

**Different place; different tastes.** Typically, ants swarm sugar, but these ants living far from a coast also crave salt.

out vials containing cotton soaked in salt or sugar solutions and waited. Within minutes, ants had swarmed the sugary balls, as Kaspari had expected. But they swarmed the salty ones just as avidly.

“It was one of the greatest things I have ever seen,” Kaspari says. “Deep in the tropics, the ants will crave sodium as much as they crave sugar.” His team even showed that this sodium craving among ants gradually rises with distance from the ocean.

For a follow-up study, they established 70 quarter-meter-square plots in a tropical lowland forest in Peru, where the earlier work indicated ants were salt-deprived. Every other day the researchers sprinkled half the plots with stream water and the other half with a more concentrated salt solution. They subsequently harvested all the invertebrates in each plot. These creatures make up the “brown” food web that breaks down leaf litter and recycles the forest’s nutrients. In the sodium-enriched plots, the number of termites and ants increased and leaf litter decomposition jumped on average by 41%, Kaspari and his colleagues reported in 2009.

The work “suggested that global carbon balance may be affected by geographical patterns of nutrient limitations,” says Daniel Hahn, a comparative physiologist at the University of Florida in Gainesville. So, Kaspari and his colleagues recently tried to

estimate how much sodium influences the carbon cycle. They set up 10 pairs of 4-meter-square plots in Peru and, twice a month for a year, sprinkled half with water as salty as rain on the coast and half with river water. The plots were seeded with filter paper disks—stand-ins for leaves—and with chunks of three different types of wood. In the salted plots, termite populations increased 16-fold, leaf litter decomposition increased 26%, and wood decomposition increased by 32% to 76%, Kaspari’s team reported at the meeting. (The results are also in press in *Ecology*.)



**Saltshaker.** Through his field studies Michael Kaspari has shown that salt can be a limiting nutrient in inland forests.

Kaspari calculates that about 80% of Earth’s landmass is more than 100 kilometers from the coast, leading him to argue that the ecological effects of sodium limitation could be substantial, particularly where the natural geology fails to provide a concentrated sodium source. An estimated 30% of soil carbon is tied up in tropical forests, and Kaspari’s results suggest that inland, the carbon stores build up faster and break down slower than on the coasts because of sodium limitation, a factor that researchers modeling the carbon cycle rarely consider. “Sodium can play an important role in regulating organic matter decomposition and thus terrestrial carbon storage,” agrees Pablo García Palacios, a plant-soil ecologist at the Center of Evolutionary and Functional Ecology in Montpellier, France.

Not everyone is convinced. Sodium “will influence the landscape-level decomposition on the short term, but I’m not sure how it will influence the global cycle,” says Michael Palace, an ecologist at the University of New Hampshire, Durham. And David Wardle, an ecologist at the Swedish University of Agricultural Sciences, Umeå, calls for more work to clarify how widespread sodium limitations are.

Still, Kaspari’s colleagues say his work has given them a new appreciation for sodium’s ecological and geochemical influence. “Mike takes [earlier observations] forward in a huge way,” Hahn says. “He’s not just looking at individual behavior and individual decisions. He’s taking it to community function.”

—ELIZABETH PENNISI

## MEDICINE

# Suspect Drug Research Blamed for Massive Death Toll

Research misconduct can ruin everything from scientific careers to institutional reputations and public confidence in science. But in a paper published 2 weeks ago, two British cardiologists claimed that misconduct in their field may have had a far greater toll. Tainted research by Don Poldermans, a disgraced cardiologist who was at Erasmus MC in the Netherlands, may have led to the deaths of 800,000 people in Europe, Darrel Francis and Graham Cole of Imperial College London wrote in a provocative article that appeared briefly in the *European Heart Journal (EHJ)* and was then withdrawn.

Poldermans, a prominent researcher who published more than 300 papers, was fired in November 2011 after a university investigation concluded that he had engaged

in misconduct, including data fabrication. He was the lead author on two influential trials examining whether  $\beta$ -blocker drugs can protect patients undergoing surgery that doesn’t directly involve the heart; those studies helped shape guidelines adopted in 2009 by the European Society of Cardiology (ESC) that recommended using the drugs. (U.S. guidelines are more cautious.) When Poldermans’s studies are omitted, Francis and Cole say, the evidence shows that the recommendations don’t save lives but endanger them.

The accusatory paper was removed from the *EHJ*’s website less than 48 hours after it appeared. It hadn’t undergone peer review, as it should have, says Thomas Lüscher of the University of Zurich in Switzerland, the

journal’s editor; an official retraction was posted on 23 January, and the paper is now under review. But Cole and Francis say the staggering number of deaths they calculated was based on published data, and their claim has reignited a debate about giving  $\beta$  blockers to patients about to undergo surgery that might stress the heart. It is also a reminder, some scientists say, of the huge effects that a few uncertain and potentially flawed studies can have on clinical practice. “This is unfortunately what happens when you write a guideline that affects large numbers of people in a relatively common situation,” Francis says.

Defenders of the guidelines counter that the estimate of 800,000 deaths is wildly inflated. It disregards explicit cautions in

the guidelines, Lüscher says. Poldermans says he has seen the paper but he declined to comment; he is waiting for the review and revision of the paper, which Francis and Cole hope will be republished shortly.

Scientists have long debated the use of  $\beta$  blockers during surgery in heart patients who need noncardiac surgery. The drugs, prescribed for conditions including high blood pressure, heart failure, and migraine, interfere with muscle cells' response to stress hormones such as adrenaline. That can protect the heart from the stresses of surgery. But  $\beta$  blockers can also exacerbate the low blood pressure that is a common and dangerous side effect of surgery. In the 1970s and '80s, doctors thought it was better to discontinue the drugs in patients who were taking them if they had an operation scheduled. But in 1996, a small clinical study suggested that the drugs could benefit patients who had heart problems by decreasing their risk of postsurgery heart attacks.

As a follow-up, Poldermans and his colleagues launched a study called DECREASE I. It enrolled only 112 patients, all with heart problems, but the results were dramatic: Only 3.4% of patients on  $\beta$  blockers—which they received starting 30 days before surgery—died of cardiac causes or had a nonfatal heart attack in the month after the operation, compared with 34% of controls, the team reported in *The New England Journal of Medicine* (NEJM) in 1999.

The study moved opinion toward starting  $\beta$ -blocker therapy in patients scheduled to have high-risk surgery. But follow-up studies had mixed results. The largest trial, published in 2008, confirmed that patients on  $\beta$  blockers had fewer heart attacks in the month after surgery. But the study, called POISE, also found that patients in the  $\beta$ -blocker group had more strokes, and more died. The POISE researchers started patients on  $\beta$  blockers 2 to 4 hours before surgery, however, which Poldermans and his colleagues criticized as too late; they also used a different drug, and at higher doses, than DECREASE I. (The POISE researchers responded that their trial was designed to reflect the likely real-life use of the drugs.) A year later, in 2009, Poldermans produced his second study on the topic, called DECREASE IV, which showed that  $\beta$  blockers were beneficial in patients at intermediate risk of heart problems.

Poldermans's view carried the day. In 2009, an ESC panel that he chaired issued guidelines concluding that  $\beta$  blockers were beneficial for patients undergoing high-risk surgery, and that the “weight of evidence or opinion” supported using them in patients at intermediate risk as well.

Poldermans's downfall, which began with findings of misconduct in a study that didn't involve  $\beta$  blockers, has called that judgment into question. In 2012, a second university panel concluded that the conduct of DECREASE IV “was in several respects negligent and scientifically incorrect.” The



**Flawed advice?** European recommendations for the use of  $\beta$  blockers before surgery that doesn't involve the heart are being revised.

committee questioned “the reliability of the findings in the publication and the validity of the conclusions.” (The paper has not yet been retracted.) In a third investigation, due to finish by early summer, Erasmus MC is examining DECREASE I, a spokesperson says.

Until that time, both DECREASE studies should be excluded as the basis for any clinical guidance, Francis says. When he and his colleagues did so in a meta-analysis of 11 trials published in July 2013, they concluded that patients who received the drugs had a 27% increased risk of dying—an increase that led to their published estimate of 800,000 additional deaths.

The paper also took aim at ESC, which publishes the journal, for being slow to react to the Poldermans affair. The society should have rescinded, or at least revised, the guidelines as soon as flaws in Poldermans's work were found in 2011, Francis says. Instead, ESC initially issued a statement saying it was “confident that our Guidelines

are supported by reliable data.” Only in March 2013 did it announce that a committee would review the guidelines; in August, ESC said that “the initiation of beta blockers ... should not be considered routine,” but should be considered on a case-by-case basis. (The review committee is expected to finish its work in August this year.) In an editorial slated for next week's issue of *EHJ*, Lüscher counters that because the validity of the *NEJM* paper on DECREASE I is still unclear, “a firm statement was intentionally avoided.”

Eric Boersma, a biostatistician at Erasmus University and a co-author on both DECREASE studies and on the guidelines, disputes Francis and Cole's risk calculations. The POISE study skewed their numbers, he says, because that study's use of  $\beta$  blockers—in high doses and starting a few hours before an operation—is potentially dangerous. “Please don't use that technique,” he adds. If the drugs are started a week or more before surgery, “my appreciation of the literature is that that is safe, and potentially doing something good”—whether or not the DECREASE studies are included.

The only way to settle the question is a new clinical trial, says Sripal Bangalore, a cardiologist at the New York University School of Medicine in New York City who authored a 2008 meta-analysis that questioned the use of  $\beta$  blockers. That won't be

easy, however, Boersma says. He and his colleagues, including Poldermans, had tried to set up a larger trial, but couldn't get funding—in part, he says, because  $\beta$  blockers are already off-patent, so industry is not interested. Today it would be even more difficult, Boersma says, because so many people are already on  $\beta$  blockers that it's difficult to find enough naïve patients who meet the high-risk criteria.

Even if 800,000 deaths is a provocative exaggeration, Francis and Cole are making an important point, says biostatistician Gerd Antes, director of the German Cochrane Center in Freiburg. After misconduct, the forces slowing down any public health response often “are far stronger than those people who are brave enough to write such a provocation,” Antes says. “I know many examples where a bit more provocation would be helpful to stir things up, so they get the attention they deserve.”

—GRETCHEN VOGEL

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Gretchen Vogel

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