and analyzed medical records for more than 200 people; 27 were invited to the National Institutes of Health (NIH) for a marathon of medical tests.

But several of those turned out to have underlying diseases that had been overlooked, including cancer, pulmonary embolism, and a muscle ailment called myositis that causes weakness and fatigue. The surprise diagnoses suggest that people told they have ME/CFS often receive inadequate care—something many patients already know. "It's a huge indictment of our medical system that they had to join a research study to find out what was wrong with them," says Mike VanElzakker, a neuroscientist at Massachusetts General Hospital.

The participants spent at least a week at NIH for "a megaworkup" that included skin and muscle biopsies, spinal taps, and energy expenditure measurements. "We took every biopsy and body fluid we could think of," Nath says. Compared with healthy volunteers, people with ME/CFS showed no differences in muscle tissue that could explain post-exertional fatigue. Cognitive and psychiatric tests were also similar across the groups.

But functional magnetic resonance imaging revealed decreased activity in brain regions that, among other functions, help control movement. The researchers suggest brain signals may flash stop signs to prevent physical activity—similar to how a bout with illness forces rest. "When we have a bad flu, [we] can't get out of bed," says Jonathan Edwards, a rheumatologist at UCL. "It's a central signaling problem" in the brain, he says. "There's nothing wrong with your muscles."

Nancy Klimas, director of the Institute for Neuro-Immune Medicine at Nova Southeastern University, who studies and treats ME/CFS, says her big takeaway from the study "is that this is a disease of the brain. … The inability to sustain energy was coming from" that organ. But why this signaling persists remains a puzzle. (The researchers couldn't find evidence of lingering pathogens, but such testing can be challenging.)

The team uncovered other biological differences between the two groups, many of which have been reported in prior studies. Among other finds, ME/CFS patients had elevated heart rates and their blood pressure took longer to normalize after exertion, both signs of autonomic nervous system abnormalities. A protein called PD-1 was also elevated in T cells from patients' cerebrospinal fluid, suggesting these immune cells were trying to fight something off, even if no invader could be detected.

Nath and his colleagues suspect the immune dysfunction may lead to the brain differences. Drugs called checkpoint inhibitors, designed to help the immune system fight cancer, might support exhausted T cells, he suggests. He hopes for more insights into ME/CFS from a new wave of studies of Long Covid; the two conditions share symptoms though their biological overlap remains uncertain.

Vastag now wonders whether the study he supported years ago was the best approach, given how long it took to complete. Vastag's partner Beth Mazur also had ME/CFS for many years, and died by suicide in December 2023. "She ran out of hope that she would ever get better," he says. "They really need to follow up with whatever findings they have," he adds. "The patient population is desperate." ■

Myalgic encephalomyelitis/chronic fatigue syndrome study participant Brian Vastag (right) with study leader Avindra Nath.

PHOTO: BETH MAZUR

GEOCHEMISTRY

Sharp shift in ice age rhythm pinned to carbon dioxide

Southern Ocean "pump" sparked deep freezes, new temperature record shows

By **Paul Voosen**

Roughly 1.5 million years ago, Earth went through a radical climatic shift. The planet had already been slipping in and out of ice ages every 40,000 years, provoked by wobbles in its orbit. But then, something flipped. The ice ages began to grow stronger and longer, with durations of 100,000 years, and overall, the planet grew cooler. And nothing about Earth's orbit could explain it.

The cause of this Mid-Pleistocene Transition (MPT), as it's known, has been a major mystery for decades. A new compilation of global temperatures covering the past 4.5 million years, published on p. 884, points a finger at a familiar molecule: carbon dioxide. It suggests that a strengthening of an ocean pump in the waters around Antarctica sucked carbon dioxide out of the air and sent it plunging to the abyss, cooling the planet and intensifying the ice ages. The study even suggests the climate, then and now, could be more sensitive to carbon dioxide than modelers expect. "The power of the [carbon dioxide] control knob on the climate system really comes out of this work," says Ruth Mottram, a climate scientist at the Danish Meteorological Institute.

This view of the MPT also represents a blow for the other leading theory for the transition: that the ice sheets were themselves responsible. According to this "regolith hypothesis," once the glaciers in the Northern Hemisphere scoured away enough soil to form on stable bedrock, they could grow taller before collapsing under their own weight, extending the length of ice ages. By reflecting more light into space and altering weather patterns, these bigger ice sheets could cool the planet more. But Peter Clark, a glaciologist at Oregon State University who pioneered the regolith hypothesis and is co-lead author of the new study, says the work represents the beginning of the end for his idea. "The indications are that the ice sheets had little influence, or no influence, essentially, on global temperature," he says.

Instead, Clark and his colleagues now argue that the linchpin of the climate about 1.5 million years ago was the Southern Ocean, and in particular an expanse of sea ice extending off Antarctica. Their global temperature record shows a gradual decline that steepens at this time. Because the record also holds regional trends, it showed that the Southern Ocean had cooled enough by then for sea ice to form more regularly on vaster scales than it has in modern times.

As sea ice grows, it sucks freshwater out of the ocean, leaving behind saltier, dense water that plunges to the ocean bottom, taking dissolved carbon dioxide along with it and cooling the planet. In a feedback, the cooling would lead to more sea ice formation, a strengthening of this ocean pump—the engine of a global conveyor belt of ocean currents—and an intensification of the ice age. Each ice age would ultimately end as traditionally envisioned: with collapsing northern ice sheets that slide into the sea. The sudden injection of freshwater into the oceans would disrupt the global conveyor belt. Carbon dioxide would escape, the planet would warm, and the sea ice would melt.

"It's a solid mechanism for starting off this MPT cascade," says Thomas Chalk, a geochemist at the European Centre for Research and Education in Environmental Geosciences. Although the study is not the first to propose that Antarctic sea ice had a role in the MPT, the temperature record fills a gap for the field, which chronically underestimates the importance of the Southern Ocean, Mottram says.

To compile the record, the researchers had to look beyond the records from cores drilled from polar ice sheets, because they only go back about 800,000 years. Oxygen isotopes in foraminifera, tiny sea creatures whose fossils are found in sediment cores worldwide, hold longer records. But these isotopes don't just capture ocean temperature; they also reflect the amount of freshwater taken up in ice sheets. Researchers have struggled to disentangle the two effects. "There are a lot of assumptions," says Jeremy Shakun, a paleoclimatologist at Boston College and co–lead author of the study. "We wanted something more direct."

The researchers began to compile published records based on other temperature proxies. One relies on alkenones, a lipid produced in the ocean only by two closely related algal species; the number of double carbon bonds in the molecule varies with temperature. Another compares the ratio of magnesium and calcium in foraminifera; at higher temperatures, more magnesium is incorporated. And the last simply compares the abundances of different microbial species that appear to be sensitive to temperature changes.

An expansion of Antarctic sea ice 1.5 million years ago may have triggered longer and stronger ice ages.

Assembling the temperature "stack" required Shakun to gather 128 of these published records. "That first little step is endless," he says. "Half the work." He had to standardize each record and line up their ages. He and his colleagues then used modern climate models to predict past global temperatures given the ocean temperatures the proxies recorded. They validated the results against modern climate records and certain well-studied points in time, such as the last ice age and the warm period before the Pleistocene.

The resulting temperature curves are profoundly different from other published records and model results. When the 40,000-year ice ages first began, 2.7 million years ago, the long-term cooling trend didn't budge—a sign that the reflectivity of the northern ice sheets wasn't an important factor in temperatures. The regional trends within the new temperature record revealed that the planet was cooling everywhere, in sync—a signature of carbon dioxide's influence, which mixes throughout the atmosphere. This global influence is also seen during the MPT, when temperatures began to drop faster, eventually settling to an average of some 4°C below preindustrial levels.

The record also shows up to 3°C more cooling across the 4.5 million years than climate models suggest should have happened. That's alarming, because researchers trying to predict how hot global warming will make the planet look to the past to understand climate "sensitivity"—how temperatures changed for a given injection or withdrawal of carbon dioxide. The new temperature reconstruction suggests climate models might be underestimating the influence of the gas, at least in their projections of the past. "If this data is to be believed, the climate system is more sensitive than we've built into these simulations," Chalk says. "We need to know which way to come down on that."

Ongoing efforts to extend ice core records beyond 1 million years will help refine this picture, adds Bärbel Hönisch, a geochemist at Columbia University. But this new record, with its regional intricacies, will likely be a foundation for much future work. "It's a pretty beautiful record," she says. Chalk says those research topics could include questions that feed into climate forecasts, such as how weather patterns could change over different continents, or how clouds respond to warming patterns in different oceans.

Regardless, the new temperature record should close the book on an "ice-sheet first" view of the Pleistocene, says Timothy Herbert, a paleoclimatologist at Brown University. "The dance of global temperature is primarily not called by ice, but more likely by [carbon dioxide]." And the record casts a spotlight on the crucial role of the Southern Ocean, where sea ice is currently vanishing fast, with implications researchers are only beginning to puzzle through. "It's the valve on deep carbon storage," he says. And today, that valve may be closing. ■

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