better than in humans. Precise effects of specific genetic variants on bristle number in flies have been mapped to several genes, and yet those same variants within a natural population have little bearing on bristle counts (*7*). Prediction of individual phenotypes is practiced in plant and animal breeding, where the genetic dimensionality is radically reduced. Modeling and prediction of complex phenotypes of inbred lines in the laboratory can be quite accurate, and yet when the same genes and phenotypes are projected into a free-living population, individual prediction entails too many additional variables and accuracy suffers.

So what comes next in complex disease research? The technology for identifying genetic differences is racing forward, with the 1000 Genomes Project (*8*) and efforts to accurately characterize copy number variation. The notion that whole-genome sequencing will become routine medical practice no longer seems so futuristic. But the biggest opportunity for making serious progress in understanding chronic disease risk lies in developing a deeper "biological awareness" into genomic approaches to the study of complex disorders. We tend to talk about pathways and processes as if they are discrete compartments of biology. But genes and their products contribute to a network of interactions that differ radically among tissues. Even our inference of gene regulatory networks suffers from being confined to a narrow biological context. A "candidate-tissue approach" still limits attention to a subset of tissues based on incomplete information and tenuous assumptions, and like candidate gene studies, there is no guarantee that these guesses are correct.

Though we have developed sophisticated statistical tools to analyze and identify genetic variants in the context of whole-organism phenotypes and to detect associations of effects that are far apart (in terms of molecular interactions), we have been unable to bridge the gap between the genetic lesion, or the biochemical effect, and the phenotype except in a few cases (*9*). A major breakthrough will be to predict and interpret the effect of mutational and biochemical changes in human cells and understand how this signal is transmitted spatially (among tissues) and temporally (spanning development) (*10*). Manipulation of induced pluripotent stem cells (*11*) may allow the analysis of diverse cell types from a number of individuals to examine the effects of genotypes in different biological contexts.

To date, GWA studies have relied on a rather unlikely model for the genetics of complex traits—that common DNA sequence variations (known as single-nucleotide polymorphisms) with widespread (but marginal) effects will predominate. This was a sensible place to start, but perhaps it should not be surprising that common variants provide little help in predicting risk. With the arrival of data for ever rarer variants in large, well-designed cohort samples, we should now decide how much emphasis to place on individual prediction, and ask how we can improve the currently unsatisfying record. Large cohort studies should provide information on candidate genes and on combinations of factors that influence groups that are at risk, even if accurate individual risk prediction is never achieved. An attainable public health goal that deserves emphasis is to identify, for each individual, life-style choices that pose particularly elevated risk of chronic disease.

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ATMOSPHERIC SCIENCE

Monsoons and Meltdowns

A counterintuitive connection between ice-sheet melting and weak monsoons helps to explain ice age cycles.

Jeffrey P. Severinghaus

What do periods of weak low-latitude rainfall have to do with the meltdown of great ice sheets? On page 248 of this issue, Cheng *et al*. (*1*) show that this counterintuitive association contains a hot clue about the much-debated causes of the ice age cycles that end every 100,000 years or so in a collapse of the great Northern Hemisphere ice sheets (a glacial termination). Understanding this collapse is relevant to human affairs both past and future, because the collapse typically causes a subsequent period of unusual climatic stability and warmth (an interglacial period), exemplified by the past 11,700 years of relatively stable climate in which human agriculture and civilization have flourished (*2*). Further, the future stability of ice sheets is an urgent question facing society today (*3*).

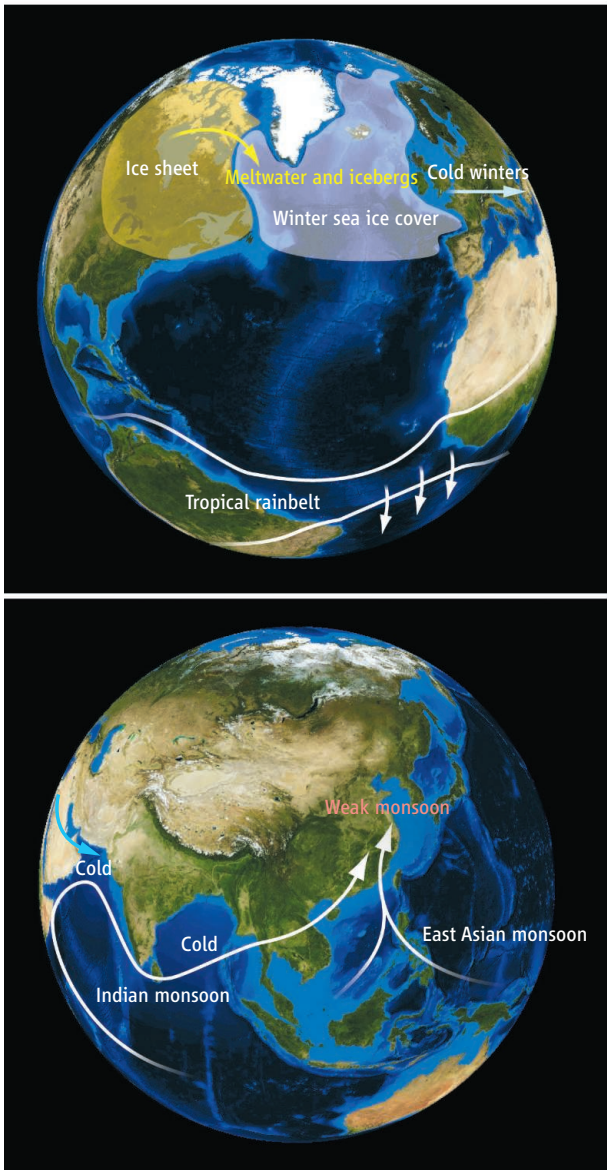
Scripps Institution of Oceanography, University of California San Diego, La Jolla, CA 92093–0244, USA. E-mail: jseveringhaus@ucsd.edu

The melting ice sheets inject so much low-density fresh water into the North Atlantic that they weaken or entirely shut down the normal sinking of dense water that fuels the ocean circulation (the meridional overturning circulation, or MOC). The loss of this circulation allows sea ice to cover the North Atlantic in winter, preventing ocean heat from warming the air and leading to extremely cold winters in Europe and Eurasia, which seem to weaken the following summer's monsoon in Asia (see the figure). The exact mechanism that links cold winters to weak monsoons is still debated, but could be simply that the more extensive spring snow cover and cold, wet soils slow the heating of the land surface that is the main driver of the monsoon. These cold winters do not, however, prevent continued summer melting of the ice sheets, because ice survival is relatively insensitive to winter temperature (*4*).

The occurrence of weak monsoons may thus provide an indirect time marker of ice-sheet meltdowns. As a record of past monsoon strength, Cheng *et al*. use the ratio of oxygen isotopes in the calcium carbonate of stalagmites (cave deposits precipitated from groundwater seepage) from the Asian monsoon region. Stalagmites are the most accurately dated paleoclimate records on the relevant 100,000-year time scale, with errors of mere decades (*5*).

The breakthrough of Cheng *et al*. is that they have achieved unprecedented dating precision, and correlate the monsoon record with ice core and marine records, providing all three with an accurate time scale for the past four ice age terminations. They can thus compare the precise timing of meltdowns with potential causes, such as the amount of sunshine (insolation) that fell on the northern ice sheets in the melting season from June to August, or the concentration of atmospheric CO_2 known from trapped air bubbles in ice cores.

The authors find that the last four meltdowns began when northern sunshine was



How meltwater from the North American ice sheet may cause weak Asian monsoons. Meltwater runoff into the North Atlantic prevents sinking of water around Greenland, because fresh water has a lower density than salt water. This leads to a collapse of the Atlantic Meridional Overturning Circulation (MOC), in turn further freshening the surface North Atlantic as a result of loss of northward transport of salt by the MOC. This fresh surface layer enhances winter sea ice formation because its low density prevents deep convection, restricting surface access to the enormous heat reservoir represented by the deep ocean. Widespread sea ice cover in turn causes extremely cold winter air temperatures downwind of the North Atlantic due to the insulating effect of sea ice. A southward-shifted atmospheric jet brings cold air into the Mideast and Indian Ocean region. Cooling of the Asian landmass and the North Indian Ocean in winter then weakens and delays the onset of the following summer's monsoon.

intensifying, in accordance with the classical Milankovitch or astronomical theory of the ice ages (*6*). By linking their cave chronology with ice cores via the spike of atmospheric methane (*7*) that accompanies abrupt increases in monsoon intensity, the authors further show that meltdowns occur hand in hand with rising CO_2. They also link the timing of their weak monsoons to Heinrich events, which are pulses of icebergs recorded in marine sediment cores as layers of ice-rafted debris. This allows them to place the sediment core records on an accurate time scale, which is important because the classical indicator of sea level (oxygen isotopes in calcium carbonate shells) is borne by sediment cores. Their finding that sea levels rose in synchrony with CO_2 during glacial terminations clears up an old confusion that came from the use of the oxygen isotopes of atmospheric O_2 as an indicator of sea level, now known to be unreliable (*8*).

These are impressive accomplishments by themselves, but the hot clue that Cheng *et al*. provide is that most of the meltdown and sea-level rise occurs during periods of weak monsoons, when the MOC is shut down and CO_2 is rising. Is there something about an "off" MOC that helps to destroy an ice sheet? Cheng *et al*.'s timing data provide support for the hypothesis (*9*, *10*) that an "off" MOC forces CO_2 out of the Southern Ocean, warming the globe by its greenhouse effect, which in turn causes more melting of the ice sheets, ensuring that the MOC stays in its "off" position in a positive-feedback loop.

In this view, the distinguishing characteristic of glacial terminations—in contrast to other periods of high Northern Hemisphere sunshine that do not trigger a termination—is a huge ice sheet that can provide sufficient meltwater to keep the MOC in its "off" position for some critical duration, allowing a large enough CO_2 rise to fatally damage the ice sheet. This critical duration entails the crossing of some threshold, beyond which the ice sheet has too low an altitude and thus cannot survive, because the air temperature increases with falling altitude. An alternative hypothesis is that massive ice sheets are inherently vulnerable and cannot survive the combined onslaught of Milankovitch and CO_2; the two hypotheses are not mutually exclusive and may both operate.

In either case, the answer to the question "Why do terminations recur roughly every 100,000 years?"—attributed to Raymo (*11*)—is that terminations require an existing massive ice sheet, and that Earth's orbit becomes nearly circular every ~100,000 years, eliminating periods of intense sunshine and thereby permitting the gradual accumulation of a massive ice sheet. An interesting exception cited by Cheng *et al*. is the anomalously weak sunshine 229,000 years ago that apparently allowed accumulation of a massive ice sheet within a short time, causing a termination that does not fit neatly into the 100,000-year paradigm.

Cheng *et al*. thus confirm the astronomical theory of the ice ages, but with a twist: The shutoff of the MOC and its associated southward shift of tropical rain belts, warming of the Southern Hemisphere (termed the "bipolar seesaw"), and rise in atmospheric CO_2 plays an integral role in the meltdown of the great ice sheets. Using monsoons to improve dating precision across the whole suite of paleodata, Cheng *et al*. show the way to the first coherent narrative that truly explains terminations and the inseparable question of what causes ice age cycles (*12*).

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12. This article neglects the role of the tilt of Earth's axis in causing terminations. Every ~400,000 years, Earth's orbit becomes really circular. At these times, the meltdowns occur when Earth's tilt is at a maximum, because the higher the tilt, the higher the Sun is in the sky in the polar regions during summer; the trigger of the meltdown is then not a minimal Earth-Sun distance, but rather a maximal tilt of Earth's axis. Milankovitch combined the effects of tilt and Earth-Sun distance by plotting June insolation (sunshine intensity) at 65°N versus time when discussing the causes of the ice ages.

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