsh brothers can't change their own past. John, however, hopes that organizations such as the COPD Foundation can change the future for others, and soon, he says: "I'm an impatient patient." ■

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