ing microelectrical mechanical systems (MEMS) or microchips are being studied. For example, microchips containing nanosized drug reservoirs might be able to deliver pharmaceuticals for long time periods in a controlled manner (see the second figure), ultimately by placing a microprocessor, power source, and biosensor in a chip. An implantable system that can deliver drug and respond to specific regulatory in vivo molecules may one day be possible (*10*).

Numerous other challenges exist. Targeting drugs to specific cells, the creation of novel vaccine delivery approaches, and the development of cell-based delivery systems are but a few examples. Recent advances point to a future where drugs are delivered only to the place where they are needed and at the levels they are required, with major benefits to patients.

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PERSPECTIVES: PALEOCLIMATE

Ice Ages, the California Current, and Devils Hole

David W. Lea

It is tempting to assume that key climate events in the past—the extent of continental ice sheets during glaciation, the coldest ocean temperatures, the response of the biosphere—occurred at the same time. But evidence is emerging from studies of marine sediments that ocean temperatures in some regions began to warm thousands of years before the melting of continental ice sheets. Inferred previously for the Subantarctic Indian Ocean (*1*), new proxies of sea surface temperature indicate that this early warming characterized the end of glacial periods in the tropics (*2–4*), the Southern Ocean (*5*), and, as Herbert *et al.* report on page 71 in this issue, on the California Margin (*6*). The temperature leads in the California Current were as large as 10,000 to 15,000 years, which implies warming during the coldest part of the ice ages; they varied spatially up and down the margin, and they are supported by diverse terrestrial evidence.

If large-scale ocean warming preceded ice sheet melting, it suggests that the oceans were responding to an external factor independent of the ice sheets. Furthermore, the early warming of the oceans is likely to have played a role in the melting of the ice sheets. In contrast, some previous scenarios have assumed that climate variability caused by the presence of the ice sheets (such as changes in the thermohaline ocean circulation) dictated oceanic conditions. The geographic distribution of the timing of change (see the figure) may help establish the regional and global patterns of climate change associated with global warming at the end of glacial periods.

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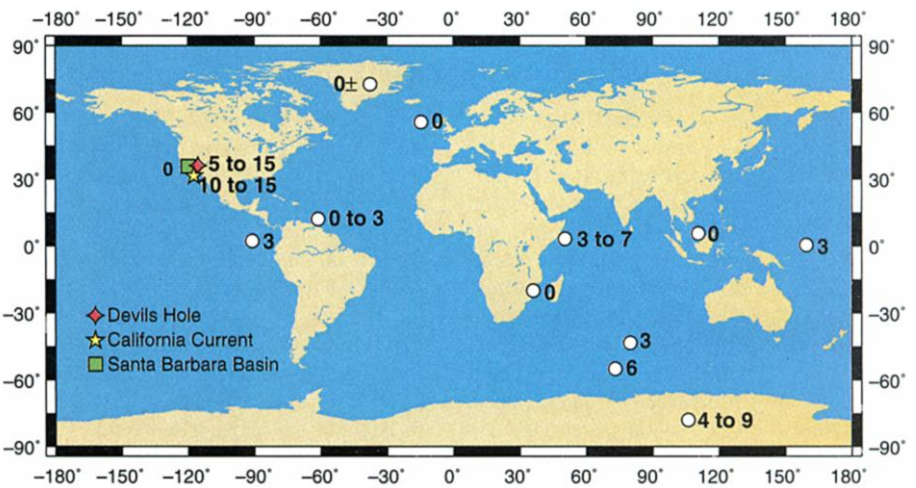
Strong support for the ocean temperature lead comes from air temperature records preserved in polar ice sheets. Proxies in an ice core from Vostok, Antarctica, show that local atmospheric warming led ice volume (the amount of continental ice) changes by 4000 to 9000 years at glacial terminations (*7*). The ice core data suggest that the temperature lead is not a purely oceanic or regional phenomenon. Rather, it reflects a large-scale response to a climate forcing, such as atmospheric greenhouse gases, which also changed before ice volume but at the same time as temperature (*7*). There is, however, ample evidence that the temperature lead was not uniform across the globe (see the figure). Sea surface temperatures in the North Atlantic, the region most directly linked to the Northern Hemisphere ice sheets, do not show a lead (*8*). Temperatures in some parts of the tropics seem to have changed at the same time as ice volume and Greenland temperatures (*2*, *9*), and the Greenland ice cap itself has an air temperature history that can be interpreted both as leading or lagging ice volume (*10*).

In their study, Herbert *et al.* exploit the fact that the number of double bonds in long-chain, unsaturated ketones (alkenones) produced by certain marine algae is correlated with the ambient temperature at the time of synthesis. Their measurements of alkenone unsaturation indices in the California Current indicate much larger temperature leads than have been observed in other oceanic records (10,000 to 15,000 years versus ~3000 years). Some proxies of California Current temperature, such as faunal abundance and oxygen isotopes in planktonic



What happens at the end of an ice age? The map shows key oceanic, continental, and ice core sites where the timing of temperature versus ice volume change at glacial terminations has been established. Lead in units of 1000 years. One of Herbert *et al.*'s California Current sites (*6*), the Santa Barbara Basin core (*11*), and Devils Hole (*13*) are indicated. The data that are mapped (*1–11*, *13*) are a composite of the last five glacial terminations, which occurred between 10,000 and 500,000 years before present and differ substantially in their orbital characteristics (*1*).

foraminifera, do not indicate such a lead (*11*), even though they were measured in a Santa Barbara Basin core also studied by Herbert *et al.*

Alkenones are mainly produced by coccolithophorids, microalgae that follow a distinct bloom pattern (*12*). The alkenones may therefore record the temperatures at which those blooms occurred and not the mean pattern of surface water temperature change. Strong support, however, for the inferences from the alkenone data comes from a continental record: a calcite vein from a submerged fissure called Devils Hole in Nevada (*13*). The lead in the independently dated Devils Hole oxygen isotope record over oceanic isotope records was first interpreted as posing a fundamental challenge to the Milankovitch theory, which argues that changes in orbital configuration drive ice age cycles (*1*). The problem was that the early onset of deglaciation in the Devils Hole record appeared to be in conflict with the orbital time scale of marine records of continental glaciation (*13*). But new temperature records from the tropical Pacific (*4*) and the more proximal California Current (*6*) suggest that Devils Hole variability is not a record of glaciation but rather a response to the temperature of Pacific source waters, which warmed early in the deglacial cycle, thus accounting for the timing mismatch. Although this eliminates the chronological mismatch with orbital theory, the early temperature response itself remains to be explained beyond the high-latitude Northern Hemisphere ice sheet forcing that Milankovitch envisioned (*1*).

If the large lead of California Current temperature is correct, it requires an explanation that is separate from the global response. Herbert *et al.* (*6*) hypothesize that the California Current collapsed during glacial maxima and that the invasion of warm gyre waters from the south produced the temperature lead. They further argue that there is a regional pattern to this effect, with the largest lead characterizing sites in the southern part of the California Current—where warm gyre waters can readily invade—and a smaller or absent lead north and south of this point.

The authors suggest that the presence of the Laurentide ice sheet—the massive ice sheet that covered much of North America—perturbed the northwesterly wind field along the California margin in a way unfavorable to the propagation of the California Current. This scenario might also explain some of the difference between the alkenone record and other temperature proxies (*11*). A seasonal invasion of warm gyre waters might favor coccolithophorid blooms, thereby leaving a particularly strong imprint of warmer temperatures in the alkenone record. Regardless of the exact causes, the timing of temperature change in the California Current and other regions challenges the paleoclimate community to understand what appears to be a globally asynchronous climate response during ice age terminations.

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PERSPECTIVES: DEVELOPMENT

The Message Is in the Translation

Joel D. Richter and William E. Theurkauf

Messenger RNAs (mRNAs) in the developing embryo must be translated into proteins at the right time and in the correct place to ensure that these proteins direct tissue formation appropriately. Assembly of multiprotein complexes on mRNAs ensures that translation is switched off until the time is right and the transcripts have reached the correct location within the embryo. Recent work on *cyclin B* mRNA (which encodes a cell cycle factor) and on other mRNAs suggests that the timing and location of mRNA translation may also control progression of cells through the cell cycle. Like protein degradation, control of mRNA translation is proving to be an elegant way for cells to modulate when and where proteins carry out their duties.

The accumulation and destruction of the crucial cell cycle factor cyclin B is essential for progression of the cell through the final stages of division (mitosis). Cyclin B binds to Cdk1 (Cdc2) protein kinase, forming activated M-phase promoting factor (MPF), and, although it is synthesized throughout the cell cycle, cyclin B begins to accumulate only during interphase. Both MPF activation and the onset of mitosis are triggered when cyclin B reaches a critical amount and the Cdk1 subunit is appropriately modified by both phosphorylation and dephosphorylation (the addition and removal of phosphate groups). Exit from mitosis requires destruction of cyclin B by an elaborate protein machine known as the anaphase-promoting complex (*1*). Although it is axiomatic that regulated protein destruction is the driving force behind cell cycle progression, recent evidence suggests that at least in early embryos, regulating the production of cyclin B is also essential for cell division. New work indicates that control of *cyclin B* mRNA translation takes place in different parts of the embryo and within different regions of rapidly dividing embryonic cells. Regulation of *cyclin B* mRNA translation appears to be part of a wider translational control network that is critical for pattern formation (the establishing of body structures in the appropriate region of the embryo) during early development of the fruit fly *Drosophila melanogaster*.

Formation of the anterior–posterior axis in the *Drosophila* embryo is specified by the localized expression of several mRNAs inherited by the egg at the time of fertilization. One of these mRNAs encodes Hunchback (Hb), a transcription factor that is required for segmentation in the anterior thoracic region of the embryo. Although *hb* mRNA is uniformly distributed, it is translationally repressed in the posterior region through the combined action of

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