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Can Biological Ageing be modulated?

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CAN BIOLOGICAL AGEING BE MODULATED?

The quest for immortality or at least extended youth is found already in the oldest written testimonies of human thinking. The epic of Sumerian king Gilgamesh (about 3 000 BC) tells about his quest to escape death. He finds a plant that renews youth but loses it to a serpent. Plants and herbs have then been used through history for such purposes – from the medieval universal medicines (theriacs) to a multitude of fancy food supplements and wonder drugs of today.

The biological ageing processes are, however, complex and not easy to influence by “pharmacological” means. During millions of years evolutionary forces have optimized the performance of human body in a hostile environment by allocating a substantial part of the available energy to growth in order to ensure survival during maturation as well as to the production and rearing of a maximum number of offspring. For repair of the body it was under these conditions necessary to invest energy enough to maintain it until the age of about 25 years to ensure the propagation of the following generations. The mean life expectancy was until about two centuries ago 30–35 years. Now, in the protected environment of the modern western societies many grow old but the capability to repair the body has not increased. The result is seen as the many manifestations of biological ageing.

The basis for these manifestations is a cascade of stochastic processes, in which destructive substances cause random damage to macromolecules, especially DNA. The most prominent of these substances are reactive oxygen species formed during the normal cellular metabolism. Although a substantial part of them is neutralized by protective enzyme systems (antioxidants) some escape and cause damage, which is partly repaired. The consequences of the remaining damage are propagated up through the hierarchical organization of the body from the macromolecules via cells and tissues to organs and organ systems and affect finally the homeostasis of the body. When the number of lesions in different organs reach certain levels declines of their physiological functions are observed. Manifestations of ageing and age-related diseases emerge gradually, which increase the vulnerability of the individual and thereby decrease the chances for survival.

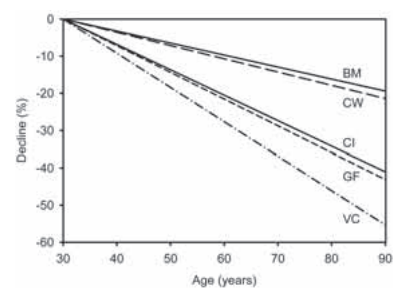
On the cellular level cells either die or continue to function normally, at least when analysing the basal (or resting) metabolic rate, which declines by about 20 percent from the age of 30 to that of 80 years (Fig. 1). The total intracellular water (a measure for the volume of cells in the body) declines at the same rate. This means that the total number of cells decreases with ageing but not their average metabolic activity.

The physiological functions of some key organs decline by up to about 30 to 40 percent (Fig. 1). These figures must, however, be treated with some caution, since they are derived from cross-sectional studies. This means that 80 year old and 30 year old people were investigated the same year, although they were born and grew up 50 years apart. The now 80 year old people grew up under less optimal living conditions and reached therefore lower peak values at the age of 30 years. If longitudinal studies (where the same people born the same year are investigated a number of times while they age) had been available for such a long span of years, they would have shown a somewhat less pronounced decline.

The ageing changes in the circulatory system are mixed with those that depend on different lifestyle factors, such as the level of physical activity, dietary habits, smoking. The slightly lower resting pulse rate is partly compensated for by a higher output with each heartbeat keeping the decline of cardiac output modest. The maximum performance, on the other hand, declines markedly due to the maximum pulse rate falling from 180 to 120 per minute. This combined with a diminishing muscle mass (see below) limits the capacity for strenuous physical activity. Lifelong physical exercise counteracts these declines and good fitness during adolescence and young adulthood means that the ageing changes begin from a higher performance level.

The changes in the respiratory system consist of stiffening of the thorax and weakening of the respiratory muscles, while the tissues of the lungs lose elasticity and undergo structural changes resulting in declining vital capacity and other physiological measures. As the “work” required for breathing thus increases strenuous exercise becomes more difficult while sedentary daily

Figure 1: Age changes in basal metabolic rate (BM), amount of intracellular water (CW), cardiac index (CI), glomerular filtration (GF) and vital capacity (VC). The value at the age of 30 years is set to 100 %. Regression lines were calculated using data from Shock NW, 1962.



living is not affected. Regular physical exercise slows down and inhaling various air pollutants accelerates the decline of pulmonary function.

Also age changes in the musculoskeletal system are slowed down by regular physical activity. The bone mass declines by about 10 percent per decade, which increases the risk, earlier in women than men because of their lower peak bone mass in young adulthood. The muscle mass declines likewise and half of it is lost at the age of 90 years but also at this age a significant part of the muscle mass and muscle power can be regained by training. Such training can enable the returning to independent living and diminish the risk of falls.

The normal ageing of the kidneys starts with such a reserve capacity that the daily living of the oldest old are not threatened, although the margin for handling extreme situations is small. Intravenous feeding can cause an overhydration that the kidneys no longer can handle. Likewise there is a risk for dehydration during heat waves.

Our knowledge of whether the normal ageing of the urinary system contributes to the urinary problems in the elderly is limited. The capacity of the urinary bladder decreases and its muscles lose some of their strength. Some urine is then left since the bladder will not be emptied completely. Also the muscles keeping the bladder closed weaken, which may cause the discharge of some urine when coughing.

The brain loses about 10 percent of its cells during adult life up to the age of 90 years but the loss is uneven when different regions are compared. Pronounced losses occur in parts of the hippocampus, a region important for memory. There is, however, neuronal plasticity, which means that surviving cells grow new branches that may re-establish some lost connections. This process is enhanced by mental stimulation and has been shown to take place up to the age of 85 years. While measurable declines take place in many organs from the age of about 30 years, changes cognitive functions (such as memory and perception) do not manifest themselves before the age of 60–65 years because of the large reserve capacity in young adulthood. Finally a stage, where the reserve capacity is no longer adequate, may be reached and symptoms like impaired memory, depression and confusion manifest themselves. Inter-individual differences increase by each decade and not all of the oldest old reach the limits of their reserve capacity.

Genetic factors play a significant role for the ageing processes although there is no "clock" that decides the lifespan. There seem to be slight variations with functional importance in a number of genes important for the ageing processes. An example is the ApoE gene, of which one variant predisposes for atherosclerosis and Alzheimer's disease while another one does not. Indirect evidence for the role of genetic factors comes from studies on monozygotic twins. One study showed that the surviving twin has an increased risk of premature death if the other one had died of myocardial infarction. Here, however, also lifestyle factors common for both twins could have played a role. It is well-known that lifestyle and environmental factors play key roles for modulating the ageing processes both in positive and negative directions.

All these factors – random damage and genetic variability as well as differences in lifestyle and environment – cause in interaction with each other an increasing diversity in the population when it ages. Not only individuals age at different speeds but there are also differences in the ageing of organs in the same individual.

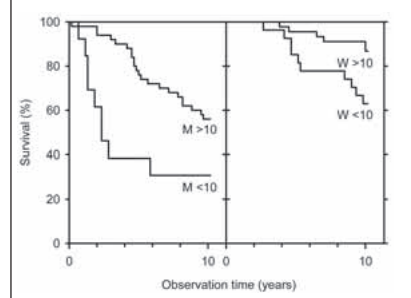
Regular physical exercise has – on population level – a pronounced effect of reducing mortality from coronary heart disease, type II diabetes and colon cancer. This effect is achieved in middle-aged men by physical activity equivalent to at least 20 km of brisk walking per week. For older men this effect seems to be achieved already by 10 km per week (Fig. 2). Fifty-six percent of physically active 60–69 year old Finnish men were alive after 10 years compared to only 30 percent of the less active ones. For women in the same age group the results were less impressive: 87 compared to 63 percent. To these benefits the above discussed positive effects the circulatory, pulmonary and musculoskeletal systems, which also enhance wellbeing, are added.

Sedentary habits and imprudent dietary habits predispose for overweight, which is a key factor for increasing the mortality from cardiovascular diseases, type II diabetes and several types of cancer. Gross obesity is also a risk factor for chronic kidney disease.

Perhaps even more important than the amount of food consumed is how the various ingredients are balanced. A high intake of red meat and dietary products rich in fat increase the risk for cardiovascular diseases, while the Mediterranean diet rich in unsaturated fatty acids has the opposite effect. Also regular consumption of small amounts of alcohol is beneficial. While some studies have linked this effect to ethanol itself, others have emphasized red wine, which contains substances with antioxidant properties. Red wine thus seems to prevent mortality from cardiovascular diseases more than enhancing cancer mortality. The "therapeutic margin" is, however, narrow, since alcohol-related liver diseases increase for men with the consumption is more than half a bottle of wine per day and a quarter of a bottle for women.

Dietary supplements have been used since Gilgamesh lost a plant that renews youth to a serpent. No positive effects have been shown for supplementing the diet with vitamins and minerals. None of the dietary supplements, for which the manufacturers claim more or less miraculous effects, have been tested in double-blind studies. Antioxidants may even be double-edged swords. Epidemiological

Figure 2: Survival of 60–69 year old men (M) and (W) over a 10 year observation period divided into those being physically active corresponding to more than (> 10) and less than (< 10) 10 km of brisk walking per week. Data from Heikkinen E et al., 1993.



logical studies have shown that diets naturally rich in antioxidants lower the incidence of cancers. Intake of beta-carotene (an antioxidant) in pills, on the other hand, has been shown to increase the risk for lung cancer in smokers. This suggests that the benefit of antioxidants is derived from a complex interaction between several of them in a mix (mostly in vegetables) developed during the evolution of plants.

The natural progress of the biological ageing processes can thus be mitigated by lifelong physical exercise, a prudent diet and avoidance of overweight – not by magic.

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