guided extension of these simple tubular structures? The arms themselves are surrounded by basement membrane, and the DTCs must migrate over other basement membranes along their migratory routes. Remodeling of those membranes appears to regulate DTC migration and gonadal expansion. Support for this comes from the demonstration that the metalloprotease GON-1 is crucial for the earliest stages of DTC migration; in the absence of GON-1 activity, the gonad arms do not migrate at all (*7*). The *gon-1* gene encodes a secreted member of a small subfamily of metalloproteases, which includes the mouse protease ADAMTS-1 and bovine procollagen I N-protease. These proteins are characterized by both a metalloprotease domain and one or more thrombospondin type 1 repeats, which may allow them to become anchored within the ECM. They would then be positioned such that they could cleave their targets with maximum efficiency. As DTCs migrate they express *gon-1*; driving expression of *gon-1* using DTC-specific promoters rescues the DTC migration defects in *gon-1* mutant gonads, thus, GON-1 activity is required for DTC migration. However, *gon-1* is also normally expressed in muscle; other experiments suggest that GON-1 is required not merely for DTC migration, but for general expansion of the gonad rudiment (*7*).

Like *gon-1*, *mig-17* appears to be specifically required for the formation of gonads in *C. elegans* (*8*). In contrast to *gon-1*, *mig-17* is involved in regulating the direction of migration of the gonad arms, rather than their general ability to migrate. Although arm extension occurs in *mig-17* mutants, its direction is strongly perturbed once the DTCs attempt to make their dorsal turn (*3*, *8*). The *mig-17* gene encodes a metalloprotease that, like *gon-1*, bears striking structural similarities to ADAM family proteases, although it lacks thrombospondin repeats. Surprisingly, using translational fusions of MIG-17 with green fluorescent protein, Nishiwaki *et al.* show that MIG-17 is initially synthesized by muscle cells rather than by DTCs. However, the protein is found on the surface of the gonad arms at the time migration defects are first observed in *mig-17* mutants. This suggests that although it is normally produced by muscle, MIG-17 diffuses to the gonad, where it is required for DTC migration. Consistent with this view, unlike GON-1, expression of MIG-17 by either muscle or DTCs is sufficient to rescue gonad arm migration defects.

How might MIG-17 and GON-1 collaborate to regulate DTC migration? Although substrates have not been identified for either enzyme, there are several possibilities. One possibility is that both GON-1 and MIG-17 are required for structural remodeling of the ECM during DTC migration. In the absence of such remodeling, DTCs may be physically unable to make appropriate changes in direction. If this is the case, then GON-1 is clearly required earlier or more stringently than MIG-17, given the severity of defects in *gon-1* mutants. In this scenario, MIG-17 could be required for more subtle remodeling events, either subsequent to the action of GON-1 or concurrent with it.

Another intriguing possibility is that one or both proteases are involved in the modification of matrix-embedded guidance cues to which DTCs normally respond. Several extracellular cues appear to guide the DTCs during their journey, the best-characterized being those affecting dorsal-ventral migration (*9*). Ventrally, UNC-6/netrin, a secreted protein structurally related to laminin, serves as an extracellular cue whose effects are mediated by its receptors, UNC-5 and UNC-40/DCC (*6*). The transforming growth factor–β family member UNC-129 may play a similar role dorsally (*10*). Remodeling of the ECM could affect how migrating cells interact with both of these guidance systems. Although there is no evidence that GON-1 plays such a role, Nishiwaki and coworkers found a marked enhancement of DTC migration defects in *mig-17/unc-6* double mutants. This suggests that MIG-17 may be involved in processing or presentation of guidance cues mediated by the UNC-6/UNC-5 system. However GON-1 and MIG-17 act, the demonstration that these proteases play an important role during organogenesis in vivo will likely stimulate the search for other proteases that regulate cell migration during development.

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PERSPECTIVES: PALEOCLIMATE

A Causality Problem for Milankovitch

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According to a theory postulated by Milankovitch in the early 20th century, changes in Northern Hemisphere summer insolation (incident solar radiation) are responsible for driving Earth's ice ages. The detailed mechanism by which small changes in insolation become amplified to drive major climatic changes remains unclear. Nevertheless, the Milankovitch theory has become central to the work of paleoclimatologists interested in the timing of climatic cycles. But in 1992, measurements were reported (*1*, *2*) that created problems for the theory (*3*). Data from a cave in Nevada, called Devils Hole, appeared to show that the timing of the penultimate termination of the ice ages, called Termination II, was incompatible with the standard Milankovitch theory. The data indicated a shift in oxygen isotopic composition to interglacial values that was essentially complete by 135,000 years ago. But at this time, the calculated Northern Hemisphere summer insolation [based on orbital calculations by Quinn *et al.* (*4*)] had not yet increased to a point at which it would be expected to trigger anything extraordinary, let alone a glacial termination. The termination event appeared to precede its own cause (see the figure).

The Devils Hole data were not the first to indicate a problem. Already in 1974, Bloom *et al.* (*5*) suggested, on the basis of uranium-thorium (U-Th) radiometric ages of coral terraces from the Huon Peninsula in Papua New Guinea, that sea level had reached a high point—presumably from glacial melting, an indicator of warm conditions—as early as 142,000 years ago. But when Imbrie *et al.* (*6*) derived the SPECMAP time scale, the most widely used model for explaining how insolation could drive ice age cycles, they did not use these results. Instead, they set Termination II at 127,000 ± 6000 years ago, on the basis of radiometric dates from Barbados corals (*7*, *8*).

In 1991, Chen *et al.* (*9*) studied U-Th ages for different coral species from two Bahamian reefs. They concluded that "the high sea level stand began possibly by 132 ky [thousand years] and certainly by 129 ky ago, when sea level reached ~6 meters above present mean low sea level" (p. 82).

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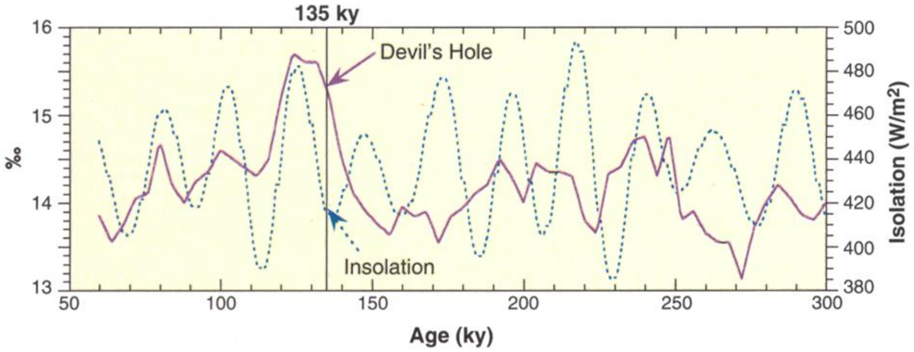
Although uncomfortably early, these dates still fell into the range proposed by Imbrie *et al.* for Termination II. But when the Devils Hole chronology was published, it was difficult to dismiss. The two standard deviation uncertainties on individual measurements relevant to Termination II were less than ±3000 years (*2*). The results suggested that the termination was virtually complete before Northern Hemisphere July insolation had risen to a substantially high level.



The "causality problem." Devils Hole $\delta^{18}O$ (a proxy for temperature and ice volume) and July 65°N insolation, the driving force of the standard Milankovitch model. The rise in $\delta^{18}O$ associated with Termination II is nearly complete before insolation begins its rise. Recent data from sediment and corals (*12*–*15*) indicate that the termination was virtually complete by 135,000 years ago, in agreement with the Devils Hole results.

A heated debate ensued in the literature. Most criticisms of the Devils Hole results were eventually addressed by the experimenters. The chronology was replicated with uranium-protactinium (U-Pa) dating (*10*). According to the additional age analysis by Winograd *et al.* (*11*), Termination II in the Devils Hole data occurred at 142,000 ± 3000 years ago—2000 years earlier than originally proposed (*1*, *2*). But given the strong evidence seen in other records that insolation affects climate, Milankovitch proponents were reluctant to strongly question the theory on the basis of a single new record. Furthermore, Devils Hole is a land-based site, and it was possible that it was only recording a local climate change [although that was unlikely given its strong correlation with the Vostok paleotemperature time series (*11*)].

Recent sea-level records from opposite sides of the globe now provide further evidence that the causality problem is real. In January 1999, Esat *et al.* published measurements of coral terraces of the Huon Peninsula in Papua New Guinea (*12*). They showed that sea level rose and peaked around 135,000 years ago, to a point only about 14 m below present levels. In March of this year, Henderson and Slowey published results from U-Th dates of aragonite-rich sediments from the slopes of the Bahamas (*13*, *14*). On the basis of three samples spanning Termination II, they arrive at an age of 135,000 ± 2500 years for Termination II. And at the Fall 1999 Meeting of the American Geophysical Union (AGU) in San Francisco, Gallup *et al.* presented new U-Th and U-Pa ages of fossil corals in Barbados that point in the same direction (*15*).

At 135,000 years ago, the date indicated by these recent studies for Termination II, Northern Hemisphere July insolation at 65°N had a value of 416 W/m^2 per day (see the figure). It had been above this level for 71 of the previous 100,000 years. There is no plausible reason to believe that this low level of insolation could have triggered an ice age termination. We conclude that the causality problem is real. Northern Hemisphere summer insolation could not have triggered Termination II; whether it accurately predicts earlier terminations awaits more precise radioisotopic ages on those terminations.

The new data confirm what Devils Hole already indicated, namely that climate is too complicated to be predicted by a single parameter, summer 65°N insolation. They also show that the standard Milankovitch insolation theory cannot account for at least one of the terminations of the ice ages. Models that attribute the terminations to large insolation peaks (or, equivalently, to peaks in the precession parameter), such as the recent one by Raymo (*16*), are thus incompatible with at least one precise observation.

More importantly, the new results create practical problems for the working scientist. Virtually all published time scales used in paleoclimate are based on Northern Hemisphere summer insolation. This includes the frequently referenced SPECMAP time scale (*6*) and the low-latitude stack of Bassinot *et al.* (*17*). The new coral data show that for Termination II, these are incorrect by 5000 to 10,000 years or more. There is no a priori reason to believe that they are not similarly in error at other terminations.

What can be done? Crowley and Kim (*18*) suggest a more complex insolation model. Another possibility that received attention at the Fall 1999 Meeting of AGU is to attribute terminations to Southern Hemisphere insolation (*13*, *15*). But if we do this, we lose the explanation for the most recent ice age termination at about 12,000 years ago, which has been successfully accounted for by the increase in Northern Hemisphere summer insolation. Do different terminations have different causes? And where does that leave Milankovitch theory?

Even if we have no simple answer, at least we can conclude that the Milankovitch theory must not be a procrustean bed into which every observation will be forced. Different aspects of climate may have different driving forces—and some may even be unrelated to insolation (*19*). There is evidence that different proxies in the same core can be measuring completely different aspects of climate. For example, the oxygen isotope record of the Vostok ice core shows a variation that matches Earth's precession cycle, yet the temperature proxy measured in that same core shows virtually no precession (*20*). In sea-floor records, eccentricity can be strong in one proxy, yet virtually absent in another (*21*). We must look at the data again, as if for the first time, regard climate to be multidimensional, and be open to new ideas unbiased by our prior theoretical prejudices.

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