

Professor Richard Hanson and his team at Case Western Reserve University in Cleveland, Ohio, thought they had embarked upon an interesting but routine experiment. They had an enzyme – PEPCK-C – that had been discovered 50 years earlier at their university. It occurs in all animals and appears mainly in their livers and kidneys where it is associated with the production of glucose. But there is also some in the muscles. Wondering what it did there, Hanson and his team decided to see what happened if they massively increased the amount of PEPCK-C in the muscles of mice.

They did this by rigging the genetics of the mice to overexpress the enzyme on skeletal muscle. Every day hundreds of such experiments are going on with millions of mice subjected to all kinds of genetic interventions. Most achieve either nothing or lots of dead mice. Genetics is still a young science in which anything may be possible, but for the moment most things aren't. Hanson wasn't expecting much from his mice.

He certainly was not expecting a long-lived, superfit, relentlessly randy, hyper-active, marathon-running mighty-mouse. But that is exactly what he got. Hanson's mice – especially the females – can run six kilometres at 20 metres a minute. They keep it up for five hours or more.

They can eat up to twice as much as an ordinary mouse but weigh half as much.

Supermice can be spotted soon after birth by their bouncing – and, I imagine, to ordinary mice incredibly irritating – hyperactivity. Later on they irritate ordinary mice even more by not ageing and, although formal experiments have not yet been conducted on this, they appear to live longer. Female supermice have given birth at almost three years old, the human equivalent of about 80.

Everything about these results is weird. Hanson's transgenic mice are minimally different from his "wild" – ie ordinary – types. But this tiny genetic change seems to affect every aspect of the organism even, judging by its hyperactivity, its mental state. Researchers (and anybody who wants to live longer or just run up Mount Everest) are queueing up to play with the Case Western colony of 500 supermice.

The big question is: will this work in humans? We have PEPCK-C in more or less the same places as mice and we are genetically similar. That's why we use them in experiments. On the face of it, we are on the brink of becoming a race of superhumans.

Of course, it's not that simple. First of all we have no idea of the side effects. Work is going on to establish the cancer rates among supermice. They are even going to have their intelligence tested – it would be no big advantage to a human to be a superfit moron (or perhaps it would). In addition, supermice are much more aggressive than their wild type cousins.

"I don't think," says Hanson dryly, "we need more aggressive humans."

What does it mean, if anything, for us? First of all, it seems to tell us something about the effects of exercise. Hanson compares his mice with Lance Armstrong, the cyclist, who has been extensively studied by the University of Texas. His freakish ability in cycle races indicates there is something fundamentally different about his metabolism, a difference perhaps shared by the supermice.

When you or I exercise, we eventually have to stop because our muscles fail us. They do so because of a build-up of lactic acid. This happens because we are burning glucose. But the supermice seem to burn only fat and thus avoid the lactic acid build-up. It also keeps them very lean. Furthermore, the supermice seem to want to exercise: they could simply choose to stop but they don't. So whatever has happened in their muscles seems to have affected their minds, as well.

They also seem to cast new light on the effects of diet. Experiments on animals since the 1930s have consistently shown that cuts of 20% or 30% of caloric intake increase lifespan, sometimes massively. It would be unethical to conduct such experiments on humans but many have been convinced that this is the way to a longer life.

Calorie restrictionists now form a world-wide club (see [www.calorierestriction.org](http://www.calorierestriction.org)). This is generally regarded by doctors in the mainstream as risky. It may cause brain damage and does seem to cause bone weakness. But there is no question that calorie restriction pushes the body into a defensive/survival mode that does affect the ageing process. However, these supermice are consuming twice the usual number of calories.

Leading British ageing researcher Aubrey de Grey, the author of *Ending Aging: The Rejuvenation Breakthroughs that could Reverse Human Aging*, thinks that something in the treatment has kicked the supermice into the same condition as a calorie restricted creature. The supermice, for example, have much higher numbers of mitochondria than their irritated cousins, exactly like animals on restricted diets. Mitochondria are, effectively, batteries; they are structures within the cell that provide its power. The behaviour of the supermice in general is similar to that of calorie restricted animals.

This suggests that we can enjoy the benefits of calorie restriction without the misery of being hungry all the time. This is, obviously, a big area of research at the moment. In particular, scientists are looking into the action of resveratrol, the substance found in red wine that seems to protect against heart disease and other ageing conditions, in the hope that we may be able to live longer while eating as much as we like. If you are persuaded and impatient, you can easily get hold of resveratrol as a food supplement.

Whether these supermice really are living longer is not yet clear. Hanson emphasises that he has not done ageing and longevity studies on the mice and his evidence is anecdotal. But it is highly suggestive. Members of his team report that they can tell the difference between an old supermouse and a wild type and the very late litters born to old female supermice do suggest that some fundamental antiageing trigger has been pulled. As usual in ageing studies, the females seem to do much better. In almost all human populations, women seem on average to live about five years longer than men.

How any of this knowledge may be applied to humans is as yet unknown. There has been a cascade of suggestive developments pouring from genetics and micro-biological labs around the world. As long as 10 years ago another form of supermouse was developed at Johns Hopkins University – they called it Mighty Mouse. This was a super-muscular creature created, again, by an intervention of skeletal muscle gene expression.

Such developments – along with announcements such as last week's World Cancer Research

Fund study that seemed to blacken the name of bacon – are indications of the scope and scale of new medical science. Crucially, they raise questions about how far we can go. Life expectancies in the developed world have continued to rise. They were expected to plateau in the 1970s. The rise up to then was well understood – it was largely thanks to antibiotics, public health measures and the suppression of infant mortality.

The rise since then is less well understood. Scientists such as de Grey in Britain and Michael West in America have been advocates of the view that we are, indeed, on the verge of achieving massive extensions in life expectancy, possibly to 1,000 years and beyond. A majority of scientists are sceptical and some believe it is downright harmful to pursue such a goal when research money could be better spent elsewhere. But to a large extent this argument is losing ground simply because so many extraordinary results are emerging from the laboratories.

The supermice at Case Western are further evidence that something big is happening in biology, something that may well mean we can take control of and even transcend our biological destinies.

By Bryan Appleyard