ulatory factors? Finally, because linker histones have been implicated in DNA repair and apoptosis (*18*, *19*), do they act in these cellular processes by compacting chromatin or through some other, yet to be discovered mechanism? The next decade of research on linker histone variants (*7*), as well as on core histone variants (*20*), may yield as much insight about cell regulation as the past decade has about histone modification.

References

1. D. Z. Staynov, C. Crane-Robins, *EMBO J.* **7**, 3685 (1988).
2. H. Lee, R. Habas, C. Abate-Shen, *Science* **304**, 1675 (2004).
3. M. Schlissel, D. D. Brown, *Cell* **37**, 903 (1984).
4. X. Shen, M. A. Gorovsky, *Cell* **86**, 475 (1996).
5. Z. F. Wang *et al.*, *J. Mol. Biol.* **271**, 124 (1997).
6. R. W. Lennox, L. H. Cohen, *J. Biol. Chem.* **258**, 262 (1983).
7. Y Fan *et al.*, *Mol. Cell. Biol.* **23**, 4559 (2003).
8. O. C. Steinbach *et al.*, *Nature* **389**, 395 (1997).
9. K. Song *et al.*, *Nature* **360**, 477 (1992).
10. E. H. Bresnick *et al.*, *Nucleic Acids Res.* **20**, 273 (1992).
11. L. A. Cirillo *et al.*, *EMBO J.* **17**, 244 (1998).
12. Y.-B. Zhou *et al.*, *Nature* **395**, 402 (1998).
13. L. A. Cirillo, K. S. Zaret, *Mol. Cell* **4**, 961 (1999).
14. V. Ramakrishnan *et al.*, *Nature* **362**, 219 (1993).
15. Y. Dou *et al.*, *Mol. Cell* **4**, 641 (1999).
16. R. N. Bhattacharjee *et al.*, *Mol. Cell. Biol.* **21**, 5417 (2001).
17. D. Pruss *et al.*, *Science* **274**, 614 (1996).
18. J. A. Downs *et al.*, *Mol. Cell* **11**, 1685 (2003).
19. A. Konishi *et al.*, *Cell* **114**, 673 (2003).
20. K. Ahmad, S. Henikoff, *Mol. Cell* **9**, 1191 (2002).

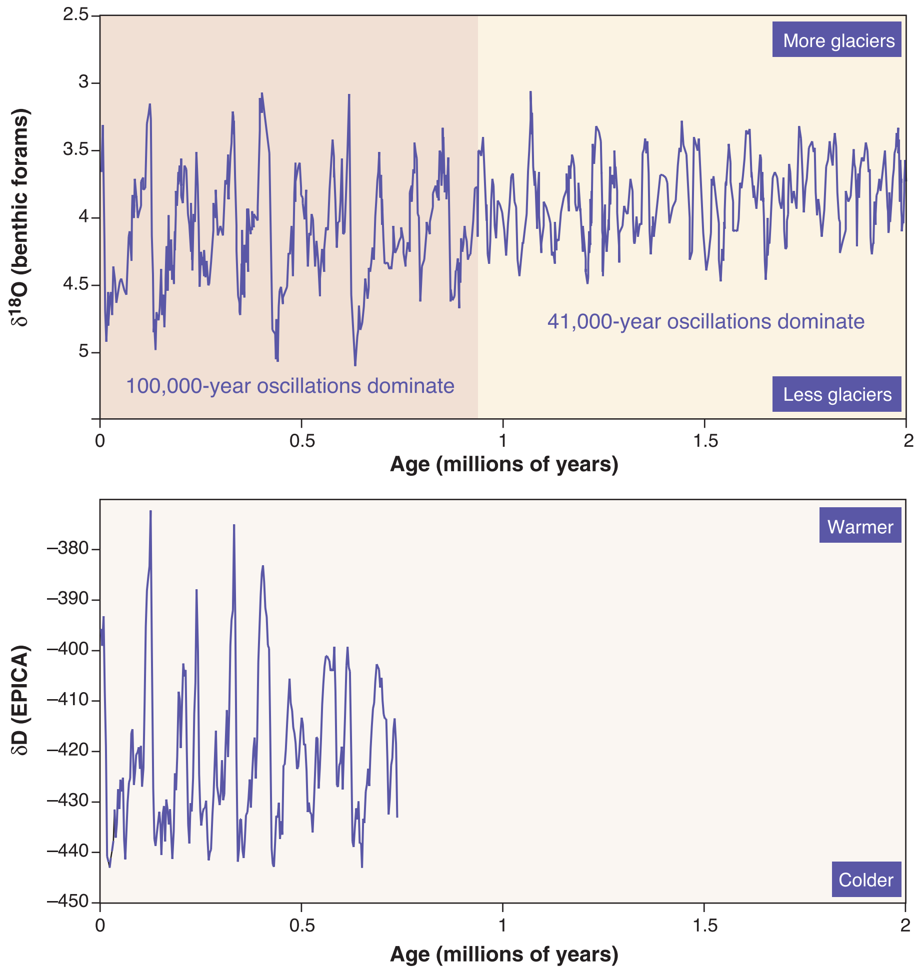
PALEOCLIMATE

Do I Hear a Million?

James W. C. White

There is a bidding war going on in Antarctica, and it has just heated up in a big way. The bidding started with 80,000 for the Byrd Ice Core. Vostok raised the bid to 160,000 and then 420,000. Now a new ice core, the European Project for Ice Coring in Antarctica (EPICA) Dome C core, has raised the bid to a startling 740,000. No, we're not talking money here, but something very precious, to paleoclimatologists at least, and that is years. At a site in east Antarctica, a team of European and Russian researchers from about a dozen countries have recovered an ice core that extends back in time 740,000 years, nearly twice as long as our previously longest ice core record. They report their findings in this week's *Nature* (*1*). Through their efforts, they have opened doors to scientific problems that we once thought were not accessible with ice cores, and raised the tantalizing possibility that 1-million-year-old ice is waiting for us somewhere near the bottom of the Antarctic Ice Sheet.

What's in a million? In this case it's not just a magical number that captures our attention, but it is also a key time in the history of climate on Earth, a time when the pattern of climate change and sea level changes shifts from a clearly Milankovitch world dominated by the obliquity of Earth's orbit, to one with larger sea level changes dominated by a periodicity of 100,000 years. Where this 100,000-year periodicity comes from is one of the still unanswered, yet fundamental questions in paleoclimatology. Records of oxygen isotopes in benthic foraminifera, tiny recorders of the volume of glaciers on the planet, tell us that about 1 million years ago, this climate shift occurred (see the figure), but they have not thus far been able to tell us why. Ice cores bring to the table new data that tell us about forcing factors of climate, including concentrations of greenhouse gases such as carbon dioxide and methane, and dust levels in the atmosphere, as well as estimates of temperature and precipitation amounts. Until recently, ice core scientists rarely spoke in terms of a million years. With the EPICA results, one can be sure that the race to get there is on in earnest. In fact, ice core scientists from around the world, at a recent meeting of the International Partnerships in Ice Core Sciences (*2*), made the goal of retrieving an ice core of 1 million years or more one of their top priorities for the upcoming International Polar Year (www.ipy.org) in 2007–2008. With a new spirit of global cooperation among ice core researchers not seen in at least a decade, the odds of finding that ice seem rather good.



The longer view. (**Top**) The $\delta^{18}O$ of benthic foraminifera from Site 849 in the Pacific Ocean, a proxy for glacial ice and sea level (*7*). (**Bottom**) The δD (deuterium/hydrogen ratio) of ice, a proxy for air temperature, in the new EPICA ice core (*1*).

The author is in the Environmental Studies Program, University of Colorado, Boulder, CO 80309, USA. E-mail: james.white@colorado.edu

But the EPICA core "only" goes back 740,000 years. Does that mean it's a bust? Hardly. The EPICA team members focus on several important climate stories that are within EPICA's long reach. About a half-million years ago, a less obvious, but potentially very important change in the nature of those 100,000-year-long cycles of glaciation occurred. Called the Mid Bruhnes Event, this time is marked by a significant increase in the amplitude of sea level changes (see the figure). In interesting contrast, at EPICA, although the glacial periods appear equally cold regardless of how much ice volume exists, the last five interglacial periods are the only ones in the past 740,000 years that are as warm as our climate is today. Prior to 430,000 years in the EPICA record, the warm periods are really cool periods, and are less obvious as "interglacials." Perhaps EPICA is telling us that we need to revisit the term "interglacial," and define a third, intermediate cool climate state between full glacials and full interglacials. It's worth noting that in the past 430,000 years, the percentage of time that climate was as warm as it is today is quite small, about 5 to 10%, and before that time, it appears to never have been that warm. Our current climate appears to be a rarity, if not an anomaly. Again, we don't know why, but it is hoped that the answers will come as the new core is analyzed for the full suite of measurements available in ice cores, and as others of equal or longer age are recovered.

Another key new finding of the EPICA team is the recovery of the full interglacial period at 410,000 years ago (Marine Isotope Stage 11, or MIS11). MIS11 is the only interglacial period in the EPICA record that is as warm as, and as long as, our interglacial period, known as the Holocene. We have basked in relative warmth for the past 12,000 years, considerably longer than the 4000- to 6000-year lengths of the previous three interglacials as seen in the Vostok ice core (*3*). This is more than a game of one-upmanship, as we have needed this long period of stable and warm climate to develop modern, complex societies. Although it is an arguable point, it seems unlikely that human societies could have evolved to their impressive level of today in interglacials of 6000 years or less. So why is our interglacial longer than most? Some would argue that it's a matter of how much, where, and during what season the Sun's energy reaches the planet (*4*). Others, notably Ruddiman and Thompson (*5*), assert that humans impacted climate as early as 6000 years ago, with extra methane generated from rice cultivation and extra carbon dioxide from biomass burning, possibly keeping the next ice age at bay. The EPICA CO_2 and CH_4 results from MIS11 don't resolve this controversy, but it's worth noting that both greenhouse gases at MIS11 don't show the steady rise during that period that they do during the Holocene. It's also worth noting that MIS11 was about 28,000 years long, so perhaps we should not be expecting an ice age any time soon anyway. Any hopes for the Holocene eventually being the longest interglacial period, by the way, appear to be dashed by recent evidence that human-caused warming began in the 1960s or 1970s (*6*), ending the Holocene and starting the Anthropocene. We'll have to settle for being number two.

The new EPICA ice core is a tantalizing mixture of wonderful new data, new questions added to unanswered old ones, and great promise once the full analyses are done. At 740,000 years, it's a remarkable record. This austral summer, the EPICA crew will go back to retrieve the last few hundred meters of ice left. Given our past experience with ice at the bottom of ice cores, it may be mixed and folded and thus climatologically unusable. Even if that's the case, and it may well not be, the ice core community now has its sights set on collecting even older ice. Do I hear a million?

References and Notes

1. EPICA community members, *Nature* **429**, 623 (2004).
2. Meeting of the International Partnerships in Ice Core Sciences, 13 to 16 March 2004, Sterling, VA. See also http://nicl-smo.unh.edu/IPICS/IPICS.html.
3. J. R. Petit *et al.*, *Nature* **399**, 429 (1999).
4. A. Berger, M. F. Loutre, in *Earth's Climate and Orbital Eccentricity: The Marine Isotope Stage 11 Question, Geophysical Monograph 137*, W. Droxler, R. Z. Poore, L. H. Burckle, Eds. (American Geophysical Union, Washington, DC, 2003), pp. 17–26.
5. W. F. Ruddiman, J. S. Thomson, *Quat. Sci. Rev.* **20**, 1769 (2001).
6. Intergovernmental Panel on Climate Change, *Third Assessment Report: Climate Change 2001: The Scientific Basis* (Cambridge Univ. Press, Cambridge, 2001).
7. A. C. Mix *et al.*, in *Proc. Ocean Drill. Prog. Sci. Results 138*, N. G. Pisias, L. Mayer, T. Janecek, A. Palmer-Julson, T. H. vanAndel, Eds. (Ocean Drilling Program, College Station, TX, 1995), pp. 371–412.

8. I thank G. Miller and T. Marchitto for thoughtful and helpful discussions.

DEVELOPMENTAL BIOLOGY

Hox Genes in the Limb: A Play in Two Acts

Jacqueline Deschamps

During embryonic development, tetrapod limbs emerge from the lateral plate mesoderm at specific positions along the embryonic axis. Nascent limb buds are already endowed with anterior-posterior (AP) polarity, as evidenced by the asymmetric expression of *dHand*, *Gli3*, and some of the *Hox* genes, including a set of genes on the 5′ side of cluster *HoxD* (see the figure). Interplay between anteriorly restricted *Gli3* and posteriorly restricted *dHand* is thought to prepattern the limb bud (*1*). This prepatterning results in the formation of the zone of polarizing activity (ZPA) in the posterior of the limb bud (*2*), which expresses the signaling molecule Sonic Hedgehog (SHH) (*3*). This marks the second phase of limb development during which SHH signaling feeds back onto the early limb controller genes, reinforcing their transcription posteriorly or repressing their expression anteriorly. This second phase initiates morphogenesis of the most distal limb structures, the digits. Mouse embryos lacking *Shh* exhibit limb truncations suggesting that this gene is essential for digit formation. Recent work shows that *Shh* and *Gli3* are dispensable for generating limb skeletal elements, but are required for specifying digit identity (*4*, *5*). Inactivation of *Gli3* rescues the digit phenotype in *Shh*-deficient mouse embryos presumably by releasing GLI3-mediated repression of the 5′*HoxD* genes that play an important part during the second phase of limb development. *Hox* genes are typically expressed along the embryonic axis in the order in which they lie in their clusters. The expression of 5′*HoxD* genes is restricted to posterior embryonic tissues. In addition, these genes are expressed in dynamic patterns in developing limb buds, and are essential for digit development (*6*).

On page 1669 of this issue, Zákány *et al*. (*7*) reveal that the 5′*HoxD* genes contribute to patterning of limb buds much earlier than the second phase of limb bud development. Early posterior re-

The author is at the Hubrecht Laboratory, Uppsalalaan 8, 3584CT Utrecht, Netherlands. E-mail: jacqueli@niob.knaw.nl