pattern of accelerated degenerative changes very similar to those seen in the human patient, not only at the molecular and cellular level, but also in terms of organ and system functions. Comprehensive analysis of gene expression in the *Ercc1*$^{-/-}$ mice compared with normal controls revealed a broad spectrum of changes, with 1,675 genes showing significantly different expression in the mutant mice. These changes included a general decrease in the activity of hormonal pathways involved in the regulation of metabolism, such as growth hormone/IGF1 signalling, and increased activity in antioxidant and DNA repair pathways.

Intriguingly, this pattern of altered gene expression in a model of accelerated ageing is reminiscent of the array of changes previously reported in the context of gene mutations that increase lifespan in the nematode worm *Caenorhabditis elegans* (a classic genetic model of ageing)[6], and also during life-extending dietary restriction in mice[7–9]. Curiouser and curiouser, as Alice observed in Wonderland.

To resolve the paradox presented by these data, we need to grapple with one of the central conundrums in ageing research. When so many molecular and cellular changes occur in concert both during normal ageing and in genetic models of accelerated or postponed ageing, which of them are causative and which merely secondary consequences? Niedernhofer *et al.* address this problem to some extent by showing that the profile of gene-expression changes in the *Ercc1*$^{-/-}$ mice is broadly reproduced not only in naturally aged control mice, but also in adult control mice subjected to an increased burden of DNA damage from the chemical mitomycin C. From this, we can infer that the systemic changes in the *Ercc1*$^{-/-}$ mice, and probably those in the XPF-deficient human condition, are a nonspecific consequence of the accumulated DNA damage that also occurs in ageing. But how particular are these changes to DNA damage, as opposed to the other kinds of damage that might affect ageing cells?

The collection of progeroid syndromes in mice and humans is intriguing, both for the similarity in age-accelerated symptoms (despite the diversity of causative mutations) and for the fact that these changes only partly mimic the normal ageing process[10]. And if, as various data indicate, reduced growth hormone/IGF1 signalling is a putative cause of increased longevity in mice, worms and fruitflies, how is it that such a pattern is also seen as a consequence of the damage that leads to the decreased longevity described by Niedernhofer *et al.*?

It is fast becoming clear that unravelling the complex biology of ageing so as to understand the true relationship between cause and effect will not be easy. We will need to move beyond essentially descriptive studies of what goes up and what goes down, and perhaps to immerse ourselves in the exciting but deep waters of systems biology. This branch of science offers a way of teasing apart the complexity that allows a change in some components of a system to act as both cause and effect. Although the study of progeroid syndromes such as that due to the XPF–ERCC1 mutation poses at least as many questions as it answers, it also represents a helpful buoy in these waters. ■

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1. Oeppen, J. & Vaupel, J. W. *Science* **296,** 1029–1031 (2002).
2. Kirkwood, T. B. L. *Cell* **120,** 437–447 (2005).
3. Finch, C. E. & Tanzi, R. E. *Science* **278,** 407–411 (1997).
4. Niedernhofer, L. J. *et al. Nature* **444,** 1038–1043 (2006).
5. Hasty, P., Campisi, J., Hoeijmakers, J., van Steeg, H. & Vijg, J. *Science* **299,** 1355–1359 (2003).
6. Hansen, M., Hsu, A. L., Dillin, A. & Kenyon, C. *PLoS Genet.* **1,** 119–128 (2005).
7. Lee, C. K., Klopp, R. G., Weindruch, R. & Prolla, T. A. *Science* **285,** 1390–1393 (1999).
8. Cao, S. X., Dhabhi, J. M., Mote, P. L. & Spindler, S. R. *Proc. Natl Acad. Sci. USA* **98,** 10630–10635 (2001).
9. Spindler, S. R. *Mech. Ageing Dev.* **126,** 960–966 (2005).
10. Kipling, D., Davis, T., Ostler, E. L. & Faragher, R. G. *Science* **305,** 1426–1431 (2004).

OPTICS

A light touch

'Being good with your hands' is not quite the badge of approval it once was: the tiny scale of the components used in most high-tech industries has made old-fashioned manual dexterity largely redundant. Yet in many sensitive applications, the unique directness of human touch is highly desirable. Now Graeme Whyte *et al.* introduce an apparatus that could go some way to putting the 'hand' back in manipulation, even on very small scales (*Opt. Express* **14,** 12497–12502; 2006).

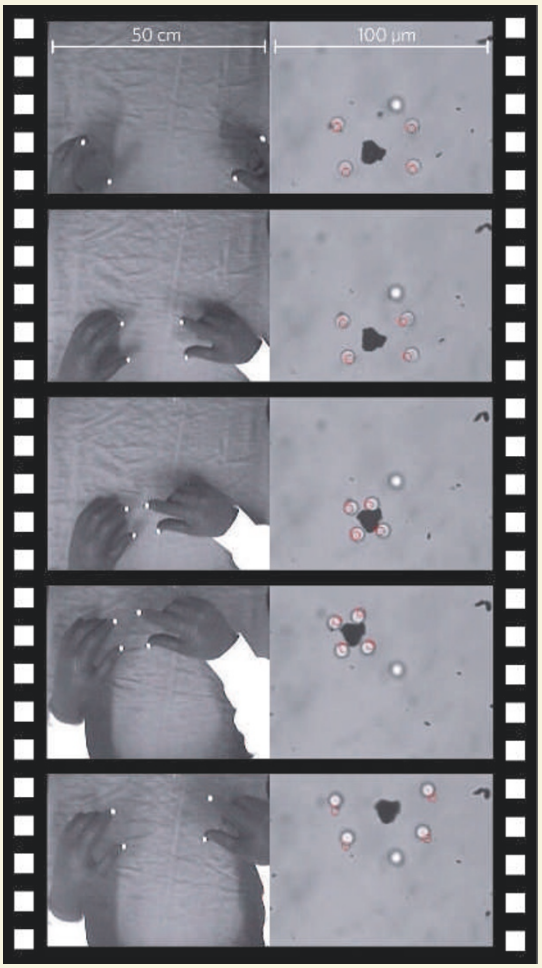
The authors' apparatus marries the skill of human digits with the laser-sharp precision of 'optical tweezers'. Such tweezers use the momentum of a highly focused laser beam to trap and move objects as small as a single atom. The technique is increasingly useful, especially in cell biology, where it can be applied to measuring the mechanical, optical and transport properties of cells and biological molecules without the need for a material probe.

Whyte *et al.* use 'holographic' optical tweezers, in which a diffractive element, known as a spatial light modulator, is used to steer the laser beam. This allows several optical traps to be created that can be moved independently in three dimensions. The authors hook up the spatial modulator to a camera that images the position of beads attached to the fingertips of two gloved human hands. A specially written hologram-calculation algorithm converts the positions of the beads in the photographic plane into the *x*–*y* position of the optical traps, and the apparent size of the bead in the image into a *z*-coordinate.

The result is a device in which each trapping beam acts as a digit of an optically controlled hand. The position of this hand on the micrometre scale is controlled by appropriate larger-scale movements of the remote, real hands. The images show how silica beads trapped at the tips of the optical fingers grasp and move a larger, irregularly shaped chrome bead. The hologram algorithm allows 8 frames per second — enough for manipulation in real time — to be processed using a standard desktop computer.

Because the manipulated object does not itself have to be optically trapped, this method could be very useful for dealing with light-scattering metallic particles or light-sensitive materials, such as some biological tissues. But more generally, such techniques could mean that the future of micromanipulation lies in our hands.

Richard Webb



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