Historical and Current Concepts of the Mechanisms of Aging

The concepts concerning the mechanisms of aging changed with the evolution of epistemology. There has been a tendency to look for universal causes, although aging does not evolve identically in living organisms. In some organisms, it is a rapid and spectacular process such as in the opossum, some marsupials and the salmon; it can be slow and progressive as in the elephant and humans, or negligible such as in lobsters, turtles, and some fishes.

In spite of these differences between the phenomenon of senescence across species and the obvious contrasts in all respects between organisms (metabolic, genetic, histological, divergence in million of years, etc.), gerontologists have been unrepentant in extrapolation from one organism to another and in the goal of reaching universal explanations. Rodents are the laboratory animals used mostly in gerontology, however, as will be described herein, there are some fundamental differences (e.g., genetic) when compared with other mammals in particular humans. The divergence of rodents to modern-day man is of more than 100 million years (Lavery 2000), that between phyla of course even greater.

The average number of heartbeats for instance during a human life span of 70 years is about 2.57×10^9; during the mouse and the rat life spans, it is 1.10×10^9 and 0.68×10^9, respectively. Some isolated attempts have been made to measure comparability (Beier 1994), but these have been voices preaching in the desert. Questionable statistical tests have also been used to correlate interspecies phenomena. Several papers use correlation coefficients with few data points leading to misleading significance (Le Bourg 1996).

This does not mean that studies performed on lower organisms along the evolutionary scale are useless in understanding human aging. Some mechanisms maybe conserved, but as an organism becomes more complex other regulations come into the picture, and as a result, the homeostatic control of life span also increases in complexity.

Moreover, along the evolutionary road, some mechanisms have remained preponderant in some species, while becoming secondary in others. It is obvious that the mechanisms controlling the life span of Drosophila, for instance, where there is no cell turnover in the mature organism, cannot be the same as those in a mammal, where permanent renewal occurs throughout the life span in many cell compartments.

Another difference concerns the information stored in the genome; at the last estimate the human genome may have anywhere between 26,000 to 90,000

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genes, that of *D. melanogaster* about 15,000, and *C. elegans* 19,000. There are other levels of information in the genome besides the expressed genes that contribute to species differences.

There is still today a tendency to look for a main cause that would explain it all, triggering a cascade of events leading to senescence. This is apparent in reviews where the main theories proposed a mechanism for the aging of metazoans. A theory that was very popular, the protein error theory, obeyed this criterion (Orgel 1963). It focused on a concept common to several cultures, that the human organism is basically perfect, but perishes because of errors committed. The wish to find errors was so ingrained that any observed change in proteins was considered as proof of the production of errors during protein synthesis (Holliday and Tarrant 1972). However, none of the numerous experimental attempts to test for the presence of proteins with errors could provide any support to the theory.

It seems that more than 300 theories have been proposed, each one was supposed to explain the mechanism of aging; we will mention the main theories showing how experimental studies led to the conclusion that they overlap. There is some truth in each of them, but of course none can explain it all. The function of the organism has to be seen as the result of multiple interactions, attempts to isolate a phenomenon in the organism inevitably distorts the picture and gives an erroneous view.

1.1 Rate of Living

One of the main theories proposed during the first half of the last century was the rate of living theory of Pearle (1928). It claimed that the duration of life varies in inverse proportion to the rate of energy expenditure because of a finite total amount of "vitality" being used up. In other words, senescence would be the result of the exhaustion of that "vitality".

This view was given a more scientific basis in the second half of the century by Selye (1970) who proposed that the organism is endowed with a given amount of adaptive energy that is progressively consumed by events that he called stress, which trigger the discharge of hormones. Aging would reflect the sum of all the stresses and of the adaptive compensatory reaction of the organism, which have acted upon the body during a life span. Selye was able to induce a progeria-like syndrome in rats using dihydrotachisterol, and to prevent it using spironolactone, which he termed a catatoxic hormone, i.e., capable of canceling the toxic effect of other hormones.

Selye's concepts are rarely cited; we believe, however, that they will be revived. It is unquestionable that stress can accelerate aging, not only through the triggering of diseases, but also by hastening changes at the molecular and cellular levels that lead to senescence. An interesting study showed that arterial smooth muscle cells from animals whose lateral hypothalamus was stimulated electrically grow faster when explanted in vitro than those of the control

donors (Gutstein et al. 1991). This work demonstrates the repercussions of a broad reaction in the organism at the tissue, cellular, and molecular levels with implications for atherogenesis. It is also representative of the influence external events can have on the proliferative history of a cell compartment, an important aspect of aging of the organism.

Many functions of the organism such as DNA repair (Niedermüller 1995) and defense mechanisms (Fietta et al. 1994) are maintained during aging under normal conditions, but fail under stress. It was, for instance, shown that a chronic stressor (caregiving for a spouse with a progressive dementia) alters the immune response to influenza virus vaccination in older adults (Kieckolt-Glaser et al. 1996). The effect of stress on morbidity is well documented. In addition to or because of its accelerating effect on senescence, stress plays a role in mortality, which becomes increasingly significant with aging, since the amplitude of the insult needed to kill diminishes as the organism ages (Fries 1984). The divergence between anabolic and catabolic metabolic processes becomes evident after stress situations; the aging brain is particularly at risk since the stress-induced demand for energy cannot be sufficiently met (Hoyer 1995).

This idea of aging as the result of inevitable events creating changes in the organism that trigger a reaction with the goal of reestablishing normality has been made more comprehensive extending it to all modifications resulting from the mere functioning of the organism and to the inevitable damage suffered by the genome (Schächter 1998). It was called the compensatory adaptation theory of aging. "In an effort to survive, the organism reorganizes its metabolism to compensate for its deficiencies; aging would be the composite outcome of irreversible alterations and partially reversible compensations".

On the other hand, it has been proposed that small doses of stress might increase survival. This has been suggested as the explanation for the prolongation of life span through caloric restriction because of the moderate hyperadrenocorticism it induces (Masoro 1998). In other words, it would correspond to a hormesis effect of stress. The same type of explanation was proposed for the beneficial effect of radiation on the life span of flies (Sacher 1963), mice and guinea pigs (cited in Masoro 1998), and for elevated temperatures on survival of *C. elegans* (Lithgow et al. 1995). Other forms of small stresses that have increased longevity are chloroform, electric shock and cool water immersion (cited in Masoro 1998). Hormesis might be the new fad looming in the field of gerontology (Calabrese and Baldwin 2000). A problem difficult to solve is what is a small dose? This is something probably unsolvable in humans.

1.2 Endocrine Theory

Selye's stress theory is related to endocrine theories of aging. It was postulated that the normal aging program is timed by a clock located in the brain (Everitt 1980). The clock drives the aging program by mediation of the endocrines and

the autonomic nervous system, whose secretions (hormones and neurotransmitters) have aging actions on their target cells. Hormones (particularly corticosteroids, thyroxine and growth hormone) increase the rate of aging in the tissues. Long-term excessive production of hormones due to life events such as pregnancy, disease, or stress can accelerate aging by producing damage in tissues.

The mammalian organism has indeed a programmed clock-type behavior through its life span where hormones seem to play a significant role. Female mammals are endowed with a finite, nonrenewable reserve of dormant follicles, which are recruited to grow and synthesize estradiol. The somatic components of the follicle (granulosa, theca, endothelial cells, supporting connective tissue) are derived from the embryonic indifferent gonad that consists primarily of mesenchyme (Hirshfield 1991). Each element of the proliferative unit is endowed with a limited capacity for proliferation. After the germ cells invade the indifferent gonad, both they and the somatic cells undergo extensive hyperplasia. The germ cells are gradually separated from one another by the somatic cells; finally there is transformation of the mitotically active oogonia into quiescent oocytes and organization of the somatic cells into follicles, each follicle surrounded by its own membrane. The pregranulosa cells enter a period of quiescence and cell proliferation will resume only when the primordial follicle begins to grow; the length of time between this arrest (primordial follicle) and the resumption of meiosis (preovulatory follicle) is extremely variable, some follicles begin to grow as soon as they are formed, others only months or years afterwards. There are a variable number of follicles in various stages of maturation in each ovary. The human oocyte remains arrested in prophase I of meiosis until the time of ovulation, then meiosis progresses until the first meiotic division is completed, and the oocyte arrests at metaphase of the second meiotic division until fertilization occurs (Battaglia and Miller 1997).

Two opposing views are presently debated: one claiming that the exhaustion of the pool of ovarian follicles triggers the hypothalamic-pituitary changes that accompany menopause when a threshold number of follicles is reached; the other view proposes that age-related changes in the central nervous system are the driving force that initiates the menopausal transition. The truth is probably in between.

There is evidence suggesting that reduction of the number of follicles in the ovarian pool disrupts the equilibrium between the dormant and growing pool of follicles, causes alterations in the regularity of cycles, and compromises the feedback to the neuroendocrine axis (Wise et al. 1996). Hence, both the ovary and the brain are pacemakers and the decline of the reproductive organs is the result of their interaction.

The life span of follicles is also probably dependent on mechanisms intrinsic to its cell constituents. The cells surrounding the oocyte have a finite proliferative potential and apoptosis can be detected in granulosa cells during adult life (Vaskivuo et al. 2001).

Both in vivo and in vitro studies showed a link between estrogen and neural aging. Estrogen increases synaptic connectivity (Yankova et al. 2001), which has a protective effect on the onset of senile dementia, and can protect neurons in culture against amyloid-induced toxicity (Morrison and Hof 1997). On the other hand, independently of these ovary–brain interactions, oocytes undergo modifications with time that decrease their viability. It is well known that with maternal aging meiotic spindle assembly, upon which chromosome movement depends, becomes compromised leading to aneuploidy.

The clock-type evolution of the mammalian organism is accompanied by decreasing circulating hormone concentrations in three hormonal systems (Lamberts et al. 1997): estrogen (in menopause) and testosterone (in andropause); dehydroepiandrosterone and its sulfate (DHEA and DHEAS; in adrenopause); and the growth hormone/insulin-like growth factor I axis (GH/IGF-1; in somatopause).

The blood circulation levels of bioavailable testosterone, DHEAS, and of the GH/IGF-1 ratio show a highly negative correlation with age (Morley et al. 1997). The bioavailable testosterone and the GH/IGF-1 levels also showed a significant correlation with cognitive measurements and with physical tests such as balance and handgrip strength.

DHEA is a universal precursor for androgenic and estrogenic steroid formation in peripheral tissues, which contain a number of DHEA-metabolizing enzymes. In humans, the plasma levels of DHEA and DHEAS are at their highest level around the age 20–25 years and thereafter undergo a progressive age-related decline, reaching 10–20% of their maximal levels in the eighth decade (Schwartz et al. 1990). Attempts to use the precursor in the prevention of aging led to inconclusive results, which is not surprising since it attempts to correct just one element in a very complex phenomenon where a multitude of factors are implicated (Bellino et al. 1995).

The relative decrease in insulin secretion and increased peripheral insulin resistance is an important aspect of the aging syndrome responsible for the high frequency of impaired glucose tolerance. In rat hepatocytes the insulin resistance that develops during senescence is accompanied by an impairment of the glycosyl-phosphatidylinositol-dependent signaling system caused by a decrease in basal levels of this lipid, so that the insulin stimulatory effect on glucose incorporation into glycogen is reduced (Sanchez-Arias et al. 1993). There are other possible mechanisms of insulin resistance like the one regulated by the islet amyloid polypeptide (IAPP; Westermark and Johnson 1995). IAPP seems to have a counterregulatory modulating and balancing effect on insulin. Increased deposits of IAPP with age could be part of the mechanisms involved in insulin resistance.

The GH/IGF-1 axis is also implicated in the proliferative potential of somatic cells and is responsible, inter alia, for the general decline of the proliferative potential of several cell compartments. IGF-binding proteins seem to play a role in senescence of the prostatic epithelium (Lopez-Bermejo et al. 2000); moreover, cells such as adipocytes (Carrascosa et al. 1998), osteoblasts