highest binding affinity, 1H, only needed minor modifications to improve its half-life in serum.

Although the serum half-life of the 1H antibody is slightly less than that of the anthrax toxin, the antibody's high binding affinity ensures that the antibody-toxin complex is removed from the serum before the complex dissociates. However, important questions remain about the safety and efficacy of the antibody under field conditions. If toxin has irreversibly bound to and damaged tissues once symptoms appear in infected individuals, the benefit of the antibody as a postsymptom treatment may be lessened. An additional concern is that an antibiotic-resistant form of *B. anthracis* might be used as a bioweapon. In this case, an antitoxin antibody might not be protective as bacteria would continue to proliferate unchecked and produce large amounts of toxin that would eventually overwhelm the host.

Vaccines to protect against prime biowarfare agents are often antiques. The current smallpox vaccines, for example, until recently were prepared from the skin of calves. Current anthrax vaccines were developed more than 30 years ago. Both vaccines are associated with adverse reactions and are not recommended for vaccinating the general public in the absence of an immediate threat. One big advantage of an antitoxin antibody is that it would be administered to people showing symptoms of anthrax or suspected of having been exposed to *B. anthracis*, so that the general population would not need to receive the antibody. Despite our increased understanding of the molecular pathogenesis of anthrax, smallpox, and other biowarfare agents, the old vaccines remain in place because few discoveries made in the laboratory are translated into new therapeutics or modern vaccines.

Maynard and colleagues still have to overcome some technical hurdles before their antibody can move to the next stage of development. For example, their *E. coli* expression system means that they can only produce a partial (single-chain) antibody molecule. Conversion of their partial antibody to a full antibody by expression in a mammalian system may be necessary before it can be administered to humans. Several production facilities that could produce sufficient quantities of such converted proteins already exist in the United States.

But the biggest hurdles to bringing a new anthrax therapeutic to market are likely to be financial and legal. First, there is no assurance of a market (the very existence of an effective drug might help to dissuade any future attack and contribute to a lack of demand). The anthrax bioterrorist assault last year killed five people and led several thousand others to seek treatment or at least purchase antibiotics. Such low demand is insufficient to warrant corporate investment. Were this an over-the-counter pill that people could stock in their homes, a large market based on fear might be imagined. But an antitoxin antibody would have to be injected, so stockpiling in individual households is unlikely to be an option. A further disincentive is presented by the biotechnology patents that cover methods (for example, antibody phage display) used to obtain the 1H antibody, even though such methods would not be involved in the actual production of the therapeutic antibody.

Thus, we face the daunting prospect of knowing how to make but not how to market a drug that, along with antibiotic treatment, could possibly eliminate the threat of a drug-sensitive anthrax bioweapon and diminish our dependence on vaccines whose safety is questionable. It is satisfying that biotechnology has proved itself capable of inventing a molecule tailored to public need. The big question is whether the substantial economic hurdles can be overcome so that this molecule can be quickly added to the therapeutic arsenal against bioterrorism. Perhaps public impatience over vulnerability to future bioterrorist attacks will instill an urgency to tackle this problem from all angles. The recent effort to purchase a safer genetically engineered anthrax vaccine by the National Institutes of Health and the Department of Health and Human Services is an encouraging step in this direction (*3*).

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PERSPECTIVES: PALEOCLIMATE

The Glacial Tropical Pacific—Not Just a West Side Story

David W. Lea

The tropical oceans—especially the tropical Pacific—serve as a heat engine for Earth's climate and as a vapor source for its hydrological cycle. The impact of the tropical Pacific on global climate is well known during El Niño events. By implication, tropical climate must have played a major role in ice age cycles. But until recently, researchers could not resolve the relatively subtle changes in tropical sea surface temperature (SST) that occurred during glacial episodes. The impact of tropical climate cycles has therefore remained elusive.

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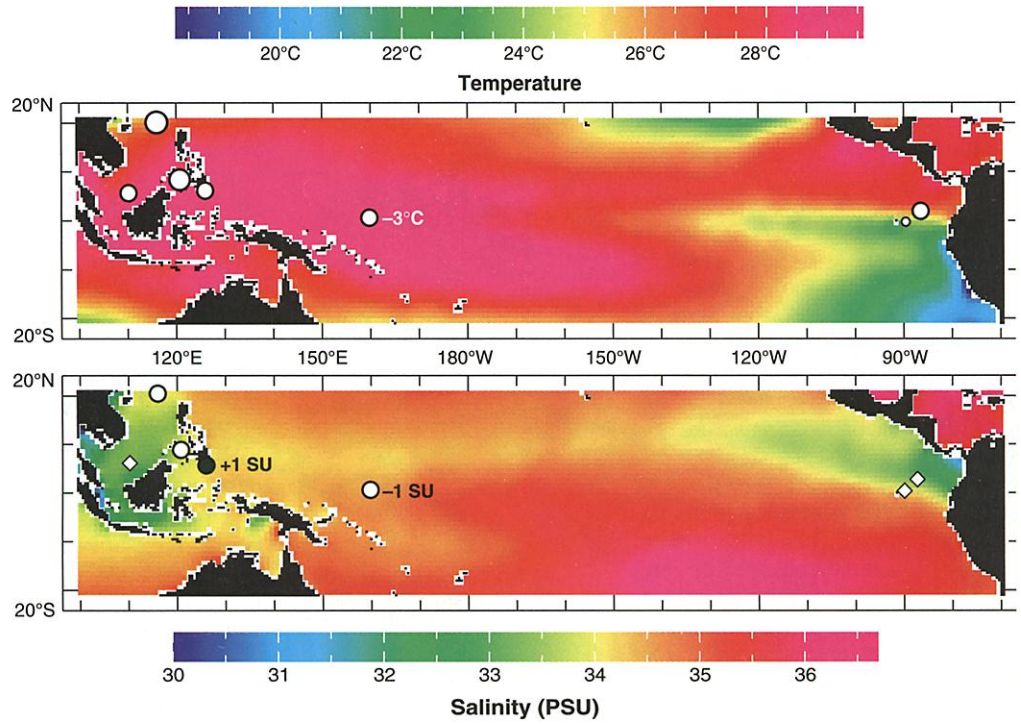
Two papers on pages 222 and 226 in this issue (*1*, *2*) now report the first high-resolution records of past climate for two key regions of the tropical Pacific: the cool waters of the Galápagos region in the east, and the warm waters south of Mindanao in the Philippines in the west. The records reveal several new aspects of tropical Pacific climate during the last glaciation.

The authors combine two recent advances to derive their records. First, two new methods, alkenone unsaturation ratios (*3*) and foraminiferal Mg/Ca ratios (*4*), enable second-hand (proxy) information on past SSTs to be obtained. Second, usable, rapidly accumulating sediments have been recovered from the tropical Pacific—a difficult endeavor because of the great depth and extensive carbonate dissolution of much of the central basin.

The Galápagos data of Koutavas *et al.* (*2*) suggest that the cold tongue of the eastern Pacific cooled less than other regions (see the figure). According to sediment geochemical data, most of the warm (>26°C) tropical Pacific cooled by about 3°C (*3*–*5*), and this inference is corroborated by the new Mindanao data (*1*). In contrast, glacial cooling may have been only 1°C in the coldest part of the eastern tropical Pacific (*2*). This finding is important because the temperature of the eastern Pacific cold tongue is a direct diagnostic of trade wind strength, thermocline depth, and the upwelling of cold subsurface waters.

This result challenges the paradigm of stronger trade winds, a steeper east-west thermocline tilt, and more intensive eastern boundary cooling during glacial episodes (*6*). It further suggests that cold (La Niña) episodes, which are characterized by such conditions, are not a suitable analog for glacial conditions (*7*).

The Mindanao record of Stott *et al.* (*1*), on the other hand, mostly demonstrates the rapid response of the hydrological cycle of the western Pacific on millennial time scales. The authors exploit



Mean annual sea surface temperature and salinity in the tropical Pacific. Modern climate is characterized by strong temperature gradients in the east and dominance of salinity gradients in the west. Symbol size and color indicate estimated changes during cold glacial periods from sediment records. Salinity changes are relative to the oceanic mean and do not include the effect of lower sea levels. The absolute magnitude of glacial salinity changes is uncertain because it depends on the oxygen-isotope composition of glacial precipitation, but the sense of change is likely to be correct. Diamonds indicate sites where there is no apparent change. [Modern climatology adapted from (*14*)]

extremely high accumulation rates (~65 cm/1000 years) and the combination of Mg paleothermometry and oxygen isotopes to pinpoint the timing and magnitude of these hydrological shifts.

Today, gradients in the western tropical Pacific are dominated by salinity rather than temperature (see the figure). The salinity gradients reflect the interplay of sites of convection and the Asian monsoon. Spatial and temporal salinity patterns respond strongly to the effects of El Niño–Southern Oscillation (ENSO) on precipitation over the modern western Pacific (*8*).

During glacial sea-level lows, the enlargement of the western maritime continent likely led to changes in patterns of precipitation and runoff. Earlier studies used patterns of oxygen-isotope change between the last glacial maximum and modern climate to suggest large-scale shifts in western Pacific salinity (*9*).

Stott *et al.* show that the rapid millennial-scale climate events (*10*) that characterize the last glaciation are marked by large shifts in surface water hydrology. They find warmer and wetter conditions during brief warmings known as interstadials, which they interpret as an indication that oscillation between cool stadials and warm interstadials (*10*) was akin to extreme ENSO cycles. During stadials the center of atmospheric convection appears to have moved east of the Mindanao site, as it does today during El Niño episodes. The hypothesis of drier El Niño–like conditions during glacial episodes is in line with the Galápagos data of Koutavas *et al.* (*2*).

The pattern of deglaciation in the two records, and in other records from this region, is another important diagnostic. Results from low-resolution equatorial Pacific records suggest that tropical SSTs warmed before ice volume shrank (*4*). No such lead is found in records from the South China Sea (*3*, *5*), where the SST response to millennial-scale climate cycles appears to follow the Northern Hemisphere pattern (*11*). In contrast, the new Mindanao and Galápagos records clearly indicate the SST lead on deglaciation, as does a record from the Sulu Sea west of Mindanao (*12*).

The temperature lead thus appears to be a robust feature of tropical Pacific deglaciation, whereas the South China Sea responds to Northern Hemisphere forcing by way of the Asian monsoon (*5*, *13*). This analysis suggests that the Northern Hemisphere pattern of deglaciation did not extend to the open tropical Pacific. The Mindanao results (*1*) imply, however, that the tropical water cycle in the western Pacific did respond to millennial-scale climate change, either through the postulated link to ENSO or, as suggested for the South China Sea, by way of the Asian monsoon (*13*).

The new Mindanao record (*1*) should help researchers to piece together a picture of the structure and climatology of the glacial western Pacific. Available data (see the figure) suggest that glacial cooling was fairly uniform, but that the pattern of hydrological change was complex. The latter may reflect the combined effects of southward migration of atmospheric convection, changes in the strength of the Asian monsoon, and shifts in ENSO.

But the Galápagos record (*2*) indicates that tropical Pacific climate evolution is not just a West Side Story. Much of the climate variability in the tropical Pacific reflects trade wind strength and the atmospheric Walker circulation. The weaker winds implied by the minimal glacial cooling in the cold tongue must therefore be linked to changes in atmospheric convergence and convection in the western Pacific. As the temperature and salinity structure of the glacial tropical Pacific becomes more certain, researchers should be able to establish how such critical linkages changed during glaciation.

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