

Further improvements can be made by reassessing the role of ethics as integral, rather than parallel, to research. As David Morton, Professor of Biomedical Science and Ethics at the University of Birmingham, UK, commented, "ethics shouldn't be a separate issue for researchers, it should be part and parcel of their daily activity. The three Rs are often a cover-up for scientists; we need more concentration on the intrinsic value of an animal and the role of the researcher as a moral agent." He would prefer the four As: Awareness (of suffering), Assessment, Avoidance and Alleviation. "Always assume that animals will suffer, rather than the reverse," he added. Reduced suffering improves the cost:benefit ratio of an experiment and makes it ethically more defensible, but it also increases the quality of the science, because pain and other forms of suffering can strongly influence physiological responses and hence scientific outcomes.

The better a species is understood, the better its welfare can be addressed. The effect of environmental factors, such as cage enrichment, on phenotype is complex and needs more research. But preliminary findings suggest that they have a significant and unpredictable effect on the results of experiments, according to Steve Brown from the MRC Mammalian Genetics Unit (Harwell, UK), who is the co-ordinator of Eumorphia. In the case of transgenic mice, the need for better phenotyping is now being addressed through large scientific networks across Europe. This is good for standardization, validation and data sharing, all of which contribute to the three Rs. Furthermore, genetic modification of animals is usually both a reduction and a refinement: it often replaces the chemical trauma that was inflicted on pregnant animals over a long period to create a particular defect in the offspring. Conditional mutants even allow the expression of a particular defect to be switched on and off. Less invasive technologies, such as magnetic resonance imaging markers and telemetry for remote monitoring, can also help to refine certain experiments, as can better definitions of humane end-points and improved knowledge of normal and patho-physiological values. In a general sense, greater knowledge minimizes suffering, which in turn improves the quality of experimental data.

Funding bodies and scientific publications can help by requiring scientists to describe in detail the suffering caused to an animal, and how it has been minimized. But nothing can improve the credibility of scientists more than ensuring animal welfare by self-regulation; there is no legislative substitute for good practice enforced in-house. Some researchers who are aware of the directive revision therefore ask why it is necessary if scientists already follow the rules and constantly improve animal use according to the best current scientific knowledge. Overwhelmingly, this is indeed what researchers do, as the tenets of the three Rs and the ethical use of animals do not conflict with sensible research.

What might be at odds with research are amendments born more out of political than scientific considerations. Many groups rightly have a stake in the revision process, and its final stages will rest in the hands of politicians. If researchers want scientific considerations to be included when the discussions become political, they are well advised to identify their nearest MEPs and correspond with them. "Keeping your head down does not work," remarked Festing. Hard-line ani-

mal rights groups will certainly not keep their heads down in the months to come.

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Skullduggery

The discovery of an unusual human skeleton has broad implications

When a team of Indonesian and Australian palaeontologists discovered a nearly complete but very strange 18,000-year-old human skeleton in an Indonesian cave in 2003, the find provoked questions about modern human origins. Do these ancient bones belong to a new human species? Are they, as many have claimed, the most important find in hominid palaeontology for decades? Or is this creature—indelibly christened 'the Hobbit' because it is so tiny—simply one of an isolated people who suffered from a deforming malady? The huge stakes in this competitive, caustic debate can be summed up succinctly: money and fame. But Hobbit investigations may eventually have less impact on the study of human evolution than they do on the standing of palaeoanthropology, and on the continuing crusade against the Darwinian account of how life on Earth evolved.

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The bizarre story so far: In 2003, a joint Indonesian–Australian team, digging in Liang Bua cave on the Indonesian island of Flores, found hominid bones and a nearly complete skeleton. The skeleton, designated LB1, was childishly tiny, but tooth wear showed the hominid to have been aged about 30 at death. In 2004 at the same site, the team uncovered another mandible and more bones and bone fragments, from a total of eight individuals. Dates inferred indirectly from materials around the finds range from about 94,000 to 12,000 years ago. This suggests that the hominids lived

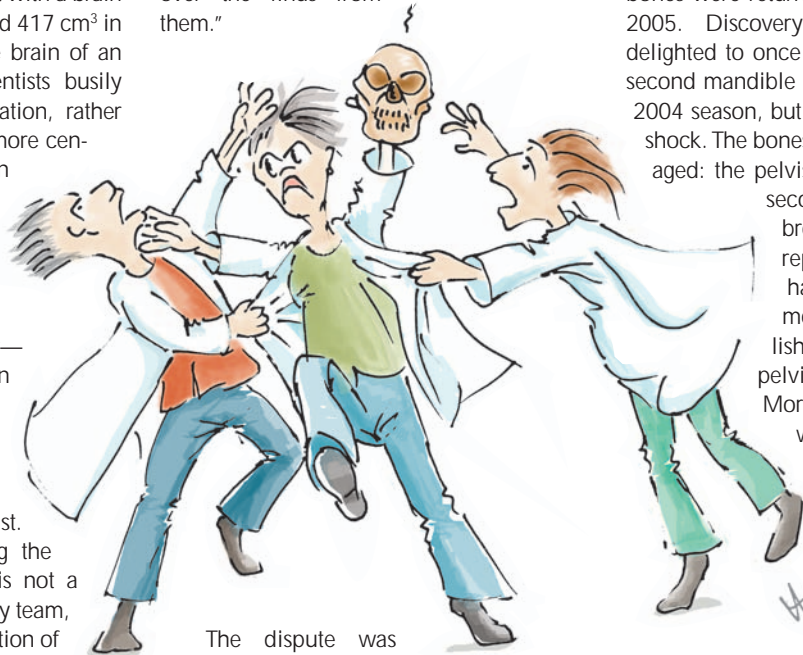
there for a very long time, overlapping with fully modern *Homo sapiens* on Flores for many thousands of years. LB1 was declared female and dated at 18,000 years old.

In 2004, *Nature* published the 2003 discovery to unprecedented commotion (Brown *et al*, 2004; Morwood *et al*, 2004). The authors declared that the bones were those of unique, unknown humans, which the scientists named *Homo floresiensis*, and were possibly descended from *Homo erectus*. Nearby tools resembled those from early *H. sapiens* in Europe. *H. floresiensis*'s small size, about 1 m, was attributed to island dwarfing, a phenomenon believed to occur when being big is a disadvantage because predators are absent and resources scarce. It seemed that they hunted an elephant that was similarly dwarfed. And—most astonishing of all—their complex culture was carried out with a brain estimated to be between 380 and 417 cm³ in size, which is smaller than the brain of an average chimp. This had scientists busily speculating that brain organization, rather than sheer size, must be even more central to human behaviour than previously believed.

The fragile bones—never fossilized and originally described as being like wet blotting paper—were kept at the Indonesian Centre for Archaeology in Jakarta, but were moved in November 2004 to the laboratory of Teuku Jacob, an eminent Indonesian palaeoanthropologist. The circumstances surrounding the transfer remain murky. Jacob is not a member of the original discovery team, but is in charge of a large collection of *H. erectus* fossils at Gadjah Mada University in Yogyakarta, about 275 miles from Jakarta. He says the move was at the request of Radian Soejono, a dig leader and one of the Hobbit paper's authors, who works at the Centre. It was normal, Jacob noted, for him to receive Indonesian bone finds while other artefacts remained at the Centre. The bones, he said, would be studied in his lab. Indonesian researchers not connected with

the find carried out some of this work, but nothing has yet been published. Jacob also allowed Australian, US and German researchers to study the bones without asking permission from the discovery team members.

Team members and other scientists were enraged over the moving of the bones. "From comments I have received or heard, most scientists are very concerned about what has happened to the material, and are hoping it can be returned as soon as possible to be studied by the original team. What has happened threatens all further research on the Flores site," said Chris Stringer of London's Natural History Museum. "The people who originally excavated and studied the material should be the ones taking forward work such as DNA testing, not someone who had taken over the finds from them."



The dispute was further fuelled when Jacob charged that the discovery team had bungled their analysis. LB1 and company, he said, were not a new species of *Homo*, they were simply short people; LB1 was male, not female, and had prehistoric microcephaly. Microcephaly is a nonspecific term for an abnormally small brain and skull; the condition has many variations and scores of known causes, both genetic and environmental. The main *Nature* paper had actually raised and dismissed some of these possibilities. This paper argued that LB1's skeletal features are not consistent with dwarfism, including microcephalic dwarfism, nor are her stature and brain size similar to pygmy populations. And although

some features, such as her canine teeth, are *sapiens*-like, her skeleton resembles australopiths, the authors of the paper noted. Palaeoanthropologists have never before seen anything like this assortment of modern traits mixed up with hominid skeletal anatomy that dates back millions of years.

In the meantime, Jacob's diagnosis has been backed up by a handful of other palaeoanthropologists, including some visitors who have seen the bones. The discovery team—and many others—think this is nonsense. Team leader Michael Morwood of the University of New England (Armidale, NSW, Australia) declared that "the vast majority" agree with their original assessment. "We don't have any credible critics. All we have is opinion in unreviewed publications."

After months of negotiation, most of the bones were returned to Jakarta in February, 2005. Discovery team members were delighted to once again have access to the second mandible and other bones from the 2004 season, but there soon came another shock. The bones had been seriously damaged: the pelvis had been smashed, the second mandible had been broken and unskilfully repaired, and LB1's skull had been mutilated by latex moulding; *Science* published photos of the damaged pelvis (Culotta, 2005). Morwood charged that bones with australopithecine traits had been almost destroyed. "The condition of some finds is absolutely appalling," he said. "This is not the action of responsible scientists."

Jacob acknowledged taking moulds, but says he has photos showing that the bones were in perfect condition when they left his care.

Meanwhile, a study of LB1's brain, based on skull endocasts made before the bones were moved, was also published (Falk *et al*, 2005). First author Dean Falk of Florida State University (Tallahassee, USA) concluded that the brain was unique and somewhat *erectus*-like, but had advanced features, such as an enlarged prefrontal cortex, that hinted at respectable cognitive capacity. Comparing it with a single skull from a microcephalic, the group also concluded that LB1's brain was not altered by disease. Falk is now studying addi-

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tional microcephalic endocasts for comparison. "This was just a thrill," she said. "We said to them, 'We stand ready. If you find any more skulls, we'd love to analyze them!'"

Ralph Holloway of Columbia University (New York, NY, USA), an eminent endocast expert, has studied an endocast he made from the original CT scan data of the skull. Holloway believes LB1 was probably not microcephalic, although the endocast has features that puzzle him. "This is extraordinarily dwarfed, with a brain size that some chimpanzees would snicker at, so I wouldn't call it normal." The extremely thin protruding frontal lobes have led him to wonder if LB1 is an example of microgyria. In this condition, the cerebral cortex has only four layers instead of the usual six, but he notes this is not a hypothesis that can be tested easily. In lab animals, microgyria leads to brain reorganization and behavioural changes, and in humans it has been associated with epilepsy and dyslexia.

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DNA studies, which could establish whether LB1 is *H. sapiens* or something completely different, are not likely to occur in the near future. A bone chip that was sent—accompanied by international outrage—from temporary residence in Jacob's laboratory to Svante Pääbo's laboratory at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, has as yet yielded no results, either positive or negative. Pääbo, one of the world's leading experts in the analysis of ancient DNA, does not give his studies a high chance of being successful, but added, "I would be delighted to work with the team excavating the site in order to explore this material further." Alan Cooper from the University of Adelaide (SA, Australia), the discovery team's designated DNA expert, reports that he does not expect his search for DNA—which has so far been confined to sediments and plant material from the site—to hit its stride until 2006, with publication a long time after that. Conditions at the Liang Bua site are the worst possible for DNA preservation: hot and wet. But even if conditions were perfect, the peregrinations of the bones—to say nothing of the covert damage—have exposed them to considerable contamination from for-

eign genetic material, which is always a hurdle for studies of ancient DNA.

The reports of the discovery team on the 2004 digging season are expected soon. Team members say the new analysis backs up their contentions about a new *Homo* species, but with debate so polarized, it is doubtful that additional reports will persuade sceptics. The second mandible, despite being broken and inexpertly repaired, is said to be very similar to that of LB1. This is the strongest indication so far that, whatever the specimen is, she—or he—is not unique. However, according to John Hawks—a palaeoanthropologist at the University of Wisconsin-Madison, USA—who has studied photographs taken in Jacob's lab, this similarity does not mean that nothing was amiss with these creatures. He says tooth and braincase oddities reported in the original paper, plus the projections in the front of the endocasts, suggest pathology, as do the postcranial bones. He notes that most of the other individuals are represented by a single bone or bone fragment. "There are mosaics of features across all the postcranial bones that suggest developmental abnormalities," he said. "If the pictures that I have seen of the post-crania had been included in the original *Nature* report, it would have never have made it past review."

The truth, Hawks argues, would emerge with wider access to the bones. "Let's get a group of people in there who don't have a stake in one side being right, and let's open it up," he said. "There's been a real lack of transparency that has led to the persistence of a legitimate scientific debate that could be settled fairly easily if there was more openness."

The Hobbit story seems designed for twenty-first century media because indeed it was. The US National Geographic Society has funded palaeontology research for many years, always promoting and portraying it as notably successful—sometimes even before journal publication. The Society has underwritten the Hobbit research, and its news on the Hobbit began appearing simultaneously with the *Nature* papers; television followed soon after. *Nature* accompanied the papers with its own press conferences, press kits, videos and news stories. The Hobbit tale is a natural draw, featured in print and broadcast media everywhere. Discovery team members have led journalists and TV crews to the dig site,

taken part in teleconferences and appeared regularly in TV studios. Formerly inconspicuous palaeontologists, anthropologists and microcephaly experts are suddenly in demand. Broadcast networks, especially in Australia and the USA, launched TV specials. And there is no end in sight; Holloway and his cast of endocasts are scheduled to star in a BBC television special in the UK.

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The sponsors probably would have preferred that the Hobbit remained one of the Top Ten science stories of 2004. Instead, it has turned into a particularly rancorous scientific dispute, to say nothing of a territorial battle that has degenerated into name-calling. Jacob has been quoted as saying the Australians on the discovery team lack expertise and has called them scientific terrorists. Morwood has countered that taking bone to Germany was unethical and illegal. Such comments have proven irresistible, even for some media that usually ignore science.

But, ultimately, the impact of the dispute on the science of human origins may be as small as the Hobbit itself. "It's extremely interesting and provocative, but it is not going to upset the apple cart on the whole picture of hominid evolution," Holloway said. "It is clearly a localized phenomenon that took place on one small island in the Indonesian archipelago."

Instead, Hawks worries that the dispute has been bad for palaeoanthropology and good for creationism. Searching the World Wide Web for information on the Hobbit, he pointed out, uncovers many creationist sites. "They're saying, 'Look! These people don't know what they're doing! They don't know what they're talking about! They're disagreeing about the most basic issues—about whether something is diseased or not!'", Hawks commented. "It's wrong for them to do what they do, but we certainly make it easy for them when we have disagreements like this one. I think that a lot of what has been said is going to have to be retracted. Given the amount of media attention, it just makes the field look incompetent." His conclusion: "Everybody wants a piece of this. Nobody is on the side of the angels now."

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Disease mongering and drug marketing

Does the pharmaceutical industry manufacture diseases as well as drugs?

Most people may not have heard of metabolic syndrome, but that is likely to change. Once known mysteriously as Syndrome X, the condition, a precursor to heart disease and type 2 diabetes, is about to be transformed into a household name by the US pharmaceutical industry and its partners in the medical profession. A society dedicated to addressing the condition has been organized, a journal has been started, and an education campaign launched. Patients are already being tested for metabolic syndrome. As the trade publication *Pharmaceutical Executive* said in its January 2004 issue: "A new disease is being born" (Breitstein, 2004).

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The situation is reminiscent of the attitude towards cholesterol. Twenty years ago, physicians were not concerned about the effects it might have on heart disease. Today, thanks to efforts by pharmaceutical companies, high cholesterol levels are now recognized as a major

health problem. In fact, IMS Health, a global healthcare information company, reports that the two best-selling drugs in 2004 were statins: Lipitor® (atorvastatin calcium) from Pfizer (New York, NY, USA)—valued at US\$10.6 billion with growth of 13.9% over the previous year—and Zocor® (simvastatin) from Merck (Whitehouse Station, NJ, USA). *Pharmaceutical Executive* noted: "The emergence of cholesterol reduction as a market was a major event for pharma. Metabolic syndrome promises to be as big or bigger" (Breitstein, 2004).

However, critics note that not every new disease for which the pharmaceutical business provides a drug is necessarily a major public health problem, but rather a venue for drug companies to increase revenues. Pharmaceutical companies research, develop and exploit drugs to prevent, control and cure diseases and treat symptoms. Companies then market these medications to recoup their investments and reward shareholders. It would seem to serve the interests of society, but some critics characterize it as a vicious circle in which businesses invent new diseases to match their existing drugs. Increasingly, industry has found itself under fire from detractors who contend that, in the pursuit of profits, companies are in league with medical doctors and patient advocacy groups to 'disease monger': convince people that their usually mild ailment urgently needs drug treatment.

The late medical journalist Lynn Payer addressed the issue in the early 1990s in her book *Disease-Mongers: How Doctors, Drug Companies, and Insurers Are Making You Feel Sick*. She wrote: "Disease-mongering—trying to convince essentially well people that they are sick, or slightly sick people that they are very ill—is big business.... Disease mongering is the most insidious of the various forms that medical advertising, so-called medical education, and information and medical diagnosis can take." Similarly, Arthur Caplan, Professor of Bioethics at the University of Pennsylvania, Philadelphia, USA, last December told the popular American TV programme *60 Minutes*, "If you want to stir up worry in the public, and you've got the advertising dollars to do it, you can turn almost anything into a disease." The focus of the *60 Minutes* report was the recent emergence of a market for adult attention deficit disorder (ADD)—the traditional view was that ADD afflicted only children who would eventually outgrow it.

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Critics such as Payer and Caplan maintain that the routine human condition—unhappiness, bone thinning, stomach aches and boredom—is increasingly being re-defined as disease: depression in its milder forms, osteoporosis, irritable bowel syndrome and attention deficit disorder. Likewise, risks factors, such as high cholesterol and high blood pressure, are declared diseases in their own right—hypercholesterolaemia and hypertension—with falling thresholds resulting in more people considered to be sick. In other cases, drugs approved for devastating illness, such as clinical depression, are indicated for milder conditions, such as shyness, which is now dubbed 'social phobia'.

One such example is Strattera® (atomoxetine hydrochloride), developed by Eli Lilly & Co. (Indianapolis, IN, USA) and approved in November 2002 by the US Food and Drug Administration (FDA) for treating ADD in children, teens and, for the first time, adults. One Lilly advertisement shows a series of photographs of an uptight-looking model, and asks in the headline: