Epidemiologists are now interested in supercentenarians. They are the subjects who had reached 110 years of age, in a validated manner. Information on their nationality, date of birth, the gender, and the year of eventual death is known. To evaluate the prevalence of supercentenarians is a complicated task. It is correlated with the same conditions which determine the ageing of the population, and particularly that of the centenarians. Therefore, it is variable region by region, and in various ethnic groups. Values have been estimated as about 0.25-0.50 per cent, or 0.15-0.25 per cent of the centenarians. Identified and alive supercentenarians were (June, 2009) 82 (74 females and 8 males). Their presence in the world is estimated as about 350-450 subjects. The International Database of Longevity estimates that during the last 50 years there have been about 1000 supercentenarians. The factors responsible for the extreme longevity are multiple, and among them the genetic ones are of fundamental importance, even if these may not be considered as exclusive ones. A comparative evaluation of the prevalence of supercentenarians in a multiracial country may be of particular importance. For example, in US, the black population represents the second large group of centenarians, contrasting that of the African countries, displaying the lowest medium life span. It is important, however, that the ratio of prosperity/longevity in a country is valid up to a certain value of the GDP. As a matter of fact, the Preston-curve has shown that this factor is valid up to an annual income of US$ 5000 per person/year. The USA with a GDP of US$ 37,650 per person/year (the highest in the world) occupies only the 45th place in the ranking of life expectancy. From these data, it should be noted that India is on the 145th place of nations in the ranking of the life expectancy, it has a modest GDP per person, but a very large sample number, and yet has a single validated supercentenarian, Lucy d’Abreu, a Scottish women born in 1892 in Dharwar (India) and died at the age of 113 years and 197 days in Stirling (Scotland). Probably a careful nosographic research and a consequent validation procedure could confirm numerous ultracentenarians in India, and also the presence of several dozens of supercentenarians. on the basis of the statistical evaluation. The ageing process cannot be considered as being only under the genetic control.

Ageing is a defense network characterized by cellular, molecular and environmental mechanisms, maintaining the integrity genetica and somatica. The genetic pathogenesis seems to be a polygenetic system, indicating the susceptibility of ageing and longevity of the individuals. The genetics of human longevity seems to be peculiar (post-reproductive genetics), where antagonistic pleiotropies may play different roles at various ages.

The longest surviving subject was Jeanne Louise Calment, who died in 1994 at the documented age of 122 years and 164 days. One of the peculiar aspects of longevity is the increase in number of women among centenarians (79% women and 21% men), while in supercentenarians these proportions are 87.5 and 12.5 per cent, respectively. This prevalence depends on numerous factors, acting in complex modes, which have been identified so far only in part. The menopause in women seems to be evolved to allow them to become independent after the young age, when they assured the survival of the species. The maintenance of the estrogen production until the menopause helps in the prolongation of the anti-atherosclerotic, anti-ageing activity, and its absence resulting in a major mortality of the males during the pre-senile period of life. It is of great interest also that one finds an independent risk factor of all-cause mortality per cardiovascular disease of the males of
medium age (45-74 yr), who live alone, compared to the similar groups of females. These events have been correlated to the particular conditions of personal deteriorations in males causing a minor capacity of adaptation, confirming the importance of environmental factors and co-morbidities in survival.

A nosographic approach to the supercentenarians is not simple. Usually the various descriptions refer to well-defined single subjects, regarding the anagraphic data, but to incomplete and modest information on the clinical aspects. The data deriving from the Okinawa Centenarians Study (OCS)\textsuperscript{11} and from the New England Centenarians Study (NECS)\textsuperscript{12}, reporting the clinical conditions revealed in the past times in 12 and 32 supercentenarians are of great importance. Case reports of this type are exceptional, considering the modest world-prevalence of supercentenarians, but even these do not allow any valid statistical evaluation. The only specific characteristic proven by these data is that certain centenarians really could reach the age of 110 years. The centenarians represent a variable world, composed by polyopathological subjects, with heavy cognitive deficits, with inability of performing both the activities of daily living (ADL) and the instrumental ones (IADL), and also by subjects who although present signs of advanced ageing, are in good health conditions showing mini mental state examination (MMSE) scores up to the maximal values, and also to perform all activities on the ADL and IADL scales\textsuperscript{13}.

For the clinical classification of the centenarians, our research team (Italian Multicentric Study on Centenarians: IMUSCE) uses generally accepted and validated terms. Based on anamnestic, objective, laboratoristic, instrumental data, as well as on the cognitive evaluation by MMSE, ADL and IADL (modified for the elderly), the centenarians have been classified in 3 groups: being in good, intermediate, and bad conditions\textsuperscript{6,13}. The percentual distribution of the centenarians in these 3 groups was 20.0, 33.4 and 46.6 per cent, respectively. However, only a minority (1.6\%) of the centenarians in good conditions displays an integral and continuous cognitive capacity, for performing not only the routine, common activities, but also several special activities, like embroiding, ironing, playing music on instruments, driving cars, bicycling, etc.\textsuperscript{13}. The cases of supercentenarians represent one part of these subjects, who reached 100 years of age without noticeable diseases. Based on the comparative data of the two studies OCS\textsuperscript{11} and NECS\textsuperscript{12} carried out on the supercentenarians, the following conclusions may be drawn:

(i) The global evaluation is very difficult, due to the individual clinical differences. A moderate prevalence of numerous chronic-degenerative, significant pathologies is widely documented in the centenarians, as compared to the elderly, seems to be present also in the supercentenarians, compared to the centenarians. Even the dementia of various clinical aspects, which is the only disease condition more frequent in the elderly than in the centenarians\textsuperscript{5}, seems to be of lower prevalence in the supercentenarians, as compared to the centenarians.

(ii) It is difficult to interpret the net difference in the prevalence of cancer. In the OCS\textsuperscript{11} study, cancer is absent, while in the NECS\textsuperscript{12} study, it is present in 25 per cent of the supercentenarians, however, all of them were treated, and none of them were active. This is a condition which justifies the presence of cancer in the supercentenarians.

An autoptic study performed on 140 ultracentenarians, showed the presence of various types of cancer in 16.3 per cent, as compared to the average elderly showing 39.0 per cent, and there was a lower aggressivity of metastases (24.0 vs. 55.0 \%).\textsuperscript{14}

The absence or extreme rarity of diabetes mellitus (one single subject in the total study pool) is particularly interesting. Because of several pathogenetic, clinical and other characteristics, type 2 diabetes (DMT2) in the elderly is distinguished in 3 subtypes, based on the age of onset: diabetes of adults manifesting itself in medium age (\( \geq 40 \) and \(< 60 \) yr), the late onset diabetes, manifesting itself at later ages (\( \geq 65 \) yr), and senile diabetes. In the elderly (65-84 yr of age), using the ADA criteria to evaluate the prevalence of diabetes we obtained a prevalence of diabetes as 15.11 per cent, of this 8.35 per cent manifested in medium age, and 6.76 per cent in senile age\textsuperscript{15}. On the contrary, in the centenarians we found that the diabetes was almost exclusively of senile type (99.66 \%).\textsuperscript{15} In addition, this diabetes had an onset always after 90 years of age. These data led us to hypothesize that the diabetes of long duration would not allow to become centenarians. The results found in the supercentenarians seem to support this hypothesis, and demonstrate also the missing expressivity of DMT2 in the extreme longevity.

In conclusion, the supercentenarians have survived the 100 years of age with good health conditions,
have not manifested the typical pathologies of the old ages (infarct, stroke, cancer, etc.), however, they are extremely fragile, showing a progressive loss of their autonomy, and rapid evolution of cellular and tissue degeneration, accompanied by limitations in functional capacities, with a compression of their disability into a relatively short period at the end of their exceptionally long lives. In this regard we have to precise that the functional network is an interconnected system, assuring a global functioning. A deterioration of one of the components causes the insufficiency of the system, and/or the loss of efficiency. The specific factors of the network favourable for the maintenance of longevity may be: genetics, environmental factors, lifestyle, etc. The biographic analyses of several known supercentenarians showed that they have been gourmands and have considered their own longevity as correlated to the consumption of several particular foods (pickled herrings, gherkins, pork fat, miso-soup, fish instead of meat…), especially accompanied by brandy or cherry with Ginger ale. Mrs. Calment, the oldest person of the world, recommended to eat some chocolate and drink a glass of red wine every day. A particular significance is attributed to the capacity of eliminating the aged or damaged molecules or cells. This capacity involves particularly the mechanisms of repair allowing the maintenance of the 3 great systems at cellular level (immunological, endocrine, nervous systems) which are the factors responsible in the maintenance of homeostasis of the organism. It becomes clear why the most frequent cause of death is the senile cardiac TTR-amyloidosis, found in 4 of 8 cases of validated autopsies of supercentenarians. Unless some extraordinary events may take place, we cannot expect any rapid increase of the human life-span. It means that we have motifs to expect a rapid and significant increase in the number of supercentenarians, and only moderate changes in their medium and maximum survival.

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References