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Healthy Aging: an Oxymoron or a Hendiadys*

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1. Introduction

In the last century, the life expectancy of Italians (lifespan), and also of all the populations in the western world, has increased remarkably, but the number of years lived in a healthy and vital manner (healthspan) has not increased in parallel with lifespan. Indeed, there has been an increase in the number of individuals affected by such chronic diseases as hypertension, diabetes, cardiac diseases and tumors, with a consequent growing increase in health and social security costs. In the near future, the ongoing epidemic of abdominal obesity and diabetes could reduce the average lifespan of our citizens, besides, obviously, reducing the healthspan. Reducing the gap between lifespan and healthspan, i.e., enabling people to remain physically and mentally healthy, happy, active, strong, independent and socially helpful for the longest time possible, is an achievable aim that will have significant positive impacts on the country as a whole.

Diet, physical activity and the environment together with knowledge about genetics are crucial factors in optimal aging. Information about the genetic factors related to aging will become ever more important as knowledge of the human genome becomes personalizable. In addition to this factor and to the environment in which we live with its myriad effects it has on us, a third age–related factor is emerging, namely lifestyle, which is constituted by the set of behaviors that depend mainly on the single individual. The life–style risk factors that are able to negatively affect the lifespan and even more the healthspan of an individual are essentially represented by an incorrect diet, lack or scarce physical activity, the intake of toxic substances such

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as drugs, alcohol and the by–products of cigarette smoke. The genes we inherit from our parents predispose us to develop some diseases during life, and regulate our resistance or intollerance to nutrients. Nevertheless, food, drugs (in the wide sense) and physical activity are able to modulate our genes thereby promoting or inhibiting the development of chronic diseases that make us ill and die prematurely. At this point, I would like to establish some concepts that may be useful for the reader, although some terms are not always used appropriately in everyday life. Aging refers to the progressive deterioration of the physiological functions linked to intrinsic processes related to age and that cause a progressive loss of vitality as well as an increase in vulnerability.

The changes that occur are progressive, universal and irreversible, at least as far as we know at present. Intrinsic aging refers to the progressive deterioration of the physical structures of an organism and of the biological functions that occur with the advance of age and that are independent of illnesses, namely, graying of hair, the loss of elasticity of the skin, a decrease in sight and hearing, loss of muscle tissue, of bone tissue etc. By senescence, one means mainly the process at cell level (also known as cell senescence) that leads to the aging of the organism in toto. Cells that senesce increase with age whereas the regenerative potential of tissues decreases. Despite all the intense effort invested in finding dosable substances that could alone or in combination substitute chronologically measured age ("biomarkers of aging"), this goal remains elusive.

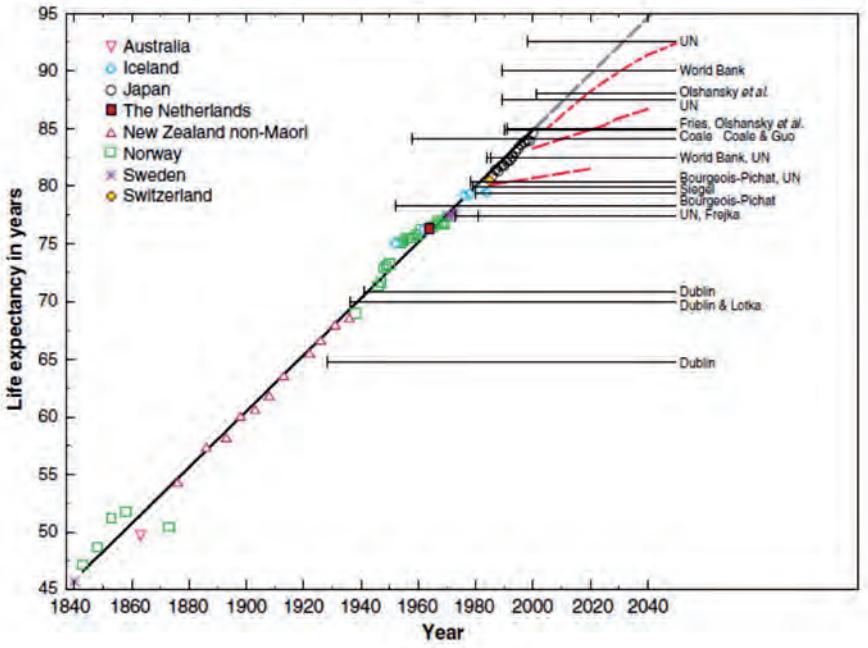
Also pentosidine, which has been shown to accumulate in aged tissues, must await further studies before it can be considered a true marker of aging. Another important concept that should be clarified is the duration of the period of life (lifespan), which is the interval between birth (the moment a new organism physically separates or detaches from the originating organism) and death, which is the occurrence of irreversible changes that no longer allow the individual to maintain the internal and external organizations that are indispensable for the existence of the single individual. Life expectancy refers to how long, on average, a person can expect to live depending on where, at which time and gender (man or woman). Longevity, on the other hand, is the period of time in which one may reasonably expect an organism to live in ideal circumstances (obviously excluding accidents

or other adverse events). The world's longest living person is Jeanne Louise Calment who was born in Arles, France in 1875 and died at the age of 122 years and 164 days (Fig. 1).

Jeanne Calment (1875-1997)

The number of super–centenarians has increased in the past few decades thereby indicating a decisive increase in the average lifespan and in life expectancy. What is interesting is, on the one hand, that projection of the geographic distribution of the elderly population (60 years and over) clearly indicates that this population is increasing in practically all areas of the globe, and, on the other hand, that life expectancy has continuously increased from 1840 to now without any rightward flattening of the curve that everyone would have expected (Fig. 2).

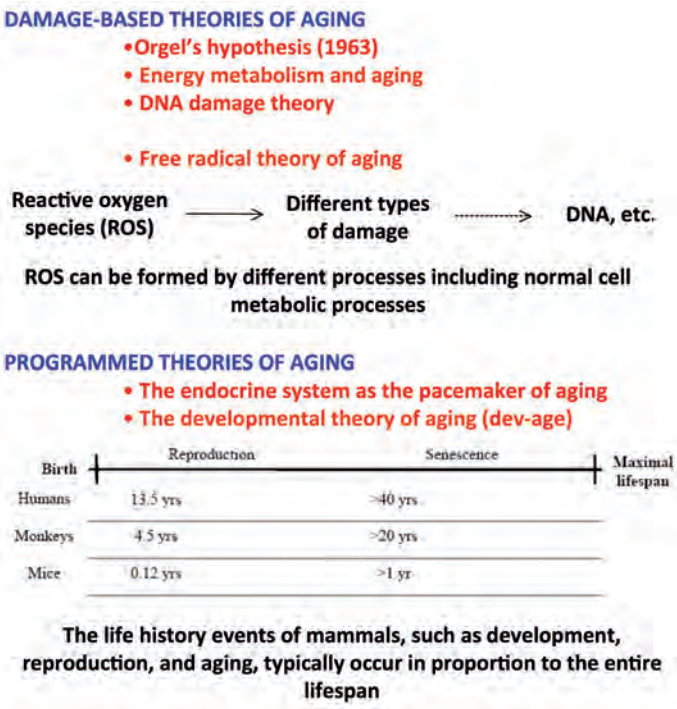
However, despite the above comments, the so–called "health map" varies greatly among populations. In fact, based on the most recent



census, the average life expectancy ranges from 84.4 years in the Macau population of Asia to only 38.2 years in Angola, whereas it is about 80.2 years in Italy. Theories and mechanisms of aging, senescence and tumors Aging theories abound and, still today, some are hotly debated with scientific, evolutionistic and, on occasions, also philosophical–ideological arguments being called into play. I shan't enter into detail about all aging theories, but it is worth mentioning several to give an idea of how many studies have been carried out and are still today being conducted in the attempt to explain this important, and, supposedly, inevitable biological phenomenon that is linked to the life of living organisms.

Theories based on damage occurring during life. Starting with Leslie Orgel's error catastrophe theory of aging and longevity, the other important theories are: a) those that attribute aging to deterioration of energy metabolism; b) that of repeated successive damage to DNA molecules; and c) that related to reactive oxygen species (ROS) that obviously damage the molecular structures of cells (Fig. 3).

Reactive oxygen species are formed in large quantities by various



metabolic processes that include, obviously, also the normal metabolic processes of the cell, thus leading to the inevitable process of aging. However, it should be mentioned that the mechanisms underlying these theories are not mutually exclusive, rather it is highly possible that they act simultaneously and that they contribute, albeit in a quantitatively different measure, to the process of cell senescence and consequently to organismic aging.

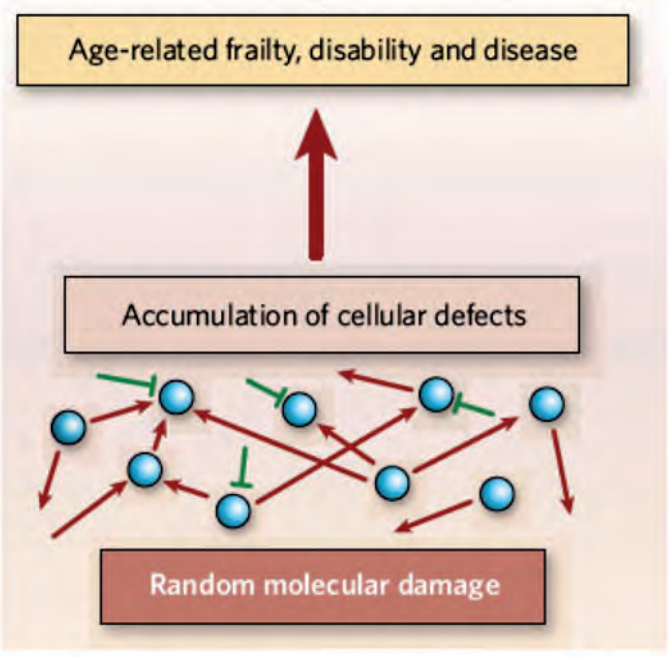
Programmed theories of aging. Like the other theories related to aging, also the programmed theories of aging have appeared over time, and should not be considered entirely mutually exclusive, indeed their underlying mechanisms may co–exist. Essentially, there are two programmed theories of aging: a) the endocrine theory, in the sense that the endocrine system acts as pacemaker of aging; and b) the development theory (Dev–Age). In actual fact, it has been found that in the life of mammals, development, reproduction and aging itself occur in proportion to the entire lifespan. For example, in man, chimpanzee and mouse, reproductive activity and senescence start

approximately in proportion to the maximum life expectancy at birth of these organisms. On average, man, chimpanzee and mouse start reproduction at 13.5, 4.5 and 0.12 years, respectively, and senescence starts at 40, 20 and 1 years, respectively (see Fig. 3). The evolution theories of aging predict some mechanisms/events underlying them: a) it is highly unlikely that there are specific genes that promote aging; b) that aging is not programmed but derives largely from the accumulation of somatic mutations and from the scarce capability of the organism in terms of repair mechanisms. Thus, based on what we now know, longevity would be essentially regulated by the capability of genes to control the activity of DNA repair mechanisms and of antioxidant defenses. In addition to these mechanisms, there may well be genes expressed in the elderly that are deleterious and that have eluded natural selection, or pleiotropic genes that provide benefits in early life but are harmful in advanced age.

Moreover, it is clear that a multiplicity of genes contribute to the aging phenotype, several are "private" to single individuals and others are "public", namely they occur in populations and species. Identification of these genes is a significant challenge and is a topic currently under extensive study. Remaining in the field of what can be considered genetic and what not, it should be stated that everything that happens in the human organism is invariably in part genetic and in part linked to external factors that collectively and in an approximate fashion is referred to as "environment". Nevertheless, in the last ten years many studies have focused on situations that fall between genetics of a Mendelian nature and other molecular/cellular situations. This branch of genetics is called "epigenetics" (*epi* — Greek: επί — over, above genetics), and in simple terms is concerned with heritable changes in gene expression that are not encoded in the DNA of the genome.

This phenomenon is based on processes of molecular regulation, first identified only in DNA methylation, and subsequently extended to changes in chromatin and to gene regulation by a class of small RNAs (micro–RNA and others) which are now known to number over one thousand of different molecules encoded by the human genome, each of which targets messenger RNA of various proteins. A frequently asked question is: why can't we consider aging to be one of the many multifactorial diseases? Obviously, we do consider aging

in this way. Indeed, both genetic and environmental factors concur to induce aging and consequently death. And again, if one or more causes of a given disease are specific for a tissue or if they are systemic, then it is also true that this disease prevails and thus becomes the cause of death (see Fig. 4).



As indicated previously, in the field of studies on the molecular mechanisms that underlie cell senescence and thus aging, a key player is represented by reactive oxygen species (ROS) that produce a series of compounds, ions and atomic/molecular species that determine tissue damage. The notoriety of ROS has resulted in a flood of antioxidants that claim to have miraculous effects against aging and against many other alterations caused by ROS. As I mentioned earlier, a tremendous number of studies have been conducted in this field; similarly numerous are the studies that have identified intracellular molecules involved in signaling and that act as intermediates between DNA damage and the effect on cell proteins and on their molecular mechanisms that ultimately lead to aging. See Table 1 for a view, in quantitative terms, of the multiplicity of molecular events occurring in the human cell and in the human organism.

Table 1. Reactive oxygen species (ROS) in the human cell and in man

A human cell	
Metabolizes 10^{12} O_2 molecules per day	Produces 3 X 10^9 ROS/hour
A man	
1% of the inspired O_2 produces ROS	Produces 3 X 10^{22} ROS/hour

Among the many studies, including studies from Italy, I would like to recall those concerning protein p66 that produces ROS (including hydrogen peroxide). Under conditions in which ROS production is reduced, for example when p66 is completely absent (as occurs in genetically modified mice) longevity is increased, as it is when certain enzymes (e.g., mitochondrial catalase) are able to abolish or annul the negative effect exerted by ROS. Protein p66 has also been indicated as a genetic factor that contributes to producing the metabolic syndrome, which is a pathologic syndrome in man that is represented by a variety of alterations the most striking of which are glucose intolerance, insulin resistance, obesity, hypertension and prothrombotic and pro–inflammatory states in general.

Turning to cell multiplication, which parallels aging because, as mentioned above, with the passage of time, cells multiply less quickly, also when cultured in vitro. Indeed, about half a century ago, it was found that a normal population of human fetal cells in a cell culture divide between 40 and 60 times after which it enters a phase of senescence (this process is known as the Hayflick limit or phenomenon after its discoverer). This finding challenged the concept that normal cells are immortal (Alexis Carrel). An exception to the Hayflick phenomenon are stem cells, which are found in small numbers also in adult

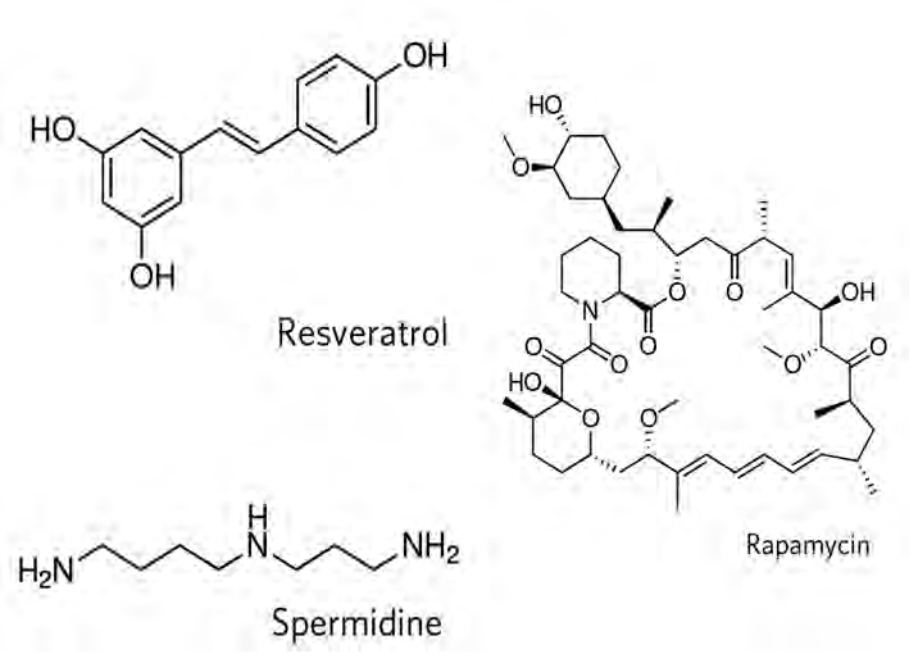
tissue (by definition, stem cells are embryonic cells present in the first days after formation of the first cells, zygotes, and are potentially able to form an entire individual). There are peculiar human diseases in which the cells divide less, but they age, as case in point is Werner's syndrome – a syndrome characterized by premature aging. People affected by this genetic disease, which is due to the alteration of a single gene that is responsible for DNA replication and repair, age and then die prematurely.

These patients have growth failure and do not usually live beyond the age of 40 years. Progeria is another genetic disease in which patients usually die just after the age of 10 years. It is a very rare disease, and is associated with altered synthesis of nucleic acids, DNA and RNA. Patients have the typical aspect of an elderly person. A step forward in our understanding of aging came in 1973 with Alexey Olovnikov's telomere hypothesis of aging. A telomere is a region of repetitive DNA sequence at each end of a cell's chromosome that protects the ends of the chromosome from deterioration and from fusion with neighboring chromosomes. However, at each cell division, telomeres become shorter and as a consequence cell multiplication decreases and the cell begins to senescence and dies.

Another major advance in our understanding of aging was the discovery in 1984 of telomerase and the demonstration of the physiological role of telomeres (a decrease of telomeres corresponds to cell senescence) and of telomerase, in the absence of which stem cells progressively senescence. This ground–breaking research showing that the presence and progressive shortening of telomeres is associated with the absence of telomerase in adult cells led to the 2009 Nobel Prize for Medicine (see below). However, although telomerase is able to reform telomeres, it is also present in stem cells and tumoral cells, precisely where cell multiplication is most active and where senescence is absent.

Therefore, although the presence of telomeres increases lifespan, it is also true that the risk of cancer is higher in telomerase–containing cells. In this context, it is interesting to note that compounds aimed at treating cancer by curbing telomerase (which is active in cancer cells) are already available and others are under study. Here is the intriguing consequence that comes from the comments to the award of the 2009 Nobel Prize for Medicine to the three USA researchers

Elizabeth H. Blackburn, Carol W. Greider and Jack W. Szostak. The consequence is: given that immortal cells, namely cells that do not senescence, are rich in telomerase but unfortunately have tumorigenic capacity and are thus not the best antidote against aging, one may ask: is it better for an organism to die from cell senescence by losing telomeres thereby becoming old, or is it better to die from a tumor with abundant telomerase without becoming old? To bring this topic to a close, Figure 5 shows the process undergone by a normal cell in the case of aging and in the case of transformation into cancer.



It is possible to treat or prevent aging? It appears that some animals are immortal, for example, lobster and a few species of turtle do not seem to undergo aging, but these observations are still under discussion. It is also true that if mankind seeks to adapt to the environment why shouldn't it fight aging? American economists have calculated that it is economically advantageous to keep people in good health in old age; indeed, it would result in a saving of 2.4 billions dollars per year for the US. In fact, as the average lifespan increases, the percentage of frail and elderly people needing healthcare services etc. increases. Therefore, it makes good economic sense to treat or

prevent aging. This brings us, as I mentioned earlier, to the concept of Healthy Aging, understood as the mental, social, physical and functional well–being also in elderly persons, in other words, we should aim at reducing the gap between lifespan and healthspan. The difference between immortality and the extension of healthy life has long been recognized — as illustrated by the Greek mythological tale of the Tithonus Error. Tithonus was granted immortality by Zeus upon the request of his daughter Eos, who omitted to ask for eternal youth.

Thus, as Tithonus aged, he became increasingly debilitated and demented, and finally asked to die to alleviate his pains! We don't know how to revert aging, but it could be possible to prevent it, that is, it could be possible to prevent the diseases, especially chronic diseases, associated to the aging process (for example cardiovascular and neurodegenerative diseases, cancer, diabetes, hypertension, inflammatory diseases, etc.). History abounds with attempts (scientific and not–so–scientific) to find substances that can prevent aging or its negative effects. The flood of such substances on the market prompted an investigation by a group of 51 American experts in aging, who concluded in 2001 that none of the remedies sold over–the–counter was a scientifically proven anti–aging remedy and that the "Fountain of Youth" did not and could not exist (see Table 2).

Table 2. Life expectancy at birth and healthy life expectancy at birth in Italy (2005)

Life expectancy	
Male	78.1 years
Female	83.7 years
Healthy life expectancy	
Male	54.5 years
Female	51.6 years

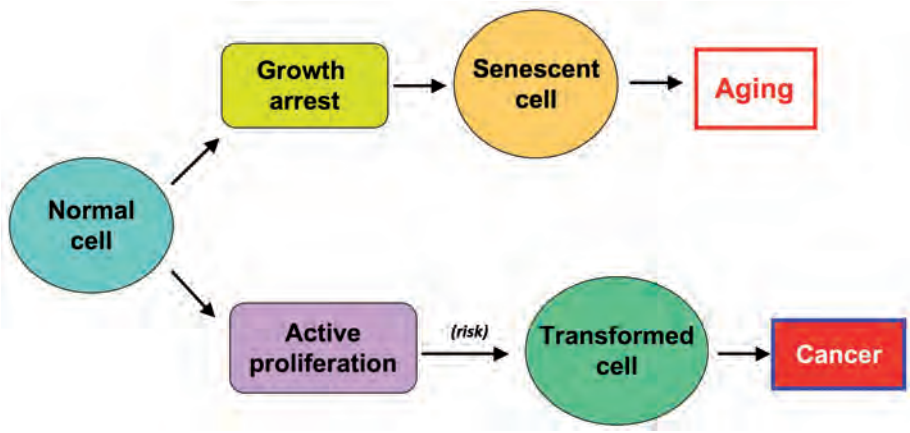
Istat. Health for All-Italia. http://www.istat.it/sanita/Health/.

It is interesting to see in Table 2 that while Italian women have a higher life expectancy than Italian men, healthy life expectancy greatly decreases in both groups and is even lower for women than for men. This is probably related to problems of reproduction and menopause in women. In summary, successful aging, namely healthy aging, is characterized by three factors: a) a low risk for diseases or disease-related disability; b) a well functioning body in both physical and mental terms; c) active involvement in work and social activities. Numerous scientists have long attempted to produce formulas of hope, or even of hermeneutic–type formulas, to understand, if it is possible to establish what lifestyle to follow in the attempt to go towards (or even reach) immortality. Suresh I.S. Rattan, professor and chairman of a large institute in the field of aging and senescence of Aarhus University in Denmark, in a light moment, produced a formula of eternal life:

$$E = GMC2$$

E is immortality or a long healthspan, G is the set of genetic factors associated to an individual, M is the milieu, namely the environment, from the microscopic cellular level to the social level, and lastly C is chance, namely the stochastic events that occur according to the rules of probability, as the world of subatomic particles has shown us. Therefore, should we conclude that chance is the main player in determining the longevity of humans? On a more serious level, studies published in the last 5 years or so have identified some drugs and/or behaviors that can promote the extension of life and decrease the incidence of diseases that occur with the passage of time; most of these studies were conducted in animal models. Essentially, these studies have shown that: a) resveratrol, contained in red wine and peanuts, which have already been tested in clinical trials for cancer, type 2 diabetes, etc.; b) rapamycin, found in the soil of Easter Island and in other western islands, is already used as an immunosuppressor in medicine (Fig. 6); c) spermidine, which promotes autophagy and increases life span in yeasts, drosophila and worms (Caenorhabditis) (see Fig. 6).

Finally, a reduced intake of calories has been shown to be beneficial in terms of age–related conditions. Other conditions/factors that promote protection from aging are an increased reaction to hypoxia,



female sex, and the assumption of omega 3 fatty acids. A reduction in dietary calorie intake has been found to be effective not only in models like yeast, drosophila, nematodes and mice, but also in monkeys in which there was a reduction of deaths and a reduction in chronic diseases such as cancer, cardiovascular diseases, diabetes, etc; moreover, brain function was much better than in monkeys not undergoing reduction of calories.

The study of the molecular mechanisms underlying these results has just begun, and despite some controversy, the findings obtained thus far are promising. The results of the first experiments conducted in man are also promising, although treatment is associated with some adverse effects (a reduction in libido, depression, etc.). It is crucial to pursue these studies because, as rightly underlined by Rita Levi Montalcini, it is of no interest to add years to our life but to add life to the years we live. Therefore, as I mentioned at the beginning of this article, besides genetics and the environment, a "third element" is usually necessary for healthy aging, which is defined as a fully functioning physical and mental status.

Accordingly, national and international studies are required to evaluate the effects of diet and physical activity in preventing chronic diseases and in promoting healthy aging. In this line of reasoning, in Naples we have created a multidisciplinary structure, at CEINGE — Biotecnologie avanzate s.c.a r.l., which, starting from the genetic analysis of factors predisposing to e.g., obesity and chronic diseases, will try to identify, by using a robust experimental approach, the most

appropriate lifestyle for a given individual to age in a healthy manner. The idea that a person can consult preventive healthcare structures, as well as structures dedicated to recovery and treatment, to have a comprehensive understanding of their state of health and learn how to prevent diseases and stay healthy is an innovative strategy that we are pioneering in Italy and that could be a model for Europe. This new healthcare policy, aimed at preventing the most common chronic diseases, e.g., type 2 diabetes mellitus, coronary diseases and some types of cancer, may also release resources/funds that can thus be used to treat diseases that are very difficult to prevent, such as rare or genetic diseases. In conclusion, after an initial understandable skepticism given the absence of robust scientific results, a series of studies are emerging indicating that it is possible to understand the cellular and molecular mechanisms that drive senescence and aging, and the mechanisms that, through adequate lifestyles and eventually drugs, can act as catalysts to prolong healthspan. Thus we are moving from the oxymoron of "healthy aging" to the more optimistic figure of speech "hendiadys", namely "healthy survival" or "healthy longevity".

Tables and Figures (captions and legends)

— Fig. 1 — Jeanne Calment (1875–1997). The world's longest living person for whom official records are available.
— Fig. 2 — Life expectancy in various countries across the time. The dots follow an almost straight line, without a rightward flattening, as one might have expected. This suggests that the average life span can continuously increase as time goes by (Reproduced with permission from the Nature Publishing Group. Copyright © 2008).
— Fig. 3 — Theories on aging that have come and sometimes gone over the years, and that still have supporters. Some of them may co–exist. (Modified from João Pedro de Magalhães, 2008).
— Fig. 4 — Plausible mechanism of aging according to the theory based on the molecular and cellular damage. (Reproduced with permission from the Nature Publishing Group. Copyright © 2008).
— Fig. 5 — Fate of a normal cell towards senescence or malignant transformation (cancer). (Modified from Robert A. Weinberg, 2004).
— Fig. 6 — Chemical formulas of the three substances found to have antiaging properties in lower organisms, and that in some cases delay the progression of some human chronic diseases.

Essential bibliography

The following articles are suggested for those readers who wish to probe further some of the topics touched upon in this paper.

Carrel A., *On the permanent life of tissues outside of the organism*, J. Exper Medicine 1912;15: 516–527.

Orgel L.E., *The maintenance of the accuracy of protein synthesis and its relevance to aging. Proc. Natl. Acad. Sci.* U.S.A. 1963;49:517–521.

Szostak J.W., Blackburn EH., *Cloning yeast telomeres on linear plasmid vectors*, Cell 1982; 29:245–255.

Greider C.W., Blackburn EH., *Identification of a specific telomere terminal transferase activity in Tetrahymena extracts*, Cell 1985; 43: 405–413.

——, *A telomeric sequence in the RNA of Tetrahymena telomerase required for telomere repeat synthesis*, Nature 1989; 337: 331–337.

Sell D.R., Primc M, Schafer I.A., Kovach M, Weiss M.A., Monnier V.M., *Cell associated pentosidine as a marker of aging in human dipoloid cells in vitro and in vivo*, Mechanisms of Ageing and Devlopment 1998; 105; 221–240.

Halloszy J.O., Fontana L. *Caloric restriction in humans*, Exp. Gerontol. 2007; 42: 709–712.

Kirkwood T.B. A systematic look at an old problem, Nature 2008; 451: 644–647.

Colman R.J., Anderson RM, Johnson SC, Kastman EK, Kosmatka K, Beasley TM, Allison DB, Cruzen C, Simmons HA, Kemnitz JW, Weindruch R.,*Caloric restriction delays disease onset and mortality in Rhesus Monkeys*, Science 2009; 325: 201–204.

Fontana L., Modulating human aging and age–associated diseases. Biochim. Biophys. Acta (BBA) 2009; 1790: 1133–1138.

Fontana L., Partridge L., Longo V. D., *Extending healthy life span–from yeast to humans*, Science 2010, 328: 321,326.

Omodei D., Fontana L., *Calorie restriction and prevention of age–associated chronic disease*, FEBS Letters 2011, article in press.

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