is needed in order to single out the key component of the neuroendocrine network relevant for the age-associated decline of thymic factor production.

In the context of neuroendocrine-thymus interactions, it should, moreover, be noted that such interactions do not seem to work only from the neuroendocrine system towards the thymus, but also in the opposite direction. A large amount of experimental evidence now supports the hypothesis that the thymus, possibly through its hormonal products, may affect the neuroendocrine balance either during ontogeny[30] or in old age[29,31]. In particular it has been shown that neonatal thymus graft onto old recipients is able to correct the altered serum level of some hormones, such as T_3 and insulin, and the abnormally low response to beta-adrenergic stimulation[31]. The recovery of this latter aging parameter seems to be achieved through a correction of the cellular membrane density of beta-adrenoceptor, which is usually altered in old age[29]. These findings strongly support the idea that the thymus exerts a widespread influence on the neuroendocrine system, that such an influence is operating throughout the lifespan of the individual and that its deterioration may represent an important component of the aging processes[29].

Conclusions and perspectives

While it is generally accepted that the immune system deteriorates with advancing age, the causes for such a decline and the impact that the age-associated immunological derangement has for the aging of other body organs and apparatus remain areas for future work. In this context a major role undoubtedly is played by the neuroendocrine system, but, due to the complexity of neuroendocrine-immune network, only a multidisciplinary approach will make it possible to step beyond the realm of speculation and finally attain consistent experimental evidence. The experimental findings and the theoretical models developed in the Gerontological Research Department of Ancona, whose foundation and organization represent one of F. Verzár last efforts, are fully confirming the validity of his multidisciplinary approch to the study of aging processes.

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Neurobiology of aging

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Time and memory have sorted out main recollections which now overshadow the details. I met Professor F. Verzar many times. One always appreciated the wonderful harmony of the human qualities, kindness, generosity and punctiliousness of the great investigator. F. Verzar, who came into gerontology already established as an eminent scientific authority, contributed tremendously to the development of the field.

With regard to the mechanisms of aging, Verzar attached much importance to the changes in the nervous system[1]. He found that changes in an organism's adaptation in old age are linked to the changes in the nervous centers[2].

At least two important tasks should be recognized in the neurobiology of aging: first, the identification of the role age changes in the nervous system play in the aging of the entire organism; second, the elucidation of molecular, structural and functional mechanisms of aging of the nervous system proper.

To date, much factual material has been collected which strongly indicates that the most essential manifestations of aging are related to shifts of the central nervous system, i.e. age changes in the psychics, behavior, memory, intellectual and muscle working ability, responsiveness to the environmental stimuli, motor activity, reproductive ability, reliability of homeostasis regulation, adaptation to the altering living conditions, development of age pathology, etc.

Moreover, the concept is being increasingly supported that primary age changes in the brain have resulted in the secondary manifestations of aging in other organs and tissues. The impairment of neural control over their metabolism and function has been observed in the activity of various organs[3]. This manifestation is related to the changes in the centers and periphery, the destruction of nerve endings, the shifts of transmitters and cell receptors. Noteworthy is the resemblance of many manifestations of aging at certain stages of tissue denervation. Changes shown in the intracentral and central-peripheral axoplasmic flow of substances in aging[4-6] which may alter the trophic of neuron and innervated tissues, are significant.

At the same time many questions concerning the implication of the changes of the neural control in old age are still to be answered. What role do the age-induced changes in the central mechanisms and pathways of information transfer to the periphery play in the shifts of the nervous control? What is the pattern of change in the neural regulation of protein biosynthesis in various tissues in aging? In what succession do the disturbances of the structure and metabolism occur in separate cellular organoids under weakened neural control? What is the regular sequence of age changes in the synapses? What changes do the number and state of receptors undergo on the postsynaptic membrane, and how are they related to the phospholipid surrounding and changes in the conformational properties and number of membrane proteins? Does the axoplasmic flow of substances in the nerves undergo only quantitative change? Is it possible to assume that changes may appear in the peptides of the axoplasmic flow of substances and hence the regulation of tissue trophic become disturbed? Is it possible that axoplasmic flow of substances provides the restoration of neuron thus permitting its longer viability? To what extent should one find that in conditions of altered central control, the role of local mechanisms of regulation increases? What is the pattern of change in the ratio between the extent of disturbances of the neural control and the degree of changes in the sensitivity to humoral factors? To what extent can the Cannon-Rosenblueth's law be applied to age changes in the neuro-humoral regulation?

Modern conceptions about the localization of function in the brain require a concrete analysis of age changes in various nervous structures and their involvement in the shifts of the organism's activity with aging. The classical studies done in Pavlov's school are a good example of such a necessary approach. They demonstrated that in aging the capacity for elaborate conditioned reflexes decreases, the internal cortical inhibition weakens, and the breakdown of physiological processes in the cerebral cortex appears more readily. Here, I would like to mention parenthetically that F. Verzar first visited the USSR in 1935 when he attended the 15th International Congress of Physiologists. At that time Pavlov was 86 years old. F. Verzar told me about his meetings with Pavlov and of the remarkable passion and activity of this man.

In recent years, rather extensive though not quite adequate studies have been undertaken on age dynamics of the structure, metabolism and function of the separate brain functions. Great attention is justifiably focused on the hypothalamic-hypophyseal area which is involved in the hormonal control of the organism's internal medium[7-10]. Some authors found the activity of this area to increase with aging, others found it to decrease. At the same time, the hypothalamus is not functionally a uniform system and some of its nuclei are formed at various stages of phylo- and ontogenesis. The functional state of separate hypothalamic nuclei is characterized by the diversely directional changes in their excitability, electric activity, and sensitivity to humoral factors in old age[3].

This causes a disruption of its integral function and jeopardizes the reliability of the regulation of the organism's homeostasis. Important is that cell genetic apparatus is controlled by the hypothalamic-hypophyseal area through the system of corresponding hormones. Owing to this fact there occurs an adaptation of regulation of the protein biosynthesis in the changed activity of the organism. It has been found that the optimal possibilities of the genetic apparatus activity are limited by age changes in the hypothalamic-hypophyseal area. There appears a situation when the periphery is 'still able' to adequately respond, but the centers do not make use of this possibility.

With increasing age, significant changes take place in the striopallidal system of the hippocampus[11-13]. The studies on the psychics, behavior and memory of the aged with regard to possibly correcting the developing disturbances have been, and will continue to be, an important issue in the neurobiology of aging.

Morphological findings reveal an irregular, hetero-

chronic pattern of structural changes in various brain areas. In one structure of the brain for example, in locus ceruleus, the neuronal number falls by 40–50% in aging, whereas in others (in some nuclei of the hypothalamus, midbrain) it does not practically change[14–16]. Moreover, the loss of neurons in various areas of the cortex and the hypothalamus is nonuniform.

It is noteworthy that there is no direct correlation between the number of dead neurons and the degree of functional changes in relation to the brain structure concerned. This is a result of mobilization of the adaptive mechanisms in the remaining neurons.

Not only morphological findings, but also biochemical data misleadingly imply that the phylogenetically younger structures are first and the phylogenetically older structures are last to undergo changes in aging. The research into evolutionary neurobiology of aging will help to answer the question concerning the true succession of aging processes in the brain of higher animals and man. In the course of evolution the mechanisms of neurohumoral regulation have acquired greater importance. How have the mechanisms of aging changed along the perfection of the nervous control over cells and tissues? The lifespan is determined not only by aging, but also by the processes of vitauct (vita - life, auctum - to prolong) aimed at an enhancement of the organism's viability. Is it possible to postulate that the perfect mechanisms of brain activity primarily determine the course of vitauct processes and then become deficient giving rise to a rapid development of aging processes? How do the most essential intracentral, cortical-subcortical interrelations and those within the limbic system, etc. change? Why was so little research carried out on the physiological characteristics of the brain stem and vegetative centers of the medulla oblongata which determine the basal level of regulation of the most vital functions of the organism? What age changes are there in the function of a number of brain structures which are characterized by a high level of transmitters (for example, substantia nigra, locus ceruleus)? Couldn't they play a special role in the mechanism of aging of the separate brain systems? What is the electric excitability, electric activity and sensitivity to humoral factors in the various central nervous structures? How do the main afferent flows in the brain change with aging? What is the pattern of change of the ratio of nervous and humoral feedback control in the system of regulation of organism's functions? Should one not extend the systemic principle, the laws of self-regulation to the brain activity in aging? Is it possible to explain many disturbances in the neurohumoral regulation by the changes occurring in the receipt of the signals at the stage of the feedback control thus resulting in peculiar desinformation of the centers about the state of the organism's internal medium? In what measure does this lead to the inadequate information at the stage of the direct control?

Aging of the nervous system limits the adaptive possibilities and facilitates the development of age pathology. With aging the course of stress, thermoregulation, digestion, reproduction, etc. undergoes changes. The arterial hypertension, ischemic disease of the heart and brain, obesity, diabetes, tumours, etc. develop more frequently among the elderly than in other age groups. To what extent does aging of the nervous system determine the biological age of animals and man? What is a concrete neurophysiological mechanism of changes in the adaptive reactions with aging, and to what structures and metabolic shifts is it related? What is the ratio of the central and peripheral links of the direct and feedback control in the forthcoming shifts of adaptation? What are the possible ways of correcting these mechanisms of self-regulation? What is the ratio of age-related and pathological changes in the brain? What are the limiting links in the system of age changes of the neurohumoral regulation predisposing an onset of the diseases? What are the peculiarities of development of the pathological processes being modeled in old animals? It has been found that the development of arterial hypertension and coronary deficiency created by chronic stimulation of the hypothalamus, denervation of the aortal arc and sinus carotid, and vasopressin administration has a different pattern in old animals than in adults[17]. Does this not evidence the specifics of pathogenesis of many diseases occurring in old age? Doesn't this indicate the nonuniform involvement of nervous and humoral factors at their onset in different age periods?

There is a clear discrepancy between the knowledge we have from the rapid development of general neurophysiology and the poorly studied age changes in the neuronal function in aging. What are the electric reactions of neurons in different populations in old age? What are the main biophysical properties of their membranes in aging? What is the pattern of change in the active ion transport, ionic canals, membrane enzymes, membrane phospholipids, etc.? What are the functional and structural changes in the presynaptic endings and on the postsynaptic membrane? What are the changes in the ability of rhythm transformation, etc.? What are the changes in the neuro-glial-capillary complex? How does the transport of substances from the glia to the neuron change? What change does the neuronal function undergo in the connection with a change of the glia?

The experimental data have shown that in aging the changes occur in the ratio of inhibitory and excitatory postsynaptic potentials, interneuronal functions, and intracentral subordinatory influences. The cortical-spinal, reticulospinal, spinal reciprocal and segmental inhibitions, the internal and external inhibition in the cerebral cortex weaken[17].

The studies on the membrane receptors and the turnover of transmitters[18-20] have contributed greatly to the explanation of the neuronal reactions. Ultimately, the structural and metabolic changes in nerve cells make their 'contribution' to an organism's aging by changing the functions of neurons and nervous structures. Therefore the studies on molecular mechanisms of the disturbance of neuronal function in aging should determine the key direction which neurobiology of aging will follow in the future. Isn't there a redistribution of various pathways of energy provision of the neuronal function with aging? Couldn't many disturbances of metabolism of the nerve cell be explained by its partial dereception? In what measure are the changes in the membrane receptors and enzymes of the plasmatic membrane related with the shifts of its phospholipid composition during peroxide oxidation reactions? Is it possible to treat the change in protein synthesis of the neuronal membrane, changes in the relationship between protein biosynthesis and electric properties of the nerve cell, as one of the fundamental mechanisms of aging of the neuron?

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Genetics

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Longevity: A trait under genetic control?

In considering the enormous differences in life spans which distinguish the species of the animal kingdom, gerontologists have repeatedly affirmed that longevity is a genetically determined trait. What does that assertion exactly mean? Does it mean that the interspecific differences in life span are genetic in origin? Or does it mean that the potentially large intraspecific differences in life span are genetically determined? Or does it mean that both the inter- and intraspecific differences are under genetic control?

Inter- and intraspecific differences in life span

If one considers the respective sizes of the mayfly and of the elephant one may claim that because these sizes are so different they are genetically determined. However, does one, by that claim, really gain any insight into the mechanism of the genetic control of size in mayflies and in elephants? For an individual to reach the normal life span characteristic of the species to which he belongs implies a proper development of the zygote and of the embryo, a harmonious growth and, once the adult stage is reached, accurately balanced maintenance activities. All these phases of development, growth and life maintenance may be affected by genetic accidents which ultimately may result in death. For example, in humans, a supernumerary chromosome may lead to an impaired development of the embryo; mutations at the loci responsible for chondriodystrophy or for progeria will considerably modify growth; the mutation of the gene responsible for insulin production will significantly impair the maintenance activities. These genetic interferences with development, growth and maintenance activities will eventually result in a premature death. Such accidental deaths, although due to genetic causes, have no relation whatsoever with the normal life span of the human species. They certainly do not demonstrate that human life span is genetically controlled. Neither do they demonstrate that the difference in life span between man and *Drosophila*, for instance, is under genetic control.

In a way which is typical, we believe, of the actual approach to the research in gerontology, Sacher and