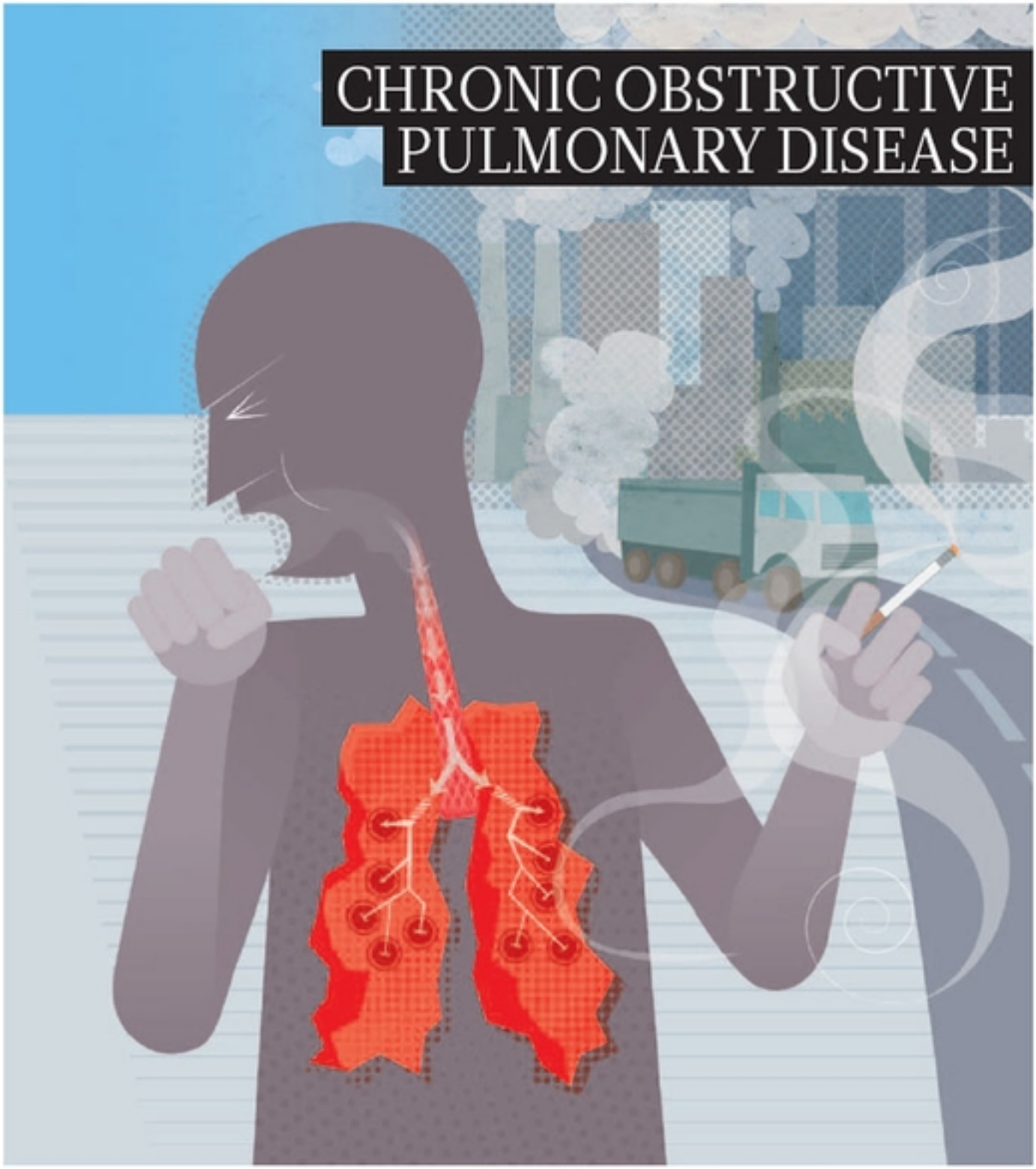
nature OUTLOOK

CHRONIC OBSTRUCTIVE PULMONARY DISEASE



Produced with support from:
NOVARTIS

Patients struggle for air, researchers struggle for answers

nature OUTLOOK

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

27 September 2012 / Vol 489 / Issue No. 7417

Cover art: Nik Spencer

Tens of millions of people around the world find it distressingly difficult to breathe owing to a combination of emphysema and chronic asthmatic bronchitis — a deadly duo known as chronic obstructive pulmonary disease (COPD).

Smoking is the most common trigger for COPD, and we have mapped the incidence of smoking and the prevalence of COPD in the United States, a country with fine-grained data on both phenomena (page S2). But there is more to COPD than smoking. Evidence is emerging that some people might be genetically susceptible to the disease (S7), while researchers are picking apart the involvement of errant immune cells (S15).

New treatments for COPD are in development. Hot areas of pursuit involve combinations of agents, as well as novel drug-delivery systems (S16). Most available treatments only abate COPD's debilitating flare-ups. One new line of enquiry is to stimulate the production of antioxidants to neutralize the free radicals that trigger the violent biochemical cascades that lead to the lungs' deterioration (S4). If the damage wrought is irreversible, artificial lungs might be an option (S12). And there are tantalizing early results that suggest that vitamin D supplements can at least slow the lungs' deterioration (S10).

No remedy for COPD will be effective if the condition is not properly diagnosed. Indeed, too often, the disease is mistaken for other, less serious ailments, and the standard doctor's office test is prone to error (S8).

While the decline in smoking in the West should lower the prevalence of COPD, other parts of the world have a rougher road to travel. COPD is expected to grow rapidly in China where tobacco use, smog and smoky cooking stoves portend a future of difficult breathing (S18).

We acknowledge the financial support of Novartis Pharma AG in producing this Outlook. As always, *Nature* has full responsibility for all editorial content.

Herb Brody
Supplements Editor

CONTENTS

COLLECTION

CHARLES THATCHER/ GETTY IMAGES

HEALTH IMPACT

Breathless

COPD is one of the world's biggest killers, but awareness is low, diagnosis is often missed, and in many countries the extent of the problem is not even well-documented.

BY AMBER DANCE

Worldwide, 65 million people with chronic obstructive pulmonary disease (COPD) are gasping for air — and with the World Health Organization (WHO) predicting the disease will vault from fifth to third in the leading causes of death globally by 2030, their breathless ranks are set to swell. Governments, scientists and pharmaceutical companies are taking several approaches to ease the burden of COPD, both on the patients and on healthcare systems.

COPD encompasses both emphysema and chronic asthmatic bronchitis; patients can suffer either problem or both simultaneously. Emphysema eats away at the lung's air sacs, or alveoli, so that less surface area is available for gas exchange. Bronchitis constricts the airways entering the lungs and clogs them with mucus. The winded masses face a disease that is incurable, even for those fortunate enough to receive a proper diagnosis and treatment for symptoms.

Surveys suggest that COPD is grossly underdiagnosed in both developed and developing nations. People don't always report the relevant clinical signs, and some doctors do not use spirometry, the gold-standard method of diagnosis, because they cannot afford the machine or haven't heard of it. A patient undiagnosed means a patient untreated, which could hasten death.

Although reliable numbers on global COPD rates are hard to come by, the WHO estimates that 90% of COPD cases occur in developing nations. COPD is likely to become an especially serious problem over the coming decades in China, the world's biggest producer and consumer of cigarettes. About a third of Chinese people smoke, among the highest rates in the world. Smoking-related diseases are the country's biggest killer, and COPD alone kills nearly two million people there each year.

Smoking is the major risk factor for COPD, but it is not the only one. Just 15% of smokers develop the disease. Presumably, their genetic makeup predisposes them to lung maladies. Scientists have known for decades that a mutation in the enzyme α1-antitrypsin, found in 1–2% of people with COPD, puts people at greater risk — especially smokers. In the past few years, genome-wide screens have netted a slew of new gene candidates, though not all have been confirmed as risk factors.

The manner in which smoke particles damage the lungs also remains uncertain. In addition to imbalances in enzymes such as antitrypsin, another potential culprit is the immune system. Most smokers suffer from inflamed airways. But those who develop COPD endure sustained inflammation, even after they quit smoking. Some scientists see this as evidence that COPD is an autoimmune disease. Supporting the hypothesis, researchers have found that some people with COPD possess antibodies against some of their own proteins.

Another potential modulator of the immune response in COPD is vitamin D. Several studies have shown that people with COPD are more likely to have a deficiency in the vitamin, and the less vitamin D they have, the worse their lungs work. Vitamin D may squelch the negative inflammatory response while promoting beneficial immunity, but researchers have yet to confirm its effect and work out the details.

Pharmaceutical companies are pursuing new and improved versions of current COPD treatments, such as the bronchodilators that relax airway muscles and ease breathing. Both Novartis, headquartered in Basel, Switzerland, and Pearl Therapeutics, headquartered in Redwood City, California, report promising data. And a collaboration between GlaxoSmithKline (GSK), headquartered in Brentford, UK, and Theravance, a biopharmaceutical company based in South San Francisco, California, is running several trials with a dual-drug combination. But another combined therapy from GSK and Theravance, Relovair, has yielded mixed results thus far. Fortunately, drugs are not the only option. Researchers are also at work on bioartificial lungs that they hope could reduce or even eliminate the need for donor organs.

Cigarette smoke is packed with free radicals, so antioxidants — which can neutralize their damaging effects — have also been tested in clinical trials. The results have been inconsistent, perhaps because each medicine only mops up a subset of the different types of free radicals ravaging the lungs. Some scientists have now turned their attention to Nrf2, a DNA-binding protein that switches on many of the body's own antioxidants.

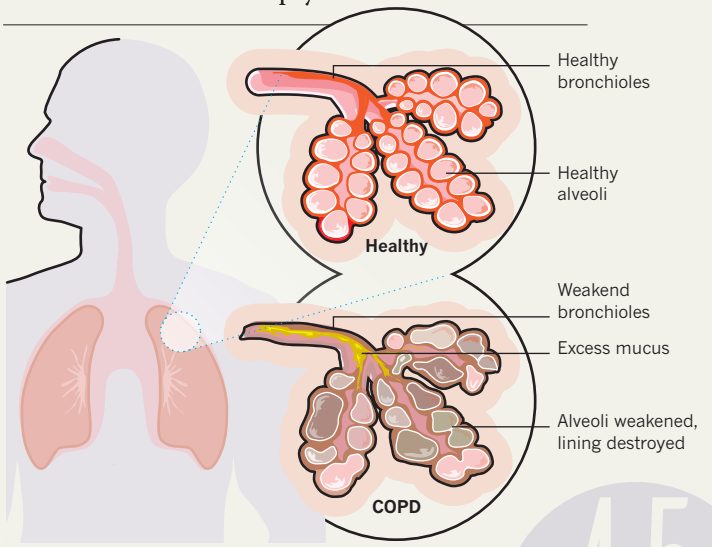
These treatments will be important weapons in the fight against COPD. But most are still confined to the lab rather than nearing the clinic — and scientists and health professionals must take aim at COPD now if they are to stem its rise. ■

Amber Dance *is a freelance science writer based in Los Angeles, California.*

COPD IN THE UNITED STATES

INSIDE THE LUNGS

It is not a single disease but a constellation of symptoms. And comes in two forms: emphysema and chronic bronchitis.



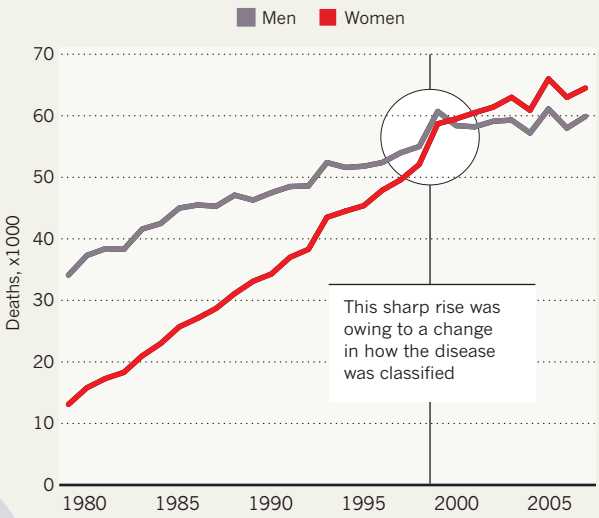
Patients with COPD suffer primarily because their alveoli, or air sacs, lose their elastic quality or are destroyed. The airways may also become thick and stiff, inflamed, or clogged with mucus, so that patients can take only shallow breaths.

4.5

A person dies of COPD-related illness every four to five minutes in the United States.

A DISEASE ON THE RISE

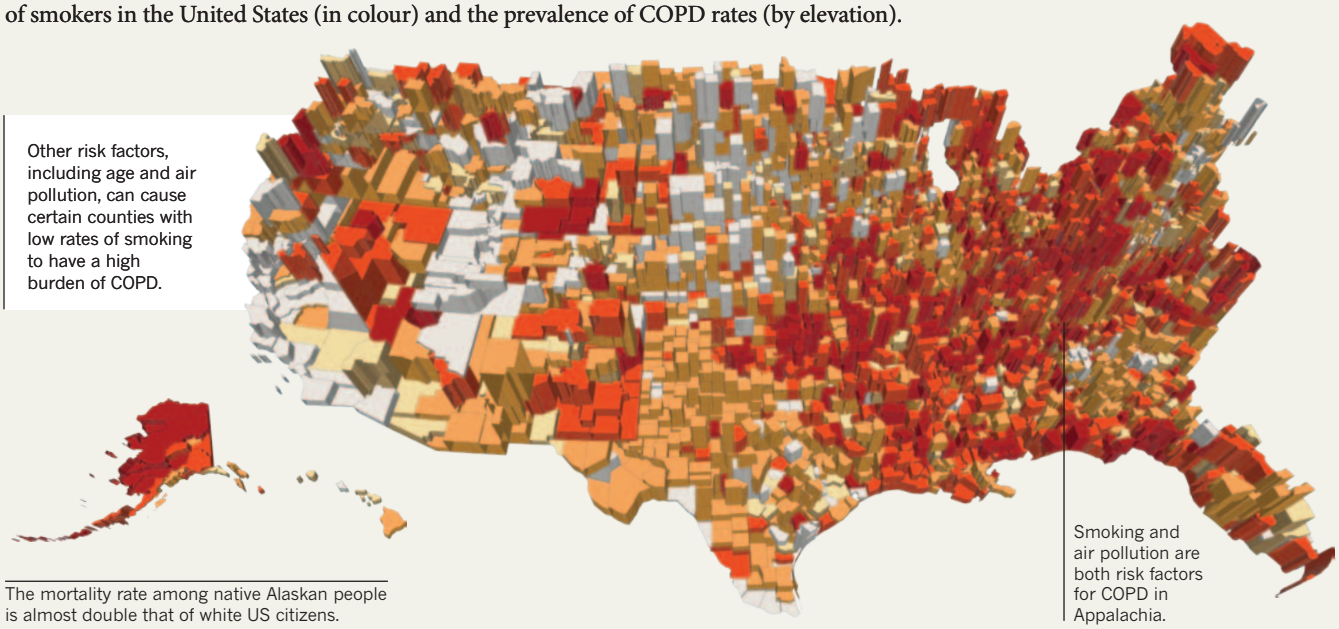
Of the ten most common causes of death in the United States, COPD is the only one with an increasing death rate.



The rise was fuelled partly by a sharp increase of COPD among women, who in 2000 became more likely than men to die of the disease owing to several trends including more women smoking at a younger age and doctors' increasing awareness of the syndrome.

SMOKE SCREEN

Tobacco smoking is the primary risk factor for COPD in industrialized countries. This map shows the prevalence of smokers in the United States (in colour) and the prevalence of COPD rates (by elevation).



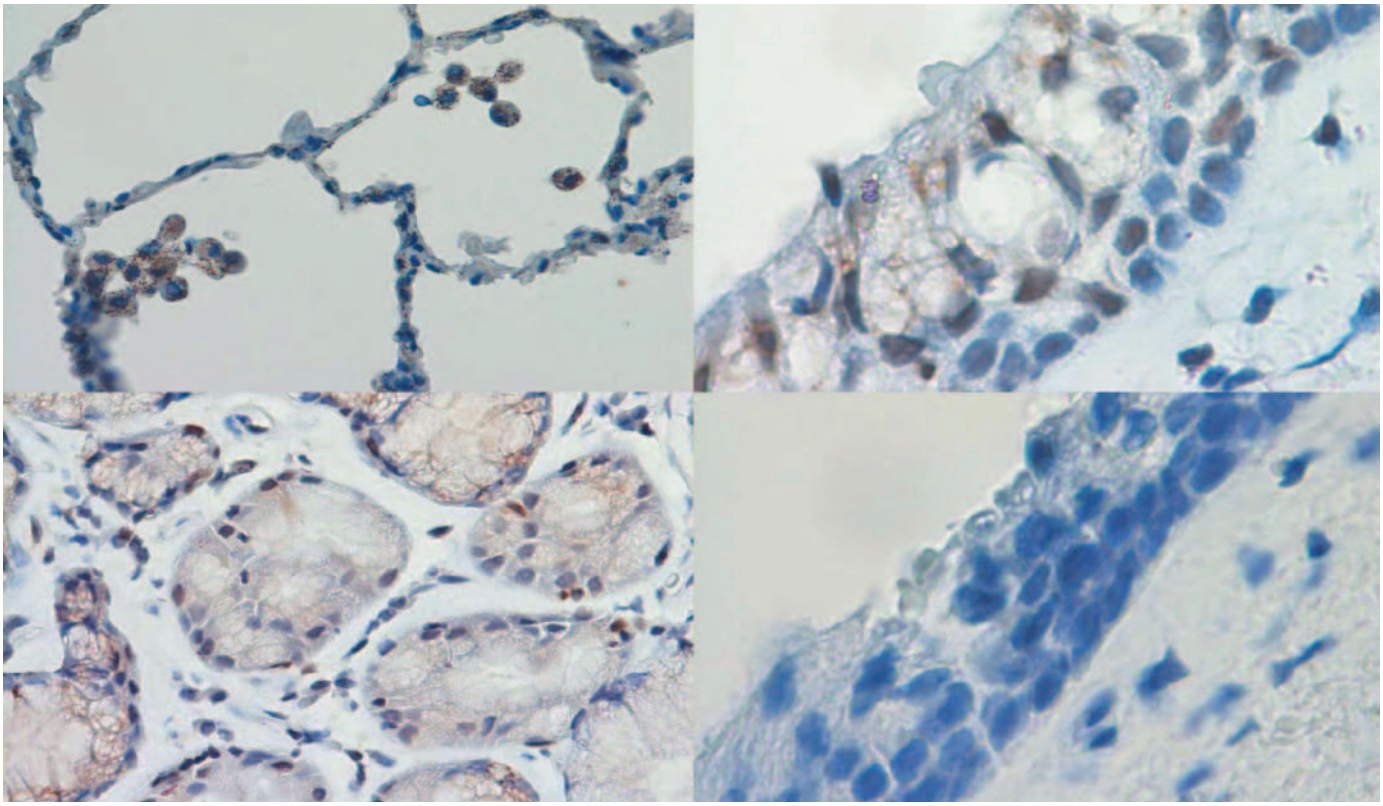
Smoking rates

>27 | 23–26 | 19–22 | 15–18 | <15

COPD rates

Counties are elevated by COPD prevalence

Data for 'A disease on the rise' came from the American Lung Association. Data for the map came from the American Lung Association and the CDC's Behavioural Risk Factor Surveillance System. Map illustrated by Chris Wilson.



IMPERIAL COLLEGE LONDON

Immune cells taken from the lung seen expressing the protein Nrf2 (brown) which acts as a master switch for genes that encode protective antioxidants.

BIOCHEMISTRY

A radical treatment

Researchers are counting on drugs that activate a master switch for antioxidant genes to protect lung tissue of COPD patients from an onslaught of free radicals.

BY KEN GARBER

Smoking is the most common cause of chronic obstructive pulmonary disease (COPD), a progressive condition characterized by lung damage, a narrowing of the airways and difficulty breathing. No surprise given that each puff of cigarette smoke contains more than 10^{15} free radicals — atoms or molecules with unpaired electrons that can react violently with other molecules, setting off chain reactions that damage proteins, lipids, and DNA. "In excess, [free radicals] will cause injury, and will cause impairment in the repair process," says biochemist Irfan Rahman of the University of Rochester in New York. "That's what happens in lungs in response to tobacco smoke."

COPD continues to progress long after a person quits smoking, and free radicals are partly to blame. COPD involves chronic inflammation, and inflammatory cells release abundant free radicals. As a result, the lungs of COPD patients exist in a constant state of oxidative stress — an imbalance of free radicals and antioxidants. Antioxidant enzymes convert free radicals to less reactive molecules, and antioxidant free radical scavengers donate electrons to halt free radical chain reactions. In COPD, the shower of free radicals overwhelms these antioxidants, causing cell death and tissue damage.

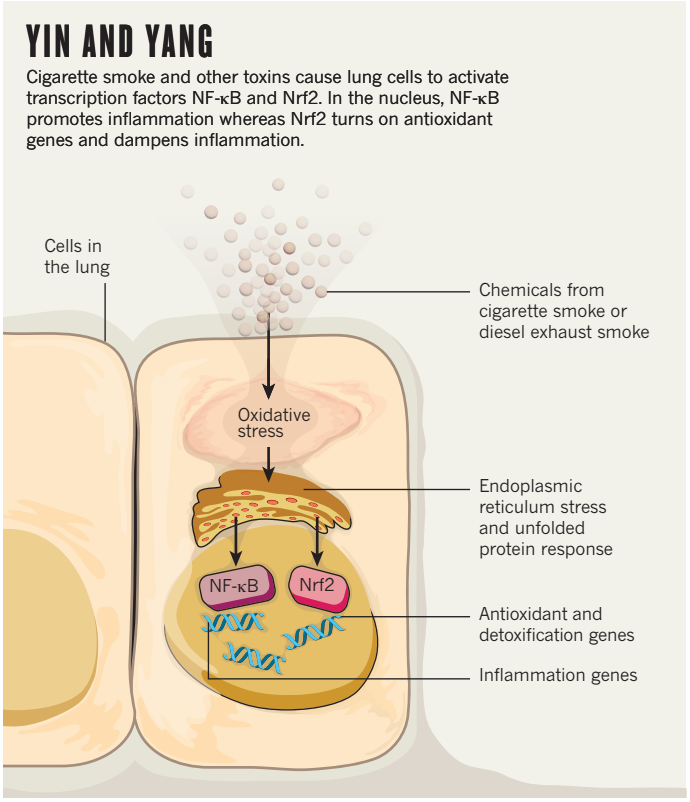
But clinical trials of antioxidants have mostly failed to prove they work as a COPD treatment. That may be because each chemical antioxidant molecule can extinguish only one target molecule; it is therefore impossible to quench more than a fraction of the excess free radicals even using high doses of antioxidants. Such antioxidants behave in a "sacrificial" manner, says Paul Kirkham, a biochemist at Imperial College London. "Once it's been used, it's gone." Another problem, says Kirkham, is that individual antioxidants may not reach the cellular compartment where they are needed most.

A new approach to COPD promises to solve these problems. Several drug companies are developing compounds that activate the DNA-binding protein Nrf2 (nuclear erythroid–related factor 2, also known as Nfe2l2), which acts as a master switch of genes that encode antioxidants. Nrf2 emerged from obscurity in 1997, when biochemist Masayuki Yamamoto at the University of Tsukuba in Japan showed that it activates an entire class of detoxifying enzymes. Among these enzymes are many that generate critical antioxidants.

Drugs that activate Nrf2, in theory, would solve the problems of dose and compartmentalization that have so far derailed other antioxidant therapies. To begin with, Nrf2-activated enzymes aren't spent each time they do their job. "They can effectively regenerate themselves — that's the beauty of an enzyme," says Kirkham. "So you need much less of it." Together, these enzymes neutralize a variety of free radical molecules, not just one, and in all important cell compartments. Finally, Nrf2 induces the expression of proteins that can repair some of the damage inflicted by free radicals.

Researchers have been studying Nrf2 in animal models of COPD for more than a decade, and in human tissue. It now appears that Nrf2

activators may potentially benefit COPD patients beyond triggering antioxidant and detoxification enzymes. Following Yamamoto's discovery, researchers assumed that Nrf2 activators would need to be administered early in the disease — in particular, before the lung tissue destruction typical of emphysema, one of the two main manifestations of COPD. (The other is bronchitis, inflammation of the bronchi, the main airways that go into the lungs.) But work by toxicologist Shyam Biswal at the Johns Hopkins University School of Public Health in Baltimore, Maryland, and others suggests that Nrf2 activators might be effective not only in preventing COPD progression but in treating advanced cases. And, unlike bronchodilator drugs, says Biswal, Nrf2 activators might not just treat the disease's symptoms but also arrest its course.



In 2004, Biswal's group found that mice genetically engineered to lack Nrf2 developed early-onset emphysema with more severe inflammation than did wild-type mice, and that this was a result of oxidative stress[1]. Moreover, exposing the mice without Nrf2 to cigarette smoke over six months caused comparatively more lung damage. Four years later, three different research groups reported that Nrf2 activity declines as COPD progresses in humans — suggesting some protective role for Nrf2. Then Biswal's group found that lack of Nrf2 activity in human COPD lungs caused defective protein clearance, which led in turn to more oxidative stress and cell death. Adding an Nrf2 activator to cells prevented these effects. The overall picture emerging from these studies is that Nrf2 is a key stress-response factor whose absence worsens COPD.

Nrf2 may also help clear harmful bacteria from the lungs of COPD patients. Such bacteria can cause COPD exacerbations — acute and potentially fatal bouts of increased coughing, mucus production and shortness of breath. Biswal's group found that adding an Nrf2 activator to cultures of macrophages (crucial host defense cells) taken from the lungs of COPD patients restored the cells' ability to clear bacteria in culture and in mice[2]. Biswal's group went on to show that Nrf2 in macrophages activates a scavenger receptor that recognizes pathogenic bacteria and enables the macrophages to clear infection — thus, in theory, limiting COPD exacerbations.

Finally, Nrf2 plays a crucial role in overcoming treatment resistance to corticosteroids, a mainstay in asthma therapy, which doctors often prescribe to COPD patients. Unfortunately these steroid hormones provide little or no therapeutic benefit in COPD. In fact, says Biswal, "steroids cause more problems in COPD than they help," mainly because steroid treatment can lead to pneumonia. An explanation for this corticosteroid resistance emerged in 2005, when pulmonologist Peter Barnes at Imperial College London reported that oxidants in cigarette smoke inactivated the enzyme histone deacetylase 2 (HDAC2), which normally blocks the expression of inflammatory genes. Corticosteroids reduce inflammation by signalling through a receptor that recruits HDAC2 and represses inflammatory gene expression. But in smokers and COPD patients, oxidative stress inactivates HDAC2 resulting in continuous inflammation and tissue damage.

"You've got to do the clinical trial and then see what happens."

By reducing oxidative stress, Nrf2 activators can reverse corticosteroid resistance, at least in cell culture. Biswal and his Johns Hopkins colleague Robert Wise are planning a clinical trial of treating COPD patients with the steroid prednisone and the Nrf2 activator sulforaphane. "This would be a logical approach," says Barnes. Sulforaphane is already in a phase II clinical trial for COPD, sponsored by the US National Institutes of Health. Cells extracted from the lungs of COPD patients will be tested to see if the drug raises levels of Nrf2.

But sulforaphane is not an ideal Nrf2 activator. It does activate Nrf2, but not always very potently, and because it targets many other proteins it could potentially cause collateral damage. And although safe at low doses (it is derived from broccoli sprouts), sulforaphane can be toxic at high doses. Hence an intense search for more selective Nrf2 activators is underway.

Drug companies are already heavily involved. In December 2011, in one of the largest preclinical deals ever, Abbott Laboratories, headquartered in Abbott Park, Illinois, agreed to pay US$400 million to Reata Pharmaceuticals, based in Irving, Texas, to license Reata's second-generation Nrf2 activators. Abbott executive vice president Thomas Freyman told investors in January 2012 that he expected the first of those compounds to enter clinical trials later in the year. Meanwhile, Cureveda, a Baltimore, Maryland, biotech firm cofounded in 2010 by Shyam Biswal, is screening compound libraries from the UK pharmaceutical company GlaxoSmithKline for pro-Nrf2 activity. Other companies are interested in targeting Nrf2, including Pfizer and Novartis, which are part of a consortium studying new therapeutic strategies for treating COPD, according to Kirkham.

Despite their great potential in COPD, Nrf2-activating drugs present possible safety issues. Nrf2 is usually inactive in cells, but is activated by spikes in oxidative stress. Using drugs to keep Nrf2 turned on could disrupt beneficial oxidative processes in cells. "The cell is actually maintained in a very fine redox [oxidation-reduction] balance, because it actually needs oxidative stress to do some of its signaling," says Kirkham. Biswal concedes that continuous activation of Nrf2 could cause side effects. "You've got to do the clinical trial and then see what happens," he says.

Then there is the evidence that Nrf2 might increase the risk of cancer. In 2008, a group at Japan's National Cancer Research Institute in Tokyo reported apparent Nrf2-activating mutations in human lung tumours and in head and neck tumours[3]. In their report, they contend that ongoing activation of Nrf2 might give cancer cells "undue protection from their inherently stressed microenvironment." In 2011, two groups reported that in mouse models Nrf2 is indirectly activated by mutations that cause hereditary kidney cancer in humans. And a group from the Cambridge Research Institute, part of Cancer Research UK, found that three common cancer-causing genes activate Nrf2, which may promote tumorigenesis by reducing oxidative stress in

pre-cancerous cells[4].

But, paradoxically, activated Nrf2 can also have anticancer effects. Several studies have found that Nrf2-activating compounds can prevent or suppress cancer in mouse models. And a recent study found that sulforaphane did not promote lung cancer in mice. Pharmacologists Mike Sporn and Karen Liby at Dartmouth College in Hanover, New Hampshire, explain that Nrf2 can either promote or suppress cancer depending on the cellular context[5].

Safety concerns about Nrf2 activators in COPD have been lessened by trials of two Nrf2-activating drugs in other diseases. Weston, Massachusetts-based Biogen Idec recently completed phase III clinical trials of dimethyl fumarate (DMF) for multiple sclerosis. Although DMF wasn't designed as an Nrf2 activator, the company claims it works at least partly that way. And Abbott and Reata are jointly developing bardoxolone methyl, another unintentional Nrf2 activator that's now in phase III trials for chronic kidney disease in type 2 diabetes. Side effects of bardoxolone methyl have been mild. Side effects reported for DMF include abdominal pain, diarrhea, flushing and headaches. On the other hand, it is too early to assess the risk of cancer — any cancers would likely take many years to appear.

Clinical trials should soon determine if Nrf2 can help resolve the many problems in COPD, from oxidative stress to inflammation. "COPD is a multifactorial disease — it's one of the worst," says Biswal. Harnessing the power of Nrf2, that prolifically protective protein, may eventually prove to be the solution. ■

Ken Garber *is a freelance science writer based in Ann Arbor, Michigan.*

1. Rangasamy, T. *et al. J. Clin. Invest.* **114**, 1248–1259 (2004).
2. Harvey, H. *et al. Sci. Transl. Med.* **3**, 78ra32 (2011).
3. Shibata, T. *et al. Proc. Natl. Acad. Sci.* **105**, 13568–13573 (2008).
4. DeNicola, G. M. *et al. Nature* **475**,106–109 (2011).
5. Sporn, M. B. & Liby, K. T. *Nat. Rev. Cancer* **8**, 564–571 (2012).
6. Lee, S.H. *et al. Nature Med.* **13**, 567–569 (2007).
7. Shan, M. *et al. Sci. Transl. Med.* **1**(4):4ra10 (2009).
8. Chen, K. *et al. PLoS One* **6**, e2033 (2011).
9. Shan, M. *et al. Sci. Transl. Med.* **4**, 117ra9 (2012).

AUTOIMMUNITY

The T-cell connection

What exactly causes the destruction of lung tissue in emphysema? Free radicals definitely contribute, but for half a century, the prevailing hypothesis has been that emphysema, one of the two main aspects of COPD, develops when the activity of proteases — enzymes that digests proteins — falls out of balance with antiprotease activity. Proteases normally help maintain lung health by clearing roadblocks from the path of migrating immune cells hunting pathogenic viruses and bacteria. But cigarette smoke stimulates immune cells such as macrophages and neutrophils to release too many proteases, and wanton destruction of proteins ensues. Mysteriously and inexorably, this process continues in COPD patients even after they stop smoking, as emphysema slowly suffocates them.

That mystery is now beginning to be solved, as clues implicate autoimmunity. Th17 cells — a specialized class of $CD4^+$ T cells, the cell type that orchestrates the adaptive immune response — appear to be central to the pathology. Therefore, therapies targeting these cells might be a promising strategy.

Early evidence for autoimmunity in COPD came in 2007, when Farrah Kheradmand, a pulmonologist and immunologist at Baylor College of Medicine in Houston, Texas, isolated $CD4^+$ T cells from the blood of ex-smokers with COPD[6]. Elastin is an important structural protein in the lungs' connective tissue, and when Kheradmand added elastin fragments to these T-cell cultures, the T cells responded by releasing inflammatory cytokines as if the cells had encountered a microbial pathogen. "A large number of patients who have emphysema [who] stop smoking and continue to have the disease will have these autoreactive T cells," says Kheradmand.

Why the body attacks its own lung tissue remains unknown. But by isolating the cells driving this autoimmunity, scientists can identify potential drug targets. Th17 cells, which secrete the inflammatory cytokine IL-17, are the main drivers of autoimmunity in rodent models of rheumatoid arthritis, psoriasis and multiple sclerosis. Th17 cells are also present in COPD. In 2009, Kheradmand's group found that culturing certain cells of emphysema patients with their own T cells drove those T cells to release IL-17, which in turn led to the production of destructive proteases[7].

Evidence for IL-17 driving autoimmunity in COPD continues to be found. In 2011, University of Pittsburgh, Pennsylvania, pulmonologist Jay Kolls reported that mice genetically lacking the IL-17 receptor did not develop emphysema despite six months of exposure to cigarette smoke[9]. More recently, Kheradmand and collaborators at the MD Anderson Cancer Center in Houston, Texas, genetically engineered mice to overexpress one form of IL-17 — IL-17A — and then exposed these mice to cigarette smoke for four months[8]. The mice developed an especially severe form of emphysema along with producing more destructive proteases. Both studies fingered IL-17 as a culprit in COPD autoimmunity.

The picture emerging from these studies is that inhalation of cigarette smoke promotes the generation of T cells that express IL-17, which, in turn, causes the production of proteases that destroy lung tissue including elastin. Then, elastin fragments trigger an autoimmune response involving more IL-17-producing T cells, perpetuating a loop and more tissue destruction.

To disrupt this vicious cycle, pharmaceutical and biotech companies could test drugs they already have in hand that target these cells and the cytokines they produce. Antibodies specific for IL-17 and its receptor have been very effective in clinical trials for psoriasis. As for COPD, "I don't know if it is on the radar screen of these companies yet, but I think [IL-17] would be definitely an intriguing target," says Kolls. He is collaborating with an undisclosed company, testing whether anti-IL-17 receptor antibodies can treat COPD in mice.

Others are more ambivalent. "It would certainly be worth studying IL-17 or IL-17 receptor blockers," says Peter Barnes, a pulmonologist and COPD researcher at Imperial College London. He adds that such trials are planned. But he cautions that Th17 cells may not play the same role in human COPD as in the mouse version of the disease; indeed, he says, the evidence for increased Th17 cells in human COPD lungs is "not as striking" as it is in mice. "The evidence for Th17 cells playing an important role in COPD is not fully established," he adds.

Kheradmand disagrees. She says that IL-17 is "very much present" in lung tissue of human COPD patients. And Kheradmand points out that each case of emphysema is different, with not all manifesting autoimmunity. Her lab at Baylor College is developing an assay to identify COPD patients with an autoimmune form of the disease driven by Th17 cells, and hopes companies will eventually test their drugs in such patients. "Wouldn't it be wonderful," she asks, "if we can just identify this particular individual… who does have this autoimmune component, to then offer him these biologics?" — **K.G.**

PERSPECTIVE

How can genetics help?

Smoking and COPD have one of the strongest relationships in clinical epidemiology. But don't forget the genetics, says **Edwin K. Silverman**.

Many people who develop chronic obstructive pulmonary disease (COPD) blame themselves rather than the tobacco industry, which continues to promote cigarette smoking though the dangers are well-known. This disturbing 'blame and sham' attitude among patients is based on one of the most well-established associations in clinical epidemiology: the causal relationship between cigarette smoking and COPD. Exposure to cooking stove smoke from biomass fuels is also an important COPD risk factor in some parts of the world.

Although these environmental risk factors are strong, recent research suggests that genetics also plays a key role in COPD. Identifying genetic determinants and investigating their functions may lead to important progress in COPD pathobiology, diagnosis and treatment. It could also help patients understand that the disease is not their fault.

Genetics provided one of the first clues regarding COPD pathogenesis. A small percentage of patients inherit severe α1-antitrypsin deficiency (A1ATD), a well-characterized, rare syndrome that often includes COPD. The discovery of A1ATD nearly 50 years ago led to the protease–antiprotease hypothesis for COPD, which postulates that lung destruction results from an excess of protein-degrading enzymes relative to their enzyme inhibitors. This hypothesis remains important in current COPD pathobiology.

Not all smokers are equally likely to develop COPD. An underlying susceptibility appears to run in families. Indeed, familial studies of severe, early-onset COPD patients without A1ATD suggest other genetic risk factors. Smokers who are first-degree relatives of these subjects are about three times more likely to develop COPD than are smokers in general. Non-smokers who are first-degree relatives of these subjects are not at increased risk[1], suggesting that genetic factors may interact with smoking.

As with other complex diseases — those influenced by multiple genetic and environmental factors — many studies of candidate genes have failed to replicate. Yet subsequent genome-wide association studies (GWAS) have found four genomic regions associated with COPD that meet the stringent standard for statistical significance in genome-wide studies[2–5].

Two of these genomic regions, near the *HHIP* and *FAM13A* genes — the former a member of the developmentally essential hedgehog pathway, the latter a gene of unknown function — are also associated with variations in lung function levels in samples taken from the general population[5,6]. An association with lung function does not in and of itself prove susceptibility to COPD; genes that influence traits that vary among healthy people, such as height, are not always the same ones that influence pathological conditions, such as dwarfism. However, the associations of COPD to genomic regions near *HHIP* and *FAM13A* are convincing. They have been replicated in several studies, and a potential functional genetic variant that regulates *HHIP* gene expression has been found upstream from *HHIP*[7]. Further study of *HHIP* and *FAM13A* may identify new biological pathways involved in COPD.

The other two regions identified by GWAS, on chromosome 15 and chromosome 19, include many genes of interest, including several related to nicotine addiction. The chromosome 19q region has been associated with smoking behaviour; it is the location of the gene *CYP2A6*, involved in nicotine metabolism. Similarly, the chromosome 15q25 region, which contains genes for several components of the nicotinic acetylcholine receptor, has been convincingly related to smoking behaviour. The same region also contains the gene *IREB2*, which encodes an iron binding protein that has been potentially linked to COPD susceptibility.

The overwhelming association between COPD and smoking provides a unique opportunity to understand the relationships between environmental and genetic influences on risk of disease. In most complex diseases, environmental factors are either unknown or difficult to measure. Cigarette smoking behaviour, on the other hand, can be accurately quantified. Of course, genes and the environment are intertwined; genetic determinants of nicotine addiction may influence exposure to COPD's key environmental risk factor. Furthermore, the risk from smoking suggests that epigenetic factors may also influence COPD pathogenesis[8].

The next generation of genetic research on COPD will include studies of rare genetic variants assessed by sequencing or genotyping the variants in patients' exomes (the protein-coding portions of the genome) and ultimately by sequencing their entire genomes. Advances in computational biology and phenotype characterization based on imaging and clinical observation will also be needed in coordination with genetic studies to dissect the COPD syndrome into groups of patients with different subtypes — an initiative with both diagnostic and therapeutic implications. COPD is highly heterogeneous, with variable amounts of emphysema and airway disease. Integrating genetic studies with chest computed tomography (CT) scans has already identified the *BICD1* gene as a potential determinant of emphysema.

GENETICS COULD HELP PATIENTS REALIZE IT'S NOT THEIR FAULT

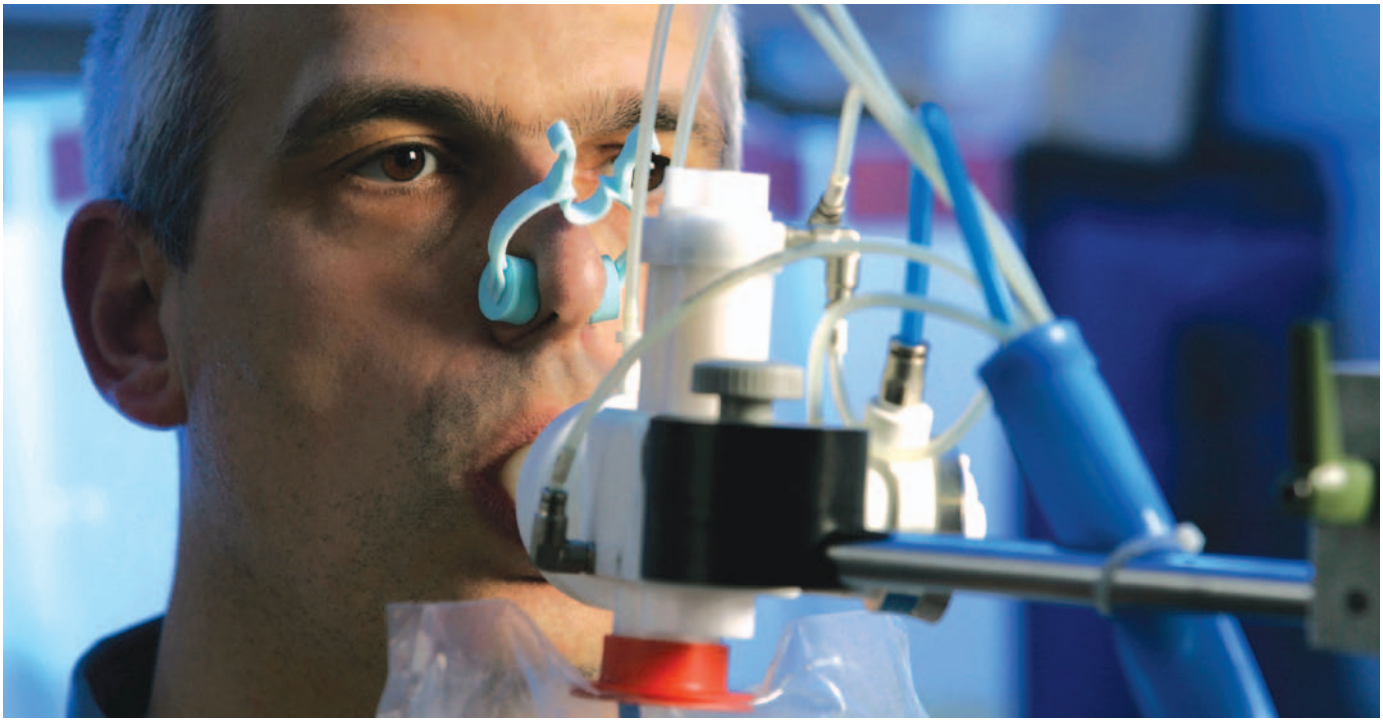
However, comprehensive understanding of the complex pathobiology of COPD will probably require the integration of multiple -omics data types (for example, proteomics, transcriptomics and metabolomics) with detailed phenotypic assessment, epigenetics, and genetic variants using systems biology and network science approaches.

Avoiding tobacco smoke will always be an essential public health message. But for millions already suffering, advances in genetics, pathophysiology and phenotyping may lead to new opportunities for specific diagnosis and personalized treatment of COPD. ■

Edwin K. Silverman *is chief of the Channing Division of Network Medicine at Brigham and Women's Hospital in Boston, Massachusetts, and associate professor of medicine at Harvard Medical School.*
email: ed.silverman@channing.harvard.edu

1. Pillai, S. G. *et al. PLoS Genet.* **5**(3), e1000421 (2009).
2. Wilk, J. B. *et al. PLoS Genet.* **5**(3), e1000429 (2009).
3. Cho, M .H. *et al. Nature Genet.* **42**, 200–202 (2010).
4. Cho, M. H. *et al. Hum. Mol. Genet.* **21**, 947–957 (2012).
5. Hancock, D. B. *et al. Nature Genet.* **42**, 45–52 (2010).
6. Repapi, E. *et al. Nature Genet.* **42**, 36–44 (2010).
7. Zhou, X. *et al. Hum. Mol. Genet.* **21**, 1325–1335 (2012).
8. Wan, E. S., *et al. Hum. Mol. Genet.* **21**, 3073–3082 (2012).

The author would like to acknowledge helpful discussions with Craig Hersh, Michael Cho, Dawn DeMeo, Scott Weiss and James Crapo. The author declares a conflict of interest go.nature.com/tah34c



ANTONIA REEVE/SCIENCE PHOTO LIBRARY

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 α1-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.

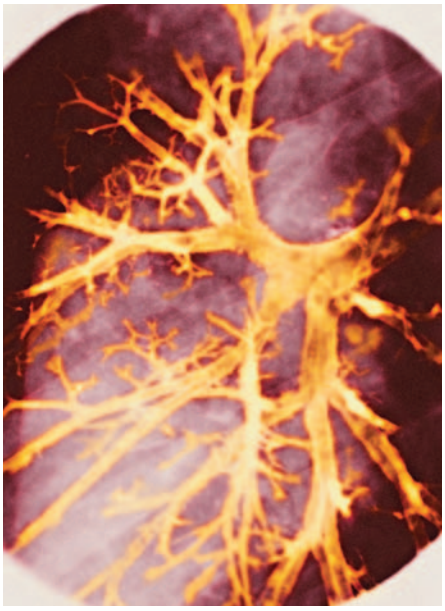
Among men and women, awareness of COPD is on the rise. In 2007, the NHLBI launched the Learn More Breathe Better campaign. And, in February 2010, an awareness campaign called DRIVE4COPD was launched by the German pharmaceutical company Boehringer Ingelheim, which markets the widely used COPD medication 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 healthcare 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 develop symptoms of COPD severe enough to require a trip to the emergency department.



CNRI/SCIENCE PHOTO LIBRARY

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

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.

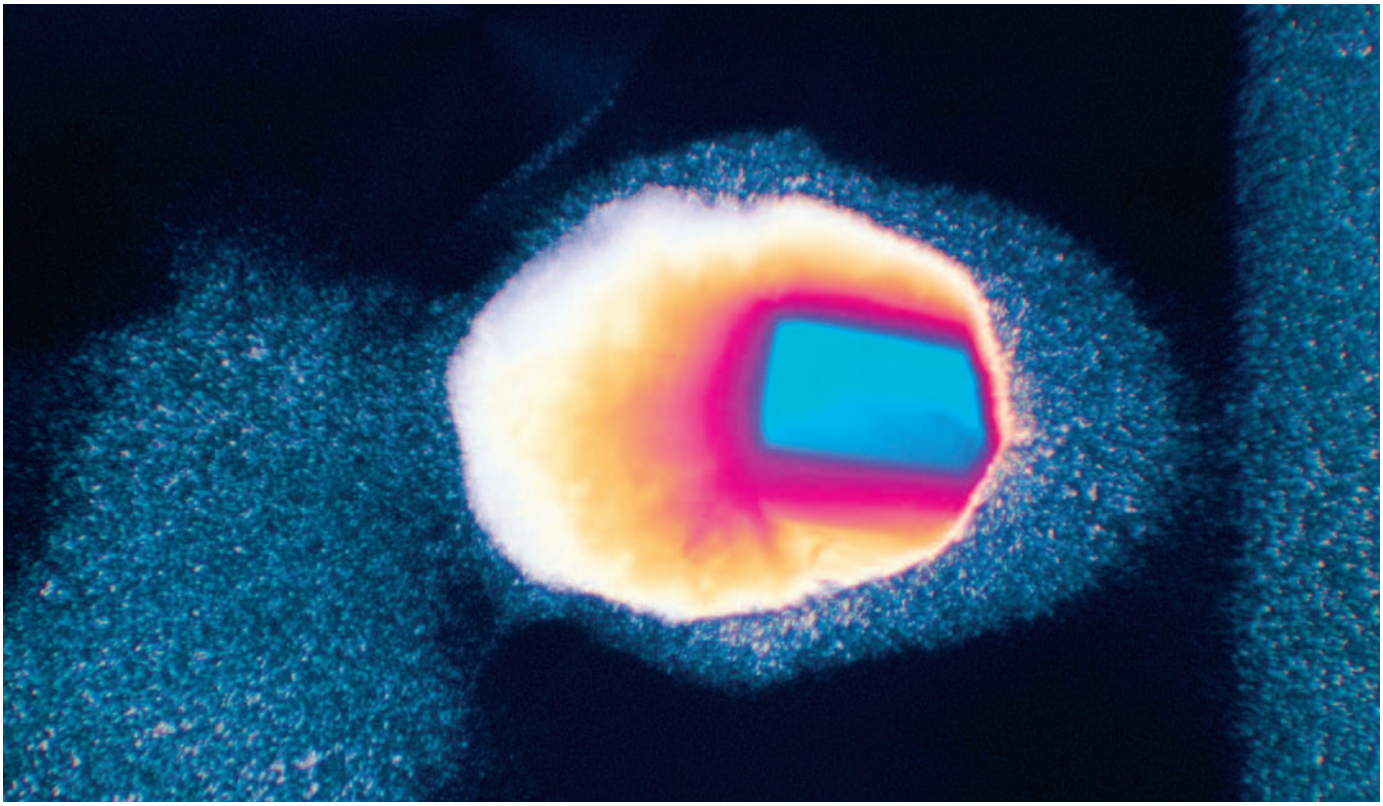
CT scans aren't likely to become a screening tool just for COPD though. "That's going to be way too expensive, and people are going to be worried about the exposure to radiation," Walsh says. However, joint guidelines issued in May 2012 by the American College of Chest Physicians and the American Society 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." ■

Cassandra Willyard *is a freelance writer based in New York.*



DAVID PARKER/SCIENCE PHOTO LIBRARY

Vitamin D_2, shown in its crystalline form, can be used as a dietary supplement and is being studied for its therapeutic effects in patients.

NUTRITION

The vitamin D complex

Many COPD patients are deficient in vitamin D, a condition that can lead to bone problems as well as difficulty breathing. Can dietary supplements be of help?

BY THEA SINGER

My sister, Candice Singer, was a smoking fiend. Hooked since age 12, she was up to two packs a day by the time she started university, eventually rolling her own cigarettes to save money. In 2010, at age 50, she was diagnosed with chronic obstructive pulmonary disease (COPD) and needed to wear an oxygen mask at night to regulate her breathing while she slept.

When she finally quit smoking, seven months ago, her vitamin D level was an alarmingly low 8 nanograms of 25-hydroxyvitamin D (25-[OH]D) — the major circulating, though inactive, form of vitamin D and used to measure sufficiency — per milliliter of blood serum. The Institute of Medicine (IOM), a non-profit group afilliated the US National Academy of Sciences, defines vitamin D sufficiency at over twice Candice's level — 20 ng/mL. And The Endocrine Society, an international group of endocrinologists, set an even higher sufficient range of 40–60 ng/mL.

That's for good reason. Vitamin D deficiency can lead to osteoporosis and osteomalacia, a fragility and a softening of the bones. Candice came to know the symptoms, with pains in her feet and back. And new research suggests that patients like Candice have other things to worry about, as vitamin D deficiency may affect more than the skeleton — even the ability to breathe.

A COPD-VITAMIN D LINK?

COPD is primarily an inflammatory disease. The predominating hypothesis holds that cigarette smoke damages the lung's tissue, sparking an innate immune response. Immune cells, including macrophages and neutrophils, rush into the lungs to protect the cells lining the airways from the smoke, releasing reactive, oxygen-containing molecules along the way. Antimicrobial peptides, a group of molecules that damage and kill microorganisms, join the fray, as do pro-inflammatory T cells stimulating the production of antibodies of as yet unknown specificity.

In smokers, this proinflammatory response is relentless. In the emphysema form of COPD, holes appear in the alveoli — the tiny, balloon-like structures in the lungs where oxygen and carbon dioxide are exchanged. And in response to noxious stimuli, the smooth muscle beneath the epithelial and connective layers of tissue contracts and expresses adhesion molecules, cytokines, chemokines and growth factors[1]. Over the years, this muscle thickens. "Think of it as weight lifting," says Reynold Panettieri Jr, professor of medicine at the University of Pennsylvania in Philadelphia. "If you keep lifting weights, your muscle bulks up — it gets thicker. And the problem with thicker is that the [airway becomes narrower] simply by the increased mass of the muscle." Hence the shortness of breath that characterizes COPD. Most of the inhalant corticosteroids and some other medications for COPD aim to relax that stiffened muscle.

This is where vitamin D comes in. Nearly every cell in the body has a surface-bound

receptor that directs vitamin D to the nucleus. In fact, about 3% of the human genome is regulated by the active form of vitamin D, 1,25-dihydroxyvitamin D[5]. Studies of human cells in culture, have shown that vitamin D stunts the growth of human airway smooth muscle cells[6]. This effect, says Panettieri, is even more pronounced than that induced by inhaled steroids. Moreover, during an infection — a common occurrence in COPD patients given their compromised lungs — vitamin D aggravates the misfiring immune response. Studies have also found a link between vitamin Ddeficiency and autoimmune diseases including multiple sclerosis and rheumatoid arthritis[2,3,4].

SEARCHING FOR PROOF

It is not known whether vitamin D deficiency can cause COPD, but there's evidence that it may be involved in its pathogenesis. One epidemiological study found vitamin D deficiency in more that 60% of patients with severe COPD, and the more severe the disease, the worse the deficiency[5]. Research presented in May 2012 at the American Thoracic Society's annual meeting found that a three-year decline in a crucial metric of breathing, forced expiratory volume (FEV1), was linked to vitamin D deficiency. The decline was so steep it is comparable to the effects of smoking[6]. And a 2011 study in mice found that vitamin D deficiency causes deficits in lung function[7].

So if vitamin D levels correlate with the severity of COPD, could a dietary supplement of the vitamin — which the body synthesizes from the sun's ultraviolet-B (UVB) — help abate the debilitating condition? There are few studies that have given vitamin D to COPD patients.

A randomized, double-blind placebo-controlled study, the gold standard of clinical trials, led by pulmonologist Wim Janssens at University Hospitals Leuven, Belgium, had mixed results. Patients 50 years of age or older with moderate to very severe COPD were given large doses of vitamin D or a placebo at 4-week intervals for a year. The researchers then recorded the incidence of COPD exacerbations — a worsening of respiratory symptoms over 48 hours — and monitored blood serum levels of 25-[OH]D.

In the supplemented group, mean levels of 25-[OH]D increased (to 52 ng/mL) compared to the placebo group. But there was no improvement in the timing and frequency of exacerbations, FEV1, or rates of hospitalization and fatality[8]. "The main message of the paper is a null message," says Janssens.

Despite discouraging results, Janssens remains convinced that vitamin D deficiency plays a role in COPD progression and that dietary supplements might slow the course of the disease. Janssens' team took another look at the trial's data and found that those with the most severe deficiency — 30 patients with baseline serum 25-(OH)D levels below 10 ng/mL — had 43% fewer exacerbations over the year.

That analysis matters, says Panettieri, noting the treatment's potential efficacy in certain subgroups. He explains that vitamin D, in high enough doses, can act as an anti-inflammatory. But, he says, the vitamin D levels induced in Janssens's study may not have been high enough to produce an anti-inflammatory effect. "They simply corrected the deficiency but didn't use vitamin D as an anti-inflammatory," he says. "We believe that if we used vitamin D in a more challenging approach to enhance the anti-inflammatory effects, maybe the study would have been positive, although more data is necessary to prove that."

"If we used vitamin D in a more challenging approach maybe the study would have been positive."

ST HELEN'S TAKETEN PROGRAM

Former smoker Candice Singer now lives with COPD.

Diane R. Gold and JoAnn E. Manson, professors of medicine at Harvard Medical School in Boston, Massachusetts, addressed the issue of vitamin D dosing in an editorial accompanying publication of the clinical trial. They cited the benefits of daily versus intermittent dosing in other, non-COPD-related vitamin D trials[9]. They also suggest that differences in participants' physiology, immunology, and genetics may partly explain the null results in the general COPD population. COPD is not a monolithic disease: muscles thicken and tissues are destroyed to varying degrees, and molecular variants in the vitamin D binding protein — which transports vitamin D in the bloodstream — affect activation of immune cells including macrophages. In fact, Janssens had found that COPD patients with two copies of a particular variant in the gene for vitamin D binding protein were more likely to be deficient in vitamin D deficiency[5].

Unraveling whether vitamin D deficiency is a cause of COPD requires more clinical data. Gold and Manson are leading one of the most extensive of those efforts. Their National Institutes of Health-funded Vitamin D and Omega-3 Trial (VITAL) is just starting; it will follow 20,000 participants age 50 and older as they receive 2,000 international units (IU) of vitamin D daily for five years.

DEFICIENCY AS CAUSE?

At least one study in mice sheds some light on the relationship between COPD and vitamin D. A team led by Graeme Zosky, who heads the Lung Growth and Respiratory Environmental Health at the Telethon Institute for Child Health Research, in Subiaco, Australia, fed one group of female mice a vitamin D-deficient diet and another group a diet with sufficient levels. They studied the offspring of both, looking for differences in lung physiology. They measured lung volume and dissected the lungs to take a look inside.

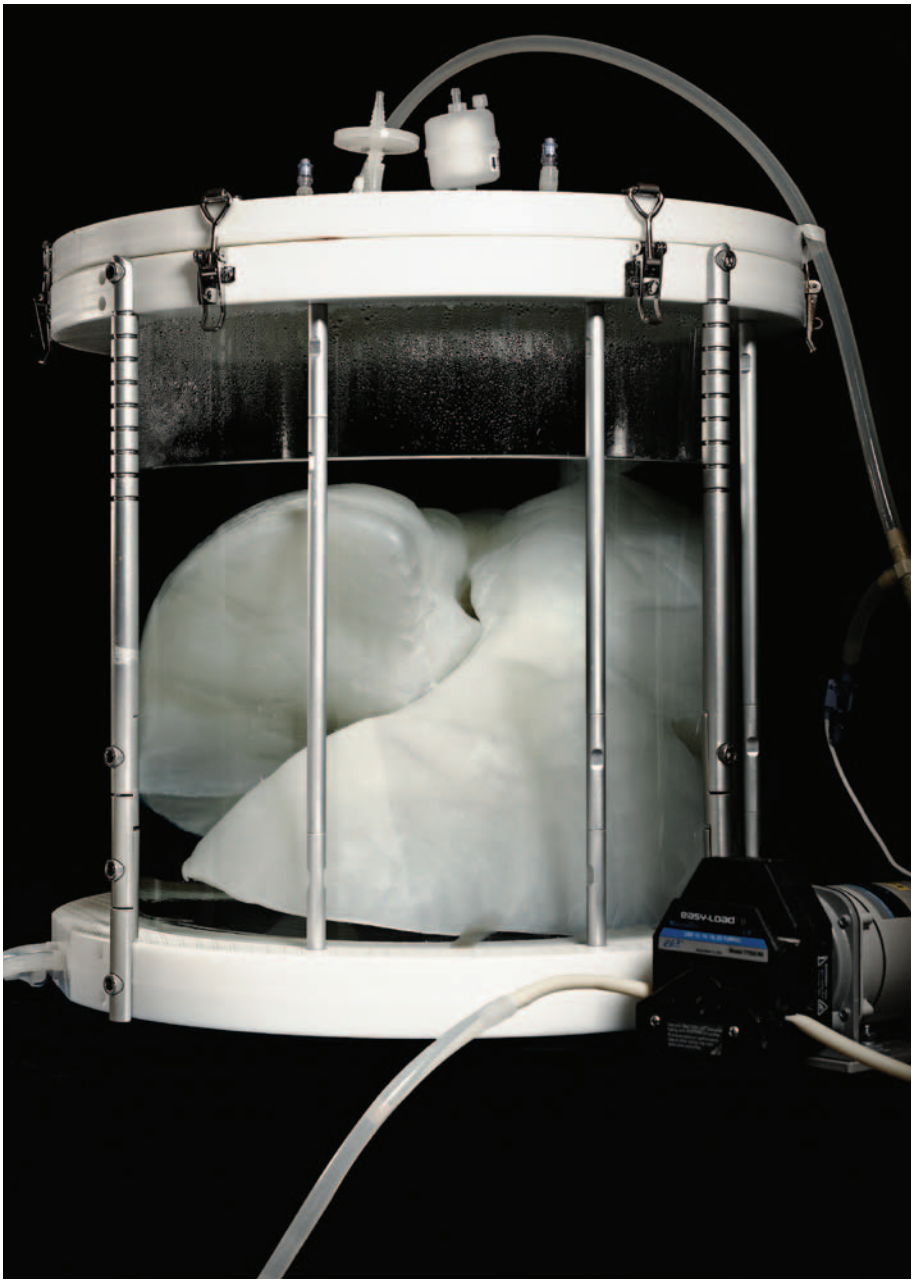
The offspring of the vitamin D deficient mice — also deficient in vitamin D — had statistically significantly smaller lungs than normal: about 18% smaller in female offspring and 28% smaller in males[7]. "Our point was that vitamin D deficiency isn't causing gross structural changes in the lung, but it might be slowing down lung growth," Zosky says. "What we don't know is what that means when you put disease on top of it. My suspicion is, if we introduced COPD pathology in these mice, the effect would be much larger."

My sister Candice, for one, believes her lung capacity has increased since she started talking vitamin D as part of a smoking cessation program. She began with a daily dose of 10,000 IUs for four weeks, and continued with a daily dose of 5,000 IU (The IOM recommends just 600 IU a day for adults up to age 70 and 800 IU a day for those 71 and older). Candice can't separate out the benefits of supplementation from those of not smoking, but she attributes her improved health to both. She has little trouble carrying her four-year-old daughter up the stairs now — whereas before, she says, "I couldn't do that without losing my breath."

Thea Singer *is a freelance writer in Brookline, Massachusetts.*

➲ NATURE.COM
Nutritional advice— The vitamin D-lemma:
go.nature.com/1jppLb

1. Banerjee, A. & Panettieri R. *Curr. Opin. Pharmacol.* **12**, 266–274 (2012).
2. Janssens, W. *et al.* Vitamins and Hormones, Vol. 86 (ed. Litwack, G.) Ch. 17, 379–393 (Elsiver, 2011).
3. Holick, M. F. *N. Engl. J. Med.* **357**, 266–281 (2007).
4. Merlino, L. A. *et al. Arthritis Rheum.* **50**, 72–77 (2004).
5. Janssens, W. *et al. Thorax* **65**, 215–220 (2010).
6. Persson, L. J. P. *et al. Am. J. Respir. Crit. Care Med.* **185**, A3889 (2012).
7. Zosky, G. R. *et al. Am. J. Respir. Crit. Care Med.* **183**, 1336–1343 (2011).
8. Lehouck, A. *et al. Ann. Intern. Med.* **156**, 105–114 (2012).
9. Gold, D. R. & Manson, J. E. *Ann. Intern. Med.* **156**, 156–157 (2012).



JOSEPH FERRARO/ MGH PHOTOGRAPHY SERVICES

Cadaveric or animal lungs might form the framework for new lungs made of a patient's own cells.

DEVICES

Artificial inspiration

The donor lungs of the future — built from collagen or silicone rubber or engineered from donor organs stripped of their original cells — might give a new lease of life to COPD patients.

BY ELIE DOLGIN

Sarah Gilpin is talking to a pair of opalescent human lungs. "You guys are so cool," she says, peering into a keg-sized glass bioreactor at Massachusetts General Hospital (MGH) in Boston. The lungs float inside, puffing up as 40 litres of soapy fluid is pumped through their network of blood vessels. Less than a week earlier, these lungs belonged to a 47-year-old New Yorker, allowing him to take one last breath before dying of cardiac arrest. Now, his donated lungs have been stripped of their cells and genetic material. All that remains are two cone-shaped objects made of collagen and other structural proteins, dangling as though in suspended animation.

Gilpin, a postdoctoral fellow, is using such protein scaffolds to try to grow a set of bioartificial lungs in the laboratory. Together with Harald Ott, a cardiothoracic surgeon at MGH, Gilpin is devising a protocol to flush out the cells from donated lungs that are ineligible for direct transplantation. Eventually, they plan to seed the support structure with stem cells and to direct these cells to develop, or differentiate, into the various cell types in the lung, thereby rebuilding functioning tissue. Using the techniques the lab has developed so far, Ott has already engineered bioartificial rat lungs that can perform the appropriate gas-exchange functions when transplanted back into living rats[1]. Now, he and Gilpin are scaling up to humans.

Success in their quest would bring good news to the estimated 65 million people worldwide who live with chronic obstructive pulmonary disease (COPD), a lung disorder mainly caused by exposure to tobacco smoke and airborne pollutants. Medication can often help treat the symptoms and complications of COPD, such as breathlessness and chronic coughing. But, for many people with severe forms of the disease, the only option is to replace a bad set of lungs with a good set. Relatively few lungs are donated, however, and most of these are damaged and therefore unsuitable for transplantation (see 'Organ refit'). So, each year, around the world, only a few thousand patients with COPD receive a life-saving transplant. New sources of healthy lungs or devices that serve the same purpose are desperately needed.

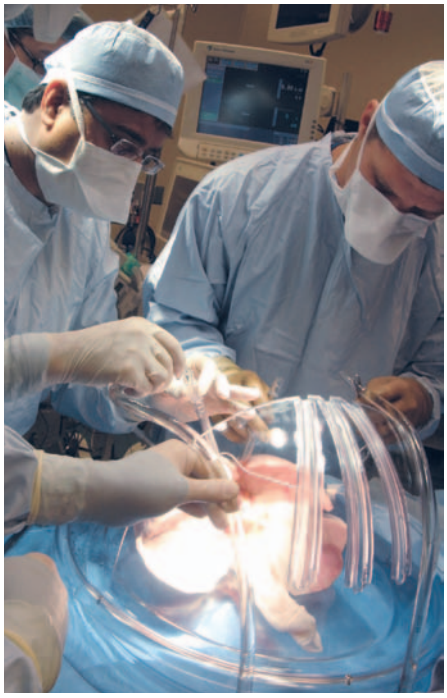
Such technologies are lacking. "Count the number of devices you can use if your heart is failing, and you can make a nice long list. But if your lung is failing, you have very few options," says Scott Merz, president and co-founder of Michigan Critical Care Consultants in Ann Arbor, a company that designs and develops 'lung-support' technologies.

Lab-grown lungs, reconstructed from damaged donor lungs and seeded with a patient's own cells, offer one attractive option. What's more, these bioartificial transplants could have a major advantage over their natural counterparts: by

➲ NATURE.COM
Artificial pancreas to make diabetes more manageable:
go.nature.com/spn6zs

incorporating a patient's own (autologous) cells, the lungs would be less prone to rejection by the immune system than lungs transplanted directly from a donor, and recipients wouldn't have to take lifelong cocktails of immunosuppressive agents. However, considering that Gilpin, on this particular July morning, was only part way through removing the cells from her second set of human lungs and that no other team has reported success with this approach on a similar scale, the research is still a long way from the clinic.

"We're a couple of decades away from having an autologous, tissue-engineered lung," says Laura Niklason, a biomedical engineer at Yale University in New Haven, Connecticut, who has independently created bioartificial rodent lungs[2]. "There are technological hurdles, and there are stem-cell differentiation hurdles. But I don't think anything is insurmountable."



UNIVERSITY HEALTH NETWORK, TORONTO

Surgeons strip lungs of their original cells.

In the meantime, many academic and industry researchers are turning to mechanical devices that can help the lungs to carry out their main function: gas exchange, specifically the removal of carbon dioxide from the bloodstream and the delivery of oxygen. The first such products are already on the market, and the next generation of 'artificial lungs' is not far behind.

OUTSIDE THE BOX

Novalung, a device manufacturer based in Talheim, Germany and spun off from Merz's company, is the market leader in lung-support technologies. The company's interventional lung assist (iLA) membrane ventilator takes blood from a patient's thigh and circulates it under ambient pressure from the femoral artery through a rod lined with hundreds of tubes full of pure oxygen. Oxygenated blood then flows back into the femoral vein. This system, which was approved in Europe and a handful of other countries in the past ten years for providing respiratory support for up to 29 days, has mainly been used as a stopgap for people urgently awaiting lung transplants. But doctors are beginning to test whether this device, and similar technologies, can be used earlier in the treatment process to avoid the need for transplants altogether.

Long before needing a new set of lungs, a patient with COPD will be well acquainted with the hospital emergency department because of frequent episodes of severe breathing difficulty. These attacks — called acute exacerbations — occur, on average, two to three times a year in people with moderate-to-severe COPD. To give the lungs a break and help the patient breathe during one of these episodes, doctors usually attempt to deliver air through a face mask. Although these masks are easier to apply and less cumbersome for patients to wear than the iron lungs of the early twentieth century, mask-based ventilation doesn't work for everybody. For example, individuals who are not fully conscious and cooperative are not considered good candidates. So, if the mask approach fails, doctors turn to more invasive techniques, in which a breathing tube is inserted into the windpipe and a ventilating machine pushes air directly into the lungs. Such mechanical ventilation can save lives during a COPD attack. But it also significantly increases the risk of pneumonia, and forcing the air into the lungs can cause injury.

Lung support devices such as the iLA might obviate the need for invasive ventilation during exacerbations. For example, in a pilot study of the iLA system reported in June 2012 at the annual meeting of the German Society for Internal Intensive and Emergency Medicine in Cologne, doctors at the University Medical Center Hamburg-Eppendorf in Germany helped 13 of 14 patients with COPD avoid tracheal intubation.

"You have something that breathes outside the patient, allowing the lungs to recover and heal rather than being forced to perform by mechanical ventilation," says Georg Matheis, a managing director of Novalung, based in Heilbronn, Germany. "This might affect the long-term cause of COPD by mitigating or avoiding the damage inflicted by these exacerbations." In this way, patients who are protected against progressive damage by a system such as Novalung's might ultimately live longer or have an easier time breathing.

Novalung is now moving towards a new iLA design, with a pump that exchanges blood through the jugular veins, in the neck. This approach gives patients greater mobility, as well as lowers the risk of heart attack and other problems associated with an arterial puncture. But Novalung is not alone in pursuing this strategy: another company, ALung

ORGAN REFIT

All donations accepted

More than 80% of donated lungs worldwide are too damaged to transplant. These lungs can still be used to study tissue-engineering techniques, such as those used for generating bioartificial lungs in the laboratory of Harald Ott, a cardiothoracic surgeon at Massachusetts General Hospital in Boston. But, with many people dying while on the waiting list for a lung transplant, researchers are beginning to explore whether the unsuitable lungs might be of immediate benefit to patients, especially if some of the tissue damage can be repaired.

In a 2012 study, a British team of doctors assessed the survival of nearly 1,300 lung-transplant recipients, some 500 of whom had received lungs from donors who smoked[5], which is permitted under UK policy. As might be expected, transplant recipients whose lung donors had not smoked survived longer. But recipients of smokers' lungs fared better than patients with COPD who remained on the waiting list. "It's better to get a lung with a smoking history than no lung at all," says Lorraine Ware, a doctor who studies lung transplantation at the Vanderbilt University School of Medicine in Nashville, Tennessee.

However, before doctors race to transplant suboptimal lungs from smokers, they might consider applying a recently developed technique called the Toronto XVIVO Lung Perfusion System. Developed by Shaf Keshavjee and his colleagues at the University Health Network in Toronto, Canada, the procedure involves pumping a protein and nutrient solution into the donor lungs and ventilating them with an oxygen gas mixture for several hours to repair damage caused by swelling or inflammation.

In a 2011 report, the Toronto team showed that only 15% of suboptimal lungs prepared in this way showed signs of acute organ injury three days after transplantation, in contrast to 30% of the supposedly healthy lungs that were transplanted without such preparation[6]. "The advantage isn't just that we can use more lungs but that we also make these transplants safer and more predictable," says Keshavjee, adding that around 20% of organs transplanted at the Toronto Lung Transplant Program undergo this perfusion treatment. (The Toronto program, like those in the UK, allows the use of smokers' lungs, which Keshavjee says make up 30–40% of lungs considered for transplant.)

"This is our first foray into partially engineering or repairing donor lungs," Keshavjee notes. If he succeeds more broadly, maybe bioartificial lungs won't be necessary after all. **E.D.**

Technologies based in Pittsburgh, Pennsylvania, is advancing a similar device as an alternative to mechanical ventilation.

In June 2012, at the 58th Annual Conference of the American Society of Artificial Internal Organs in San Francisco, California, ALung reported success with its Hemolung device, showing that patients with severe exacerbations of COPD experienced, on average, 28% reductions in their blood levels of carbon dioxide within 24 hours of the start of Hemolung treatment. "We're bringing the technology down to a level of safety, simplicity and superior efficacy, all with a lower level of invasiveness," says Scott Morley, a biomedical engineer who heads product management at ALung. The company plans to file for European approval of the Hemolung system later this year.

POOR EXCHANGE

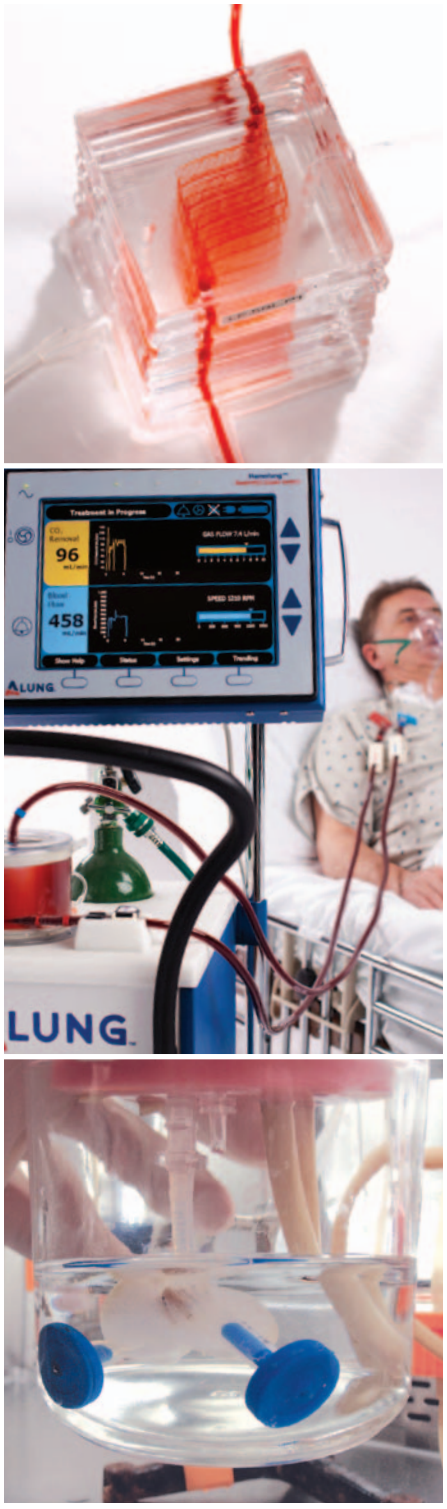
Not everyone is convinced that lung-support devices offer any real advantage over mechanical ventilation for treating COPD. "Right now, the risk–benefit ratio of those two is very close, and it's hard to tell how that's going to play out," says Joseph Zwischenberger, a cardiothoracic critical-care doctor at the University of Kentucky in Lexington, who has been working on artificial lungs for about 30 years. "There are those who think the technology has evolved to the point where the risk of the devices is less than the risk of being on a ventilator, and then there are a large majority who say, 'Nope, it's just not there yet.'"

One of the biggest problems with the existing technologies is their tendency to clot: rapid blood cells encounter something akin to a traffic jam as they flow into and out of the devices. The devices are also bulky, and only limited gas exchange happens as the blood passes over the oxygen-filled fibres. Thus, many advocates of lung-support systems are looking to completely redesign the technology and are turning to the science of very small volumes — microfluidics.

Using microfluidics "enables you to get much more surface area for gas exchange per unit blood volume than the traditional devices," says William Federspiel, a bioengineer at the University of Pittsburgh and a co-founder of ALung. "That could allow for a more compact device that is potentially efficient enough to run off room air," unlike existing devices, which typically require a tank of pure oxygen.

Some success has been achieved already. Air delivered at near ambient pressures was able to oxygenate blood in a microfluidic device designed by Joseph Potkay and his colleagues at Case Western Reserve University in Cleveland, Ohio. In a proof-of-principle test published in 2011 (ref. 3),

Only a pair of healthy human lungs can reverse the downward progression



A lung-on-a-chip (top), a lung-support machine (middle) and a bioreactor containing a rat lung removed of cells and ready for regeneration.

Potkay and his team created a credit-card-sized device with artificial capillaries that achieved gas-exchange rates far surpassing those of current devices, without the need for pure oxygen. "We're pushing the size limits of this technology," says Potkay, who is now at the Veterans Affairs Medical Center in Ann Arbor. But "through [such] microfabrication, we can get devices on the same size scale as the structures in the natural lung."

SIZE MATTERS

The device still has some kinks that need to be worked out. For one thing, it would take more than 1,000 of them on top of one another to provide just one-quarter of the body's baseline gas-exchange support. And Potkay's team designed the device to maximize gas exchange but didn't optimize it to prevent clotting. By more closely mimicking natural blood-vessel architecture, however, a few research teams have designed microfluidic chips that circumvent the clotting problem, paving the way for long-term lung-support devices that could aid even mobile patients with COPD.

Joseph Vacanti, a transplant surgeon at MGH, is leading one such effort. Vacanti helped Ott to engineer bioartificial rat lungs, but he is now focused on developing a microfluidic device. Vacanti's group has built a device with a bifurcating architecture that closely matches the branching of blood vessels in the body[4]. With an eye to miniaturization, his group is now working to make the system out of collagen instead of silicone, a material that introduces much dead space into the device. "We've got a lot of work to do on choosing the best material and making it in the thinnest possible way so the size of the thing is either wearable or implantable," says Vacanti.

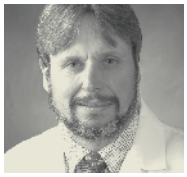
Across the river from MGH, Jeffrey Borenstein, director of the Biomedical Engineering Center at the Charles Stark Draper Laboratory in Cambridge, who has his own microfluidic lung prototype, is focused on optimizing another part of the design. To reduce the possibility of clotting, Borenstein and his colleagues are seeding the channels of their branching gas-exchange device with the cells that line blood vessels — endothelial cells — and, so far, they have seen no decline in the rates of gas transfer. "As we think about clinical implementation we really want to make this as natural a device as possible so we're not always dealing with these blood interactions with synthetic surfaces," Borenstein says.

Gilpin, the MGH postdoc, praises the efforts to develop lung-support devices and hopes they will soon provide some relief for people with COPD. But, ultimately, she says, only a pair of healthy human lungs can reverse the downward progression of this devastating condition. She leans her elbows on the lab bench, props her face in her hands, and gazes at the stripped set of lungs. "Seeing this makes me think we have the platform," she says. "You'd never be able to create this. Only nature can create this." ■

Elie Dolgin *is a news editor at* Nature Medicine.

1. Ott, H. C. *et al. Nature Med.* **16**, 927–933 (2010).
2. Petersen, T. H. *et al. Science* **329**, 538–541 (2010).
3. Potkay, J. A. *et al. Lab Chip* **11**, 2901–2909 (2011).
4. Hoganson, D. M. *et al. Lab Chip* **11**, 700–707 (2011).
5. Bonser, R. F. *et al. Lancet* **380**, 747–755 (2012).
6. Cypel, M. *et al. N. Engl. J. Med.* **364**, 1431–1440 (2011).

PERSPECTIVE



Clues, not conclusions

Scientists have some way to go before they can prove that COPD should be treated as an autoimmune disease, says **Steven R. Duncan**.

Chronic obstructive pulmonary disease (COPD) has many enigmatic traits. A progressive respiratory disorder that causes severe breathing difficulties, it can worsen even after patients stop smoking, may flare up unpredictably without apparent cause, and is often associated with other medical conditions such as atherosclerosis, osteoporosis, renal dysfunction and cancer. Many characteristics of COPD could be attributable to pathologic autoimmune processes[1]. And there are increasing numbers of reports that autoantibodies against many different lung proteins are often present in COPD patients[2,3].If the underlying cause of COPD were indeed autoimmunity, new treatments might improve quality of life for patients.

Nonetheless, scepticism about the role of autoimmunity in COPD still abounds and is probably justified, albeit with several qualifications.

Some of the uncertainty may be explained by the nuanced and complex biology of autoimmunity[4]. Low-level reactivity to most (or maybe even all) of the body's own proteins is common, and is probably critical in preventing the immune system from mistakenly launching an injurious inflammatory response against our own cells and tissues. But in several studies, patients diagnosed with certain diseases, including COPD, have shown significantly higher levels of one or more antibodies that bind to the body's own proteins, compared to demographically matched healthy people. These findings are generally considered evidence of autoimmunity.

Several investigators have used variations of this approach to identify a "COPD autoimmune response." The increasing availability of high-throughput antigen array chips that can detect the presence of autoantibodies against thousands of proteins simultaneously, and the ease by which antigen-specific autoantibodies can be discovered, may soon spur a profusion of similar studies.

However, not all of these autoantibodies should be considered pathogenic, even if their presence is abnormal. The problem lies in understanding whether a particular one causes or contributes to disease.

Autoimmunity often develops as a consequence of chronic inflammation caused by distinct disease processes[4]. In all but a few cases, it is unknown how or why initial, narrowly targeted, and appropriate immune responses become misdirected to attack normal tissues and cause disease. One plausible explanation goes that in COPD patients, host defences triggered by microbial infection of the airways promote the development of autoimmune responses[1,2]. The tobacco smoke that is the number-one risk factor for COPD in industrialized societies is a complex mix of highly reactive chemicals that can modify native proteins. These modified proteins may no longer be recognized as 'self' by the immune system, and can be targeted by an immune response[3].

Most autoantibodies have no apparent pathogenicity. A few, however, are profoundly pathogenic and cause severe tissue damage[4]. The trick for researchers is to determine whether observed autoimmune responses are actually pathogenic, or simply abnormal and harmless. Many studies have found links between autoantibodies and the severity of COPD. That's a good start. But because underlying inflammation could be proportionally driving harmless (epiphenomenal) autoimmune responses, it is a less than wholly compelling explanation. Some researchers maintain that particular COPD autoantibodies can be meaningful only if they are not associated with other diseases. In reality, however, fundamental immunologic processes are often shared among very different clinical syndromes. Hence, the presence of a superficially similar autoantibody in two or more clinical syndromes says little about the pathogenicity in any one of those diseases. Someday someone might discover the autoantibody that is the exclusive cause of COPD, and then the respective assay will be absolutely sensitive and specific for this disease. For now, though, this seems unlikely.

In the meantime, establishing the contribution of any given autoimmune response to COPD requires, at the least, a demonstration of pathogenicity. Autoantibodies can be isolated from patients and tested for their effects on human cell targets *in vitro*[2]. If auto-immune responses are truly pathogenic, there should also be clear evidence of characteristic injuries within the target organ[2,3]. T cells have exquisite specificity for antigens and considerable potential pathogenicity, and are inert to self-antigens in healthy patients. Accordingly, the presence of autoreactive T-cells is highly abnormal and is strong evidence for the presence of a pathogenic autoimmune process.

NOT ALL OF THESE ANTIBODIES SHOULD BE CONSIDERED PATHOGENIC, EVEN IF THEIR PRESENCE IS ABNORMAL

So far, however, few mechanistic studies show specific COPD autoimmune responses that cause injury. Proof that a particular autoimmune response contributes to COPD will probably require recreating the disease in an animal model through adoptive transfers of patient-derived pathogenic autoantibodies or lymphocytes — a task that may prove difficult because of key differences between the immune systems of mice and humans.

When, as many of us working on COPD anticipate, autoimmune mechanisms are more convincingly demonstrated to be factors in COPD pathogenesis, clinical trials will have the potential to yield unprecedented medical advances. Currently available treatments for COPD primarily ameliorate symptoms. Some treatments do attack the underlying inflammation, but not very effectively, and they do not dramatically alter the overall progression of the disease. But modalities to remove autoantibodies or minimize their subsequent production are already available, and several more agents are now being developed that could also work[5]. We may soon have the rationale and tools to implement novel, and potentially better, therapies for this extremely morbid and otherwise unremitting syndrome. ■

Steven R. Duncan *is a pulmonary and critical care medicine physician at the University of Pittsburgh in Pennsylvania.*
email: duncsr@upmc.edu

1. Agusti, A. *et al. Thorax* **58**, 832–834 (2003).
2. Feghali-Bostwick, C. A. *et al. Am. J. Resp. Crit. Care Med.* **177**, 156–163 (2008).
3. Kirkham, P. A. *Am. J. Respir. Crit. Care Med.* **184**, 796–802 (2011).
4. Marrack, P. *et al. Nature Immunol.* **7**, 899–905 (2001).
5. Cancro, M. P. *et al. J. Clin. Invest.* **119**, 1066–1073 (2009).

B. BOISSONNET/SCIENCE PHOTO LIBRARY

Drugs to treat COPD, such as Spiriva, aim to relax the smooth muscle of the airways.

THERAPEUTICS

Strength in numbers

Several new drugs for treating chronic obstructive pulmonary disease are about to hit the market, with more in the pipeline.

BY DUNCAN GRAHAM-ROWE

Shortness of breath, a tightening of the chest, wheezing and that desperate feeling that you can't get enough air into your lungs: these are all familiar to asthma sufferers. For people with chronic obstructive pulmonary disease (COPD), however, such symptoms are not fleeting. They are constant and aggravated by a steady build-up of sputum, shallow breathing and a persistent cough. The most that patients can hope for in terms of treatment is merely to manage their symptoms as they steadily worsen over time.

COPD, unlike asthma, is associated with tobacco smoking and long-term exposure to airborne toxicants, which irreparably damage the lungs, causing inflammation and airway narrowing. But traditionally, COPD has been treated in much the same way as asthma. For relief, patients can inhale short-acting bronchodilators, which relax the airways: for example, salbutamol, which is marketed as Ventolin by the London-based drug giant GlaxoSmithKline (GSK). Inhaled corticosteroids also reduce inflammation in the lungs and therefore decrease the risk of acute episodes known as exacerbations, which can leave patients hospitalized for days. For managing symptoms over the longer term, there are bronchodilator–corticosteroid combinations such as salmeterol–fluticasone propionate (Advair; also marketed by GSK), which can ease symptoms for up to 12 hours. Another long-term option is tiotropium bromide (Spiriva), which acts by a different bronchodilation mechanism to provide 24-hour relief, and is marketed by pharmaceutical companies Boehringer Ingelheim, based in Germany, and Pfizer, based in Groton, Connecticut.

Now, several new drugs for COPD treatment are on the verge of being approved by regulatory authorities (see 'Long-acting, daily medications'). The new candidates are not cures, but they may offer genuine hope that COPD sufferers can have a better quality of life.

FAST ACTION

On the surface, the offerings look like simple replacements for Spiriva and Advair. The closest to market is glycopyrronium bromide (NVA237; Seebri), which is awaiting approval in Europe and has been developed by the pharmaceutical giant Novartis, headquartered in Basel, Switzerland. Like Spiriva, this once-daily drug acts on a set of nerves in the smooth muscle around the airways. "Acetyl-choline acts on muscarinic receptors found in the muscles surrounding the airways, causing the muscle in the airways to contract and the airways to narrow," explains Dave Morris, who heads global development for primary care at Novartis. In patients with COPD, the new drug competes with acetylcholine, blocking the receptors and preventing the airways from closing up. It is therefore classified, together with Spiriva, as a long-acting muscarinic antagonist (LAMA).

Novartis has carried out three large-scale phase III trials of Seebri. In May 2012, it reported the results of the second trial, GLOW2, at the American Thoracic Society International Conference in San Francisco, California. GLOW2 was conducted over one year and involved 1,066 individuals: Seebri not only improved lung function to the same extent as its analogue, Spiriva, but also took effect quicker. At both 5 minutes and 15 minutes after inhalation, it produced a doubling in FEV_1, the amount of air that can be exhaled in 1 second (as measured by blowing into a spirometer). It has also been clinically shown to produce greater bronchodilation in the first 4 hours of use than Spiriva.

GSK is taking a different tack. In July, together with Theravance, a biopharmaceutical company based in South San Francisco, California, it applied for regulatory approval in both Europe and the United States for a new drug combination: vilanterol–fluticasone furoate (previously known as Relovair but now called Relvar or Breo). Relvar is similar to Advair in that it consists of a long-acting β2-agonist (LABA) bronchodilator and an inhaled corticosteroid. Like Seebri (and Spiriva), Relvar works on the nerves in the smooth muscles, but it does so by stimulating β2-adrenergic receptors, which triggers a biochemical cascade that leads to the relaxation of the smooth muscle in the airways. In phase III trials, Relvar improved lung function compared with placebo or Advair when taken over a 12-week period, as measured by standard spirometry tests.

GSK has not yet published numbers showing the extent of the improvement. But, according

LONG-ACTING, DAILY MEDICATIONS

Do combination therapies really add value to COPD treatments? The pros and cons of long acting therapies in the pipeline.

Name	Main benefit	Type of drug	Active components	Delivery method	Doses per day	Adverse effects	Stage
Advair	Improves lung function for a period of time	Long-acting β2-agonist (LABA) and corticosteroid	Fluticasone/ salmeterol	Dry powder inhaler	2	Increased risk of non-fatal pneumonia	Available
Spiriva	Improves lung function for a period of time	Long-acting muscarinic antagonist (LAMA)	Tiotropium bromide	Dry powder inhaler	1	Hives, rash, swelling and dry mouth	Available
PT003	Efficient delivery, improved lung function	LAMA + LABA (two molecules)	Glycopyrrolate and formoterol (LAMA + LABA)	Metered dose inhaler (MDI)	2	Headache, dry mouth and coughing	Phase II completed and Phase III to begin 2013
NVA237	Improves breathing in a matter of minutes	LAMA	Glycopyrronium bromide (LAMA)	Dry powder inhaler	1	Headache, dry mouth and coughing	Phase III completed and approval sought in Europe
Relvar	Once daily instead of twice	LABA + inhaled corticosteroid	Vilanterol and fluticasone furoate	Dry powder inhaler	1	Fatal pneumonia reported	Phase III completed and approval sought in USA and Europe
MABA	Dual action molecule improves lung function	LAMA + LABA	MABA	Most likely dry powder inhaler	Unknown	Unknown	Phase II

to a spokesperson, Relvar's effects last longer than those of Advair, so it need only be taken once a day rather than twice. A once-daily dose should significantly increase compliance. "Patients frequently don't take their second dose," says James Donohue, a pulmonary diseases specialist at the University of North Carolina at Chapel Hill, who has been involved in trials of Spiriva and has worked as a consultant to both GSK and Novartis.

DYNAMIC DUOS

Patient compliance concerns are also driving the development of combination therapies — the rationale being that patients find it easier to take a single medication. Combination therapies also have another advantage. Inhaled corticosteroids don't seem to have strong anti-inflammatory effects when they are used in isolation. When used in conjunction with separate bronchodilators, however, they've been shown to reduce the frequency of exacerbations. This synergistic effect probably arises because "the β-agonist facilitates the entry of the steroid into the [cell's] nucleus", Donohue says. So delivering them as part of a combination therapy has the potential to optimise this synergy.

Another effect with ramifications for treating COPD involves the simultaneous use of a LAMA and a LABA. The idea is to open the airways further by simultaneously switching off the nerves that tighten the passages while stimulating the ones that relax them, says Chris Cates, a population health researcher at St George's University of London who studies COPD.

Such LAMA–LABA combinations are being developed by a company called Pearl Therapeutics, based in Redwood City, California. Pearl has already carried out eight clinical trials on a combination therapy called PT003, and phase III trials are set to commence in the first half of 2013, says Colin Reisner, Pearl's chief medical officer.

PT003 is notable not so much for its chemistry as for its novel method of delivery, says Donald Tashkin, medical director of the Pulmonary Function Laboratory at the David Geffen School of Medicine, University of California, Los Angeles, who has consulted for the company. Both the LAMA and LABA components — glycopyrrolate and formoterol fumarate, respectively — are established drugs. But PT003 delivers them together, bound to particles with a diameter of less than 5 micrometers. In this way, the drug molecules are suspended in solution and can be dispensed through a metered dose inhaler, a device that many patients find easier to operate than the commonly used dry powder inhalers. The molecular vehicle also provides an efficient means of delivery, ensuring that around half of the drug reaches its target, as opposed to as little as 5% with some delivery systems, says Tashkin.

Synergistic effects can occur in the lungs even when LABAs and LAMAs are inhaled separately, but one after the other. However there is preclinical evidence that the approach of administering them simultaneously through a single device, as for PT003, may enhance their effect even further, says Darrell Baker, a senior vice president who oversees GSK's respiratory portfolio.

"The big question of drug combinations is whether the costs outweigh the benefits."

If this is the case, then another novel drug, being developed jointly by GSK and Theravance, could prove successful. The drug is a single molecule with both LAMA and LABA properties. Phase II clinical trials of this muscarinic antagonist–β2 agonist (MABA) have been promising, says Baker, which when compared to salmeterol "improved bronchial dilation across a range of doses".

Even so, no trial data have been released so far, and the company's plans for this MABA are unclear. "We are keen to see how it works as a bronchodilator by itself," says Baker. "However, we also see the opportunity for a triple-mechanism action with an inhaled corticosteroid."

Ultimately, this is where the greatest value may lie — not in the pharmacological precision of a single molecule with a dual mechanism of action, but rather in the ease with which it could pass through the drug regulatory system. "The beauty of this is when it is approved, MABA would count as one drug," says Baker.

In principle, companies hoping to develop a triple therapy by adding one drug to this MABA would therefore have a low regulatory bar, says Tashkin. Normally, triple combination therapy would require a six-way study — demonstrating improvement over not just the individual constituents but also their various combinations — but combining the MABA with an inhaled corticosteroid would require a simpler burden of proof.

The big question, says Cates, is whether the costs outweigh the benefits. For instance, adding corticosteroids may lower the risk of exacerbations but increase the risk of pneumonia. Indeed, there have been fatal cases of pneumonia associated with Relvar (although it is not the only drug to carry that potential risk). According to Baker, the company is likely to market the drug at lower doses than those given to trial subjects who developed pneumonia.

Although many of these new drug candidates hold promise and have short-term benefits, none of them has yet been shown to improve lung function year on year, says Cates. So until drug companies start to find ways to help repair damaged lungs and reverse the effects of COPD, there is only one long-term 'treatment' available to patients, he adds, and it does not involve taking drugs but abstaining from them: quitting smoking. ■

Duncan Graham-Rowe *is a freelance science writer based in Brighton, UK.*

GUY VANDERELST/ GETTY IMAGES

The Pearl River runs through Guangzhou in China, where high levels of smog increase the incidence of COPD.

PUBLIC HEALTH

Where there's smoke

Air pollution and smoking have made COPD a major problem in China, now compounded by outdated diagnostics and treatments — and experts say it's bound to get worse.

BY VIRGINIA HUGHES

A visitor to China may well notice the country's smog problem as the plane descends. Smog levels in large cities such as Beijing and Shanghai frequently dwarf those of other metropolitan centres. Then there's the cigarette smoke. China, the world's most populous country, claims about one-third of the world's smokers — at least 300 million people — who collectively puff 1.7 trillion cigarettes a year. In rural areas, cigarette smoke permeates buses, shops and even doctors' offices.

Beyond cigarette smoke and outdoor air pollution, hundreds of millions of Chinese people breathe unclean air while working in factories and on industrial-scale farms or while cooking at wood-burning stoves inside their homes.

These airborne toxicants — many of which are by-products of China's economic boom — are risk factors for chronic obstructive pulmonary disease (COPD), an incurable respiratory disorder that can cause severe breathing difficulties. And they have public-health officials worldwide worried about a coming epidemic. "We're just seeing the tip of the iceberg on COPD in China," says Don Sin, a respiratory medicine specialist at the University of British Columbia in Vancouver, Canada, who researches COPD. "In 30 years, [the number of cases] is going to explode."

A large-scale study in China put the prevalence of COPD in 2004 at roughly 8% in people who are 40 or older[1], in line with rates in the United Kingdom and the United States. But because China has seen soaring rates of industrialization and tobacco use over the past few decades, and because COPD symptoms aren't typically noticed until after age 50, public-health experts say the future is bleak. According to Sin, projections based on current trends and World Health Organization estimates show that by 2030, COPD will kill 3 million Chinese people a year — a million more than die annually now.

➲ NATURE.COM
Nature China covers the best of Chinese research:
go.nature.com/xuaofu

SMOKE SIGNALS

Since the late 1970s, disposable income has been on the rise in China and so has the Chinese tobacco industry, which has ramped up production and advertising. (However, recent laws have banned cigarette advertisements on television, the radio and in newspapers.) Cigarettes are cheap: as little as 30 US cents per pack, says Sin.

Because of a strong cultural stigma, only about one in fifty Chinese women smoke. But more than half of all men, and about two-thirds of middle-aged men, do. Smoking is popular among men in the city and the country, among those of all educational levels. And a survey of doctors in six Chinese cities, published in 2007, found that 41% of male doctors smoke, and about 15% have smoked in front of their patients[2].

Smoking-cessation programmes exist, but their impact is minimal. Chunxue Bai, director of the Respiratory Research Institute at Fudan University, in Shanghai, says he has launched

smoking-cessation clinics at 58 hospitals across China. But the clinic at his own hospital sees only about 300 people a year.

Despite the known link between smoking and COPD, most Chinese smokers do not fully appreciate the harm caused by smoking or are unconcerned. "They have some knowledge, but it doesn't go deep enough to change their behaviour," says Frank Hu, a nutrition specialist and epidemiologist at the Harvard School of Public Health in Boston, Massachusetts, who grew up in China.

China's high smoking rates explain only part of its COPD problem though, because non-smokers are also at risk. For example, even though few women smoke, women still have high rates of COPD.

One explanation is that women — 82.5%, according to one study[3] — are exposed to second-hand cigarette smoke. Two large studies in China have pointed to a link between this 'passive smoking' and COPD. The first of these studies, published in 2007, relied on the Guangzhou Biobank Cohort Study, a collection of blood samples and extensive medical data from more than 20,000 people over age 50 from Guangzhou, the largest city in southern China. In this group, the longer the duration of exposure to second-hand smoke, the higher the likelihood of COPD. The authors of this study also estimated that, of the 240 million people in China who were 50 years or older at the time of the study, 1.9 million non-smokers would die because of second-hand smoke[4].

Similarly, the second study, published in May 2012 by Hu and his colleagues, followed 910 non-smoking Chinese women for 17 years. They found that women who were exposed to second-hand smoke were 2.3 times more likely to die from COPD than those who were not exposed, with cumulative exposure increasing the risk[5].

But these data are controversial. Studies of second-hand smoke in Western countries have shown a suggestive but not definitive link to COPD. Three other studies in China also did not find an association between second-hand smoke and COPD. And COPD rates are up to three times higher for non-smoking Chinese women who live in rural areas than for non-smoking Chinese women who live in cities, even though their levels of second-hand smoke exposure are similar.

"There's no question that second-hand smoke is bad, but the [estimate] for how much COPD it causes in China is still not known," says David Christiani, an environmental geneticist at the Harvard School of Public Health. "It's much more than just a simple linear connection."

Christiani became interested in the non-smoking causes of COPD in the late 1970s, when US health officials were pushing for regulations to limit workers' exposure to cotton dust in textile factories. The process of turning fluffy cotton flowers into strong thread throws off particles of plant matter, pesticides and bacterial endotoxin, and textile workers had high levels of respiratory disease. But, at the time, the US cotton industry suggested that workers' lung problems stemmed from cigarette smoking rather than conditions at the mills. "Most workers were smokers, so it was very hard to tease these things apart," Christiani says.

Thanks to a serendipitous partnership with a university in Shanghai, Christiani realized that China offered a natural experiment to settle the debate. In Chinese factories, men and women work side by side; however, whereas most of the men smoke, hardly any of the women do.

For the past 30 years, Christiani has followed hundreds of people working at two cotton mills and one silk mill in Shanghai. His research has shown that even in non-smokers, breathing cotton dust causes significant airway blockage.

Although China has passed some labour laws to limit exposure to cotton dust, they're often not enforced. And many other industries pose similar threats or worse ones. Coal mining, welding, construction, grain processing and animal breeding produce their own airborne toxicants — including silica crystals, asbestos and faecal matter — all of which can contribute to COPD.

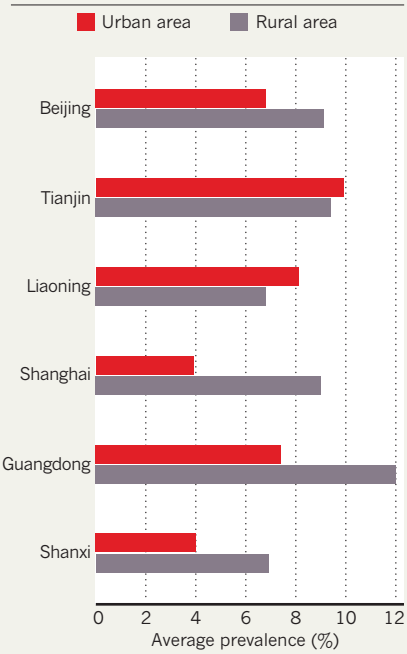
The impact of these occupational hazards is evident even in the layout of Chinese hospitals, notes Peymané Adab, an epidemiologist at the University of Birmingham in the UK and an investigator on the Guangzhou Biobank Cohort Study. "There are specific wards for people who have been exposed to certain dusts or people with lung disease related to a particular toxin," she says.

Another key factor is indoor air pollution. More than 70% of all Chinese households, and 90% of rural ones, use stoves that run on wood, crop residues, coal or animal dung. Burning these fuels releases particulate matter, as well as fumes laced with carbon monoxide, formaldehyde and free radicals. In 2007, China's Ministry of Environmental Protection set emissions standards for pollutants inside the home, but studies that measure air quality in rural homes have found levels exceeding the standards many times over. And exposure to biomass smoke increases COPD risk by 2.4 times, according to a 2010 meta-analysis of 15 studies[6]. "Women being the predominant cooks for families, they would be exposed to more of that," says Sin. That might partly explain why the COPD rates in non-smoking Chinese women are higher in rural areas than in cities — the dangerous types of stove are more common in the countryside.

Sin points to a slew of other factors too. About 1.5 million people in China have tuberculosis, and many areas of China have high rates of childhood pneumonia and malnutrition. All three factors increase the risk of COPD later in life.

COPD IN CHINA: WHERE IT'S WORST

In four of six provinces included in one study[1], the disease was more common in the countryside, which has its own risk factors — such as home cook stoves that throw off toxins and poor healthcare.



DEVICES WANTED

As recently as a decade ago, COPD research in China was scant. Although awareness has grown considerably in the past few years, scientists still have trouble gauging the full extent of the disease.

COPD prevalence ranges widely from region to region, from 5.5% in the province of Shanxi to 13.7% in the city of Chongqing, according to the large prevalence survey of 2004[1]. Other studies have found even greater discrepancies (see 'COPD in China: Where it's worst').

One reason for this variability is inconsistency in the methods of diagnosis. Spirometry, in which the patient blows as hard as possible for as long as possible into a machine that measures lung capacity, is the global gold standard. But spirometers are rarely used in China, especially outside the big cities. Even though these machines are relatively inexpensive for specialized medical equipment — several thousand dollars apiece — many doctors, especially in the countryside, do not use them. The large COPD prevalence study found that less than 7% of participants diagnosed with COPD had previously been tested by spirometry[1].

Instead, Chinese doctors tend to rely on subjective descriptions of symptoms to make the call, which can lead to misdiagnosis as asthma or a non-chronic form of bronchitis. "People go to see their doctor complaining of shortness of breath, and responses would be, 'You're getting old' or 'You have bronchitis, take some antibiotics'," Sin says.

Even for individuals who receive a bona fide COPD diagnosis, medical care and drug treatments can be lacking. In Western countries,

©GETTY IMAGES

One study found that fewer than 7% of COPD patients in China had been tested by spirometry.

common treatments for COPD include several kinds of inhalants, such as corticosteroids and β-agonists, that open up the airways in the lungs and provide immediate relief from symptoms. In the later stages of the disease, many patients use portable oxygen tanks. But these options are far too expensive for most Chinese patients.

In China, the most common COPD treatments are two inexpensive tablets. One, called carbocisteine, helps break up mucus and phlegm in the respiratory tract and has antioxidant properties that may slow the progression of COPD (see 'A radical treatment', page S4). The other, called theophylline, is a decades-old bronchodilator, or respiratory muscle relaxant, and anti-inflammatory. Theophylline is structurally similar to caffeine and is known for its erratic absorption and harsh side effects, including nausea, headache and life-threatening changes to heart rhythms.

Chinese researchers are focused on rigorously testing the effectiveness of their small drug arsenal. Studies of Western patients have found little benefit to adding carbocisteine or theophylline to other, reportedly more effective, treatments. But, in China, where most patients use nothing else, research has shown that the two drugs can help. For example, a 2008 report found that in Chinese patients with COPD, carbocisteine treatment for one year reduced the number of exacerbations, or sustained disease flare-ups, better than a placebo[7]. The same was found for theophylline given in a slow-release formulation at doses low enough to prevent severe side effects[8].

Both drugs are much cheaper than inhalants. In 2008, the average annual cost of carbocisteine therapy in China was 650 renminbi (about US$90 at the time) for each patient, compared with 4,320 renminbi ($580) for treatment with the standard combination of inhaled medications used in Western countries. Yet even the cheap drugs present an economic burden for most families, who shoulder the bulk of their healthcare costs without insurance or government assistance. One study found that the total cost for a patient with COPD in China was US$1,732 a year — a tremendous amount, given that the average urban Chinese household pulled in only $3,000 per capita in 2010, according to an analysis of government statistics by the China Market Research Group.

Beyond cost, the difference in quality of life is enormous. The inhalers used in Western countries slow down lung deterioration and give patients years of additional mobility. They are also better at preventing exacerbations, which cause intense anxiety and often take weeks to recover from. These flare-ups often mean time off from work, making treatment costs even harder to bear.

"Only about one in fifty women smoke, but more than half of all men do."

HAZY FUTURE

For now, inhalers are available only to wealthy Chinese citizens. But, as China's economy continues to grow, so too will its middle class — and its market for more expensive drugs.

Pharmaceutical giants have taken notice. A spokesperson for Novartis, headquartered in Basel, Switzerland, says the company recently approached a regulatory agency in China about one of its inhalers, a once-a-day bronchodilator. Jinping Zheng, deputy director of the Guangzhou Institute of Respiratory Disease, says that London-based AstraZeneca is investigating COPD in China. And he says that four years ago, GlaxoSmithKline (GSK), also headquartered in London, launched COPD Academy, a programme that has reached more than 20,000 general practitioners across China. A third of the programme focuses on a COPD drug called Seretide, a combined anti-inflammatory and bronchodilator that is marketed by GSK. The other two-thirds — developed with the help of the top 18 respiratory experts in China, according to GSK — aims to deliver unbiased education on the basics of COPD diagnosis.

There has also been some regulatory movement on the antismoking front. In the past few years, major cities in China have banned smoking in hospitals, restaurants, public transport and other indoor public places, and a similar nationwide ban was instituted in 2011. These laws are difficult to enforce, however, and many smokers blatantly ignore them.

Smoking regulations promoted by prominent doctors and China's Ministry of Health have a powerful enemy in the Chinese tobacco companies, which are controlled by the government at the local and national levels. "The tobacco companies are much stronger [than the health department] because they have the money," says Tai Hing Lam, director of the School of Public Health at the University of Hong Kong. "That's why the progress has not been as good as we would like." Lam and other experts say that China's COPD problem will not be curbed until the public makes demands for more-sweeping political changes from its government.

There is a precedent. It happened in the summer of 2008, when the Olympic Games were held in Beijing, and China shut down dozens of nearby factories and ordered half of all private cars off the road. The Beijing government also passed smoking bans in schools, hospitals and government offices, and required non-smoking sections in hotels and restaurants. Air pollution dropped quickly.

But as soon as the festivities were over, business continued as usual, and many of the smoking bans were lifted.

All China needs is a wake-up call to realize the significant human and economic burden of COPD, according to Christiani. "Once China starts recognizing the problem as something that needs to be tackled, it can make some significant strides." But for millions of older Chinese people, any hope of avoiding COPD risks has gone up in smoke. ■

Virginia Hughes *is a freelance science writer based in Brooklyn, New York.*

1. Zhong, N. *et al. Am. J. Respir. Crit. Care Med.* **176**, 753–760 (2007).
2. Jiang, Y. *et al. Am. J. Prev. Med.* **33**, 15–22 (2007).
3. Han, J. X. *et al*. [in Chinese with English abstract] *Wei Sheng Yan Jiu* **35**, 609–611 (2006).
4. Yin, P. *et al. Lancet* **370**, 751–757 (2007).
5. He, Y. *et al. Chest* http://dx.doi.org/10.1378/chest.11-2884 (23 May 2012).
6. Hu, G. *et al. Chest* **138**, 20–31 (2010).
7. Zheng, J. P. *et al. Lancet* **371**, 2013–2018 (2008).
8. Zhou, Y. *et al. Respirology* **11**, 603–610 (2006).