tered-light imaging of other disks. The disk of β Pic is viewed nearly edge-on, extending like a thin ribbon of light from within 5 AU to more than 1000 AU from the star. The data indicate that at least three different regions of the disk are tilted or warped with respect to each other (*7*). The perturbation of material in this way has been modeled successfully under the assumption that a giant planet orbits within it (*8*).

Around HR 4796A, a star with slightly more infrared excess than β Pic, dust is largely confined to a narrow ring of material 70 AU from the star (see the figure, left panel) (*9*). One endpoint of the ring is brighter than the other, suggesting a clumpy distribution of dust along the ring. In our solar system, Saturn's narrow rings are shepherded dynamically by its moons, and it is tempting to invoke the effects of planets in the HR 4796A system as a dust-confining mechanism.

The disks imaged to date form a heterogeneous group, with little in common in terms of structure even when the central stars are quite similar. All are considerably larger than our known solar system, raising the question of whether they (or we) are typical.

But many more excess stars may soon be found by targeted observations. In the last few years, a large number of fairly young stars (ages of <50 million years) has been identified close to the Sun (<100 pc) (*10*). Young stars generally have more dust, and close stars can be studied with the best spatial resolution, so these stars should be a boon to disk studies both from the ground and from space. NASA's next great observatory, the Space InfraRed Telescope Facility set to launch in January 2003, will search for dust at solar system levels around 300 stars with a wide range of ages, including mature stars like the Sun.

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PERSPECTIVES: PALEONTOLOGY

East of Eden at the Paleocene/Eocene Boundary

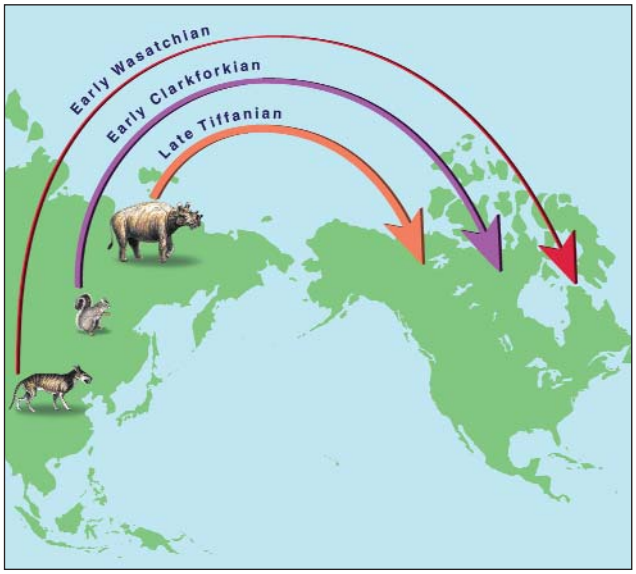
Chris Beard

Geologists divide the long saga of Earth history into chapters known as eras, periods, and epochs. Even before Darwin published *Origin of Species*, these intervals were recognized on the basis of the distinctive fossil assemblages that characterize them. Understanding how, when, and why these ancient ecosystems replaced one another remains a central question for both the earth and life sciences.

On page 2062 of this issue, Bowen *et al*. (*1*) present data bearing on the most dramatic biotic change of the last 65 million years (the Cenozoic Era), popularly known as the "Age of Mammals." This radical reshuffling of Earth's biota coincided with a brief but intense episode of global warming at the Paleocene/Eocene (P/E) boundary, about 55 million years ago (*2*).

The climatic perturbation was fleeting, but its biological effects were permanent. Across the Northern Hemisphere, a wave of anatomically modern groups of mammals appeared in the Eocene, at the expense of archaic forms that became extinct (*3*). Other major components of the ecosystem changed at the same time (*4*). Given the brevity of the P/E boundary events, how did such a rapid overhaul of terrestrial ecosystems occur?

The pattern of biotic change at the P/E boundary is documented best in the Bighorn Basin of Wyoming, USA, where a nearly continuous sequence of fossiliferous rock strata provides a uniquely detailed window on mammalian turnover across the P/E boundary. The Bighorn Basin record shows that the mammalian fauna changed abruptly at the P/E boundary, when the earliest North American primates, artiodactyls, perissodactyls, and opossum-like marsupials (Didelphidae) show up en masse (*5*). This cohort of modern mammals was accompanied by other groups, such as the carnivorous Hyaenodontidae and the enigmatic Hapalodectidae, that later fell prey to extinction.



East of Eden. Phylogenetic data suggest that Asia was the geographic source for many mammalian groups that later spread to Europe and North America. The fossil record implies that Asian mammals invaded North America at least three times near the P/E boundary. The three waves of Asian mammals included uintatheres (order Dinocerata), which dispersed to North America 57 million years ago (Late Tiffanian); rodents, which first appeared in North America 56.3 million years ago (Early Clarkforkian), and hyaenodontids, which migrated to North America 55 million years ago at the P/E boundary (or Early Wasatchian). New geochronological evidence from China supports this iterative biogeographic model.

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Each new type of mammal marking the beginning of the Eocene already sports the characteristic anatomy that defines its group. The newcomers differ so fundamentally from North American Paleocene mammals that they could not have evolved in situ. A similar pattern of biotic change occurred in western Europe, although the fossil record is less densely sampled there (*6*).

Faunal turnover across the putative P/E boundary in Asia differs from that observed in North America and Europe. In Asia, the carnivorous Hyaenodontidae and the odd-toed Perissodactyla (horses, rhinos, and tapirs) are recorded from fossil sites assigned to the Gashatan

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Asian Land Mammal Age (ALMA), traditionally viewed as late Paleocene. The first Asian primates and artiodactyls show up in the succeeding Bumbanian ALMA, widely regarded as early Eocene.

However, all hypotheses about how the Gashatan and Bumbanian ALMAs relate to the P/E boundary are based purely on fossils. Paleontologists have been forced to estimate the ages of Gashatan and Bumbanian fossils on the basis of the fossils themselves, and no consensus has emerged on how to do this (*3, 7–8*). In the absence of independent geochronological evidence, it is difficult to test the possibility that Asia was a Paleocene "Garden of Eden" for many groups of modern mammals (*9*).

Bowen *et al*. (*1*) take a crucial first step toward untying this Gordian knot, thereby illuminating the processes that underlie the biotic turnover at the P/E boundary. Their solution is based on a geochemical anomaly that provides a datum for P/E boundary strata worldwide, much like the well-known iridium anomaly at the Cretaceous/Tertiary boundary. Marine and terrestrial strata near the P/E boundary have revealed a consistent negative spike in the $^{13}C/^{12}C$ ratio, known as the carbon isotope excursion (CIE). The CIE is attributed to large-scale "melting" of oceanic methane hydrates, which would have released massive volumes of methane and its oxidation product CO_2 into Earth's atmosphere (*10*). Hence, the CIE is indicative of intense global warming at the P/E boundary.

In the Bighorn Basin, the incoming wave of Eocene mammals shows up about 10,000 years after the peak of the CIE (*11*). Bowen *et al*. (*1*) now document the CIE in Asia, in an area in China's Hunan Province that is less densely fossiliferous than the Bighorn Basin. Their results show that the Bumbanian ALMA is at least as old as the CIE. The hyaenodontid and perissodactyl specimens from the underlying Gashatan ALMA must therefore be Paleocene in age, older than any similar fossils from North America and Europe.

The new geochronological data of Bowen *et al*. (*1*) strengthen Asia's claim as the birthplace of numerous modern groups of mammals, including our own order, the Primates (see figure) (*7, 9*). They also point toward global warming as the driving force behind the most profound biotic reorganization of the Age of Mammals. Further field work is needed to clarify whether the biogeographic dominance of Asian mammals at the P/E boundary extends to other organisms and across a longer time interval. Such efforts will go a long way toward integrating the diverse fields of climate change, phylogenetics, geochronology, and biogeography.

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PERSPECTIVES: IMMUNOLOGY

A Perfect Mismatch

Klas Kärre

Patients with leukemia or certain genetic diseases can be treated by transplantation of bone marrow or hematopoietic stem cells. The patient's own bone marrow (and leukemia cells residing in the marrow) are destroyed by irradiation or cytotoxic drugs and are replaced with marrow or stem cells from a donor (allogeneic transplantation). As in organ transplantation, there is a risk that the immune system of the recipient will reject the transplant, termed a host-versus-graft (HvG) reaction. However, because the donor graft gives rise to a new immune system in the recipient, hematopoietic cell transplantation also involves the risk of a tissue-damaging reaction in the opposite direction, called graft-versus-host (GvH) disease. GvH can also be favorable for the patient, as it may help to eradicate residual leukemia cells (the graft-versus-leukemia or GvL effect). T cells of the immune system, which recognize differences between individuals in HLA molecules of the major histocompatibility complex (MHC), are crucial mediators of these reactions.

In a model example of preclinical-to-clinical translational research, Ruggeri *et al*. (*1*), reporting on page 2097 of this issue, demonstrate that another cell of the immune system can influence the outcome of hematopoietic cell transplantation in a surprising and favorable way. So-called natural killer (NK) cells in the donor graft can prevent leukemia relapse in leukemic recipients, and at the same time seem to prevent the destructive complications of GvH and HvG.

One normally tries to avoid complications during hematopoietic cell transplantation by matching the HLA tissue type of donor and recipient at as many loci as possible. The chance that a sibling carries the same HLA type as the patient (that is, has inherited the same combination of HLA genes from the mother and father) is 25%. In many cases there is no familial match, nor can a matching unrelated donor be easily found. In such situations, it is possible to transplant tissue from a family member for whom only one of the HLA-carrying chromosomes is matched with that of the recipient (haploidentical transplantation). Such a partial match is provided by either parent of the patient, and by 50% of the siblings. T cells do not react to the self HLA proteins but do recognize the presence of nonself HLA. In the haploidentical match, there will thus be strong reactivities against the nonmatched HLA molecules, and therefore the graft must be exhaustively depleted of T cells. T cell depletion dramatically reduces GvH reactions, but at the price of a higher incidence of leukemia relapse because the GvL effect is reduced.

The rationale for the Ruggeri *et al*. study in leukemia patients and mice was that NK cells should also influence hematopoietic cell transplantation in a manner determined by HLA, albeit by different rules. It is well established that NK cells can be activated by sensing the absence of self MHC on other cells (missing self recognition) (*2*). They express killer cell inhibitory receptors (KIRs) that recognize self HLA molecules on target cells (*3, 4*). The receptors then transmit an inhibitory signal that cancels a program for cytotoxic action previously triggered by contact with the target cell. In the absence of the inhibitory signal, cytokine secretion and killing of the target cell proceeds by default. Furthermore, NK cells distinguish groups of HLA molecules rather than single allelic variants. This meant that Ruggeri *et al*. could classify their haploidenti-

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