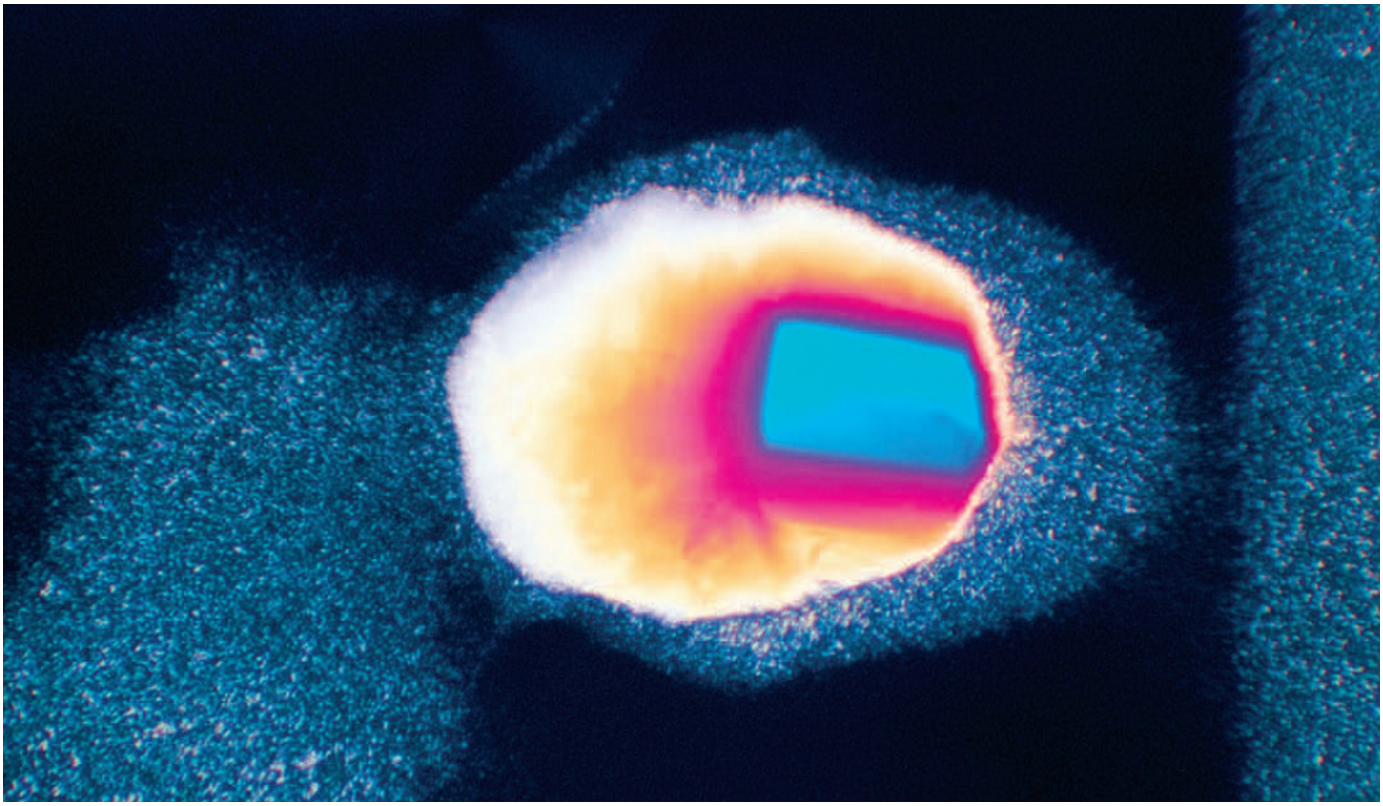

DAVID PARKER/SCIENCE PHOTO LIBRARY

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).