Natl. Acad. Sci. U.S.A. **90**, 883 (1993); G. Gill, E. Pascal, Z. H. Tseng, R. Tjian, *ibid.* **91**, 192 (1994).
28. C.-M. Chiang and R. G. Roeder, *Peptide Res.* **6**, 62 (1993).
29. D. I. Chasman, J. Leatherwood, M. Carey, M. Ptashne, R. D. Kornberg, *Mol. Cell. Biol.* **9**, 4746 (1989).
30. M. A. Blanar and W. J. Rutter, *Science* **256**, 1014 (1992).
31. A. Hoffmann, C.-M. Chiang, R. G. Roeder, unpublished data.
32. A. J. Courey and R. Tjian, *Cell* **55**, 887 (1988).
33. We thank K. Hisatake for recombinant HA:230 baculovirus; J. L. Chen and R. Tjian for Sp1 proteins; R. Kageyama and S. Nakanishi for the human placental cDNA library; B. Cullen, Y.-S. Lin, F. Liu, H.-C. Liou, Y. Shi, and J.-B. Yoon for plasmids; A. Hoffmann (anti-TBP and anti-$TAF_{II}20$), M. Kretzschmar (anti-p50), E. Martinez (anti-YY1), P. Pognonec (anti-USF), S. Stevens (anti-$TAF_{II}135$), R. Takada (anti-$TAF_{II}230$, anti-$TAF_{II}95$, and anti-$TAF_{II}80$), and N. Tanese (anti-CTF1) for antibodies; S.-Y. Wu for constructing f:USF and f:50 expression plasmids and performing yeast two-hybrid analysis; X. Zhang for preparing nuclear extracts; J. Huang for maintaining cell lines; E. Hendricks for assistance in generating polyclonal antibodies; H. Ge and Z. Wang for discussions about chromatography; and the protein sequencing facility of the Rockefeller University for synthesizing the FLAG peptide and performing protein microsequencing analysis. Supported by NIH and by grants from the Pew Trusts to Rockefeller University. C.-M.C. is a Helen Hay Whitney Foundation and Aaron Diamond Foundation postdoctoral fellow.

8 September 1994; accepted 29 November 1994

TECHNICAL COMMENTS

Paleotopography of Glacial-Age Ice Sheets

W. R. Peltier (*1*) presents a model that reconstructs the paleotopography of glacial-age ice sheets on the basis of sea level curves and the viscoelastic properties of the earth's crust and mantle. The model has profound implications because it suggests that the elevation of northern hemisphere glacial-age ice sheets was much lower than previously believed. The low topography has implications for atmospheric general circulation models of ice age climate. Furthermore, the model suggests that the glacial-age Antarctic Ice Sheet was significantly larger than today's.

Such models can now be tested more rigorously because of the advent of sea level curves that have high resolution and cover most of deglaciation. Before the late 1980s, most deglacial records covered only the very last portion of deglaciation and chronologies were established with ^{14}C dating. In the late 1980s the development of thermal ionization mass spectrometric (TIMS) techniques for measuring ^{234}U (*2*) and ^{230}Th (*3*) provided the capability to obtain high-precision ^{230}Th ages of coral skeletons (*3*). TIMS ^{230}Th dates have advantages over ^{14}C dates because they (i) have higher precision and (ii) do not require independent calibration. The advent of TIMS ^{230}Th dating provided impetus for researchers to drill for deglacial sequences of corals, with the goal of obtaining long, high-resolution records of deglaciation.

Two sequences that cover most of deglaciation have been drilled and analyzed: the Barbados sequence (*4*), which covers the complete deglaciation, and the Papua New Guinea sequence (*5*, *6*), which covers the last half of deglaciation. Peltier (*1*) used the Barbados sea level record to tune his model and tested model output against the Papua New Guinea record. Model output matched the Papua New Guinea record well, apparently supporting the model's validity.

However, Peltier (*1*) used depths for the Papua New Guinea and Barbados data that were not corrected for tectonic uplift. The Barbados uplift rate is small, 0.34 m per thousand years (*4*), amounting to a correction of 7 m for the deepest portion of the core. Thus, the Barbados correction can be excluded without serious consequence. The model results disagree only slightly with the corrected Barbados record (Fig. 1). On the other hand, the uplift rate at the Papua New Guinea site is much larger. The rate of 1.9 m per thousand years is well known and documented (*5*–*7*), and amounts to a correction of more than 20 m for the oldest portion of the record (*5*, *6*). Model results disagree with the corrected Papua New Guinea record (Fig. 1). Because the Barbados curve was used for tuning, the Papua New Guinea record is the only long independent sea level curve upon which to test model results. The inability of the model to reproduce the Papua New Guinea curve would appear to cast doubt on other model results, including those related to the paleotopography of the glacial ice sheets. Thus, resolution of the discrepancy between the Papua New Guinea data and the modeling results is a central issue.

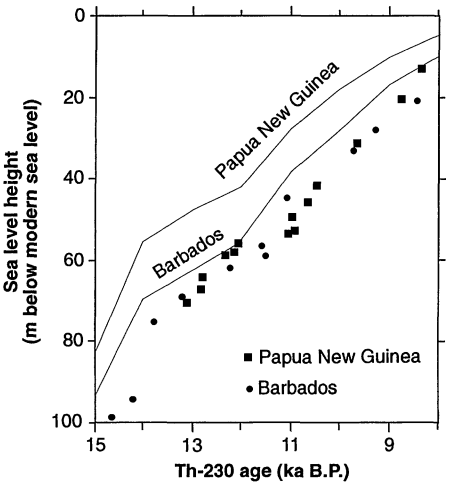

Fig. 1. Discrepancy between model results (*1*) and sea level data (*4*, *6*). Deglacial sea level rise as recorded in Papua New Guinea [squares, (*6*)] and Barbados [circles, (*4*)] corals. Data points are corrected for tectonic uplift at each site. Curves represent sea level rise at each of the two localities, as predicted by Peltier's (*1*) model.

R. Lawrence Edwards
Minnesota Isotope Laboratory,
Department of Geology and Geophysics,
University of Minnesota,
Minneapolis, MN 55455, USA

REFERENCES

1. W. R. Peltier, *Science* **265**, 195 (1994).
2. J. H. Chen, R. L. Edwards, G. J. Wasserburg, *Earth Planet. Sci. Lett.* **80**, 241 (1986).
3. R. L. Edwards, J. H. Chen, G. J. Wasserburg, *ibid.* **81**, 175 (1987); R. L. Edwards, J. H. Chen, T.-L. Ku, G. J. Wasserburg, *Science* **236**, 1547 (1987).
4. R. G. Fairbanks, *Nature* **342**, 637 (1989); E. Bard, B. Hamelin, R. G. Fairbanks, A. Zindler, *ibid.* **345**, 405 (1990).
5. J. M. A. Chappell and H. A. Polach, *ibid.* **349**, 147 (1991).
6. R. L. Edwards *et al.*, *Science* **260**, 962 (1993).
7. J. M. A. Chappell, *Geol. Soc. Am. Bull.* **85**, 553 (1974); A. L. Bloom, W. S. Broecker, J. M. A. Chappell, R. K. Matthews, K. J. Mesollela, *Quat. Res.* **4**, 185 (1974); A. L. Bloom and N. Yonekura, in *Models in Geomorphology*, M. J. Woldenberg, Ed. (Allen & Unwin, Winchester, MA, 1985), pp. 140–154.
8. Sea level work supported by NSF grants EAR-8904705, ATM-8921760, and OCE-9402693.

28 July 1994; accepted 23 November 1994

Response: I am grateful for having attention drawn to one of the secondary aspects of the work described in my article (*1*). My purpose was to advance a methodology whereby the continental ice sheets that existed at the Last Glacial Maximum (LGM) might be "weighed," even in absentia. The limited application of this methodology (*1*) was based on several assumptions, mainly that (i) the ice sheets could be safely assumed to be in isostatic equilibrium at LGM, (ii) the viscosity of the planetary mantle was approximately a function of radius only, and (iii) the records of relative sea level history based on coral sequences from Barbados and the Huon Peninsula of Papua New Guinea could be analyzed without making the usual correction for a presumed constant local rate of tectonic uplift. Edwards questions the reasonableness of (iii), given the extent to which the 0.34 mm $year^{-1}$ and 1.9 mm

year^{-1} rates of tectonic uplift for Barbados and Huon, respectively, are established in the literature. Before addressing this issue, it would be useful to ask: Does this assumption affect the central conclusion of my article, namely, that the LGM ice sheets must have been less voluminous than suggested by the CLIMAP MAX model (*2*)?

The raw data of relative sea level (*rsl*) (raw implying uncorrected for a *presumed steady* rate of tectonic uplift) from Barbados demonstrate that the 21 ka (thousand years ago) horizon is now at a depth near 118 m below present sea level [figure 3A of (*1*)]. Even if this observed depth were increased by about 7 m to account for a *presumed steady* rate of uplift of the above cited amount, the total rise of sea level at Barbados since 21 ka would be increased to 125 m, less by 3 m than the 128 m eustatic sea level rise delivered by the CLIMAP MIN model of Denton and Hughes (*2*) and 33 m less than that predicted by the CLIMAP MAX model. If one were to assume that the average amount by which sea level has risen over the globe since LGM is well approximated by the observed rise at Barbados, then one would still be obliged to conclude that the CLIMAP MAX model contains an excessive amount of ice, equivalent to a eustatic sea level rise of 33 m. The issue is therefore not whether the CLIMAP MAX model contained excessive ice (which was the main argument in my article), but rather whether the Barbados or Huon coral record can be used directly to infer the amount of this excess.

The amount of LGM ice that is allowed by a detailed theoretical model of postglacial relative sea level change (*1*), when the model is required to fit the (raw) *rsl* curve from Barbados, is such as to imply a eustatic sea level rise of only 105.2 m (*1*). This theory implies that the Barbados *rsl* record overestimates the eustatic rise by about 13 m. Why might this discrepancy be expected? On a viscoelastically deforming Earth, water is continuously redistributed over the ocean basins to ensure that the ocean surface, everywhere and at all times, coincides with a gravitational equipotential, the "geoid." My theory of the glacial isostatic adjustment process (*1*) includes an accurate calculation of this phenomenon. One can observe in the present (Fig. 1) the relatively rapid rates of falling relative sea level characteristic of once deglaciated regions (Canada, Fennoscandia, and Antarctica), the slower but still significant rates of *rsl* rise characteristic of the surrounding regions undergoing postglacial forebulge collapse, and the regions of falling sea level over the centers of the major ocean basins. Analyses of ^{14}C-controlled records of *rsl* change at hundreds of sites on Earth's surface (*3*) show that the theoretically predicted pattern (Fig. 2) [figure 3A of (*1*)] characterizes well the observed variability.

This continuous redistribution was shown in my article in the form of predictions of *rsl* history for three sites from which coral based records are available, two of which are long and only one of which (Barbados) extends back to LGM. Although the theoretical model was tuned for the purpose of my analyses to fit the Barbados record, this tuning simply refined the good fit that was delivered by the ICE-3G model (*3*) in the construction of which the Barbados record was not used to constrain the deglaciation model, but rather to verify its validity. The ICE-3G model embodied a eustatic sea level rise of approximately 108 m, insignificantly different from that delivered by the ICE-4G model (*1*). Therefore, a model with modest eustatic sea level rise is independently suggested by postglacial rebound data from sites that were once ice-covered (the only data employed to construct ICE-3G) and by the coral record of *rsl* rise at Barbados. The validity of this coincident inference depends on the validity of the assumptions numbered (i) and (iii) in the first paragraph of this response. If both of these assumptions were relaxed, then one could explain the additional 7 m *rsl* rise at Barbados by invoking slight isostatic disequilibrium at LGM (detailed analyses of this scenario will be described elsewhere), thus slightly thickening the LGM ice sheets beyond that characteristic of ICE-4G. This result would not significantly affect paleotopography: An increase in *rsl* of 7 m at Barbados results in an additional thickness of each of the LGM ice sheets of only 200 m, about one-third of which would be compensated. This increase implies an additional topography of only 133 m, an insignificant amount in the context of an atmospheric general circulation model simulation of LGM climate. Furthermore, since recent detailed analysis of the coral data

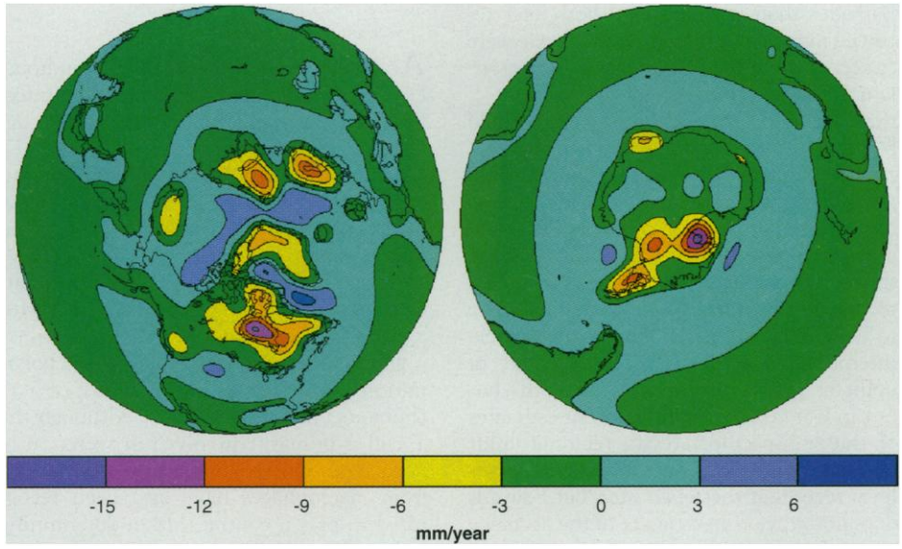

Fig. 1. Present-day rate of change of sea level predicted by the ICE-4G model of the last deglaciation event of the current ice age. Blue regions denote rising sea level driven by proglacial forebulge collapse.

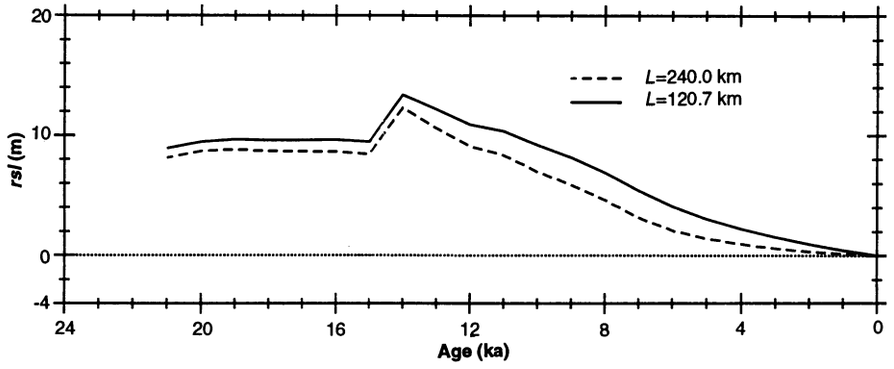

Fig. 2. Magnitude of the *rsl* offset predicted between the Barbados and Huon Peninsula curves for models with radial visco-elastic structures that differ only with respect to the thickness assumed for the surface elastic lithosphere, *L*. ICE4-Model D3g O(512), first iteration.

from Barbados (*4*) indicates a net sea level rise since LGM that is essentially identical to that delivered by the ICE-4G model, it is unclear as to whether even this small adjustment to the model will be required.

My article included a further characterization of the continuous meltwater redistribution that accompanies glacial isostatic adjustment. The theory tuned to fit the raw *rsl* record at Barbados also predicted an *rsl* history at the Huon Peninsula that fit the (raw) record there also. Because there is a significant offset between the *rsl* records at Barbados and Huon [the Huon record indicating a lower *rsl* rise, at the same age, than that at Barbados (by about 10 m at LGM)], and because this offset was predicted, it seemed that the theory could be accurately predicting the redistribution of meltwater driven by glacial isostatic adjustment. The predicted (*1*) net *rsl* rise at Huon since LGM is near 108 m (close to the 105.2 m eustatic value), whereas the predicted value at Barbados is near 118 m, so that, according to the theory, water depth increased by 10 m more at Barbados than at Huon, and both sites received more water than eustatic. If one were to accept the standard correction for tectonic uplift at the Huon site of 1.9 mm year^{-1}, then the Barbados and Huon curves could be brought into closer coincidence (figure 1 of the comment by Edwards), which would imply that meltwater redistribution during the adjustment process had zero differential impact at these two sites. The fact that the theory (*1*) predicts the differential impact recorded in the raw *rsl* data would then have to be seen as fortuitous. An equally tenable interpretation is that the tectonic rate of uplift at Huon (or Barbados, or both) has not in fact been constant. Current estimates of the site-specific rates of tectonic uplift eliminate the discrepancy between the sea level records at these two sites, but Edwards does not provide an estimate of the accuracy with which these rates have been inferred.

Deviations from the eustatic *rsl* rise at ocean basin sites might conceivably be reduced from those predicted by my analyses (*1*) if the radial viscoelastic structure of the model were modified in a way that did not violate the constraints used to derive this structure. Before suggesting that the usual constant rate of tectonic uplift assumed for the Huon Penninsula might be in error, this alternative possibility should be investigated. As one plausible flaw in the assumed radial viscoelastic structure (*5*, *6*) concerns lithospheric thickness, I have investigated for comparative purposes the result on the predicted *rsl* histories of doubling this thickness.

This maximum plausible increase of the thickness of the elastic lithosphere decreases the offset between the predicted *rsl* histories at Barbados and Huon, as expected on physical grounds, but only by about 1 m at LGM (Fig. 2). Although some modification of the radial viscosity profile in the sub-lithospheric mantle (or perhaps the influence of gravitational disequilibrium at LGM or of lateral viscosity variations) may allow the reconciliation of the theoretical prediction of the model with a constant rate of tectonic uplift of 1.9 mm year $^{-1}$ at Huon, it seems equally plausible that this rate has not been constant. The question of the origin of this offset does not affect the main conclusion (*1*) that the LGM ice sheets contained significantly less ice than posited in the CLIMAP MAX reconstruction. The topography of these ice sheets was therefore significantly lower than that previously calculated. Computations of climate state that use the revised LGM topography as a lower boundary condition for the atmospheric general circulation model are therefore expected to be significantly different from those previously derived.

W. R. Peltier
Department of Physics, University of Toronto, Toronto, Ontario, Canada M5S 1A7

REFERENCES

1. W. R. Peltier, *Science* **265**, 195 (1994).
2. CLIMAP Project Members, *ibid.* **191**, 1131 (1976).
3. A. M. Tushingham and W. R. Peltier, *J. Geophys. Res.* **96**, 20053 (1991); *ibid.* **97**, 3285 (1992).
4. P. Blancon and J. Shaw, *Geology*, in press.
5. J. X. Mitrovica and W. R. Peltier, *Geophys. J. Int.* **114**, 45 (1993); in press.
6. W. R. Peltier, *J. Geophys. Res.* **89**, 303 (1984).

19 September 1994; accepted 23 November 1994

T_H2 Downregulation of Macrophage HIV-1 Replication

Acquired immunodeficiency syndrome (AIDS) is a disease characterized by infection of T cells and macrophages and a decline in the number of CD4 T cells (*1*). Mechanisms that mediate the resulting immunodeficiency in AIDS and regulate viral load continue to be a primary focus of human immunodeficiency virus–type 1 (HIV-1) research. Cytokines have been postulated to play a major role in pathogenesis with particular emphasis on the viral and immunological consequences of a proposed polarization into a T_H1 (cell-mediated), or T_H2 (humoral) host response (*2*). Although the T cell is primarily involved in secretion of both types of cytokines, cytokines derived from macrophages have also been recognized to play a central role in determining induction and effector pathways of immunity. Likewise, for HIV-1 infection and replication, macrophages provide viral reservoirs that may be subject to regulation by T cell–derived cytokines (*1*). These possible consequences of altered T cell cytokine expression in AIDS have meaning for recent reports by E. Maggi *et al.* (*3*) and by C. Graziosi *et al.* (*4*).

Maggi *et al.* studied preferential viral production in T_H2 T cell clones. We and others have found that T_H2-type cytokines produce opposite results in isolated macrophages (*5*–*8*). We also believe that the reported in vitro data concerning macrophage and T cell viral regulation by T_H2-type cytokines, not discussed in the report by Maggi *et al.*, bear on their findings.

T_H2-type cytokines [interleukin-4 (IL-4), -10, and -13], while not inhibiting the establishment of infection, induce a potent virostatic latent state in infected macrophages in vitro (Table 1). By contrast, IL-4 upregulates viral production in T cells, unlike other T_H2-type cytokines tested. We postulate that the finding by Maggi *et al.* of preferential replication of HIV-1 in T_H0 and T_H2 clones might result from in vitro positive feedback mediated by endogenous IL-4. In this macro-

Table 1. HIV replication in T cells and tissue culture-derived macrophages (TCDM) treated with T_H2 cytokines (IL-4, IL-10, and IL-13) in vitro. T cell and macrophage cultures were prepared as described (*5*) and infected with HIV-1 RF (MOI 0.03) and HIV-1 ADA (MOI 0.12), respectively. Treatment with 20 ng/ml of IL-4 (Genzyme, Kent, United Kingdom), IL-10 (DNAX, California), and IL-13 (Sanofi-Elf, Labege, France) was started 72 hours before infection and replenished with cytokine every 3 days. Samples for viral production were obtained every day for T cells and every 2 days for TCDM until the end of culture on day 10 and 16, respectively. T cell values indicate virus production following the first round of replication (2 to 5 days after infection). Viral production was measured by in-house adapted enzyme-linked immunosorbent assay (ELISA) as described (*5*), which is one-tenth as sensitive as commercial ELISA kits. Results are the average of duplicate independent cultures and representative of multiple experiments where cytokines have been tested in different donors.

Cell type	Control	p24 (ng/ml) HIV			
		Control	IL-4	IL-10	IL-13
T cell*	0	1.39	9.11	1.30	1.12
Macrophage†	0.08	3.73	0.23	0.11	0.38

*Day 10 after infection. †Day 16 after infection.