CHARLOTTE STODDART/NPG

Lorna Stewart (far left) quizzes young researchers John Lee, Claudine Gauthier and Alina Solomon (far right) about what they think happens as our bodies age.

GERONTOLOGY

Will you still need me, will you still feed me?

As the Lindau Nobel Laureate Meetings turn 64, laureates and young researchers discuss growing old — and whether exercise and stress reduction can slow the ageing process.

BY LORNA STEWART

"What is the life expectancy of the world population today?" asks Hans Rosling, a global-health researcher at the Karolinska Institute in Stockholm, during the opening ceremony of this year's Lindau Nobel Laureate Meeting. The 700-strong audience of young researchers and Nobel laureates reach for their keypads. "Is it 50, 60 or 70 years old?" he continues. The audience casts its vote. The correct answer, 70, gets the fewest hits.

"Even chimps do better than that," jokes Rosling, hinting that the audience would have got closer to the correct value had they answered at random. But the serious point he is making is that our notions of global demographics are outdated. And scientists need to know the facts if they are to set priorities for future medical research. Global life expectancy has risen dramatically during the past century, raising profound issues concerning the role of medical practice and the demands on scientific research.

The science and ethics of ageing was a theme at the meeting, and also the focus of a series of discussions, captured by the *Nature Video* team (see www.nature.com/lindau/2014). During those conversations I kept returning to one question: should we concentrate efforts on treating conditions that affect us in old age or devote resources towards earlier stages in life, when exercise or stress reduction could have greater long-term benefits?

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At Lindau, I discussed this issue with three young researchers and two Nobel laureates, and since then I have also put the question to other researchers in the field of ageing.

Ageing is linked to a multitude of biological processes, but scientists know suprisingly little about why, and how, we age and die. "It's a large and complicated business, the biology of ageing," says Thomas Kirkwood, who is associate dean for ageing at Newcastle University, UK. "We age because it was never a priority for our genomes to invest in the kind of maintenance and repair that could keep you going very much longer — or hypothetically forever," he adds.

To date, hundreds of genes connected to ageing and longevity have been identified, but there is no master switch. Instead, most of these genes perform functions that help to

maintain cells, such as repairing damage to DNA or regulating antioxidant levels.

Individually, genes have a relatively small impact on lifespan, but together they account for 25% of our longevity, Kirkwood says. That means that one-quarter of your chance of living into old age comes from your parents, he explains, with the remainder left to chance and environmental factors. "We don't know yet exactly how the remaining 75% breaks down, but I wouldn't be surprised if it turns out that as much as half of that is influenced by things like exercise and healthy nutrition," he says.

The difficulty in ageing research is in identifying the physiological and psychological changes that are attributable to an underlying ageing process and those that are caused by age-related diseases. In the hunt for the recipe for long life, scientists have frequently turned to individuals and populations who show exceptional longevity. Earlier this year, researchers gained a fresh perspective on the biology of ageing when they analysed[1] DNA isolated from tissues obtained during the autopsy of a Dutch woman named Hendrikje van Andel-Schipper, who had lived disease-free until the ripe old age of 115.

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Studying van Andel-Schipper's body after her death in 2005, Henne Holstege, a geneticist at the VU University Medical Center in Amsterdam, the Netherlands, and her co-workers concluded that stem cells hold the key to understanding the limits of an individual's lifespan. They found that, by the end of her life, the majority of van Andel-Schipper's white blood cells had come from just two stem cells. At birth, humans have 20,000 stem cells; it is not unusual for someone in old age to have so few remaining stem cells, but scientists had been uncertain whether it was old age or disease that causes this loss. Van Andel-Schipper had been particularly healthy, so they proposed that it was the ageing process that had caused the reduction in her stem-cell count. Mouse studies[2] have found that stem cells decrease in number steadily throughout the mouse's lifespan — researchers suspect that this is also the case in humans. The chromosomes in van Andel-Schipper's two remaining blood stem cells had much shorter telomeres — caps at the ends that protect the chromosomes from deterioration— than those found in other cells. They suggested that her stem cells had reached the end of their ability to keep replenishing.

Each time a cell replicates, its telomeres shorten. When telomeres are too short, the cell will either stop replicating and become senescent or it will die. If a cell with shortened telomeres continues to replicate it can become abnormal. Exactly why some people's telomeres shorten more slowly than other people's is not fully understood, but clues are emerging.

Elizabeth Blackburn, who won the 2009 Nobel Prize in Physiology or Medicine for her work on telomeres, is taking steps to keep hers long. She says that the key is to avoid getting stressed. Since uncovering the link between stress and telomeres[3], Blackburn has taken up exercise and meditation, and at Lindau she encouraged me to do the same. Her view is that focusing on medical and lifestyle interventions when you're young benefits not just the individual — families will have more time to spend with their loved ones, too.

MARATHON TASK

Alongside the mechanisms of biological ageing, researchers are also interested in conditions that are related to growing older, such as Alzheimer's disease, cardiovascular diseases, diabetes and cancer. Such diseases are becoming more prevalent as people live longer, and understanding and treating them is the focus for some of the young researchers who took part in the *Nature Video* discussion.

Alina Solomon, a neurologist at the Karolinska Institute, works with people who have dementia. She sees commonalities across diseases of old age. "Several of these non-communicable diseases at older ages have common risk factors, so if we address them we can address several of these problems at the same time," she says. She thinks that the best approach for biomedical sciences is to focus on helping us live healthier, not just longer, lives. "We should consider a balance between adding years to life and adding life to years," she explains.

Solomon's view is shared by Oliver Smithies, joint winner of the 2007 Nobel Prize in Physiology or Medicine for his work on embryonic stem cells. He says that older people should not be the priority for medical science. At the age of 89 and still working in his laboratory at the University of North Carolina in Chapel Hill every day, not to mention piloting light aircraft in his spare time, Smithies is well placed to comment. "We have to be realistic about it," he says, but notes that facing facts is where the problems start. "We are sentimental and we say everybody has a right to life, which is true, but we can't afford to preserve every life. Why live to be 80 with aches and pains?"

Claudine Gauthier, a postdoc working on blood-vessel ageing at the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig, Germany, also thinks that there are good reasons to focus medical science on a younger cohort — people aged 40–50 years old. She sees middle age as an inflection point in the ageing trajectory, a period when a body might be particularly sensitive to intervention. "If you look at any health parameter, the variance of it increases dramatically once you get to middle age," she says. This means that interventions or lifestyle changes might have a bigger impact here than at any other age. "Maybe the way to be healthy when you're 30 is not the same way to be healthy when you're 50."

It comes down to prevention, she adds. "If you want to tackle ageing you've got to do it in a younger population because I don't think it's sustainable in the long term to just cure every disease." Blackburn agrees. "We can't think of them as diseases of ageing," she says. "Cancer unfolds silently, often for years, and then you say: 'I got cancer'. No, you didn't 'get' cancer, that's a process that's been going on for ages."

LIVE HEALTHIER FOR LONGER

'Health-span' is a phrase that came up a lot at the meeting. The idea is to focus on the number of years that you remain healthy and active, rather than on the number of years that you live. Many people I spoke to said that the focus for biomedical science should be on extending good health, not just on extending life. But are living longer and being healthy really at odds with one another?

It depends on how you view health, says Kirkwood. A large-scale survey[4] of people over 85 years of age in Newcastle, UK, showed that most have multiple health problems but still regard themselves as in good or excellent health when comparing themselves to their contemporaries. "People have this notion that they will be bundles of misery suffering all kinds of illness and woe," he says. "What we found was very far from the case. A large number of people were living very active, full and busy lives." Perhaps, then, part of ageing healthily is about adjusting what we expect to be able to do. The good news, says Kirkwood, is that is there is nothing in our bodies to programme our death. "Our bodies are designed for survival, they're just not built well enough to survive indefinitely."

John Lee, a PhD student at Drexel University College of Medicine in Philadelphia, Pennsylvania, understands this problem. He wants to live to 150, but thinks that it is more likely that his grandchildren will achieve this feat, rather than him. He is working on developing exoskeletons to help people who have had a spinal-cord injury, and believes that technological solutions may ultimately fix our crumbling bodies and help us to age better. "We don't expect to be running marathons at 150," he says. But, with this kind of help, we could be over 100 and still doing things "as if we were 30 again — or maybe 50". ■

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1. Holstege, H. *et al. Genome Res.* **24,** 733–742 (2014).
2. Orford, K. W. & Scadden, D. T. *Nature Rev. Genet.* **9,** 115–128 (2008).
3. Epel, E. S. *et al. Proc. Natl Acad. Sci. USA* **101,** 17312–17315 (2004).
4. Collerton, J. *et al. Br. Med. J.* **339,** b4904 (2009).