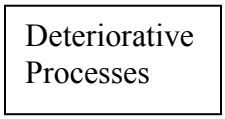
Mechanisms of Biological Aging – Four Concepts

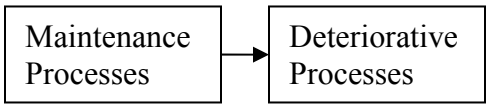
This section summarizes four concepts regarding the mechanisms that cause biological aging in humans and most other mammals. All of these concepts are based on the existence of deteriorative processes and each successive concept incorporates and is built upon the previous concept and is consequently more complex. Successive concepts provide progressively better fit to empirical evidence and additionally suggest more points at which intervention could be attempted.

1. Simple Deterioration



Premise: Aging is simply the result of accumulative deteriorative processes such as oxidation, telomere shortening, other molecular damage, wear and tear, and disease-specific processes such as accumulation of cell mutations (cancer), or accumulation of blood vessel deposits. Potentially many deteriorative processes are involved although some theorists believe one or another such as oxidation or telomere shortening dominates.
Empirical Evidence: There is wide agreement that deteriorative processes exist and cause gradual deterioration in inorganic and organic systems. However, the simple deterioration concept provides a poor fit to empirical evidence. In particular, it does not explain the very large differences in life spans observed between very similar species that presumably have very similar exposure to generic deteriorative processes.
Intervention: Agents such as anti-oxidants could be sought that directly interfere with a deteriorative process. It is common practice to seek agents that interfere with disease-specific deteriorative processes such as anti-cholesterol medications.

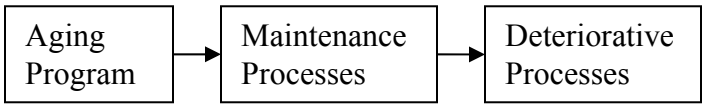
2. Maintenance and Repair



Premise: Deteriorative processes exist but are countered and offset by maintenance and repair processes whose effectiveness varies between species. The existence of these processes, corresponding to the respective deteriorating processes, slows accumulation of the deteriorating effect.

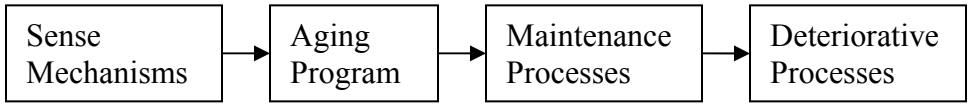
Empirical Evidence: This concept fits *gradual* aging and the multi-species life span variation. Additionally, it is known that various maintenance processes exist: hair grows, wounds heal, dead and damaged cells are replaced, infections are combated.
Intervention: In addition to the above, agents could be sought that increase the effectiveness of the maintenance processes, e.g. increase production of naturally occurring anti-oxidants or telomere repair enzymes.

3. Programmed Aging



Premise: Deteriorative processes exist and are offset by maintenance processes but the maintenance processes are in turn modulated (attenuated) by a species-specific genetically specified biological program to result in the observed species-specific life spans. The program involves some sort of biological clock or method for determining when to slow the maintenance functions. The program and clock could be common to multiple maintenance processes suggesting that signaling is involved.
Empirical Evidence: In addition to fitting the multi-species life span observations, this concept fits discoveries of genes that cause aging in various species. It also fits observations of species that die suddenly or age very rapidly at some point in their lives (e.g. salmon) in that a program calling for that behavior is easily visualized whereas the gradual accumulation of un-repaired damage postulated in concept 2 has difficulty. Further, this concept fits observation of genetic diseases that simultaneously cause acceleration of many (progeria) or most (Werner syndrome) symptoms of aging as these conditions could be affecting a common program.
Intervention: In addition to all of the foregoing, agents could be sought that interfere with the operation of the clock or interfere with associated signaling.

4. Regulated Programmed Aging



Premise: Deteriorative processes exist and are offset by maintenance processes but the maintenance processes are in turn modulated by a genetically specified species-specific biological program, which in turn can be adjusted by sensing of external conditions.
Empirical Evidence: In addition to all of the above, this concept fits observations of explicit life span regulation in various organisms (Kenyon, et al). It also fits observations that life spans are *increased* by external conditions that would nominally be expected to *increase deterioration* such as caloric restriction or stress because

sensing of these conditions could be adjusting life spans. Known biological clocks are commonly adjusted by sensing of external conditions (e.g. mating seasons and circadian rhythms are synchronized to planetary cycles).
Intervention: In addition to all of the above, agents could be sought that interfere with sense functions or associated signaling.

All of these aging mechanism concepts have **associated evolutionary rationales** that attempt to explain why the particular mechanism should have evolved or been retained in the designs of the possessing organisms. The evolutionary arguments involve **evolutionary value-of-life concepts** that attempt to explain why evolution would select more effective or less effective maintenance mechanisms (concept 2) or even select mechanisms that purposely limit (concept 3) or regulate (concept 4) organism life span. Concept 4 requires substantially the same evolutionary assumptions as concept 3 but provides a better match to empirical evidence.

Since all four concepts involve deteriorative processes, research into direct intervention (concept 1) is the least controversial. However, ignoring the other concepts is likely to result in missing major opportunities for successful intervention in aging processes and consequent treatments for age-related diseases and conditions.