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EVALUATION OF THE BIOLOGICAL AGE

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Summary. Based on researches carried out at the National Institute of Gerontology and Geriatrics, a synthesis is presented of the criteria used in the evaluation of the biological age and aging rhythm, which express the fundamental traits of the aging process, the diminution in the adaptability and reactivity of the organism. The age indicators are grouped in organizational and integratory types: molecular, cellular, tissular and organismic.

Molecular aging is pointed out by the intensification of crosslink formation with age. The cellular and tissular aging process is selective, asynchronous. Normal aging is characterized by a marked lability of the general homeostatic balance. At this level, the evaluation of the age indicators under stress is particularly important. Functional age can be evaluated only by means of complex battery of tests. The main criteria are pointed out in the evaluation of the cardiovascular, nervous, renal, immune systems and internal medium.

The researches carried out at the National Institute of Gerontology and Geriatrics have led to the elaboration of certain synthetic indicators used in the determination of the biological age at populational and individual levels. The concluding part of the paper presents the main directions of future researches. The biological age will be most exactly determined by means of: complex tests, including some stress indicators in the program, the study of areas in the longevous, the thorough use of statistico-mathematical method.

The assessment of the age criteria is an obligation of gerontology, aimed at appreciating the biological age and studying the evolution of the aging process. We began this study in 1951 also with a view to objectivizing the therapeutic action.

From this standpoint, the criteria should be representative, easily applicable and, if possible, reversible.

The speed of the biological phenomena — the aging rhythm results in either concordance or discordance between the chronological age and the morphofunctional condition of the organism. The significant differences between the rhythm and manifestations of the biological aging process in different individuals determined thorough gerontological studies with a view to identifying the indicators of the biological age.

The researches on the determination of the biological age carried out recently have defined quite a number of tests which allow a better understanding of the biological aging process at individual and populational levels. The process of aging implies a complex of biochemical and biophysical changes which can be morphofunctionally pointed out at the end of the growth period in different organs and tissues.

The dissimilar aging in different tissues and organs is due, in the first place, to the genetic inheritance, and secondly to the environmental factors — geographic conditions, climate, socioprofessional environment, nutrition — which induce great variations in the aging rhythm of each individual and between the members of

the same population. The pathological conditions injure different systems, induce a faster and severer degradation by stressing the integratory mechanisms.

The evaluation of the biological age is organically dependent on these factors; usually, it does not correspond to the chronological age of the individual, which expresses the morpho-functional condition of the organism in relation to the outlived years.

In the longevous, the chronological age precedes the biological age, whereas in premature aging the ratio is reversed.

The physiological aging defines the normal, slow, continuous, asynchronous, heterogeneous aging and allows the individual to reach advanced ages despite certain adaptative difficulties. The physiological aging, Bürger biomorphosis is clinically known as orthogeria or orthobiosis. The peculiarities of the aging process in humans are generated by the elements specific to the onto- and phylogenetic development of this species. The evolution of the nervous system and psycho-social activity, the early and marked cardiovascular involution [1], [2], are areas where the human aging acquires essential importance and individualizing elements.

The finding of the factors which induce the accelerated involution, or the discovery of the premature aging in a certain function or organ, are of major importance from the medical standpoint.

This implies a complex biological investigation, by means of a battery of tests allowing the evaluation of the biological age, different functions and the comparison between performances recorded and the standard curves.

The morpho-functional involution specific to the human aging becomes obvious at the end of the growth period and results from the decrease in the active metabolic tissues, increase in the adipose and connective tissues as well as the qualitative changes in the function of different tissues and organs.

The involutive process is based in the first place on the physico-chemical and biochemical mechanisms the result of which is the primary aging of the organism.

The secondary aging is particularly dependent on the insufficiency of the autoregulation mechanism of the complex reactive, dynamic and biological systems.

Beside the chronological age, the evidence of other criteria in evaluating the functional age and aptitudes is a medico-social imperative.

At present, in the absence of a comprehensive estimative criterium, the biological age and the aging rhythm are evaluated in terms of numerous tests expressing the fundamental peculiarities of the aging process: the decrease in reactivity and adaptability. The lack of specificity in the data on the physiologic involution entitles us to present a synthesis of the most significant clinical and paraclinical indicators. Undoubtedly the age criteria are not present in each and every individual; nevertheless, because of their statistical value, they compel recognition as age indicators.

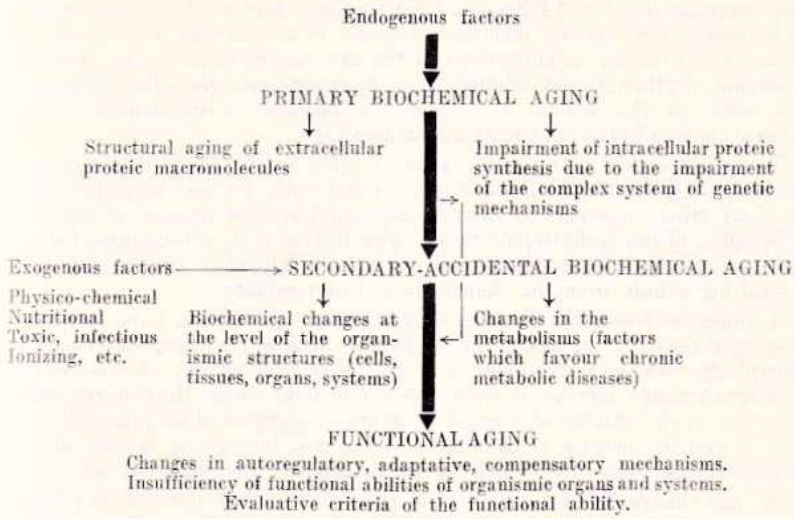
The biological aging can be followed at all levels of organization and integration: molecular, cellular, tissular, organic and organismic.

The modern biochemical, electrochemical and histochemical research methods allowed the thorough examination of the ultra-structure in the living matter and consequently the better understanding of the aging process (Table 1) at all organizational and integrational levels [3, 8]: molecular, cellular, tissular, organic and organismic. This allowed multiple organic and functional parameters (indicators) to be established, which differentiate the young and old organisms.

A large number of morpho-functional indicators (structural, physiological, biochemical, clinical) have been included in the biological evaluation.

Table 1

Biological bases of the pathogenesis of aging



CRITERIA OF AGING, BASED ON CHANGES IN THE STRUCTURE OF THE ORGANISM

The molecular aging includes changes in the structure, stability and specificity of the proteic macromolecules, of great biological significance, with slow or absent turnover: nucleic acids (particularly the DNA from the fixed postmitotic cells) and the connective tissue proteins in which the morphologic evolution is greatly dependent on age. The aging of the collagen macromolecule appears as the spontaneous evolution of the adult collagen and is characterized mainly by the increasing number of covalent, intra- and intermolecular crosslinks and the decreasing amount of soluble material (proline, hydroxyproline). With the nucleic acids, the increasing number of stable bindings between histones and DNA triggers the impairment or loss of genetic information, or the ability of synthesizing the proteins with highly significant biological value (enzymes, hormones). The cell genetic control apparatus is known to represent the key of the primary aging process at the molecular and cellular level.

The aging of the cells and tissues should be analysed in relation to their degree of differentiation. With the higher organisms it is not uniform, manifesting an asynchronous evolution in the various structures. A series of quantitative and qualitative changes define the morphologic aging in cells and tissues: the diminished regularity in the distribution of the cells through the tissues, greater variability in the size of the cells, reduction of the nucleo-cytoplasmic ratio, aspects of cellular atrophy and degeneration, as well as compensatory hypertrophy, variation in the size, form and staining of the nucleus, nucleolus and organelle, fatty or pigment infiltrations into the cytoplasm, vacuolar or hyaline degenerations.

The biochemical aspects of the cellular and tissular aging, which are the substrate of the morphological aging consist mostly in the decrease of the cellular proteic nitrogen, reduction of DNA and RNA synthesis, increase in Ca, lipid, cholesterol, lipofuscin, etc., cellular inclusions, increase in the amount of Ca from the cell membrane, complex modifications of the cell enzymatic activities, decrease in the amount of vitamins and cofactors from the tissues, changes in the cell electrolytes (increase in the amount of cellular Na, decrease in the amount of K), biochemical changes in the cell energy metabolism [3].

The morphological and the biochemical aging in the bradytrophic tissues with decreased O_2 consumption (cartilages, arterial walls, tendons, crystalline lens, cornea, etc.), where it occurs as dehydration and increased density, is different from the aging of the tachytrophic tissues with increased O_2 consumption (brain, muscles, etc.) where it means loss of active metabolic substance, atrophy and sclerosis, resulting mainly from the changes in cell permeability.

In numerous researches the connective tissue is granted an important part in the aging of the entire organism. The biophysico-chemical age changes are connected particularly with the intercellular structures of this tissue: the increase in the total collagen amount, increase in the covalent crosslinks within the collagen molecule, increase in the number of fibrillar structures, expansion of globular collagen, decrease of elastin, increase in the action of elastase, increase in density of the argentaphil fibres, diminution of the basic, amorphous fundamental substance.

The age changes in the structures of the organism considered as a unitary entity are essentially characterised by a linear regression in the number of units which make up the metabolically active cellular mass. The regression of the active cellular mass is asymmetric and asynchronous with different organs or even within the same organ. A nearly 30% regression was estimated in the metabolically active cellular mass (10 to 50% according to the type of cell) in parallel to the decrease in the water amount of the organism and to the increase in total lipid amount.

As an adaptation to the regression of the cellular mass attended, the reduction occurs in the blood globules with the aged (with no obvious functional impairment and a relatively constant plasma volume, directly proportional to the vascular capacity).

METABOLIC CRITERIA IN AGING

The essential peculiarity of the biochemical framework with normally aging elderly and old individuals is a marked lability of the general homeostatic balance, manifest through the decreased adaptative abilities under stress. The classical pattern of the metabolic aging at the humoral level is characterised by a general tendency to increase during the VI and VII decades of the biochemical values for the factors involved in the lipid metabolism and blood coagulation.

The serum albumins and heparinoid substances tend to decrease; the diminution of the former is part of the general so-called 'anabolic deficit', the decrease of the latter is highly significant for the concomitant total disorders in hypercoagulability, hypofibrinolysis and dyslipemia, similar and closely correlated with the atherosclerotic and thrombotic types of fundamental biochemical lesions (Tables 2, 3, 4, metabolic indicators in normal aging) [3].

Table 2

Biochemical indicators of lipid metabolism in aging

Main peculiarity: THE DECREASE IN THE RATE OF THE LIPID METABOLISM IN SENESCENCE

DEPENDENT ON:

1. *Impairments in the intestinal absorption of neutral fats*
2. *Abnormalities in plasma lipid transport*
   - abnormalities in the proteic support
   - abnormalities in plasma hydrolysis
3. *Decrease in lipid catabolism*

   dependent on:
   - glucose insufficient metabolism: insufficient amounts of NADP-H_2 (through the hexoso-monophosph. cycle) and alphaglycero-phosphate
   - changes proper to the adipose tissue (cytological and of the vessels)
   - changes in the factors of *hormonal regulation* (decrease in the action of gonads and hypophyso-adrenal axis), *enzymatic balance* (L.P.L., elastase, transaminase) and *vitamin balance* (particularly pyridoxine)

MANIFEST BY:

Dysmetabolism of the adipose tissue

- increase in the total fat amount of the organism
- decrease in the metabolism of the adipose tissue, pointed out by:
  - incorporation of C14-acetate and C14 palmitate
  - O_2 uptake
  - decrease in reactivity to catabolic factors: epinephrine, norepinephrine, growth hormones.

Plasma lipid dysmetabolism

- Hyperkilomicronemia
- Increase in most of the lipid fractions levels
- Alteration of the lipid uptake dynamic curve.

Table 3

Biochemical indicators of glucide metabolism in aging

Main characteristic: DECREASE IN THE TISSULAR GLUCOSE UPTAKE IN SENESCENCE

DEPENDENT ON:

Primary tissular changes in aging

- decrease in number of active cells and glucose uptake, for synthesis or energogenetic reasons
- decrease in tissular enzymatic equipment

Age changes in the efficiency of the glycoregulatory mechanisms

- deficiency of the precocious insulin response
- decrease in the biological efficiency of circulatory insulin

MANIFEST BY:

- Decrease in the rhythm of extracellular glucose renewal
- Diminished glucose supply to the tissues
- Decreased glucose tolerance, in senescence

Table 4

Biochemical indicators of protein metabolism in senescence

Total proteinemia within physiological limits

Hypoalbuminemia (with moderately decreased turnover)

Hyperglobulinemia

alpha	compensatory
beta	or
gamma	sum total of accumulated
fibrinogen	immune reactions

Decrease in the A/G ratio

- positivity of routine tests in dysproteinemia
- electrophoretic: frequent aspects of secondary dysglobulinemia

Changes in the content of some free amino acids
Hyperpolypeptidemia
Increase in oxidated glutathion
Blood urea levels at highest upper limit
Moderate hyperuricemia, with decreased uric acid clearance
Discrete normo- or hypercreatininemia
Hypercreatinemia, with creatinuria (frequent with the age 50–70)

In the normal aging, the entire metabolic activity in close correlation with the structural age criteria is carried on under conditions of slow, progressive regression of the metabolically active cellular mass (advanced as total indicator in the evaluation of age), decrease in O_2 consumption and general biologic activity. The age criteria of the intermediate metabolic activities (decrease in total hydration and hydroelectrolytic turnover, tissular and humoral lipid dysmetabolism, decrease in glucide tolerance, frequent onset of a negative nitrogen balance), present particularly under stress, appear largely dependent on the impairment of cell enzymatic equipments, intermetabolic feed-back connections and age-induced morpho-functional peculiarities of the neuro-endocrine system.

CRITERIA OF FUNCTIONAL AGING

As a result of the structural and metabolic involution, the impairment in adaptative reactions, the functional parametres of the organs and systems change. The functional age can be estimated based on a complex of criteria. The Romanian gerontologists have had a remarkable contribution in pointing out the most characteristic indicators.

1. Cardiovascular criteria. The cardiovascular age indicators reflect the interrelationship of the functional complex heart — circulatory system. They are pointed out by the main clinical, electrocardiographic, metabolic, radiologic, coronarographic, plethysmographic investigations [1, 5, 7]. The evaluation of the cardiodynamic parametres revealed a latent insufficiency in the aging heart. Among the factors which induce the decrease in the cardiodynamic performance with advanced age, the changing in geometry of the left ventricle is one of the most important [6].

2. Criteria of aging in the nervous system. Starting with the VIth decade, a significant decrease was noticed in the conduction speed of the nervous influx along the axons as well as a gradual increase in the latent period. At the level of the cortical neuronal networks, the slowing of the alpha rhythm was found as well as the progressive increase in the percentage of slow waves which become significant with the Vth decade. The neuraxial aging is more obvious in the psychometric tests. The progressive decrease of the subjects' reliability was pointed out, which follows an exponential curve starting with the age of 20. This phenomenon was noticed both with the simplest and the integrated functions (cognitive, creative).

3. Criteria of aging in the respiratory apparatus. The involutive changes which occur in the lungs are in the first place the result of the diminished elastic retraction force. The pulmonary mechanisms display an increased static compliance, dependent on frequency.

4. Kidney age indicators. The elementary, minimum combined and complex combined criteria point out the decrease in the glomerular filtrate, secretion capacity and tissular resorption, decreased ability to adapt to take up tests or to hydric restriction tests.

5. The peripheral hematologic indicators reflect the diminution of the medullary hematopoietic tissue, the decrease in the medullary mitotic and maturation indices.

6. The lability of the internal homeostasis. The decreased adaptative ability leads to the impairment of the acido-basic balance and electrokinetic processes from the internal medium. The changes in the electrokinetic potential of the blood elements are quite important in the case of platelets, because they favour hyperadhesiveness and thrombocytic aggregability. The researches carried out at the National Institute of Gerontology and Geriatrics have pointed out a humoral context characterised by dyslipemia, dysglycoproteinemia, increased concentration of coagulation factors, antithrombine decrease, impairments in the vascular wall, thrombocytic hyperadhesiveness; all these elements reveal the onset of thrombophilia in the aged.

7. The hypofunctionality of the immune system. This involves the ability to detect the non-self and to recognize the self, either normal or changed, which is equivalent with the loss of the born tolerance to some autocomponents. The insufficiency of the 'immune control' on the accumulation of new antigen carrier cells — resulting mainly from the wear of the thymodependent system — is considered by some authors the essential cause of senescence.

Beside the clinical, biological and psychological criteria individually elaborated research efforts aimed at finding new synthetic indicators at populational level [3].

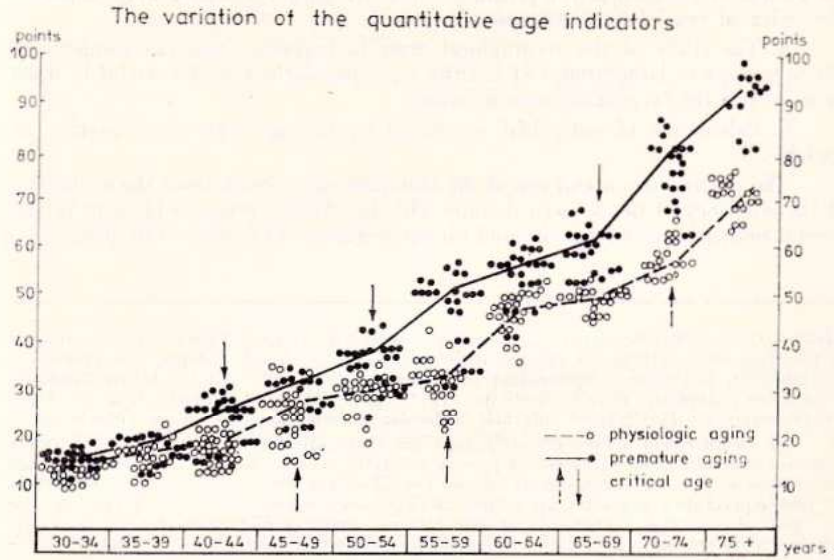


Fig. 1

Such an indicator is the 'mean biological age', which takes into consideration clinical, morphological, physiological, biochemical and morbidity data. The statistical and mathematical analysis of cohort morbidity data resulted in the elaboration of morbidity tables, used in the determination of the mean biological age and aging clock.

The static analysis of the age criteria is the quantitative expression of the age-induced qualitative changes (Fig. 1). The proportional quantification in relation to the importance of each criteria in the aging process allows the evaluation of the biological age both for individuals and communities, by means of sum totals.

In conclusion, the present methodology can be used for the evaluation of the biological age at individual and populational levels. Despite the progress achieved in the elaboration of criteria to define the morpho-functional age, there are still many unknown facts which have escaped researchers' attention.

Nevertheless, there are a few facts to point the way of future researches:

1. The Romanian gerontologists consider that the biologic condition of the individual can be evaluated by means of a large number of tests. The use of such batteries of tests in the course of longitudinal studies — as the one carried out at the National Institute of Gerontology and Geriatrics — will allow a comparison between the indicators specific to individuals with premature or accelerated aging and those of the longevous [2].

2. Elaboration of tests under stress.

3. The tests which proved useful should be maintained and the same prospective indicators included in the program, such as: anthropometric, work capacity, the index of cranial bone osteoporosis, etc.

4. The study of the geographical areas in longevous and the incidence of the longevous in large groups of healthy aged populations is also useful in order to point out the favourable natural factors.

5. Calculation of individual age based on the age regressive equation, as variable.

The determination and use of the biological age criteria allow the evaluation of the efficiency of the modern therapy with Dr. Aslan's products [4] with fundamental contribution to longevity and the prolongation of the active life-span.

Résumé. On présente, basée sur les recherches effectuées à l'Institut National de Gérontologie et Gériatrie, une synthèse des critères utilisés pour évaluer l'âge biologique et le rythme de vieillissement. Ces critères représentent les caractéristiques fondamentales du vieillissement, la baisse de l'adaptation et de la réactivité. Les indices de l'âge sont groupés dans les types d'organisation et d'intégration suivants: moléculaire, cellulo-tissulaire et de l'organisme.

Le vieillissement moléculaire est indiqué par l'intensification des « crosslinks ». Le vieillissement cellulaire et tissulaire est un processus sélectif, asynchrone. Le vieillissement normal est caractérisé par une labilité accentuée de l'équilibre homéostatique général. A ce niveau, est très importante l'évaluation des indices de l'âge sous conditions de stress. L'âge fonctionnel peut être évalué seulement par une batterie complexe d'épreuves. On mentionne les principaux critères pour l'évaluation des systèmes cardio-vasculaire, nerveux, rénal, immunologique et du milieu interne.

Les recherches faites à l'Institut National de Gérontologie et Gériatrie ont mené à l'élaboration des indices synthétiques qui servent à la détermination de l'âge biologique au niveau populationnel et individuel.

À la fin de l'article on indique les directions principales des recherches ultérieures. L'âge biologique sera déterminé avec plus d'exactité par des tests complexes, par indicateurs d'effort, l'étude des zones de longévité, en approfondissant les méthodes statistico-mathématiques.

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