Telomeres

# Ageing hard or hardly ageing?

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The potential rewards of understanding ageing are vast, yet the field remains greatly underexplored. Physiological changes in old age — ranging from poor wound healing and a compromised immune system, to cardiovascular problems — can reduce the quality of life for an ever-increasing fraction of the world's population. Reporting in *Cell*, Rudolph *et al.*[1] now provide the first direct evidence that at least some of these changes can be caused by telomere erosion.

Why and how do we age? Ageing is a side effect of optimizing an organism's evolutionary fitness[2]. Because it affects so many different systems, however, it would be naive to expect a single cause or a central 'clock'. The main factors in cognitive decline, for example, may make little contribution to cardiovascular degeneration. Many causes of ageing have been suggested, such as free-radical damage[3], replicative senescence[4] and mitochondrial dysfunction. But these complement rather than exclude each other, and data that support one in no way detract from the potential effects of the others.

One hypothesis concerning ageing of regenerative tissues (as opposed to those that cannot divide) is cell senescence[4]. Normal cells in culture divide a variable, but limited, number of times. They then enter senescence, a state in which they are alive but no longer dividing. Several types of human cell, notably fibroblasts, use the DNA sequences that protect the ends of their chromosomes (telomeres) to count how many divisions they have been through. They can do this because every time a cell goes through DNA replication, a small portion of the end of each telomere is not duplicated, so the telomeres get progressively shorter[5]. This shortening is used as a clock. In experiments where the telomere-maintenance enzyme, telomerase, which is normally repressed in fibroblasts, was expressed, both telomere shortening and senescence were prevented[5]. Such telomerase-positive cells divide indefinitely in culture, but show no other apparent change in behaviour[6,7]. The simplest interpretation is that, in fibroblasts at least, human cell senescence is 'telomere driven'.

How could senescent cells contribute to ageing? They have an altered behaviour and pattern of gene expression[4] from dividing cells, and have been shown to accumulate with age. They may alter their local tissue microenvironment and contribute to the shift from young to aged tissue. But even if they behaved normally, or were rapidly cleared by programmed death, a finite limit to division could still alter tissue function in later life. *In vivo*, cells divide either to maintain routine tissue function or in response to damage or infection. Division rates are species specific and depend on a cell's position within the tissue[8]. Cell division can be frequent, as in the epidermis or intestinal lining, or relatively rare, as with endothelial cells, T cells and fibroblasts, which may divide just once a month or even only once every few years. In such tissues, can a finite limit to division ever be of physiological significance?

Rudolph *et al.*[1] now show that if they reduce the capacity of mouse cells to divide, the function of division-competent tissues is compromised in later life. They followed a cohort of transgenic mice bearing a germline knockout of the *mTR* gene, which encodes an essential component of telomerase. There are few data to suggest that this mutation affects rodent cell senescence, which seems to be triggered through a telomere-independent mechanism[9]. But the continual loss of telomeric sequence does eventually reduce the production of viable cells, probably because,

Table 1 **Ageing syndromes in mouse and man**

| *Symptoms* | *mTR*$^{-/-}$ *mice* | *Werner's syndrome* |
|---|---|---|
| Shortened division capacity | + | + |
| Accelerated cell senescence | – | + |
| Premature greying | + | + |
| Poor wound healing | + | + |
| Increased cancer incidence | + | + |
| Gut defects | + | ? |
| Infertility | + | + |
| Shortened lifespan | + | + |
| Decreased adipose tissue | + | + |
| Hair loss | + | + |
| Brain changes | – | – |
| Osteoporosis | – | + |
| Diabetes | – | + |
| Atherosclerosis | – | + |
| Cataract | – | + |


**100 YEARS AGO**

**Aitken (*Proc. R. S. E.*, vol. ii p. 472, 1882) has given a complete theory of the colour of sea water as observed at various places, based upon the principle that sea water is a blue liquid. According to this view, the green tint often observed in sea water, especially near land, is to be explained by the presence of fine yellow particles. During a recent voyage by the Messageries steamer *Polynesien*, I was permitted, through the kindness of the Commandant Bullard, to erect a tube 736 cm. long against the rail of the after-deck, and to pass through it a continuous stream of water from the ship's salt water service. ... it is useless to comment on most of the results obtained, except in so far as they give a means of easily reproducing the exact tint of pure sea water as seen through a column 736 cm. long. Make up the following solution:- Water, 500 c.c.; Soluble prussian blue, 001 gram; Saturated lime-water just precipitated by the smallest excess of bicarbonate of soda, 5 c.c.. This mixture, when viewed through a tube 18 cm. long, will show with considerable precision the colour of a sample of water from the Mediterranean, lat. 36° 24′ N., long. 17° 51′ E. of Paris.**

From *Nature* 16 March 1899.

**50 YEARS AGO**

**An extensive analysis of the energetic disintegrations produced in the silver and bromine nuclei of nuclear emulsions exposed to cosmic radiation indicates that the emitted particles, consisting of α-particles, protons and neutrons, generally escape from the nucleus after the excitation energy has been statistically shared among the constituent nucleons. The disintegration process is then analogous to the evaporation of molecules from a drop of liquid. Occasionally, however, stars are observed in which highly charged nuclear splinters are ejected from strongly excited nuclei before equilibrium has been attained. From a total of six thousand stars, we have observed two examples in which we can identify such heavy fragments. These events are not so rare as this might imply, since their tracks can only be identified when they have a considerable length in the emulsion. The two stars were obtained in 'sandwich' emulsions exposed on the Jungfraujoch (3,500 m.).**

From *Nature* 19 March 1949.

if chromosomal ends are no longer protected by telomeres, genomic instability results[10,11].

Mice lacking the *mTR* gene show progressive telomere shortening in successive generations. After three generations (G3) of inbreeding, the mice start life appearing normal, but their telomeres are so short that the effects of their compromised division capacity soon become evident. After 18 months, the G3 mice start to show impaired wound healing — a process that requires substantial cell division — after minor surgery. They also show premature greying and hair loss, probably because they cannot maintain the populations of proliferative cells in their hair follicles. By the sixth generation, $mTR^{-/-}$ mice show structural changes in the lining of the gut that are intriguingly similar to those seen in normal aged mice[12]. These observations strengthen the argument that, in the gut, ageing is associated with a compromised ability to replace cells.

The premature onset of some features of old age is known as a segmental progeroid syndrome. An example is Werner's syndrome, a human premature-ageing disease[4]. The main biological feature of Werner's syndrome is accelerated cell senescence, and the disease has several features in common with the $mTR^{-/-}$ mice. In both cases, tissues that cannot divide are largely unaffected. However, the progeroid symptoms are not identical between the two diseases (Table 1), and it will be interesting to compare the $mTR^{-/-}$ mice with those carrying a germline knockout of the mouse Werner gene[13].

Is there any way to slow the rate of ageing? The only intervention that seems to work reliably in a range of species is calorie restriction. There is evidence that calorie-restricted mice (the human equivalent would be less than 1,500 calories per day) have fewer senescent cells in their tissues[14]. It would be interesting to see whether the onset of progeroid features in the $mTR^{-/-}$ mice could be delayed by calorie restriction. Whatever the outcome, $mTR^{-/-}$ mice are sure to be a powerful tool for analysing the effects of compromised cell replacement on mammalian ageing. □

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**High-temperature superconductivity**

# Research enters a new phase

**A. J. Millis**

"The only difference between the rich and other people is that the rich have more money", Molly Colum once remarked to Ernest Hemingway. Is the only difference between cuprate (copper-oxide) superconductors and conventional materials the high value of the superconducting transition temperature $T_c$, or do they exhibit fundamentally new physics? The work of Corson and collaborators reported on page 221 of this issue[1] opens a new experimental window onto this fascinating issue, by showing that it is possible to measure the short-time phase-coherence properties of high-$T_c$ materials.

The technical achievements of this paper are remarkable. Corson and collaborators have measured the frequency-dependent conductivity, which relates the alternating currents flowing in the superconductor to an applied alternating electric field. They have obtained data in the frequency range of 100–600 GHz, which has hitherto been difficult to access because it is uncomfortably high for conventional microwave measurements and uncomfortably low for conventional optical experiments. Corson *et al.*[1] have developed the coherent time-domain spectroscopy technique pioneered by the groups of Auston and Grischkowsky[2] into a powerful tool for probing this interesting but inconvenient frequency range. In this technique the conductivity is determined from the way in which an electric field pulse is distorted as it propagates through a material. High quality thin-film samples are also essential, and these have recently become available following the success of Eckstein and Bozovic at using the molecular beam epitaxy techniques, familiar from semiconductor processing, to grow transition metal oxides[3].

The binding of electrons into 'Cooper pairs' causes superconductivity. This binding opens the familiar 'Bardeen, Cooper and Schrieffer' gap in the electron energy spectrum, but the fundamental manifestations of the superconducting state — namely zero resistance and expulsion of magnetic fields — require in addition that Cooper pairs separated by macroscopic distances have the same quantum-mechanical phase. The strength of this long-range phase coherence is usually described by a 'phase stiffness' $\rho_s$, which measures the rigidity of the superconducting state in the same way that the shear modulus measures the rigidity of a solid. If $\rho_s = 0$ the material is not superconducting. The current carried by Cooper pairs is proportional to the gradient of the Cooper pair phase, and so the phase stiffness may be extracted from a conductivity measurement.

In two-dimensional superconductors one may have Cooper pairing without long-range phase coherence. Above a Kosterlitz–Thouless temperature $T_{KT}$, related to the phase stiffness by $T_{KT} = 8\rho_s/\pi$, long-range phase coherence is destroyed by the presence of vortices (singularities in the phase field corresponding to circulating current patterns). For temperatures only slightly greater than $T_{KT}$, the material retains phase coherence on short length and time scales, but as $T$ is further increased no trace of phase coherence remains.

This behaviour was essentially observed by Corson *et al.*[1] (Fig. 1). Although their work will undoubtedly stimulate much interesting

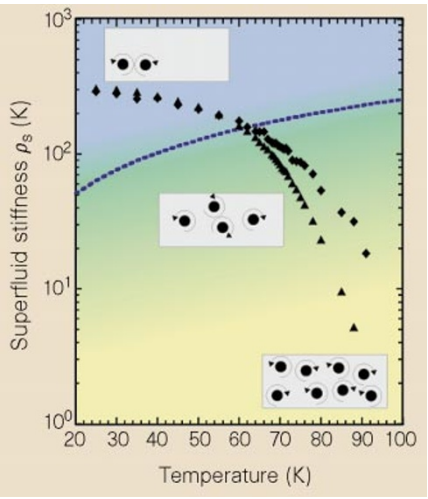


Figure 1 **Phase stiffness $\rho_s$ as a function of temperature at frequencies of 100 GHz (triangles) and 600 GHz (diamonds) as determined by Corson *et al.*[1]. Dotted line follows the Kosterlitz–Thouless temperature $T_{KT}$ as a function of phase stiffness. The Kosterlitz– Thouless superconducting transition is predicted to occur when $\rho_s$ intersects this line. Insets show behaviour of vortices in the superfluid phase field. At low temperatures, any vortices present are tightly bound in pairs of opposite circulation, so the phase stiffness is large and frequency independent. At $T \approx T_{KT}$ a few unbound vortices are present and $\rho_s$ is non-vanishing at high frequency (short-length scales) but vanishing at low frequency (long-length scales). At $T \gg T_{KT}$, a proliferation of vortices causes $\rho_s$ to vanish at all scales.**