I WANT TO LIVE FOREVER...

2B. CELLS AND CELL DIVISION

You are a researcher in the LifeSpan project. Like all of the other students in the class, you are conducting research on ageing. Your specific research is on the role played by cells and cell division in the ageing process. Ultimately you will be presenting your results to the rest of the class. The following assignments will help you to study the results, and to prepare your presentation.

Have fun!

Caspar Geraedts, Jennifer Verkleij & Yuri Matteman

De Praktijk

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Assignment 1. Telomeres

As we get older, we develop wrinkles. One of the reasons for this is that old skin cells are replaced less often the older we get. But what about the lifespan of cells? Do cells age too? And can cells continue to divide indefinitely?

1. There are huge differences in lifespan among the cells in your body. Your brain cells live roughly as long as you do, whereas your epidermal cells (those that form the top layer of skin) are constantly being replaced. Give another example of a cell type that the body is always producing.

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In 1978, a study appeared by biologist (and later Nobel prize winner) Elizabeth Blackburn. She demonstrated that the two ends of a chromosome, or *telomeres*, contain dozens of repeats of one particular sequence of nitrogenous bases (in humans TTAGGG). Every time the cell divides, the telomeres become a little bit shorter. Why is this? You may know that during DNA replication, the two strands are pulled apart, and the enzyme *DNA polymerase* creates a new chain using individual nucleotides. However, DNA polymerase can only move along a DNA strand in one direction (from 3' to 5'). A short piece of RNA, or *primer*, is also required to 'kick-start' the DNA polymerase. After replication, this piece of RNA is deleted, making one of the DNA strands shorter than the other. This is referred to as the *end-replication problem*.

2. The figure below contains a schematic diagram of the end-replication problem. Label the following elements in the diagram: *cell*, *chromosome*, *telomere*, *DNA strand*, *DNA polymerase* and *RNA primer.*

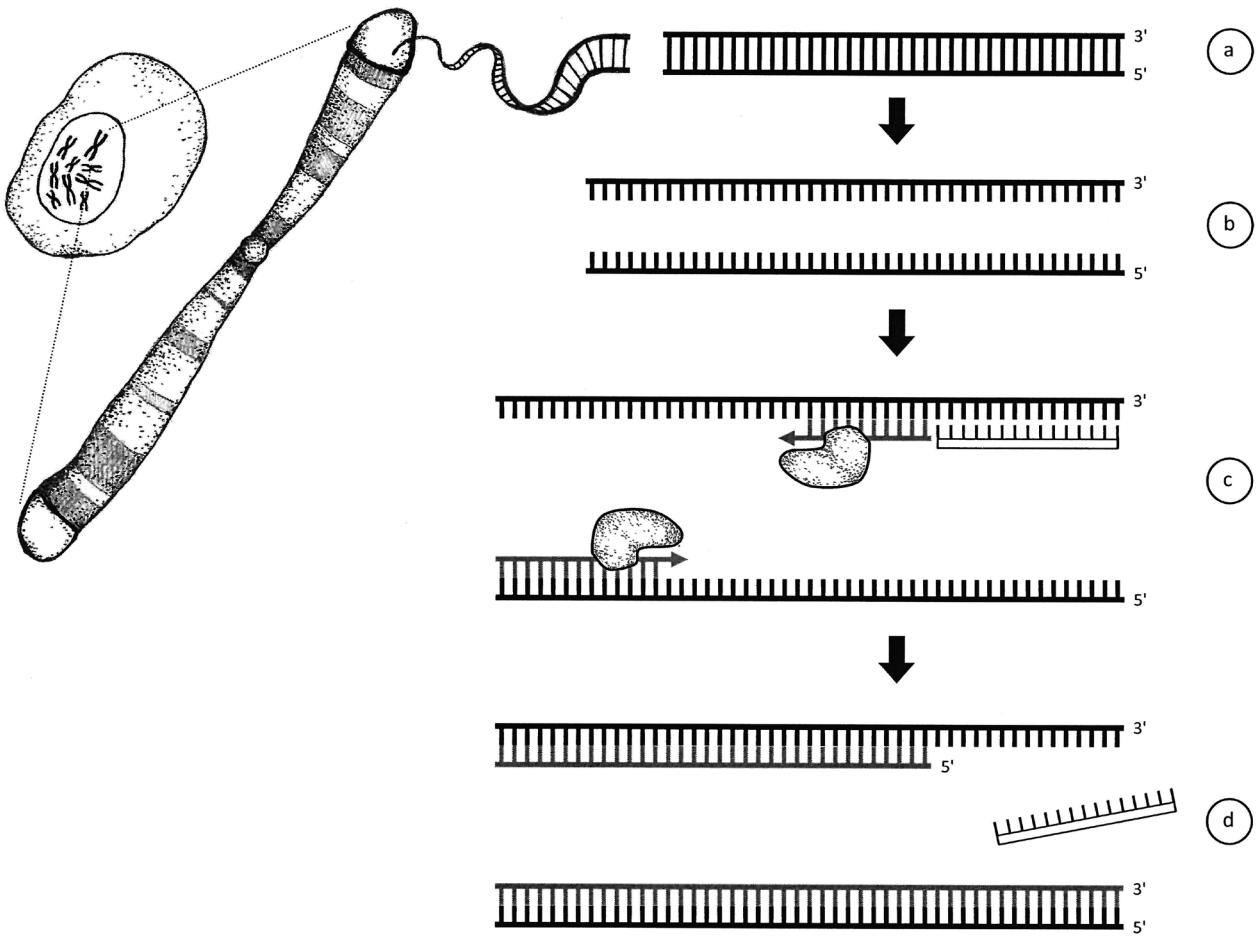

Figure 1. The end-replication problem. Diagram: C. Geraedts.

3. Telomeres become shorter every time the cell divides. After several dozen divisions, most human cells lose the capacity to divide any further. If cells were to continue to divide after the telomeres had disappeared completely, the functioning of the cell would be endangered. Explain why.

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The stem cells in our skin, however, continue to divide for our entire lifetime. How is that possible? Elizabeth Blackburn and her fellow researchers discovered that stem cells (and some other cells) that can continue to divide 'forever' contain an enzyme called *telomerase*. This enzyme maintains the length of the telomeres. Telomerase simply lengthens the ends of the chromosomes by adding repeats of the same sequence of bases as in the original DNA.

4. Four types of cells are listed below. For each type, state whether the cell will contain telomerase or not. Explain your answer.

single-celled organisms

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the cells in our salivary glands

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stem cells that produce sperm cells

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cancer cells

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Assignment 2. Free radicals

Wrinkles do not only appear due to cell division. The proteins that keep our skin strong and elastic (collagen and elastin) also become increasingly damaged as we get older. Why is this?

1. Watch the following video:
Daryl Shanley 1 – Trade-off between longevity and reproduction

In the video, Daryl Shanley mentions antioxidants. In order to understand what these molecules do, you first need to understand what free radicals are. You already know that in all cells, energy is extracted from glucose ($C_6H_{12}O_6$). This oxidisation process takes place in the mitochondria. In the electron transport chain, charged electrons and hydrogen ions (H^+) bond with oxygen (O_2), producing water (H_2O).

2. Complete the (net forward) chemical equation below so that it is correct.

$$C_6H_{12}O_6 + \ldots\ O_2 \longrightarrow \ldots\ \ldots\ldots + \ldots\ H_2O$$

Sometimes, *superoxide* (an oxygen radical) is produced instead of water in the electron transport chain. Superoxide is an oxygen molecule with an unpaired electron in its outer shell ($O_2^{\bullet -}$, the black dot stands for the unpaired electron). External factors such as UV radiation (present in sunlight) cause yet other types of *free radicals* to appear ($R^\bullet$). Free radicals are highly reactive, and can react with substances such as DNA, phospholipids and proteins. This process is called *oxidative stress*. To help prevent damage, cells contain *antioxidants*. See below for two examples of antioxidants and the reactions they produce.

superoxide dismutase (SOD)

$$2\ O_2^{\bullet -} + 2\ H^+ + SOD \longrightarrow H_2O_2 + O_2 + SOD$$

ascorbate ($AscH^-$)

$$R^\bullet + AscH^- \longrightarrow RH + Asc^{\bullet -}$$

[NB: Ascorbate is derived from Vitamin C]

3. One of these two reactions is sometimes referred to as a 'suicide reaction'. Which one do you think it is? Explain your answer.

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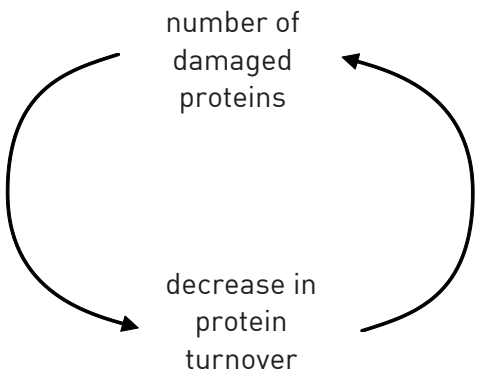
Daryl Shanley also mentions 'protein turnover': the replacement of damaged proteins. Of course, breaking down and repairing proteins in turn requires still more proteins. This results in a type of feedback loop. The more the proteins are damaged, the slower the process of protein turnover.

4. In the diagram below, indicate a positive or negative feedback loop using plus signs (+) and/or minus signs (-).



Assignment 3. Eat less, live longer?

Burning glucose produces free radicals. Are these free radicals related to ageing? During the 1980s, Roy Walford and Richard Weindruch carried out several studies in which they had mice follow a certain diet. The researchers were particularly interested in how the caloric content of the food would affect the lifespan of the mice. The table below summarises some of their research results.

Table 1. The effects of caloric restriction in mice. The diets listed began at the age of four months. From: Weindruch & Walford (1982).

no. of calories in diet	average lifespan
125 kcal/week *(the mice ate as much as they wanted)*	27 months
40 kcal/week	45 months

A diet containing fewer calories but still the necessary amounts of vitamins, minerals and protein therefore has a positive effect on average lifespan. The effects of *caloric restriction* (i.e. a considerable reduction in calorie intake) have since been demonstrated in other species.

1. Over time, various explanations have been offered for the effects of caloric restriction. Two are given below:

I. Less food is metabolised, producing fewer free radicals.

II. Cells produce more antioxidants, reducing the number of free radicals.

Recent research has shown that the level of oxidative stress does indeed drop as a result of caloric restriction. Tumour rates also decrease. Metabolic rates hardly change at all on a low-calorie diet. Which of the above explanations does this data support?

explanation I / II, because

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2. Think back to the game that you played – *I want to make babies!* Each turn, you received a number of energy points that you could divide between maintenance and reproduction. What do you suppose the influence of caloric restriction will be on the fertility and libido (sexual urge) of laboratory animals? Explain your answer.

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3. Of course, scientists are very keen to know whether caloric restriction also works in humans. For this reason, experiments began with rhesus monkeys in the 1980s. The initial results of this research were published in 2009. Why is it that this research took 20 years to produce relevant results?

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Assignment 4. The LifeSpan conference

At scientific conferences, researchers from a range of universities come together to share information and discuss research results. You are going to do this too. To conclude this assignment you will hold a kind of scientific conference, in which you will give a short presentation on the subjects you have studied thus far. You will also write a short proposal for further research.

The presentation will consist of three sections:

A. Telomeres

Use the diagram on page 10 to explain the following:
- what telomeres are,
- what the end-replication problem entails.

B. Oxidative stress

Use the diagram on page 11 to explain the following:
- what free radicals are,
- which mechanisms cells possess to counteract damage resulting from oxidative stress.

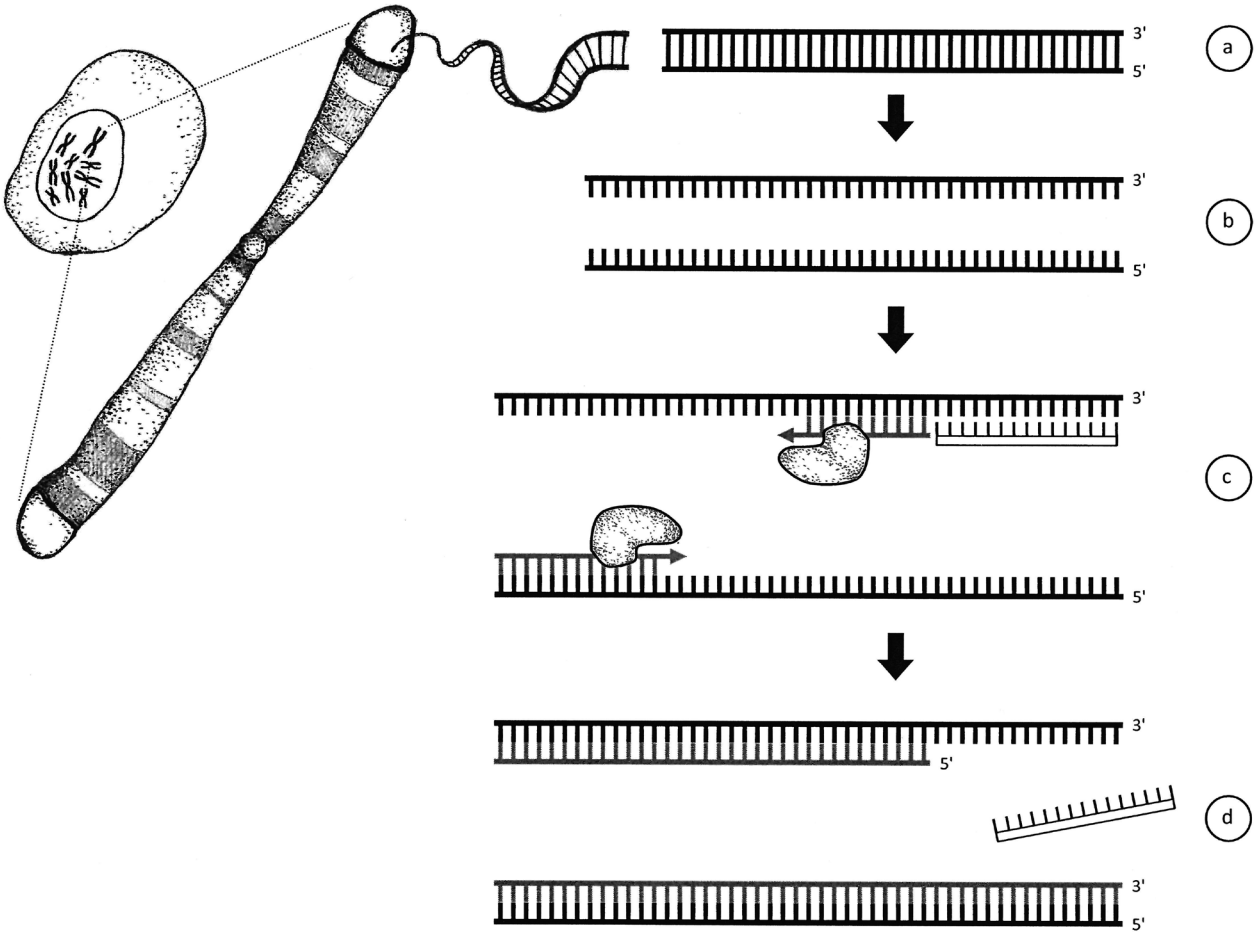
C. Proposal for further research

You wish to research the effects of caloric restriction on fertility and sexual urge among mice. Briefly describe the steps you will take to answer your research question (see the template on page 12).

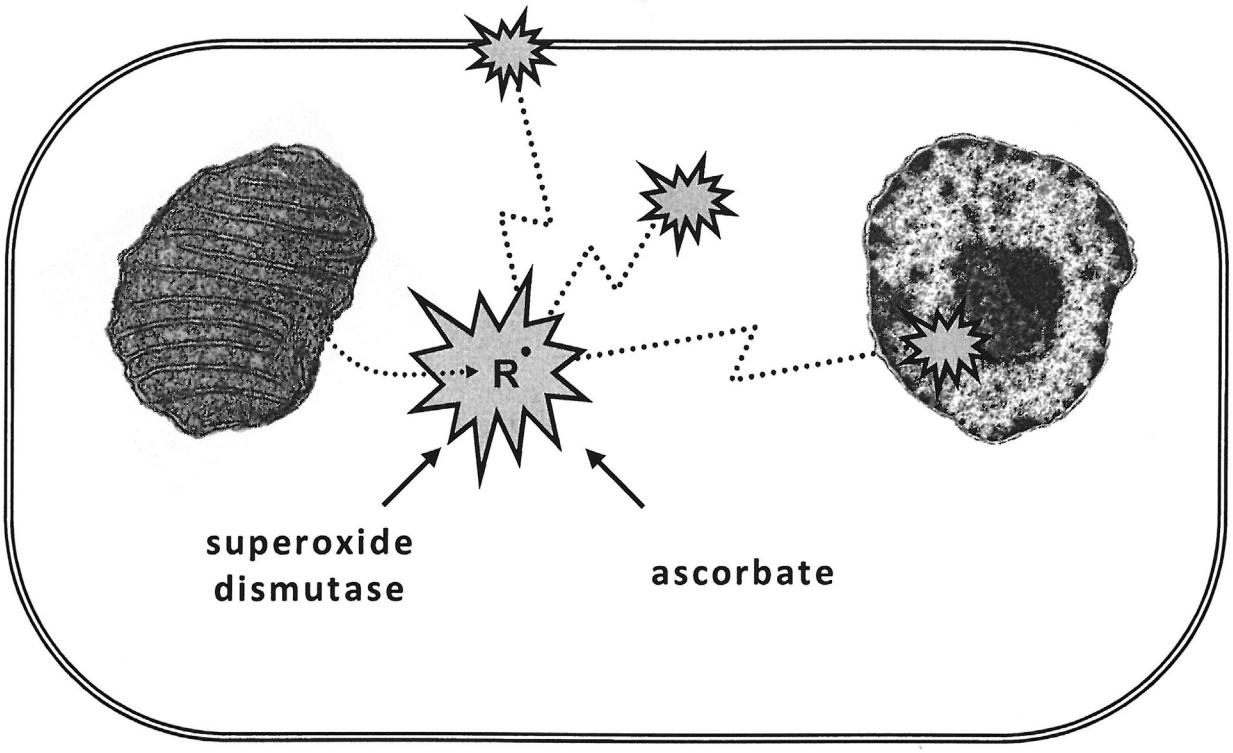
Preparation
PowerPoint slides have already been made for you, containing the images on pages 10 and 11. Use these copies to make your notes. Write your research proposal using the template on page 12. Make a rough copy first if necessary.

The conference
Using your PowerPoint slides, give a short presentation on what you have learned. You may refer to your notes if you wish. Also present your research proposal to the rest of the class. The teacher will determine whose turn it is.

A. Telomeres



B. Oxidative stress



C. Research proposal

Title of research project
Introduction (approx. 50 words)
Research question
Hypothesis
Research plan (including materials and methods)