often by a factor of 100 to 1000.

If we can measure one conductance unit at the jump to contact, we should be able to measure conductance quantization in integer multiples of $2e^2/h$ if we increase the constriction atom by atom. Recent progress has shed some light on this issue. By using the MCB junction to change the constriction size atom by atom, we observe conductance steps every time atoms are forced into the constriction region (*5*, *6*). The measurements indicate that all of the atomic positions inside the constriction region are relevant for determination of the conductance. In semiconductors, the electron wavelength is much too large for the measurements to be sensitive to the individual atomic positions. In metals, the electron wavelength is on the order of the interatomic distance; thus, the atomic configuration is responsible for electron interference effects in the constriction, just as in the quantum coral measurements of Crommie *et al.* (*3*).

The MCB junction offers another interesting difference: Each time the wire is broken, a new atomic arrangement is, in general, formed; unlike the semiconductor case of a configuration fixed by the lithography, the MCB performs a unique measurement each time. Thus, although a specific atomic configuration may not yield an integer quantization for its conductance, the average over many measurements should. This averaging is exactly what Olesen *et al.* (*7*) did. They found that integer conductance values are favored over other values in this ensemble of contacts. MCB results on gold and copper contacts (*8*) confirmed their finding. Other measurements indicate that besides the atomic positions, the metal's electronic character (that is, the extent to which electrons feel the atomic potential) also plays a role in these microscopic contacts (*9*). Although the measurements showed that an accurate description of atom-sized constrictions is complex and needed, they also showed that confinement of the electrons in the two dimensions perpendicular to the electron current leads to quantization effects very similar to those of 2D electron gases.

Also, in the tunnel regime, when the MCB is broken, impressive results have been obtained. Small tunnel sensors have been fabricated where the electrodes are held stable within a few atomic distances. The way these gadgets work is simple: two electrodes can move to and from each other by means of an electrical steering signal. Because the dependence of the tunnel resistance on the electrode separation is exponential, it is essential that electrodes in a tunnel sensor be placed initially close together, otherwise the tunnel resistance becomes immeasurably high. In one type of sensor, electronics continuously monitor the tunnel resistance and correct the steering signal to maintain a constant tunnel resistance and thus a constant distance between the electrodes under all circumstances. When a force is exerted on one electrode, the steering signal counterbalances it. Thus, the mechanical force is transduced into an electrical signal. These devices can be used in a microphone, accelerometer, infrared detector, or magnetometer (*10*). Another type of tunnel transducer has been introduced by Zhou *et al.* (*11*), who showed that by making a very small MCB junction in silicon, no force rebalancing is necessary. The two electrodes are designed so that the separation never exceeds a few angstroms (which can be measured by the tunnel resistance). In contrast with the force-rebalancing device, the actual movement of one electrode over a few angstroms provides the signal. The small size gives the device exceptional stability because of the mechanical advantage; the distance noise between the electrodes was ~0.01 atomic diameters (*11*).

In addition, these silicon microfabricated sensors can be mixed with other chip electronics, for applications such as sensors, actuator control, and basic physical measurements. The field is only at the beginning of its development, but it offers great potential in a number of industries. As these new technologies continue to develop, Feynman's microworld continues to expand.

References

1. R. Feynman, paper presented at the American Physical Society Annual Meeting, 29 December 1959; reprinted in *Miniaturization*, H. D. Gilbert, Ed. (Reinhold, New York, 1961).
2. For a review, see C. W. J. Beenakker and H. van Houten, *Solid State Phys.* **44**, 1 (1991).
3. M. F. Crommie, C. P. Lutz, D. M. Eigler, *Science* **262**, 218 (1993).
4. J. K. Gimzewski and R. Müller, *Phys. Rev. B* **36**, 1284 (1987).
5. N. Agrat, J. G. Rodrigo, S. Vieira, *ibid.* **47**, 12345 (1993); J. M. Krans *et al.*, *ibid.* **48**, 14721 (1993); J. I. Pascual *et al.*, *Phys. Rev. Lett.* **71**, 1852 (1993).
6. C. J. Muller, J. M. van Ruitenbeek, L. J. de Jongh, *Phys. Rev. Lett.* **69**, 140 (1992); J. I. Pascual *et al.*, *Science* **267**, 1793 (1995).
7. L. Olesen *et al.*, *Phys. Rev. Lett.* **74**, 2147 (1995).
8. A. M. Bratkovsky, A. P. Sutton, T. N. Todorov, *Phys. Rev. B* **52**, 5036 (1995).
9. J. M. Krans, J. M. van Ruitenbeek, V. V. Fisun, I. K. Yanson, L. J. de Jongh, *Nature* **375**, 768 (1995).
10. T. W. Kenny, S. B. Waltman, J. K. Reynolds, W. J. Kaiser, *Appl. Phys. Lett.* **58**, 100 (1991); H. K. Rockstad, T. W. Kenny, J. K. Reynolds, W. J. Kaiser, Th. B. Gabrielson, *Sens. Actuators A* **43**, 107 (1994); and references therein.
11. C. Zhou, C. J. Muller, M. R. Deshpande, J. W. Sleight, M. A. Reed, *Appl. Phys. Lett.* **67**, 1160 (1995).

Glacial Climate in the Tropics

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One of the many unresolved puzzles about Earth's climate during the Pleistocene glaciations concerns the tropics. In a report on page 1930 of this issue, Schrag *et al.* (*1*) describe oxygen isotope results that directly indicate greater cooling in the tropics during glacial cycles than previously believed.

The findings of the now famous CLIMAP (*2*) program conducted during the 1970s convinced most paleoclimatologists that the ecology of the planktonic foraminifera implied a glacial cooling in the tropics of only 1° ± 1°C. However, over the last several years, evidence based on strontium-calcium ratios in corals (*3*) suggests that the ocean cooling might have been as much as 5°C. Further, the descent of snow lines on tropical mountains (*4*) and noble gas temperatures from Brazilian ground waters (*5*) point to a similar cooling for tropical land masses and islands. Finally, the combination of the lowered snow lines (*4*) and the large glacial-to-Holocene ^{18}O shift found by Thompson *et al.* (*6*) in an ice core drilled at an elevation of 6 km in the Andes appears to demand a substantially lower water vapor content for the tropical atmosphere during glacial time.

These new results have caused the pendulum to swing toward a consensus that during times of glaciation, climatic conditions in the tropics were quite different from those today. But, as the evidence in hand is not self-consistent, the pendulum is by no means locked. Still to be explained is why strontium-calcium measurements on corals (*3*) and noble gas measurements on ground waters (*5*) suggest a tropical cooling of 4° to 6°C while foraminifera speciation (*2*), oxygen isotope (*7*, *8*), and alkenone results (*9*–*11*) suggest a cooling of no more than 3°C. Does this disagreement reflect regional differences in the extent of cooling, or is one group or the other of these proxies misleading us?

My thoughts on this subject have been strongly influenced by the oxygen isotope results on planktonic foraminifera. The glacial-to-interglacial change for these surface dwellers is equal to or less than that for deep

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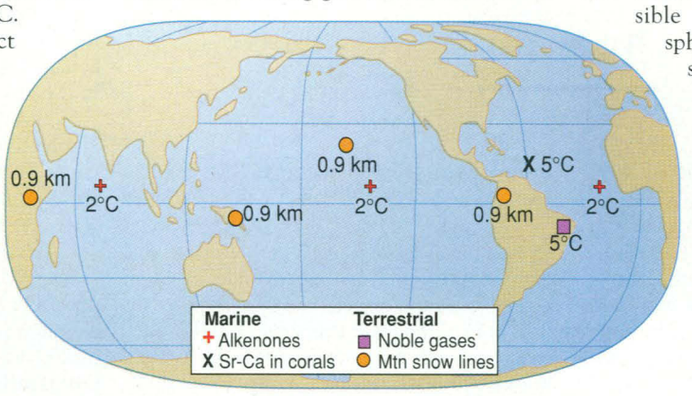
water. This difference has been interpreted as a requirement for the temperature change in the surface ocean to be equal to or less than that for deep water (*7*, *8*). Further, because deep waters in today's ocean have potential temperatures within 3°C of the freezing point, the oxygen isotope results seem to place a firm maximum on the extent of the cooling of tropical surface waters. Because no way exists to reliably estimate the contribution of preferential storage of isotopically light water in continental ice sheets, the actual cooling could be less than 3°C.

Schrag *et al.* (*1*) provide direct evidence that the cooling of deep waters was indeed close to the limit imposed by the freezing point. They exploited a proxy for the actual isotopic composition of glacial deep water (*12*) by analyzing a depth profile of pore water samples from a profile of hydro piston cores at 3 km below the sea surface on the Ceara Rise in the western basin of the tropical Atlantic. Kudos go to the chief scientists of the Ocean Drilling Project, N. Shackleton and W. Curry, who had the foresight to sacrifice the sediment from an entire hole to destruction by the pore water squeezer for this work. In much the same way as Cuffey *et al.* (*13*) computed mean glacial air temperatures from a thermal profile in the hole created by the ice core recovered from Greenland's Summit locale, Schrag *et al.* computed the mean glacial $\delta^{18}O$ composition of deep water from an isotopic profile in deep ocean sediment. They conclude that during glacial time, the $\delta^{18}O$ at this site was 0.8 ± 0.1 per mil lower than the current value. Having only one such profile, they attempt to extrapolate this result to the world ocean. Such an extension is not simple because the Ceara Rise site is located near the confluence of the world's two major deep water masses, the North Atlantic Deep Water (NADW) and Antarctic Bottom Water (AABW). Today, these two water masses differ in $\delta^{18}O$ values by about 0.5 per mil. Thus, the magnitude of the $\delta^{18}O$ change at this site may have been influenced by a shift in the water mass boundary as well as by the global ice storage. Indeed, carbon isotope results on benthic foraminifera of glacial age suggest that this was almost certainly the case (*14*). On the basis of the quasi-conservative property PO_4^* (*15*), the current mix at this site is 90% NADW and 10% AABW. The glacial-to-Holocene shift in carbon isotope ratios for benthic foraminifera from this site strongly suggest that the water mass boundary shifted to the north during glacial time, dropping the contribution of NADW to 40 ± 20%. Assuming that the ^{18}O contrast between deep waters forming at the two locations remained the same during glacial time, this shift would have lowered the $\delta^{18}O$ for deep water at this site by 0.2 per mil. Correcting for the impact of this change yields an ice volume–induced change of 1.0 ± 0.15 per mil for the world ocean. A similar result is obtained if, as assumed by Schrag *et al.*, during glacial time the ocean's deep waters became isotopically homogeneous. Because benthic foraminifera during glacial time had a $\delta^{18}O$ value averaging 1.7 per mil more than that for their Holocene cousins (*7*) after correction for the ice volume impact, a 0.7 ± 0.15 per mil residual remains, which must be attributed to temperature. Such a shift suggests a 2.6° ± 0.5°C cooling for deep waters during peak glacial time [at deep ocean temperatures T, $\Delta\delta^{18}O/\Delta T$ is –0.27 per mil per degree Celsius (*16*)].



Key estimates of the magnitude of the peak glacial to peak interglacial changes in temperature and snow line elevation in tropical regions. From (*3–5, 9–11*). Not shown are the large number of sites at which oxygen isotope measurements on planktonic foraminifera have been conducted.

A recent summary of the glacial-to-interglacial change in $\delta^{18}O$ for the surface-dwelling species *Globigerinoides sacculifer* and *G. ruber* in the latitude range 20°N to 20°S (*17*) reveals a range from 1.4 to 2.2 per mil. Assuming the same isotopic shift for tropical surface waters as for global deep water (that is, 1.0 per mil), this range corresponds to a 1.5° to 5.5°C glacial cooling [at tropical temperatures, $\Delta\delta^{18}O/\Delta T$ is –0.21 per mil per degree Celsius (*18*)]. What could explain this large range of isotopic values? First, it is likely that shifts in the distribution of $^{18}O/^{16}O$ ratios in tropical surface waters complicate the picture. Second, the extent of cooling of the tropical boundary layer might show sizable regional differences with larger temperature changes for the continents and adjacent oceans. Three sets of results—noble gases from Brazilian ground waters (*5*), strontium-calcium ratios from Barbados corals (*3*), and $^{18}O/^{16}O$ ratios from Ceara Rise planktonics (*14*) and Barbados corals (*3*)—suggest that the western tropical Atlantic cooled by 5°C. By contrast, the alkenone results (*9–11*) suggest that, at least along the equator, the central Pacific, Indian, and Atlantic oceans cooled by only 2°C (see figure). Consistent with atmospheric dynamics, the depression of mountain snow lines shows no geographical pattern (*4*). In Hawaii, New Guinea, Columbia, and East Africa, snow lines descended about 900 m (*4*). This drop in elevation requires a cooling of at least 5°C aloft and translates to a cooling of 2° to 3°C for those parts of the ocean responsible for setting these mid-troposphere temperatures. Hence, the snow line depression is not inconsistent with alkenone-based estimates of surface ocean cooling. However, because lower mountain temperatures are accompanied by lower snowfalls and because lower snowfalls result in an up-mountain snow line retreat, the 5°C cooling computed by assuming no change in snowfall must be a minimum. The actual cooling could be 1° to 3°C larger.

Although we have as yet to fully resolve the riddle posed by the glacial climate of the tropics, the pore water measurements of Schrag *et al.* constitute a step toward this goal by relaxing a bit the constraint placed by the oxygen isotope record for planktonic foraminifera. Although this first oxygen isotope profile needs to be supplemented by others, it seems clear that the ecology-based tropical-temperature estimates made by the CLIMAP group underestimated the extent of glacial cooling in the tropics. We must determine the cause of the apparently larger cooling, looking carefully at the factors controlling the atmosphere's water vapor inventory. In my estimation, Thompson's ice core $\delta^{18}O$ record demands substantially lower inventories during glacial time, leading to cooler and drier conditions in the tropics. While I suspect that this reduction is a repercussion of the change in ocean circulation, the nature of the link to atmospheric dynamics has yet to be discovered.

References and Notes

1. D. P. Schrag, G. Hampt, D. W. Murray, *Science* **272**, 1930 (1996).
2. CLIMAP Project Members, *Geol. Soc. Am. Map Chart Ser. 36* (1981).
3. T. P. Guilderson, R. G. Fairbanks, J. L. Rubenstone, *Science* **263**, 663 (1994).
4. D. Rind and D. Peteet, *Quat. Res.* **24**, 1 (1985).
5. M. Stute *et al.*, *Science* **269**, 379 (1995).
6. L. G. Thompson *et al.*, *ibid.*, p. 46.
7. W. S. Broecker, *Quat. Res.* **26**, 121 (1986).
8. G. E. Birchfield, *Paleoceanography* **2**, 431 (1987).
9. M. W. Lyle, F. G. Prahl, M. A. Sparrow, *Nature* **355**, 812 (1992).

10. F. Rostek *et al.*, *ibid.* **364**, 319 (1993).
11. E. L. Sikes and L. D. Keigwin, *Paleoceanography* **9**, 31 (1994).
12. D. P. Schrag and D. J. DePaolo, *ibid.* **8**, 1 (1993).
13. K. M. Cuffey *et al.*, *Science* **270**, 455 (1995).
14. W. B. Curry, in *The South Atlantic: Present and Past Circulation*, G. Wefer, W. H. Berger, G. Siedler, D. Webb, Eds. (Springer-Verlag, Berlin, in press).
15. W. S. Broecker, *Oceanography* **4**, 79 (1991).
16. L. D. Labeyrie, J. C. Duplessy, P. L. Blanc, *Nature* **327**, 477 (1987).
17. T. Guilderson, personal communication.
18. H. Craig, in *Proceedings of the Spoleto Conference*, E. Tongiorgi, Ed. (Consiglio Nazionale Delle Ricerche, V. Lischi e Figli, Spoleto, Italy, 1965), pp. 3–24; N. J. Shackleton, in *Les Methodes Quantitatives d'Etude des Variations du Climat au Cours du Pleistocene* (Colloques Internationaux, CNRS, Verrières-le-Buisson, France, 1973), vol. 219.
19. R. G. Fairbanks, *Nature* **342**, 637 (1989).

Tickling Memory T Cells

Rafi Ahmed

Shortly after an organism is infected by viruses, type I interferons (IFN I, which includes IFN-α and IFN-β) are induced (*1*). This rapid, nonspecific immune response is critical in limiting the extent of viral spread before antigen-specific responses can more fully control the infection. Type I interferons also augment proliferation and activation of natural killer cells, further enhancing immune defense (*2*). A report by Tough *et al.* in this issue shows that IFN I has a third function; it can also assist in the generation of T cell responses and immunologic memory (*3*).

Injection of mice with IFN I or poly(I:C), an IFN inducer, results in proliferation of T cells. Only one subset of T cells proliferates—the $CD44^{hi}$ T cells (increased expression of CD44 is a marker for activated and memory T cells)—and this proliferation occurs independently of signaling through the T cell receptor (TCR). In other words, IFN I can tickle memory or activated T cells in an antigen-independent manner.

The massive T cell proliferation (especially of CD8 cells) that characterizes viral infections in vivo (*4*, *5*) could in theory result from a number of mechanisms: antigen-driven expansion of specific T cells, stimulation of cell division by cross-reactive antigens, or cytokine-mediated bystander activation (*4–7*). Although functional assays indicate that the contribution of antigen-specific T cells is relatively low [10% or less of the total activated T cells at the peak of the response (*4*, *5*, *8*)], this value may be an underestimate: Studies with TCR transgenic T cells (in which it is possible to directly visualize the antigen-specific cells) show that the transgenic T cells can expand from less than 1% of the population to more than 50% of CD8 T cells after viral infection (*9*). Thus, much of the expansion during viral infections may represent antigen-driven proliferation of specific T cells.

The results of Tough *et al.* (*3*) implicate a second mechanism for cell proliferation: induction by IFN I cytokines. Indeed, CD8 $CD44^{hi}$ cells are the cell type most responsive to IFN I (*3*), and it is this same T cell subset that shows the most striking expansion during viral infections (*3–5*, *8*, *9*). More than 80% of CD8 $CD44^{hi}$ T cells are dividing after either poly(I:C) injection or viral infection (*3*), although overall CD8 T cell numbers do not change substantially after poly(I:C) injection (*3*). This is because IFN I alone results in only a single round of cell division (only a twofold increase), in striking contrast to the 1000- to 10,000-fold expansion of antigen-specific T cells seen after viral infections (*4*, *5*, *8*, *9*). Thus, after a viral infection, such as infection of mice with lymphocytic choriomeningitis virus, it is likely that IFN I induces many CD8 T cells ($\sim 5 \times 10^6$ per mouse) to undergo a single round of division, whereas, by antigen-driven proliferation, a few cells ($\sim 10^3$ per mouse) undergo multiple cell divisions (10 to 13 divisions over a period of 5 to 7 days) so that the total number increases to between 10^6 and 10^7 (*3–5*, *8*, *9*). Does IFN I also play a role in the antigen-driven proliferation? Possibly. Type I IFN has profound effects on lymphocyte trafficking (*10*) and may contribute to mobilization of the specific immune response.

Perhaps the most interesting implication of the results of Tough *et al.* (*3*) is the possibility that IFN I may be involved in the maintenance of T cell memory [reviewed in (*4*)]. The idea that cytokines produced during responses to unrelated antigens can stimulate preexisting memory T cells is not new (*7*), but Tough *et al.* (*3*) provide the first direct evidence that cytokines cause bystander T cell proliferation in vivo. Thus, periodic stimulation with IFN during intermittent viral infections may help to maintain the pool of memory T cells.

IFN-mediated bystander proliferation may not be obligatory for sustaining long-term T cell memory. Nevertheless, the new results (*3*) suggest a potential mechanism for maintaining memory and underscore the hyperresponsiveness of memory T cells to nonspecific stimuli. Memory cells may also be hyperresponsive to other cytokines and to activation of signaling through adhesion molecules (*4*), as well as to signaling through the TCR by cross-reactive antigens (*6*). Thus, memory T cells can be tickled in many ways that are independent of their specific antigens (*4*). This notion is consistent with data showing that some of the memory CD8 T cells are cycling but that CD8 T cell memory persists in the absence of specific antigen (*4*, *11*).

The finding by Tough *et al.* (*3*) that IFN I selectively stimulates memory T cells raises several interesting questions. Does IFN act directly on T cells or through production of other mediators? Do memory T cells have higher affinity receptors for IFN I? In addition to inducing proliferation, does IFN I also preferentially induce an antiviral state in memory T cells in vivo (a nice protection from viruses)? Why was the proliferative response after poly(I:C) injection seen preferentially in CD8 memory T cells and not in CD4 memory T cells? Does this suggest that the rules for maintaining CD4 and CD8 T cell memory are different (*4*)? Does IFN I stimulate memory T cells and natural killer cells by similar mechanisms? Is maintenance of T cell memory impaired in IFN I–deficient mice? Future studies will provide answers to these questions, but the present report of Tough *et al.* (*3*), in addition to describing an interesting property of IFN I, provides another elegant example of how the nonspecific innate immune system interacts with and shapes the specific immune response (*12*).

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References

1. U. Muller *et al.*, *Science* **264**, 1918 (1994); J. Vilcek and G. C. Sen, in *Fields Virology* (Lippincott-Raven, Philadelphia, ed. 3, 1996), p. 375.
2. M. Gidlund *et al.*, *Nature* **273**, 759 (1978); C. A. Biron, G. Sonnenfeld, R. M. Welsh, *J. Leukocyte Biol.* **35**, 31 (1984).
3. D. F. Tough, P. Borrow, J. Sprent, *Science* **272**, 1947 (1996).
4. R. Ahmed and D. Gray, *ibid.*, p. 54.
5. R. M. Zinkernagel, *ibid.* **271**, 173 (1996).
6. P. C. L. Beverly, *Immunol. Today* **11**, 203 (1990); P. Matzinger, *Nature* **369**, 605 (1994); R. M. Welsh *et al.*, *Semin. Virol.* **7**, 95 (1996); W. Cao *et al.*, *Nature* **378**, 295 (1995).
7. D. Unutmaz, P. Pileri, S. Abrignani, *J. Exp. Med.* **180**, 1159 (1994).
8. M. S. Asano and R. Ahmed, *ibid.* **183**, 2165 (1996).
9. C. Zimmermann *et al.*, *ibid.*, p. 1367.
10. M. Degre, *Int. J. Cancer* **14**, 699 (1974); I. Gresser, D. Guy-Grand, C. Maury, M. Maunoury, *J. Immunol.* **127**, 1569 (1981); R. Korngold, K. J. Blank, D. M. Murasko, *ibid.* **130**, 2236 (1983); R. Ishikawa and C. A. Biron, *ibid.* **150**, 3713 (1993).
11. L. L. Lau *et al.*, *Nature* **369**, 648 (1994); S. Hou *et al.*, *ibid.*, p. 652; A. Müllbacher, *J. Exp. Med.* **179**, 317 (1994); L. Bruno *et al.*, *Immunity* **2**, 37 (1995).
12. D. T. Fearon and R. M. Locksley, *Science* **272**, 50 (1996).