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Review

Longevity and aging. Mechanisms and perspectives

Longévité et vieillissement. Mécanismes et perspectives

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ABSTRACT

Longevity can mostly be determined with relative accuracy from birth and death registers when available. Aging is a multifactorial process, much more difficult to quantitate. Every measurable physiological function declines with specific speeds over a wide range. The mechanisms involved are also different, genetic factors are of importance for longevity determinations. The best-known genes involved are the Sirtuins, active at the genetic and epigenetic level. Aging is multifactorial, not "coded" in the genome. There are, however, a number of well-studied physical and biological parameters involved in aging, which can be determined and quantitated. We shall try to identify parameters affecting longevity as well as aging and suggest some reasonable predictions for the future.

RÉSUMÉ

La longévité peut être déterminée avec une bonne précision si on dispose des registres de naissances. Quant au vieillissement, sa quantification est difficile, car il est multifactoriel et la vitesse de déclin des facteurs déterminants est très différente, certains sont rapides comme la perte d'élasticité, d'autres très lents comme la vitesse de passage de l'influx nerveux. Les mécanismes impliqués dans ces deux fonctions sont aussi très différents, la longévité est en partie (maximum 35 %) sous contrôle génétique, le vieillissement est post-génétique. Parmi les facteurs génétiques identifiés ce sont les Sirtuines qui ont été les plus étudiées, actives au niveau génétique et épigénétique. Plusieurs mécanismes impliqués dans le vieillissement ont été étudiés et leur rôle dans le déclin avec l'âge de l'organisme précisé. Certains des paramètres impliqués dans la longévité et dans le vieillissement seront analysés dans cette brève revue.

1. Introduction

Humanity, since the existence of written records, thrived for longevity, celebrated long-lived individuals. Examples can be found in the Bible, in inscriptions of ancient Egypt and even in older Sumerian tablets. Life expectancy was, however, low during millennia after the emergence of Homo sapiens. Even in 18th century France, less than 20% of women reached 65 years (Fig. 1). This proportion increased to over 90% at the end of the 20th century [1–3]. Similar trends were observed in most advanced countries also. In the 16th century, a famous French physician, Ambroise Paré (1510–1590) proposed four periods of life (Fig. 2), starting "old age" after 35 years. Life expectancy increased slowly over the centuries. Some exceptional individuals reached a respectable age as Ramses II in Egypt who lived to 91 years, Louis, the XIVth, in France reached 77 years. During the early periods of our times, women could reach about 30 years as shown by the famous Fayoum portraits painted for their burial [1–3].

A few years ago, centenarians became a celebrated subject of popular literature. Dr. Allard's book, from the IPSEN-Foundation [4] published in 2000, gathered and studied a number of French centenarians, among them Jeanne Calment, who reached 122 years, the oldest living person with certified date of birth. More recently age-related diseases, especially Alzheimer's disease (AD) and Parkinson's disease (PD) attracted the interest of scientists all over the world [4–8]. The aging process itself inspired a limited number of scientists who proposed interpretations for its mechanisms. One

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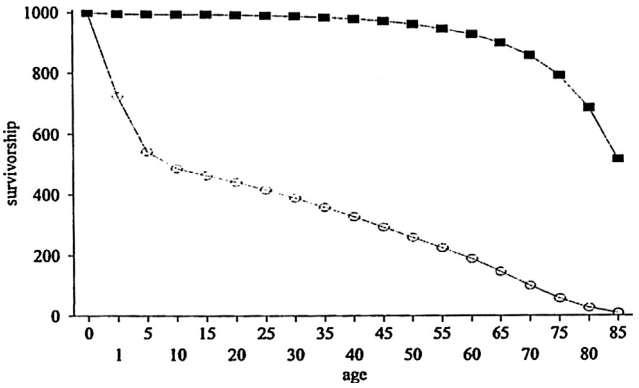

Fig. 1. Survival curves of women in France in the 18th century (1740–49) –0— and in the 20th century --■--.
Reproduced with permission from ref [2].

major difference between these two processes and concepts, longevity and aging, is the importance among longevity determinants of genetic factors. Aging, however, is not "coded in the genome", even if some of its aspects and mechanisms involve gene-related processes. The mechanisms of both of these concepts, longevity and aging, will be discussed, analyzing some specific aspects of both, without however attempting an exhaustive coverage of these subjects, such tentative could fill (and did) several books and encyclopedias [7,8].

2. Longevity

Average life expectancy and maximal longevity of human populations were and are recorded, available at several sources, among them the WHO. Aging, on the contrary, is more difficult to quantify, because it is multifactorial. Measurable physiological functions decline with different speeds as exemplified by Weale [9] by extrapolation of the decline of several physiological functions to zero value, reached at very different ages (Fig. 3). The decline of functions can be slow or fast, variable according to the nature of functions, with also large person-to-person variability. Longevity, determined by age in years at death, is a relatively reliable marker of individual fitness, depending also on environmental factors, among them fatal pathologies. As shown on Table 1, longevity was determined for several animal species and found to be exceedingly variable, from several hours for some insects to over a century for men and some animal species as some whales and tortoises. "Lonesome George", a tortoise at Galapagos Islands died over 100 years some months ago.

Longevity has a significant genetic component, studied essentially with model organisms, starting with yeast. Len Guarente at the MIT studied the genetic components of yeast longevity [10,11]. These studies resulted in the identification of a family of genes, the Sirtuins, playing a role in longevity determination. The detailed study of these genes led to the conclusion that their main function is to code for enzymes and processes of defense mechanisms postponing fatal issues [12,13]. A number of genetic pathways were shown to be longevity determinants, mostly indirectly by reinforcing defense mechanisms and improving the efficiency of metabolic functions. Contributions of genetic factors to longevity are, however, limited, estimated by several authors from 5% to 35% of all contributing factors, no more. We can assume however that "environmental factors" might well affect genetic factors, also by epigenetic mechanisms [8]. One of the strongest arguments against major genetic determination of life expectancy comes from the study of identical twins raised apart. With identical genomes, these twins died at different ages with a variety of causes or pathologies [14].

The increase of centenarians in France over the period 1900 to 2015 (Table 2) excludes also most probably a predominant genetic factor and suggests a great importance for "environmental" and possibly epigenetic factors [15,16].

3. Aging

Aging, on the contrary, is not "coded" in the genome, its mechanisms, a number of them were identified, limit vital functions. As we stated some time ago, we age in "spare parts", largely as a result of progressive loss of vital functions, some slow, others relatively fast, as for instance elastic functions as accommodation or blood vessel elasticity [9,17,18]. As opposed to longevity determinants, for aging the post-genetic mechanisms produce a slow-down of most vital functions. The slowest decline determined is the speed of nervous conductivity, the fastest, elastic recoil [9]. Rapidly declining elastic functions, such as accommodation, vascular and pulmonar elasticity, skin elasticity, concern important physiological functions. Some aging mechanisms are not the result of loss of function, but the consequence of "illegal" chemistry in the body, without built in defenses, such as non-enzymatic glycosylation (glycation), the Maillard reaction. As recorded by the British physician Weale [9], the loss of functions can be rapid, slow or intermediary (Fig. 3). This "aging in spare parts" [8] is the result of uneven loss of individual functions, depending on cellular-molecular

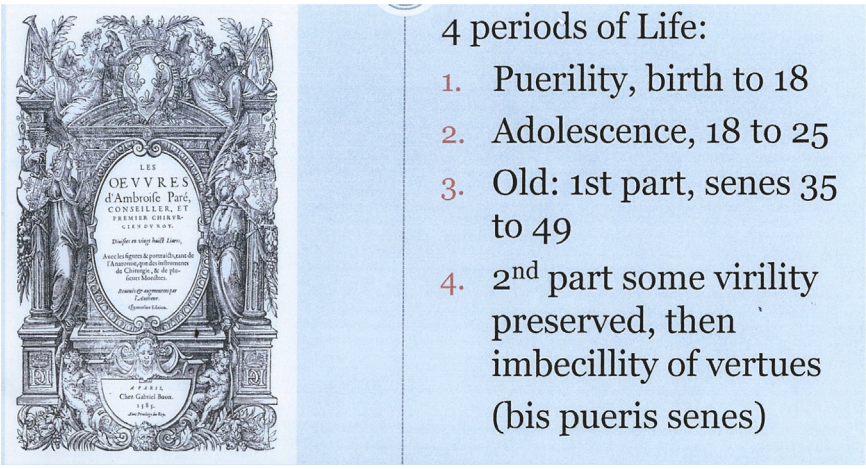

Fig. 2. The facsimile of Ambroise Paré's treatise from the 16th century with his division of human life in four periods as shown on the figure.