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Longevity and Predictive Medicine

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Our society is characterized by a progressive phenomenon of aging of the population, with a high prevalence of chronic and degenerative diseases and an increasing level of disability (1-2-3). World-wide the average life of man is 80 years, while the Maximum Life Span, which is species-specific, is approximately 120 years, twice the maximum age of the chimpanzee, the animal most closely correlated with man from a genetic point of view (only 0.6% genomic differences). Everyone at birth receives a patrimony of resources which form a functional reserve and will be used during lifetime: as demonstrated in many studies, this reserve is genetically programmed. Every man is subjected to an astronomical clock that beats its time in seconds, minutes, hours, but this clock is subordinated to a biological clock that, for every individual, begins to run after conception and differentiates time in development and successive impoverishment of the initial patrimony, not only of the organism, but also of its organs, tissues and cells, each and one of them having a different biological age. The speed of the biological clock depends on the interaction between genetic patrimony and environment. An unfavourable interaction will lead to a premature death, while an optimal interaction will lead to natural death at 120 years. In this context we can define aging as a complex cascade of processes which carry to the progressive reduction of the functional reserve of the entire organism, of the single organs and apparatuses. Longevity is obtained when aging proceeds gradually, that is when the rate of reduction of the functional reserve is not too fast, avoiding that the collapse of a function involves the entire organism (4). Aging processes, increasing the vulnerability of the old and the loss of adaptability, are the substrate for environmental factors: if we are not to decide our genetic patrimony we can make so that our genes are expressed to the maximum of their potentiality diminishing the aggression of external risk factors. Excluding pathogenic noxae, external factors commonly considered as capable of modifying the expression of the genetic program are: eating habits, smoking and drinking habits, physical activity and psychic factors.

GENES AND AGING

Thanks to the genomic map sequenced by the Human Genome Project, a data bank will soon be available in order to facilitate the location and the study of those genes involved in the development and in the manifestation of the character of man, that is both of normal (physiological) characters, of rare (variant) and of anomalous (pathological) characters. The somatic differences that can be observed between persons (phenotypic differences) are basically in relation to two genetic events that confer the so-called "genetic variability": rare mutations, which are present in the population with a frequency $<1\%$, and common mutations, which are present in the population with a frequency $>1\%$, these last ones also called polymorphisms. Each and one of us contains in his genome both rare mutations and polymorphisms. While mutations, more recent from an evolutionistic point of view, are rare genetic variations responsible for important phenotypic changes as happens in "mendelian" diseases, the polymorphisms, much older from an evolutionistic point of view, are common genetic variations responsible for minor phenotypic changes (for example different blood types), which often mediate the interaction with the environmental factors. Polymorphisms are the genetic variations most often involved as risk factors in complex diseases. They are moreover involved in the phenomenon of aging. For example the fact that there is a great variability in lifespan between healthy subjects of the same race living in the same geographic area, is due to the presence of polymorphisms, which can be defined as minor differences of the genetic equipment of everybody (5-6).

Improvements in our genetic acquaintances will enable us to classify the genotype of all diseases and to find new metabolic ways involved in their pathogenesis. Knowing the genotype, the physician is enabled to prescribe a therapy aimed on the cause and not on physical characteristics. Moreover, understanding how common pathogenetic mechanisms can be involved in different diseases, a therapy developed for a single disease could be used in order to cure other diseases. One of the most interesting applications of knowing the genomic sequences is represented by pharmacogenomics. In a certain population, some persons are complete responders to a therapy, others are only modest or marginal responders, some are non-responders and some persons express adverse reactions. The variability of the clinical response to a particular drug is not only due to the physiological mechanisms of the drug and environmental factors, but above all to the genetic constitution of the single subject, which is responsible for more than 85% of the total variability, according to some authors. The genetic profile of an individual determines in fact the characteristics of the target of the drug as well as of the proteins involved in the process of its absorption and metabolism. The variation of a nucleotide of a single gene can result in a different structure and function of a certain protein and therefore in a modification of the metabolic pathway of the drug. Subjects with a particular genotype can be unable to metabolize a particular drug and may therefore present a greater risk of adverse reactions or interactions with other drugs, while other genes are in a position to determine a faster metabolism of some drugs, reducing consequently their efficacy.

PREDICTIVE MEDICINE AND CHRONIC DISEASES

As a result of the recent discoveries in genomics and pharmacogenomics, we must attend an enormous progress in the ability to diagnose diseases, to identify new risk factors and to identify the optimal pharmacological therapy for each patient. These characteristics are the

basis of the predictive medicine. This new therapeutic strategy aims at preventing a disease to reveal itself through a genetic diagnosis of susceptibility and through treating the disease at a pre-clinical stadium with a drug that will be specific for each patient. The predictive medicine warns a person about his fragilities and permits to determine the proneness to certain diseases for himself and his children; permits to change life style (for example dietary habits and kind of work) in order to avoid the environmental factors involved in the development of a certain disease, and to monitor the predisposition to a determined disease by periodic screening. The future of this new branch of medicine is in chronic-degenerative diseases like Parkinson's disease and Alzheimer's disease, in oncology and metabolic diseases (7-8). The Parkinson's disease is the most common disease of the movement, interesting approximately 1% of the population >60 years. The pathological characteristic of this disease is the loss of dopaminergic neurons in the substantia nigra, which causes the main clinical signs; bradykinesia, rigidity, tremor and the postural instability. At the beginning it was believed that this disease was due to the exposure to particular environmental factors (comprised viral infections and chemical toxics). Later the high frequency of Parkinson's disease in some families has been demonstrated and the idea of a genetic origin of the disease became reality. Today we know that some types of Parkinson's disease might be due to mendelian mutations (for example the PARK-gene) and that other types can be correlated with the presence of specific genetic polymorphisms, which means that many types have a multifactorial mechanism. Studies have shown how some metabolic ways are altered in various types of Parkinsonism, resulting in an anomalous production of ROS (mutations of DJ-1 and PINK1), in a change of the proteic aggregation (mutations of α -sinucleina), or in stress due to misfolded proteins (mutations of UBCH-L1 or Parkin). These mechanisms are responsible for the creation of the bodies of Lewy, typical proteic residuals present in the brain tissue of Parkinson's ill patients, as well as for a condition of toxicity and neurodegeneration. The genetic therapy of Parkinson's disease begins in the United States, studied by a team of researchers guided by Michael Kaplitt from the New York Presbyterian Hospital/Weill Cornell Medical Center. A virus containing the GABA gene is injected in the subthalamic nucleus, the area which regulates the motor circuit. The GABA neurotransmitter "calms" the hyperactive neurons and is lacking in patients with Parkinson's disease which, consequently, have motor problems and tremors. Injecting the GABA gene in the brain, the researchers have tried to stimulate the production of the neurotransmitter in order to standardize the function of the motor circuit (9-10). In the disease of Alzheimer, some rare types with a premature onset are due to mutations of a single gene, while types with a late onset are known to demonstrate a familiar aggregation and are correlated to polymorphisms that confer susceptibility to the disease. In some families with premature onset Alzheimer's disease the responsible gene has been located on chromosome 21. Dominant autosomic mutations involving the gene for the amyloid precursor protein have been described. In several families with premature onset Alzheimer's disease it has been demonstrated a linkage with DNA markers on chromosome 14. The gene is a membrane protein called presenilina 1. Mutations in this gene are responsible for approximately 70% of all types of premature onset Alzheimer. A second gene called presenilin 2 and structurally correlated to the previous one, has been isolated on chromosome 1. At last, in those families with late onset Alzheimer's disease a statistically significant association between the presence of the allele epsilon 4 in the gene of the apolipoprotein E (apoE), located on chromosome 19, has been demonstrated (11). The apolipoprotein is the main carrier of lipids to the brain and has a high affinity for the β -amyloid protein. The Alzheimer's disease seems therefore to be a heterogeneous disease from an etiopathogenetic point of view and several authors think that both genetic and

environmental factors may interact on a common metabolic way leading to the intraneuronal deposition of b-amyloid and of other anomalous proteins having a neurotoxic effect.

CONCLUSIONS:

Aging is a complex systemic process due to multiple genetic components such as interindividual variations of the DNA and environmental factors including life style and interactions with the atmosphere. The challenge of Geriatrics is to identify those factors leading to a survival of hundred years keeping in mind that longevity is not an extraordinary event but a right to conquer for everyone.

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