

KILLER CLONES

Overgrowth of mutant blood cells is common in older people—and a risk factor for serious disease

By Mitch Leslie

Kenneth Walsh was looking forward to a nice dinner and some interesting talks when he joined colleagues for a 2014 meeting of the venerable Medical Exchange Club in Boston. A cardiovascular biologist from Boston University's School of Medicine, Walsh didn't imagine that the presentations, on a peculiar blood cell imbalance, would have any relevance to his research. Then he saw the data. "I almost fell off my chair," he says.

The evening's speakers, hematologist and oncologist Benjamin Ebert and molecular biologist Steven McCarroll, both of Harvard Medical School in Boston, revealed that the phenomenon, an excess growth of certain blood cells known as clonal hematopoiesis, is far more common than expected, affecting about 10% of people over the age of 70.

Even more surprising, Ebert reported, was that the condition roughly doubles the odds of developing heart disease or suffering a stroke.

Walsh had spent years studying how abnormal tissue growth in the circulatory system promotes cardiovascular disease.

But the talks that evening galvanized him to retool his lab to probe the connection between clonal hematopoiesis

and heart disease. Earlier this year, his group reported its first results, revealing a potential mechanism through which clonal hematopoiesis might help clog our arteries.

Walsh isn't the only researcher fascinated by the phenomenon, which is emerging as an almost universal companion of aging—and may be far more widespread than even Ebert and McCarroll estimated 3 years ago. "Clonal hematopoiesis is probably going to happen to all of us if we get old enough," says geneticist Kári Stefánsson, CEO of deCODE genetics in Reykjavik who has studied its prevalence. In recent years, researchers have pinpointed some of the mutations that spur the condition, and now they're uncovering evidence that clonal hematopoiesis may be harming our health in multiple ways, by boosting the odds not just of heart disease but of leukemia and many other conditions as well.

OUR 10,000 TO 20,000 hematopoietic stem cells, most of which dwell in our bone marrow, divide to produce 100 billion new blood cells every day. From time to time these stem cells also pick up mutations—about one per cell every decade. Some of these genetic glitches are damaging, snuffing out the stem cell and its lineage, and others have no effect. But occasionally a hematopoietic stem cell hits the jackpot, acquiring a beneficial mutation that dramatically increases the number of its progeny. They form a genetically identical population, or clone, that becomes disproportionately abundant in the blood. In a person with clonal hematopoiesis, Ebert and his colleagues found, a single clone typically accounts for about 20% of the blood cells.

Although researchers have known about clonal hematopoiesis for decades, they had no idea what effect it had on our health. The first hints that these outside clones might be common came in the 1990s, when hematologist Lambert Busque of the Maisonneuve-Rosemont Hospital in

As we get older, groups of mutant cells can become overabundant in our blood.

Montreal, Canada, and colleagues used a tricky and inexact test to try to gauge its prevalence. Their results suggested that the incidence of clonal hematopoiesis surged in older women. But few scientists followed up on the finding. Says Busque: "I was a bit lonely in the field for a while."

Faster, cheaper DNA sequencing, however, made it possible to quickly scan blood cells for genetic evidence of clones. McCarroll's and Ebert's groups were among the first to try, although their initial goals were very different. McCarroll and his colleagues wanted to figure out whether rare mutations that occur early in life boost the odds of developing schizophrenia. They analyzed sequence data from blood samples taken from more than 12,000 Swedish patients, about half of whom had schizophrenia or bipolar disorder. "We found thousands of acquired mutations," McCarroll says. The problem was, they were in the wrong genes. "They were concentrated in blood cancer genes," he says—not in genes that are active in the brain. "We realized we had discovered something much more important than what we had set out to find."

About a hundred meters away at Brigham and Women's Hospital in Boston, Ebert and his team were closing in on the same discovery. "We were interested in the question of whether there was a premalignant state for [certain blood cancers], and if so, how common it was," Ebert says. To find out, he and his team pored over genome sequence data from more than 17,000 people who were taking part in long-term studies of diabetes or heart disease, and they identified an unexpected role for clonal hematopoiesis in illness. McCarroll says he learned about Ebert's work during a phone call to a colleague. Within a few hours, the two labs were comparing notes, and they published companion papers in 2014.

"It was amazing how well our data and theirs aligned," Ebert says. Both groups determined that the incidence of clonal hematopoiesis shoots up as we age. Only about 1% of patients younger than 50 had the condition, compared with 12% to 16% of people older than 80. Both papers also reported that people with clonal hematopoiesis often sported mutations in a few genes that spur the growth of blood cancers, including *TET2*, *DNMT3A*, and *ASXL1*.

Recent work has provided new estimates of how many of us have clonal hematopoiesis. Separate studies led by Stefánsson and Alexander Hoischen, a molecular geneticist at the Radboud University Medical Center in Nijmegen, the Netherlands, indicated that about 20% of people in their 60s have clonal hematopoiesis; the incidence

soars to more than 50% in people older than 85, Stefánsson's team discovered. Pediatric hematologist Todd Druley of Washington University School of Medicine in St. Louis in Missouri and colleagues found clonal hematopoiesis in 95% of women between the ages of 50 and 70.

The results of these studies don't clash, McCarroll says. The sequencing technique Druley and colleagues used was so sensitive that they were able to identify smaller clones than other studies.

CLONAL HEMATOPOIESIS MAY BE COMMON and silent, but it is not harmless. Ebert's and McCarroll's groups had access to comprehensive health records for their patients, which they could comb for links between clonal hematopoiesis and illness. The condition hikes the risk of blood cancers by more than 10 times, the medical records suggested.

That's a big increase, but the absolute cancer risk remains modest. More than 90% of people with clonal hematopoiesis never get leukemia, making it analogous to other precancerous conditions such as a colon polyp or an abnormal mole, says hematologist and oncologist Rafael Bejar of the University of California, San Diego. That the mutations don't boost risk further is a puzzle, says hematologist Ross Levine of Memorial Sloan Kettering Cancer Center in New York City. "Millions of people have clonal hematopoiesis, but only some get leukemia. Why?"

But clonal hematopoiesis may be killing us in other ways, Ebert's group has revealed. Someone with clonal hematopoiesis has a 40% higher likelihood of dying from any cause, possibly because of the condition's dramatic impact on the odds of developing atherosclerosis. "It looks like clonal hematopoiesis is equivalent to hypertension or diabetes" as a cardiovascular disease risk factor, Walsh says.

To work out why, Walsh and his team replicated clonal hematopoiesis in mice by giving them bone marrow transplants that replaced some of their hematopoietic stem cells with cells that carry faulty ver-

sions of *Tet2*. After recovering from the procedure, the rodents nibbled on an artery-plugging diet. The genetically altered strain of mice the researchers used is prone to plaque buildup, but the animals with clonal hematopoiesis accumulated 60% more plaque than usual in just 9 weeks, the team reported in *Science* earlier this year.

Immune cells known as macrophages help drive cardiovascular disease by lodging in the lining of the arteries and stoking inflammation. The mice with clonal hematopoiesis didn't produce more macrophages than normal, Walsh and colleagues found, but the cells were more pro-inflammatory. Among the inflammation-inducing molecules these cells pumped out was the potent cytokine interleukin-1 β (IL-1 β). Ebert and his team have also linked IL-1 β to atherosclerosis in mice that have the equivalent of clonal hematopoiesis.

Those findings suggest that targeting IL-1 β could stymie clonal hematopoiesis's effects on the arteries, Walsh says. A drug that blocks IL-1 β , the antibody canakinumab, cuts the odds of a second heart attack in patients who have already suffered one, a study reported in August. The improvement was small—a moderate dose lowered risk by only 15%, with many people showing no benefit. But Walsh predicts the drug would work better in people who have clonal hematopoiesis.

THAT MAY NOT BE THE END of the ways in which our blood betrays us. Studies have also linked clonal hematopoiesis to chronic lung disease, type 2 diabetes, and a rare skin inflammation known as Sweet syndrome, although how it might contribute to those conditions remains uncertain. The blood imbalance may even be a common factor in many diseases of aging, including

arthritis and kidney disease, Walsh says. No one knows why these illnesses are more likely to strike us as we get older, but Walsh speculates that clonal hematopoiesis could be the culprit. "I think it's going to explain a lot of chronic disease processes." ■

A multiplying effect

Most people walking around with clonal hematopoiesis are just fine. But this imbalance of blood cells can damage our health in several ways.



Cancer

Although most people with the condition never develop leukemia, their risk is more than 10 times higher.



Diabetes

For unknown reasons, it slightly increases the odds of developing type 2 diabetes.



Heart disease

By promoting plaque accumulation in the arteries, it doubles the risk of cardiovascular disease and stroke.



Skin inflammation

The fever and painful lesions of Sweet syndrome, a rare skin condition, can result.

Science

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Mitch Leslie

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