Organ system	Cells expressing telomerase	Defect in dyskeratosis congenita
Hair	Hair follicle	Alopecia
Oral cavity	Squamous epithelium	Leukoplakia (precancerous oral lesions)
Skin	Basal layer of epidermis	Abnormal pigmentation Nail dystrophy
Lungs	Type 2 alveolar epithelial cells	Fibrosis
Liver	?	Cirrhosis
Intestine	Intestinal crypts	Gut disorders
Testes	Spermatogonia	Hypogonadism
Bone marrow	Progenitor stem cells	Failure to produce blood cells

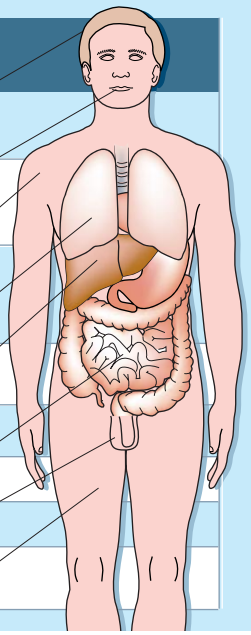

Figure 1 **Characteristics of the human disease dyskeratosis congenita. Defects are seen most often in tissues in which cells divide rapidly and often. Many of these cells express telomerase, an enzyme that maintains telomeres (the ends of chromosomes), and Vulliamy *et al.*[3] have shown that one form of dyskeratosis congenita can be caused by mutations in the gene that encodes the RNA component of telomerase.**

it needs to replicate its DNA. But, because of the directional nature of DNA synthesis, the telomeres that cap the ends of linear chromosomes are incompletely replicated, and are eroded a little with each cell division. Certain mechanisms can compensate for this loss — for example, telomerase adds sequence back to chromosome ends.

Not all cells express telomerase, however. For instance, human fibroblasts do not, and have a finite ability to replicate in culture. This phenomenon, termed replicative senescence, is caused by progressive telomere shortening[4]. The importance of this process to the ageing of whole organisms has been unclear, but it was first tested in mice by disrupting the gene that encodes the RNA part of telomerase, creating animals with undetectable telomerase activity[5]. Early generations of these mice developed without significant abnormalities; defects were seen only in later generations, mostly in highly proliferative tissues[6,7], in which the erosion of telomeres is expected to be more severe.

If dyskeratosis congenita indeed results from telomerase deficiency, one would expect that people with this disease and the late-generation telomerase-deficient mice would have similar defects. This has proved correct — both show abnormalities in the production of blood cells and in the gut, as well as poor wound healing. This is despite the fact that mice lacking telomerase RNA have no detectable telomerase activity, whereas people with the autosomal form of dyskeratosis congenita do — there is at most a partial loss of function. Moreover, the features of the X-linked form of dyskeratosis congenita are seen even in the first generation, although this could be because human telomeres are much shorter than those of laboratory mouse strains.

But do the symptoms of the mutant mice and of people with dyskeratosis congenita shed any light on the involvement of telomere shortening in human ageing? These mice and the human patients have only a few features — such as premature greying of hair and higher incidence of cancer — that are also seen as humans age. If telomere loss during ageing is a key determinant of the age-related decline in tissue function, why aren't more stereotypical features of premature ageing seen? The answer may lie in the tissue-specific regulation of telomerase expression (Fig. 1).

Telomerase activity has been detected in precursor (progenitor) cells in tissues that have high rates of cell turnover, including those of the blood system and the intestinal crypts. By contrast, some tissues that have the capacity for cellular replacement, but do not undergo continuous cell turnover, do not express telomerase in their progenitors. It is these tissues — such as the deep layers of the skin or the lining of the blood vessels — that might be expected to suffer most from age-associated telomere depletion, as they have no ability to regenerate telomeres. These tissues would also be greatly affected by defects in other pathways that maintain telomeres, such as DNA-recombination processes. This might explain why Werner's syndrome, in which an enzyme involved in DNA processing is affected, yields a closer

100 YEARS AGO

Among the local *fêtes* of parts of the north of France the procession of giants forms the most original and picturesque custom. Each Flemish town formerly possessed its giant, but this curious custom preserves its ancient ceremonial in only a few localities. Lille has not seen for a long time the procession of the giant "Phinar", which was vilified as was its colleague "Annéen" at Valenciennes. The festivals of giants are still preserved at Dunkirk, where "Papa-Rœusse" is the idol of the inhabitants, at Cassel, at Gand, at Brussels, and especially at Douai, where every June "Gayant" has a triumphal procession accompanied by his wife, "Marie Cageon", and their three children, "Jacquot", "Fillon" and "Bimbin".
From *Nature* 26 September 1901.

50 YEARS AGO

In describing and assessing the results of artificial rain-making experiments, which attempt to induce precipitation by 'seeding' suitable clouds with pellets of dry ice, crystals of silver iodide or small water-droplets, Mr. Mason said that there has been a distinct tendency to draw spectacular conclusions on the basis of too few observations, and that too little attention has been paid to the need for adequate control experiments. However, many cases have been reported of rain falling from clouds a few minutes after seeding. Although in any particular case it is not possible to ascertain that this would not have happened without seeding, in many careful dry-ice experiments carried out in Australia… rain has been observed to fall from seeded cumulus clouds, while similar clouds in the immediate vicinity produced no precipitation. Since, for a high probability of success in the dry-ice experiments, the cloud top must be colder than − 7 °C. and rain is likely to fall naturally if it is colder than − 12 °C., there is only a narrow range of conditions in which seeding with dry ice can anticipate natural events. The position is still more unfavourable in the case of silver iodide, which suffers the additional disadvantage that it becomes inactive as an ice nucleus when exposed to strong sunlight for about one hour. Calculations indicate that spraying small water-droplets into the base of the cloud should be a more efficient method of releasing showers from warm cumuli, and the results of recent experiments in Australia are encouraging.
From *Nature* 29 September 1951.