Going back to our roots

What can genetic techniques tell us about human origins and diversity?

The Journey of Man: A Genetic Odyssey

by Spencer Wells

Allen Lane: 2002. 256 pp. £20

Princeton University Press: 2003. \$29.95

Reflections on our Past: How Human History is Revealed in Our Genes

by John H. Relethford

Westview Press: 2003. 320 pp.

US\$26, Can\$40, £19.99

Rebecca Cann

How can a non-specialist, eager to keep up with the deluge of human genome diversity studies but not attuned to the details and limitations of each particular paper, let alone the context in which they become important, hope to cope? These two books provide a solution. Their intended audiences are rather different, I suspect, but reading a sample from both offers a more balanced understanding of the current state of knowledge than the focus assumed by each author individually.

Spencer Wells chronicles the history of genetic population studies, starting with Darwin's puzzlement over the diversity of humanity he saw first-hand from the deck of the *Beagle*, and ending with the various attempts to classify human variation on the basis of different political and social agendas. This theme is also introduced by John Relethford, who reveals the arbitrary nature of classification schemes imposed by the human mind when conditioned to think about pattern recognition, by using as illustration his failure to answer an IQ-test question correctly.

Both books start with the big picture but rapidly diverge from it. They eventually light on some of the same topics, including Indo-Europeans, Basques, Polynesians and Native Americans, but with different mindsets. Wells assures us that the answers to old questions are at hand, whereas Relethford always cautions prudence. These different approaches to the same topics reminded me of when I was 16 and took my father's new sports car for a spin down a California freeway with my terrified oldest sister next to me in the front seat and my little brother hanging out in the back, yelling and mooning his friends.

Wells offers a quick summary of Richard Lewontin's revelation from 1972 that the human racial classifications commonly used at the time were not founded in modern evolutionary biology. A demonstration of just how creaky our understanding of human diversity, and by extension all biological anthropology, really was first appeared with studies of mitochondrial DNA from living humans. Wells tells the story of how we got

Looking back: geneticists are studying diversity to try to piece together our evolutionary history.

into this mess, and how Luigi Luca Cavalli-Sforza laboured for years to bring order to the field, and honours the work of his mentors (Lewontin was Wells' PhD supervisor and he was a postdoc with Cavalli-Sforza).

But Wells ignores the contributions of their competitors, including Masatoshi Nei, Morris Goodman, Bob Kirk, Naoyuki Takahata, Newton Morton and Robert Sokal, in his haste to cut to the real story he wants to tell. This is the 'inside scoop' on human history provided by the Y chromosome. It reveals the uncomplicated unilineal genetic patrimony of our species, and fits the archaeological record like a dream, except for one tiny detail: modern humans carrying the ancestral M168 Australasian Y haplotype had already expanded into Australia 10,000 years before they swept out of Africa. Never mind, underwater archaeology will eventually clear up the discrepancy.

Wells excels when he explains genetic drift, molecular clocks, climate, the geographic barriers that limited genetic exchange between local groups, and the human Y-chromosome genealogy. In contrast, his assumption of neutrality for Y markers, which would complicate the estimates of when different Y-chromosome groups split from common ancestors, is rather glib. Sexual selection is never specifically mentioned, nor is female mate choice, however cryptic.

Testosterone rules the day: his target audience wants a good 3-hour travel narrative, and he intends to deliver. You won't find the Yagnob people on the Silk Road now, they're

driving taxis in Dushanbe, Tajikistan's capital. This is the MTV version of modern human diversity and genetics. Wells has an insider's knowledge of the science and its excitement, along with a conviction that the African-replacement hypothesis has been proved. But his writing lacks the thoughtfulness of the essays in Steve Olson's *Mapping Human History* (Bloomsbury, 2002), for example, which link ethnicity, gender politics, commercialization of the genome, globalization and gene scans of indigenous people.

Relethford takes a different approach, striving behind the scenes to ensure that readers don't automatically dismiss biological anthropology grounded in morphometrics as data-poor and hypothesis-empty, ready to be picked off by computers full of genotypes. His pleading for the continued examination of the multi-regional hypothesis, in its latest metamorphosis, should be required reading for law students. What constitutes proof in science? People who assume that Y-chromosome DNA tests prove that Thomas Jefferson was the father of Eston Hemings may be surprised.

I enjoyed Relethford's analogy between car makers and haplotypes; the definition of a haplotype (linked genetic markers from the same piece of DNA) is a difficult idea to convey to non-geneticists. How can we be absolutely sure that Neanderthals were replaced, let alone constitute a different species? His explanations of how the chimp genome should inform our judgements about classifying extinct human groups are

clear, as are his discussions of drift and measures of diversity. Some of these ideas will be familiar to readers of his earlier book *Genetics and the Search for Modern Human Origins* (Wiley, 2001).

He does make one glaring error, however, in his discussion of ancient DNA sequences, stating that nuclear DNA degrades too quickly to be reliably extracted from fossils, and that this is why most studies resort to amplification of mitochondrial sequences. He misses the point that it is target template number (2% of the genome bulk is in multi-copy mitochondrial DNA, providing broad comparative possibilities), not quality of DNA, that accounts for the concentration of research effort on maternal gene genealogies.

This book would be an excellent choice for a seminar introducing advanced undergraduates in molecular biology to topics in anthropological genetics, or anthropology graduate students to genetics and historical analyses. Not flashy, far too cautious for my taste, straining to keep the lid on things, he is the exact opposite of Wells. Read them together. ■

Rebecca Cann is in the Department of Genetics and Molecular Biology, University of Hawaii, Manoa, 1960 East-West Road, Honolulu, Hawaii 96822, USA.

Crossing the species barrier

How the Cows Turned Mad

by Maxime Schwartz

transl. Edward Schneider

University of California Press: 2003. 238 pp.

\$24.95, £17.95

Richard E. Race

Until 1996, the diseases of animals known as transmissible spongiform encephalopathies (TSEs), such as scrapie and bovine spongiform encephalopathy (BSE, or 'mad cow disease'), were regarded as agricultural problems with no known medical implications for humans. But then it became apparent that BSE had done what no other animal TSE had done before: transmit to humans. Suddenly, TSE diseases were of great interest to scientists and the public, who wanted to know which other TSE diseases might also pose a risk to people, and how significant the BSE problem would be.

In *How the Cows Turned Mad*, Maxime Schwartz, a molecular biologist at the Pasteur Institute in Paris, develops the history of TSE as a mystery novel. Beginning with clinical descriptions of sheep scrapie three centuries ago, he follows the chronology of TSE evolution through to BSE and its human form, variant Creutzfeldt-Jakob disease (vCJD). Schwartz poses questions, suggests possible

A change in structure turned a harmless prion protein into a fibril that causes scrapie.

answers, and then describes the scientific advances that produced the answers. The book, which was first published in French in 2001, should appeal to a wide range of readers.

Schwartz discusses the basic science behind these discoveries in numerous asides. The general public will find these diversions informative, but those with a reasonable knowledge of TSE diseases might find them distracting. They might also be concerned by the limited bibliography and the oversimplifications that are used to explain many of the controversies that still exist in the TSE field. These oversimplifications include discussions about the nature of the causative agent, the mechanisms of agent replication, the importance of various cell organelles, how infectious aggregates form, and the concept of 'spontaneous' disease. In many cases, seminal research has been omitted and the research of some scientists has been misattributed. Several TSE issues also warrant further comment.

The public's greatest concern regarding TSE diseases is the risk of transmission from animals to people. On this topic, the author is inconsistent, stating on one occasion that TSEs are easily transmitted from one species to another, but elsewhere he suggests that the likelihood is remote. In general, TSE diseases will cross the species barrier if brain homogenates from one species are inoculated directly into the brain of a different species. However, transmission is more difficult or impossible if the material is presented in a natural way, such as by being fed to the second species.

So far, knowledge about which TSE agents are transmissible to which other species has been based on epidemiological observations over the past decades or centuries. But a cell-free analysis that allows the determination of which cross-species transmissions are possible has been developed by my colleague Byron Caughey of the

Rocky Mountain Laboratories in Hamilton, Montana, who has produced results that mimic previous empirical observations very closely. This important work, which is not mentioned in the book, is the basis for recommendations of the World Health Organization and the Centers for Disease Control and Prevention on TSE issues.

The book is also vague about the mechanism by which infectious aggregates of abnormal prion protein are formed. Schwartz mentions two ideas that predominate: one theory suggests that infectious aggregates start off with monomers and dimers of prion protein, whereas the second theory favours a nucleation event. The latter theory is more consistent with the experimental data and is more widely accepted by scientists working on molecular aspects of TSE disease.

A large portion of the discussion involves the idea that, in some situations, normal prion protein can spontaneously convert to abnormal prion protein. Some scientists believe that this phenomenon accounts for cases of sporadic CJD. It seems unnecessary to me to invoke such a mechanism, because it is known that sporadic CJD is infectious and can be transmitted to non-human primates or humans by organ grafts. It is unlikely that we could determine the circumstances of infection, as the incubation periods may be decades and the disease has an incidence of one in a million. This is no reason to believe that an infectious event did not occur.

The author also misrepresents the status of chronic wasting disease (CWD) in wild elk. Although the incidence of CWD in captive or farmed elk can be quite high, it currently affects fewer than 1% of wild elk, even in areas where CWD is endemic. In wild cervids the disease primarily affects mule and white-tailed deer, with variable incidence.

Schwartz wonders why BSE occurred in Britain instead of, or in addition to, other countries with large sheep populations, such as the United States. There are several potential explanations for the lack of BSE in the United States. First, there are far fewer sheep in the United States than in Britain. Second, scrapie has been present in US sheep populations in low numbers only since 1947, compared with more than 200 years in Europe. Finally, the United States has had scrapie-eradication programmes in effect since 1952.

When Carleton Gajdusek won a Nobel prize in 1976 for his discovery of the transmissibility of kuru, a human TSE, the nature of the infective agent was unknown. Another Nobel prize was awarded to Stanley Prusiner 21 years later for his 'protein-only' theory of TSE aetiology. In his discussion of this theory, Schwartz mentions experiments that support the idea, but leaves out data that suggest other possibilities. He points out that even though the critical experiments to prove the theory have not yet been successful, the