der of 1 in 10^{18}, with major impacts in physics and metrology.

References and Notes

1. M. A. Kasevich, E. Riis, S. Chu, R. G. DeVoe, *Phys. Rev. Lett.* **63**, 612 (1989).
2. F Riehle *et al.*, *IEEE Trans. Instrum. Meas.* **48**, 613 (1999).
3. C. W. Oates, F. Bondu, R. W. Fox, L Hollberg, *Eur. Phys. J.* **D7**, 449 (1999).
4. H. Katori, T. Ido, M. K. Gonokami, *Atomic Phys.* **17**, 382 (2001).
5. R. J. Rafac *et al.*, *Phys. Rev. Lett.* **85**, 2462 (2000).
6. J. E. Barnard *et al.*, *Phys. Rev. Lett.* **82**, 3228 (1999).
7. G. P. Barwood *et al.*, *IEEE Trans. Instrum. Meas.* **50**, 543 (2001).
8. Th. Becker *et al.*, *Phys. Rev. A* **63**, 051802 (2001).
9. C. Tamm, D. Engelke, V. Buehner, *Phys. Rev A* **61**, 053405 (2000).
10. M. Roberts *et al.*, *Phys. Rev. A* **62**, 020501(R) (2000).
11. J. Reichert, R. Holzwarth, T. Udem, T. W. Haensch, *Opt. Commun.* **172**, 59 (1999).
12. R. Holzwarth *et al.*, *Phys. Rev. Lett.* **85**, 2264 (2000).
13. S. A. Diddams *et al.*, *Phys. Rev. Lett.* **84**, 5102 (2000).
14. S. A. Diddams, L. Hollberg, L.-S. Ma, L. Robertsson, *Opt. Lett*, in press.
15. J. Stenger, Ch. Tamm, N. Haverkamp, H. R. Telle, preprint available at http://xxx.lanl.gov/abs/physics/0108062.
16. S. A. Diddams *et al.*, *Science* **293**, 825 (2001).

17. The author would like to acknowledge the numerous other excellent papers presented at the symposium. It has been impossible to mention all these in this short article given here.

PERSPECTIVES: GEOLOGY

North American Devastation or Global Cataclysm?

Tim Flannery

Sixty-five million years ago (Ma), our planet was struck by a carbonaceous meteorite (*1*), a relic from the formation of the solar system. This errant piece of celestial real estate was around 10 km in diameter and was traveling at 90,000 km/hour, in a trajectory from the southeast. It struck the southern margin of North America, in what is now Yucatan but was then a shallow, tropical sea. The impact released as much energy as 100 million megatons of high explosives. The glancing blow, much like a chip shot in golf, sent a divot of debris straight into the heart of North America (*2*). It was far more devastating than a perpendicular collision would have been, releasing thousands of times more energy.

This scenario, developed over the past few decades, has led paleontologists to suspect that the extent of damage suffered by North America's ecology was unique. The continent's bountiful fossil deposits have indeed revealed extensive evidence of ecological devastation. The Gulf Coast was swept almost clean of life, and evidence of giant tsunamis exists. The dinosaurs perished, as did many smaller life forms, including most mammals. North America's forests were flattened, and four out of five plant species were driven to extinction (*3*).

It has been suggested that for decades or centuries after the impact, much of the continent resembled a vast muddy field devoid of live. Many of the life forms that eventually recolonized the land are thought to have come from refuges in the Arctic north—as distant as you can get from the impact point and still be in North America. Others came from other continents and perhaps from especially sheltered locations such as the lees of mountain ranges.

The author is in the South Australian Museum, Adelaide, 5000 Australia. E-mail: flannery.tim@saugov.sa.gov.au

The recovery of North America's ecology was slow. For thousands of years, much of the continent was little more than a field of ferns. The most dominant of the handful of species that reclaimed the wasteland belonged to the genus *Stenochlaena*, which includes the Malayan climbing fern so beloved of greenhouse owners (see the figure). The same fern covered the bared ground of Krakatoa after the 1883 eruption, where it remained dominant for decades (*4*) and formed thickets of such impenetrability that biologists examining the return of life to the island became lost in them.

Malayan climbing fern.

"Fern spikes"—extremely high abundances of fern spores preserved in sediments where evidence of other plants is scarce—are now widely recognized as evidence of catastrophic ecosystem disruption. They are characteristic of North American and far-eastern Eurasian sediments dating to just after the meteorite impact of 65 Ma. The fact that sediments of a similar age from the Southern Hemisphere did not show fern spikes has been regarded as prime evidence that the celestial chip shot uniquely devastated North America. Indeed, (rather limited) pollen and spore data indicated that southern forests suffered remarkably little extinction or disturbance at the time (*5*).

Zoogeographic studies have tended to support this view, indicating that the Southern Hemisphere may have acted as a refuge for certain groups of ancient organisms, such as araucarian conifers and ratites (emus, ostrich, and rheas), which have predominantly southern distributions. Unfortunately, very little is known about the relevant part of the fossil record of much of the Southern Hemisphere. In places such as Australia and Antarctica, clear evidence of how the impact affected land animals has remained elusive. On the basis of the fossil record of these regions alone, it is not even clear whether the dinosaurs became extinct there at the time of the impact: The fossil record is so poor that we simply do not know.

On page 1700 of this issue, Vajda *et al.* (*6*) provide the first clear evidence for a fern spike from the Southern Hemisphere. It comes from the South Island of New Zealand, about as distant from the site of the impact as it is possible to be. The pollen from this remote location speak eloquently of ecological devastation on the same order as in North America.

Before the meteorite impact, the area around what is now Moody Creek, New Zealand, supported a swamp forest rich in ferns, southern conifers, and flowering plants. In contrast, above the layer marking the impact, fern spores dominate, making up around 90% of the pollen assemblage. Flowering plants, which would dominate forests worldwide a few million years later, vanish from the local record, and the conifers suffer a serious decline. The devastation does not seem to be quite as complete as it was in North America but is still awesome. It will probably force a rethinking of some zoogeographic theories and of the overall impact of the asteroid strike.

Vajda *et al.*'s evidence also reveals some curious longer term consequences of the impact. After the initial devastation, the New Zealand data reveal a pattern of long-term environmental disruption that may relate to a massive injection of CO_2 into the atmosphere. Rapid oscillation between warmth- and cool-loving species and the advance and retreat of tree ferns occurred for at least a million years after the impact, indicating that once CO_2 levels in the atmosphere are disturbed, they take quite a while to return to

equilibrium. In an age threatened by greenhouse gas emissions, these data should be of special interest. But the ecological damage documented in the New Zealand sites persisted even longer: It took several million years for New Zealand's flowering plants to regain the prominence they enjoyed in southern forests before the impact.

What is needed now is evidence of fern spikes on other southern continents at the time of impact. Fossil deposits may reveal just how the fauna of the Southern Hemisphere fared through these remarkable perils.

References
1. F. T. Kyte, *Nature* **396**, 237 (1998).
2. S. D'Hondt *et al.*, *Geology* **22**, 983 (1994).
3. K. R. Johnson, D. J. Nichols, M. Attrep, C. J. Orth, *Nature* **340**, 708 (1989).
4. I. Thornton, *Krakatau: The Destruction of an Island Ecosystem* (Harvard Univ. Press, Cambridge, MA, 1996).
5. R. A. Askin, S. R. Jacobson, in *Cretaceous-Tertiary Mass Extinctions: Biotic and Environmental Changes*, N. MacLeod, G. Keller, Eds. (Norton, New York, 1996).
6. V. Vajda, J. I. Raine, C. J. Hollis, *Science* **294**, 1700 (2001).

PERSPECTIVES: GENOMICS

Genetic Association by Whole-Genome Analysis?

Pui-Yan Kwok

Geneticists have long dreamed of determining the genetic basis of disease susceptibility by comparing variations in the human genome sequences of a large number of individuals. But it has been considered an impossible dream because of the technical difficulties involved in obtaining human genome sequence data. For example, it took an international team consisting of hundreds of scientists many years just to produce a "working draft" DNA sequence of a reference human genome (*1, 2*). Furthermore, humans are diploid organisms containing two genomes in each nucleated cell, making it very hard to determine the DNA sequence of the haploid genome. Yet, armed with the complete DNA sequence of one of our smallest chromosomes, human chromosome 21, scientists at Perlegen Sciences (a subsidiary of Affymetrix Inc.) have undertaken a pilot study to demonstrate that this dream is within reach. On page 1719 of this issue, Patil *et al.* (*3*) report their scan of some 21.7 million base pairs of unique (nonrepetitive) DNA sequence in human chromosome 21.

These investigators set out to identify all sequence variations—called single nucleotide polymorphisms (SNPs)—in human chromosome 21 and to group them into blocks called haplotypes. First, they established human-rodent hybrid cell lines, each containing one copy of human chromosome 21 from a different individual. Then they performed long range–polymerase chain reaction (LR-PCR) to amplify the regions containing unique DNA sequences. Finally, they obtained the complete DNA sequences of all of the copies of human chromosome 21 using high-density oligonucleotide arrays. The Perlegen team scanned 20 different copies of human chromosome 21 across the unique two-thirds of the chromosome, and an additional 19 copies of human chromosome 21 across one-eighth of the unique DNA sequence. The authors conclude that just three common haplotypes can describe variations among 80% of the human population, a far smaller haplotype number than previously thought.

Although only 65% of all the bases on the microarrays yielded high-quality data, the 20 sets of data each containing 14 million base pairs still constitute one of the largest sequence comparison studies ever. For the most part, the results agree with other large-scale sequence comparisons in terms of the rate of discovery of SNPs, the unpredictable pattern of haplotype structure across the chromosome, and the lack of haplotype diversity along much of the chromosome. The haplotype patterns observed across such a large span of DNA are certainly interesting, but broad conclusions about haplotype structures within the human genome cannot be made with a high degree of certainty because the number of chromosomes analyzed is still quite small.

Although human geneticists and population geneticists will continue to debate the merits of the conclusions of this study, all will agree that it marks a dramatic shift in strategic thinking. Traditionally, one looked at a limited set of markers (even at 1 million SNPs, one is still looking at just 0.03% of the human genome) in a genetic association study where the genetic makeup of individuals with a disease is compared with that of healthy individuals. Now, one can aspire to analyze all of the unique DNA sequences in the genome simultaneously.

To ensure technical success, Patil *et al.* wisely adopted the best features of several previous approaches. First, they realized that haplotype information had been helpful in genetic association studies, and so they decided to physically separate the two homologous copies of human chromosome 21 up front. Although this was quite laborious, the resulting DNA samples yielded not only haplotype data but also data that were much easier to analyze on high-density oligonucleotide microarrays. Second, they avoided amplification of background rodent DNA (from the somatic cell hybrids) by designing LR-PCR assays with uniquely human PCR primers. If they had amplified human DNA sequences in short PCR assays, some amplification of the rodent background would have been unavoidable. Third, high-density oligonucleotide microarrays are most effective when the experiment requires only a small number of reactions (exemplified by gene expression studies where one RNA preparation is used to study the global expression pattern of a particular cell type). The authors followed the lead of previous groups (*4, 5*) and used LR-PCR products as the DNA targets in their experiments. This made it possible to have ~400 LR-PCR products for each hybridization experiment and thus to interrogate roughly 4 million bases simultaneously.

Patil *et al.* emphasize the "common haplotype structure" of the human genome. Their whole-genome scanning approach has defined and produced a dense set of SNPs that then have been used to select the most common haplotypes of the human population. Instead of endorsing this strategy, I suggest that we adopt the new thinking provoked by this study and work toward comparing whole human genomes when performing genetic association studies. To achieve this, a number of improvements will be needed. We must be able to convert diploid cells to haploid cell lines readily so that even very large population studies are possible. Likewise, the generation of DNA targets needs to be accomplished with much less effort. Patil and colleagues performed 3253 LR-PCR assays to scan the unique sequence of 1% of the human genome. Clearly, performing 325,300 LR-PCR assays is not practical. Perhaps a whole-genome amplification strategy would solve the problem. Resequencing by hybridization has obvious limitations. For example, duplicated sequence motifs cannot be analyzed by hybridization on microarrays. Similarly, certain sequence contexts will always yield low-quality signals. Some of the low-quality data points could

The author is in the Department of Genetics and the Division of Dermatology, Department of Medicine, Washington University School of Medicine, St. Louis, MO 63110, USA. E-mail: kwok@genetics.wustl.edu