

NEWS

ceived through a non-visual system. This requires further confirmation, as mammals do not possess an ability to perceive extraoptic light signals⁴.

P. Subramanian (Annamalai Univ., Annamalainagar) presented data on the circadian patterns of expression of *per* in *Cry^b* and *vg* mutants of *Drosophila melanogaster*. He reported expression of *per* in the salivary gland of 3rd instar larvae, suggesting the presence of peripheral oscillators during the developmental stages of *D. melanogaster*.

DST is playing a crucial role to increase scientific activities in the domain of chronobiology in our country. The PAC-approved five-year cycle of the SERC School in Chronobiology is currently on. DST, ICMR and CSIR supported this symposium.

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RESEARCH NEWS

Telomere shortening: A marker of atherosclerosis?

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Telomeres are nucleoprotein complexes at the ends of chromosomes, consisting of tandem arrays of TTAGGG nucleotide repeats¹ (Figure 1). They are essential for chromosomal stability and for preventing degradation and abnormal chromosomal recombinations. Telomeres are considered as a replicometer, which counts cell divisions and ultimately triggers replicative senescence, and they act as cellular 'sentinels' for genomic damage (Box 1). The fact that telomeres trigger replicative senescence has been supported by three observations. First, telomeres shorten with each population doubling in primary human cell cultures, but stop shortening in non-dividing cells². Second, immortal cells, whether single-cell organisms, germ line cells or tumour cells express in their vast majority active telomerase, the enzyme that binds to the single-stranded 3' end of the telomere and re-elongate it³. Third, human fibroblasts, which display telomere shortening and senescence, can be immortalized solely by transfection with the catalytic subunit of human telomerase, hTERT; this transfection results in the restoration of functional telomerase and elongation of telomeres⁴. *In utero*, telomere length is similar in most tissues⁵ but during extrauterine life, telomeres progressively shorten in proliferative somatic cells and their length diminishes with age. Based on studies in twins, telomere length seems to be famil-

ial^{6,7} and recently, its mode of inheritance has been described to be X-linked⁸.

Recent studies propose that telomere shortening is a marker of biological ageing

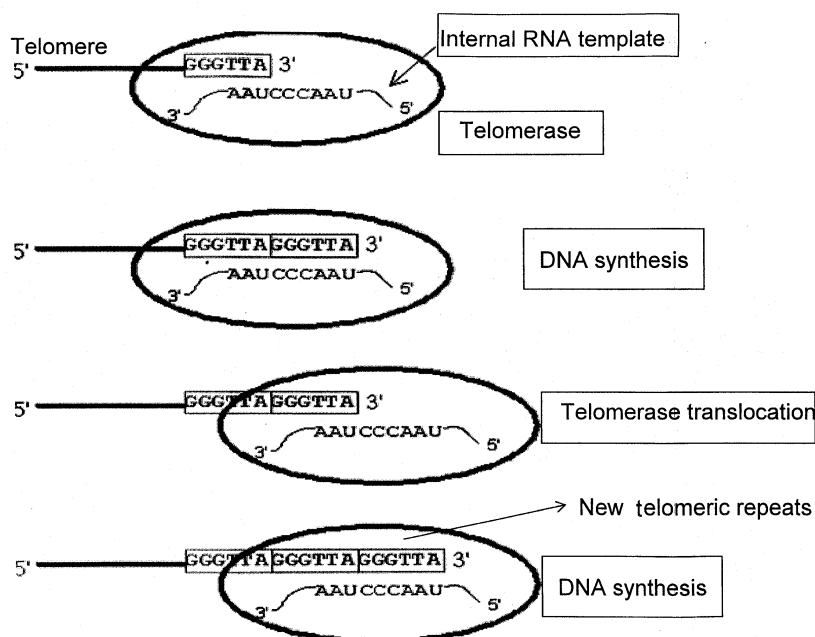


Figure 1. Telomere in a human chromosome is composed of the tandem repeat sequence TTAGGG. The telomerase contains an essential RNA component which is complementary to the telomere repeat sequence. Therefore, the internal RNA can serve as the template for synthesizing DNA. Through telomerase translocation, a telomere may be extended by many repeats. This protects the genome from the potential loss of information. In the absence of telomerase, the telomere will become shorter after each cell division. When it reaches a certain length, the cell may cease to divide and die. The successive shortening of the chromosomal telomeres with each cell cycle is also believed to influence the vitality of the cell, thus contributing to premature cellular senescence in various cell types.

Box 1. Telomeres

Telomeres are snippets of DNA at the ends of chromosomes that function in part like the plastic tips on the ends of shoelaces, preventing chromosomal fusions and offering genomic integrity and stability. Apart from ensuring chromosome stability, telomeres also provide a mechanism for 'counting' cell divisions, and thus signal replicative senescence. Since DNA polymerase requires a labile primer to initiate unidirectional 5'–3' synthesis, some bases at the 3' end of each template strand are not copied unless special mechanisms bypass this telomere 'end-replication' problem. Immortal eukaryotic cells, including transformed human cells, apparently use telomerase, an enzyme that elongates telomeres, to overcome incomplete end-replication. However, telomerase has not been detected in most normal somatic cells, and these cells lose telomeres with age.

Box 2. A long story on short telomeres

- In 1961, Leonard Hayflick reported that human cells in culture divide a certain number of times, reaching a maximum 'Hayflick limit'.
- In 1972, James Watson described the 'lagging strand problem' (end-replication problem), which predicts telomere shortening with each division.
- In 1972, Alexy Olovnikov connected Hayflick's and Watson's ideas and proposed that each DNA replication depletes telomere material to a point that signals the cell to stop dividing and attain cellular senescence.
- In 1987, Blackburn and Greider named the enzyme 'telomerase' – a reverse transcriptase that elongates the telomeres.
- In 1990, scientists identified the six-base sequence (TTAGGG) repeats in human telomeres – which become a yardstick to measure telomeres in 'telomere restriction fragment' assay.
- During the 1990s, cancer cells were shown to ignore the 'Hayflick limit' by having long telomeres and active telomerase. In addition, transfecting telomerase genes into cultured human cells gave them an unlimited capacity for cell division. In contrast, telomeres in most somatic cells in multicellular organisms, including humans, shorten with each cell division and they lack telomerase or telomerase is undetectable in those cells.
- In 1995, Chang and Harley observed short telomeres as a marker of accelerated aging in cells forming blood-vessel inner linings. Subsequent studies to-date strongly support that telomere length might be useful in predicting the onset of atherosclerosis and other cardiovascular diseases.
- Recent research¹⁹ suggests that the relationship between telomere length and cell/organism longevity is strong. Worms/birds with longer telomeres have been shown to have long lifespan.

and atherosclerosis, and that individuals with shorter telomeres than might be expected based on their chronological age, are prone to various diseases. Alterations in cellular turnover of cardiovascular tissue contribute to the many factors leading to cardiovascular diseases, and none of the conventional biomarkers directly measures them. In this context, recent investigations have demonstrated the potential of employing telomere length measurements (expressed in terms of mean telomere restriction fragment (TRF) length) as a marker of replicative history and future replicative capacity of normal somatic cells². It is likely that not only the loss of replicative capacity, but also the alteration in gene expression seen in senescent cells contributes to age-related cardiovascular disease. If senescent endothelial cells accumulate at focal sites of high cell turnover, then their reduced

ability to divide and form a continuous monolayer will expose the underlying media to blood-derived mitogenic and adhesive factors, which would contribute to the formation of the expanded intimal morphology characteristic of an atherosclerotic plaque⁹.

TRF length was shorter in patients with atherosclerotic heart disease than in age-matched controls¹⁰. It is also demonstrated that telomere shortening could be involved in the development of atherosclerotic disease in patients with metabolic diseases such as hypercholesterolemia and diabetes mellitus¹¹. Shortened telomere length was also observed in white blood cells of patients with Type 1 diabetes¹² and Type 2 diabetes¹³.

It appears that there are common molecular mechanisms accounting for atherosclerosis in which expressions of genes related to glucose metabolism, lipid meta-

bolism and vascular function are altered. Oxidative stress could be one such common mechanism¹⁴ underlying insulin resistance, diabetes and cardiovascular disease. Telomeres are less efficient in single-strand break repair than the bulk of the genomic DNA¹⁵ and oxidative stress accelerates telomere loss, whereas antioxidants decelerate it¹⁶. In fact, telomeres, as triple-G-containing structures, are highly sensitive to damage by oxidative stress¹⁷. It will be interesting to know the causal relationship between the molecular mechanisms underlying the metabolic/cardiovascular diseases and telomere shortening.

Interestingly, several studies^{6,8,13} indicate that age-adjusted telomere length is longer in women than in men. Independent of age and mean arterial pressure, arterial stiffness and pulse pressure were also inversely correlated with TRF length in men¹⁸. Such enigmatic findings suggest that the biology of aging differs between men and women and warrant further investigations.

Accelerated telomere shortening appears to be related to 'lifestyle diseases' that accompany certain concomitant metabolic factors such as obesity, hypernutrition and lack of exercise. Will this accelerated telomere shortening be prevented by tight control of blood glucose, pressure and lipids and/or by caloric restriction and antioxidant supplementation? The answer heavily relies upon advancing telomere biology research (Box 2). Given that aging is a multifactorial and highly variable entity and that biological aging (premature cellular senescence) may alter functional status of several tissues, the use of telomere length provides a new dimension to the study of metabolic and cardiovascular diseases with special reference to atherosclerosis.

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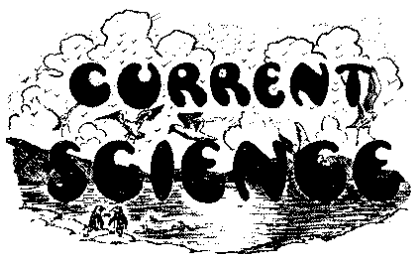
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FROM THE ARCHIVES



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Future citizens

Compulsory education for a population of thirty crores is the gigantic enterprise framed by the Sargent Scheme, short name of the plan for post-war Indian educational development laid by the Central Advisory Board of Education, whose report thereon was released last March. It will not be an exaggeration to say that if this plan can be made operative, the result will be a New India, fitted to assume the burden of world responsibility to which she is entitled by history, numbers, natural resources and the genius of her people. The difficulties of accomplishment are great, and the effort demanded by their solution enormous: but they must be surmounted if India is to take her proper place among cultivated and progressive nations.

A bare outline of the plan will facilitate its consideration. Pre-primary, con-

veniently called nursery education, will begin at age 3 and remain voluntary until 6, at which the compulsory system begins with junior basic (primary) school until age 11 followed by senior basic (middle) school until 14. Dovetailed with basic will be the high school whose course should cover 6 years, normally beginning at age 11 for only those pupils who show promise of benefiting fully by the opportunities provided; and preparation being made for at least one child in every five of the appropriate age-group. There follows the university, conditions of admission to which will be adapted to ensuring entrants' capability of profiting by the classes. It is contemplated that ultimately the intermediate course will be merged in high school, when the minimum degree course will be 3 years; meanwhile, only the first year will be transferred to high school, the second year being taken at the university. Finally, provision is made for technical, commercial and art education, for adult education and for training of teachers...

From the foregoing it follows that the age-limits of compulsions will be 6 and 14. This period of education without any charge to the parents is considered sufficient to equip the pupils for citizenship provided the training of character proceeds conjointly with training of intellect at every stage. There is great scope for improvement in both fields. An overall

illiteracy of 85 per cent is a ragged garment for democracy, and would bode ill for this country if that form of government is finally adopted. Citizenship has been usefully defined as an activity of the personality to secure certain benefits for the community to which the citizen belongs, and its proper exercise involves such qualities of character as consideration for others, commonsense and self-discipline. That these are sadly lacking is apparent in many little ways, notably the misuse of roads, where animals wander and children play while bicycles dart here and there regardless of rules; and controllers of the slowest traffic have no compunction in occupying the middle. It is noteworthy that in Travancore, with an overall 45 percentage of literacy (56 for men; 34 for women), these abuses are not observable...

Thomas Jefferson, who wrote (1776) the declaration of American Independence, also wrote (1786): 'I think by far the most important bill in the whole code is that for the diffusion of knowledge among the people. No other sure foundation can be devised for the preservation of freedom and happiness.' Lovers of this country, whether Indian or British, will devoutly hope that these brave words may find fulfilment in the Sargent Scheme.

M.O.F.