oped that were larger and more numerous than those observed in mice injected with parental CTC cell lines. Metastases were reduced by treating mice with combination therapy whereby one drug inhibited the elongation step of protein synthesis (i.e., inhibiting translation) and another suppressed cell cycle progression. Such therapies might be efficacious in patients whose CTCs show high RP gene expression, although this requires clinical corroboration. The association among epithelial-like CTCs, high RP gene expression, poor clinical outcome, and drugs that inhibit translation would need to be experimentally confirmed in other cancer types to determine whether this can be generalized.

Cellular, cell-free, and particulate components of whole blood provide a dynamic database of functional information. CTCs and circulating tumor DNA (ctDNA) provide evidence of tumor recurrence sooner than radiologic changes, but their utility as clinical assays is limited by factors such as specificity and sensitivity as well as the availability of effective drugs. Although ctDNA may be more easily measured, CTCs are advantageous for elucidating metastatic processes and identifying treatment targets for clinical testing or drug development because they represent cancer cells that survive after drug therapy. Unfortunately, only a fraction of cancer patients will have sufficient numbers of CTCs available to grow, analyze, and therapeutically test using cell culture or mouse models (*12*–*15*). Such models may take months to generate, and patients with advanced cancer may not be able to wait that long. Future research must include the development of new technology platforms to enable real-time drug testing to better understand disease progression. ■

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OCEANOGRAPHY

Surprises for climate stability

An ocean sediment record reveals chaotic ocean circulation changes during warm climates

By **Thomas F. Stocker**

Instabilities in Earth's climate system have intrigued scientists ever since analyses from Greenland ice cores revealed climate variations over the last hundred thousand years (*1*, *2*). Abrupt changes were not singular events but a pervasive feature of the last ice age. Studies pointed to the ocean, specifically the Atlantic Meridional Overturning Circulation (AMOC), as a possible origin of these large swings (*3*, *4*). Their occurrence in the distant past of the last ice age and their absence in the past 8000 years suggested that we are living in times of relative climate stability. On page 1485 of this issue, Galaasen *et al.* (*5*) report that over the past 500,000 years, there were disruptions in the formation of the North Atlantic Deep Water mass—an essential driver of the AMOC—during interglacial periods. This suggests that substantial reductions or instabilities of the AMOC could also occur in a future warmer climate.

The AMOC transports warm surface waters from the Southern Hemisphere to the north. When these waters reach the northern North Atlantic, they lose heat, and the increased density causes them to sink, creating the North Atlantic Deep Water mass. Galaasen *et al.* provide a high-resolution sediment record from a core situated in the deep return path of the AMOC. It shows substantial and rapid changes in past warm periods.

The Eirik Drift, located south of Cape Farewell, Greenland, is formed by the North Atlantic deep current. The sedimentation rate at site U1305 in the deep parts of this drift permits an unprecedented view into the dynamics of the deep northern North Atlantic ocean. Galaasen *et al.* discovered large and abrupt water mass changes during each of the warm interglacial periods during the last 500,000 years. At a resolution of better than a century, stable isotope ratios of carbon, measured on the calcareous shells of bottom-dwelling foraminifera, exhibited large and irregular swings of water mass distribution, a frequent push and pull between waters of northern and southern origin.

High values of carbon isotope ratios indicate that the formation of North Atlantic Deep Water is vigorous and associated with strong AMOC. Low values, by contrast, suggest a weak or absent overturning with deep-water mass characteristics suggestive of a southern origin. Transitions between apparently two states occur rapidly, whereas either AMOC state can last for several centuries. This signature, so familiar during the last

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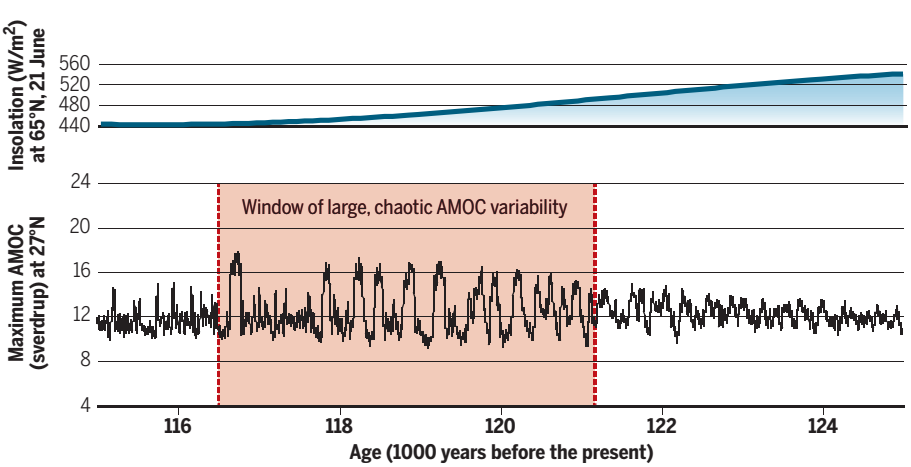
Ocean circulation growing chaotic

Simulated Atlantic Meridional Overturning Circulation (black) during 10,000 years of the last interglacial warm period about 120,000 years ago. Amplitudes of the AMOC grow and become chaotic within a limited window of the slowly changing solar energy input (blue).



ice age (*6*) and before (*7*), was unexpected in warm climates. That Galaasen *et al.* observed this during the interglacial periods suggests that this ocean circulation system may be much less stable than previously thought.

In the Holocene (the present warm epoch), fluctuations in the carbon isotope ratio in deep-ocean sediments are small, except for a well-documented 8200-year cooling event. But in previous warm periods, most notably during Marine Isotope Stage 11c some 400,000 years ago, many century-scale fluctuations in deep-water mass characteristics are registered at site U1305 of the Eirik Drift. Changes in deep ocean circulation are often associated with ice-rafted debris that originates from large ice sheets surrounding the North Atlantic basin. This debris is found in many sediment cores in the North Atlantic (*8*). However, in the record of Galaasen *et al.* from Eirik Drift, these fluctuations occur primarily in the absence of such debris, which suggests that the deep ocean circulation system may be naturally unstable or sensitive to rather small perturbations.

Galaasen *et al.* underpin their climate reconstruction with simulations over 10,000 years, using a coupled climate model of reduced complexity. Their results show that under the climate conditions of 125,000 years ago (the previous interglacial), the AMOC evolves from small-amplitude centennial variations through a period of nonperiodic self-sustained fluctuations of the AMOC with large amplitudes (see the figure). Fluctuations manifest themselves as two states: a stronger one with an AMOC close to the mean of today and a weaker state. Transitions between these two states are faster than the residence time in either state. This resembles the fingerprint of a nonlinear system with two attractors (*9*). Their model is forced by the Milankovitch cycles (*10*), the slow changes of solar energy input caused by variations in the orientation of Earth's rotation axis with respect to the Sun. This results in small changes of the seasonal distribution of solar irradiation. In a certain window lasting several millennia, the simulated AMOC shows fluctuations with amplitudes larger by as much as a factor of 5. Beyond this window, the variability decreases and the circulation again becomes more stable. In a nonlinear system, unstable chaotic behavior can emerge when a parameter is changed slowly and moves into a critical range of this parameter (*9*). Outside this range, the same nonlinear system may be strictly periodic or even stationary.

Large changes in overturning circulation without an external perturbation were also identified in other coupled ocean-atmosphere models in a specific parameter window (*11*). The largest amplitudes of these self-sustained oscillations are found close to the location of the sediment core that Galaasen *et al.* studied. However, in that study, self-sustained oscillations are periodic and predictable, which is in contrast to the more chaotic fluctuations in the paleoceanographic reconstruction from Eirik Drift and in the model simulation depicted in the figure.

Models show that a reduction of AMOC causes a cooling of the sea surface of the North Atlantic with consequent substantial regional cooling. Galaasen *et al.* do not provide a reconstruction of concurrent surface ocean conditions and their changes on the centennial time scale during the past four interglacials. It would be an important avenue of further research to quantify the climatic impact of these AMOC fluctuations.

Nevertheless, Galaasen *et al.* add to the debate on tipping points in the climate system. So far, climate models seem to agree that the AMOC will gradually decline over the 21st century, owing to the increase in atmospheric CO_2 concentrations and the consequent heating (*12*). This evolution may actually be irreversible. In addition to slow, irreversible, or abrupt transitions of the AMOC, there may also be the possibility that a gradual anthropogenic push of the climate system would move it into a state where variability becomes larger in amplitude and more chaotic. Galaasen *et al.* show that this was a possibility for the AMOC in the past and that such behavior should be factored in when assessing the risk of tipping points in the future.

Much will be learned about tipping points in the climate system through research within the European Commission's Horizon 2020 program, and continued monitoring, which is essential (*13*). But a comprehensive assessment about tipping points, their risks, and their impact is still missing. To provide robust and actionable information to decision-makers and people, this should be a priority for the seventh assessment cycle of the Intergovernmental Panel on Climate Change. ■

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GENOMICS

Quantifying mutations in healthy blood

Mutated clones in healthy tissues may hold clues for the earlier detection of malignancy

By **Christina Curtis**

Over time, somatic mutations accrue during normal cell division and tissue self-renewal. The patterns of age-associated somatic mutation have been perhaps most extensively characterized in the blood. Although many mutations are functionally benign, a subset represents premalignant initiating events in hematopoietic stem cells that result in clonal expansion. This clonal hematopoiesis confers an increased risk of hematologic malignancy (after the accrual of additional cooperating mutations), as well as cardiovascular disease and overall mortality (*1*). On page 1449 of this issue, Watson *et al.* (*2*) investigate the clonal architecture and evolutionary dynamics of healthy blood by analyzing targeted DNA sequences of ~50,000 blood cancer–free individuals. They find that positive selection for beneficial mutations, rather than neutral genetic drift, dictates the genetic diversity of normal blood. The identification of mutant clones and their associated fitness benefits could improve disease risk stratification.

The high mutational burden in rapidly dividing tissues such as the colonic epithelium was initially described in 2000 (*3*). The application of modern sequencing techniques has since revealed that other healthy tissues, including the blood, are littered with somatic mutations that accrue during normal cell division (*1*, *4*–*6*). However, the relative contributions of random (neutral) genetic drift, arising from fluctuations in allele frequencies in the population, versus positive selection for advantageous mutations on clonal expansions are unknown. Indeed, cancer is thought to arise from a mutated cell that clonally expands while

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