sportsmen and -women are less than 40 years old—can be seen in Area 6 with its early shrinkage of the neurons. However, we do not find a loss of neurons. But, the mental activity continues at least up to the age of retiring. This can be explained by the behaviour of Area 11, in which the decrease of perikaryon size does not begin until the 60th to 65th year of age. This result also supports the "use it or lose it" position. Our findings on the stability of the cortical capillary wall may explain why the brain is able to reconstitute a part of its functions, for example, after damage such as a stroke.

Our findings of the human brain concerning the biological aging permit the following statement: without a noteworthy loss of neurons but within a genetically determined decline of the finer brain structures and their functions during the older aging, "use it or lose it" can inhibit the speed of the functional decline. But, of course, "use" is not able to preserve the brain and its function permanently. Nothing of our findings speaks for "wear and tear."

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From Here to Eternity: Brain Ageing in an Evolutionary Perspective

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There is plenty of evidence to show that a high metabolic rate slowly destabilizes the optimal differentiated state of cells as a result of nonenzymatic processes. Because of the continuing high energy demands of the brain in homeothermic organisms, an evolutionary expansion of this organ has to go with the development of maintenance systems which effectively counteract these degenerative processes. Thus the nerve cells in more encephalized and longer-lived species are probably inherently more stable in maintaining their cellular and molecular integrity in the presence of destabilizing insults than do low encephalized species with short life spans.

"WHY do we live as long as we live?" This question, related to the classical philosophical problem of transiency and the finitude of life, has fascinated mankind ever since the dawn of civilization (2). Although age changes are one of the few universal properties of living organisms it is only in this century that a number of serious theories have been proposed to explain the nature of biological ageing [for reviews, see (10,11)]. These theories, which explore the mechanisms of ageing from the molecular level up to that of the whole organism, can be divided into two basic categories, viz., stochastic theories, which rely on the random accumulation of detrimental events, such as free-radical damage, and nonstochastic or genetic theories which suggest that a series of ageing processes is innately programmed within the genome of each organism.

In his remarkable comprehensive and scholarly review of the literature dealing with studies on neuronal ageing, Swaab (23) discusses a new hypothesis on the etiology of brain ageing in which both stochastic and genetic concepts are involved. Swaab argues that in the brain, as in other organs, enhanced cellular metabolism results in increased cell damage, e.g., through the formation of free radicals, and, consequently, in a reduction of the neuronal life span. On the other hand, activation of nerve cells within the physiological range would not only stimulate the cell metabolism and thus the possibility of increased cell damage, but would also activate protecting mechanisms against oxygen toxicity and DNA repair mechanisms, which effectively counteracts the continuous deterioration of DNA. The protective mechanisms, according to Swaab, would outbalance the deleterious effects of oxygen metabolism after intense neuronal stimulation and so protract or even prevent neuronal ageing. In other words, the brain is a unique organ: the more active it is, the more adequate it functions and the longer it lives.

ENERGY METABOLISM AND AGEING

It could be expected, however, that natural selection acts on protective mechanisms for increasing the stability and functional integrity of the whole organism, not only that of the brain. The evolution of increasing body size in mammals, for instance, has been accompanied by a reduction of the mortality rate and a corresponding increase in longevity (19, 20, 24). The correlate of body size, most often associated with mammalian longevity, is the rate of energy metabolism prompted by observations that life span in homeothermic organisms has a strong inverse relation to the metabolic rate per unit body mass. In other words, large mammals would tend to live longer because they metabolize at a lower rate, leading to a slowing of all long-term processes, including ageing. The rationale behind the link between metabolic rate and life span is that life at a high constant body temperature requires a high oxygen consumption which slowly destabilizes the optimal differentiated state of cells as a result of nonenzymatic processes (3, 5, 9–11). An increase in body size, therefore, which results in a lower specific metabolic rate, would be a relatively simple means of reducing the deleterious effects of the energy transformation required to maintain the cellular and molecular integrity of the system.

Although energy turnover may indeed be a major determinant of longevity, the metabolic life span concept is an oversimplified view of ageing, because it cannot account for certain conspicuous differences in maximum life span among species of equal metabolic rate and body temperature (2, 6, 13, 15, 17). Exceptions like man indicate that the thermodynamic "efficiency" of some organisms may be higher than that of others. Some species may indeed have evolved counterentropic mechanisms. This hypothesis is an accord with the model of dysdifferentiation, proposed by Cutler (3–5), which says that the ageing rate of an organism is directly related to the innate ability of the cells of that organism to maintain their proper state of differentiation as a function of time. Since cells are inherently unstable as a consequence of natural instability of DNA and the long-term interaction of the genetic apparatus with epigenetic-mutation-like processes, the ageing of an individual is considered to be largely a result of a time-dependent dysdifferentiative process, in which the proper differentiated state of cells slowly destabilize. A reduction of these continuously acting biosenescent processes such as the oxidative metabolic reactions producing free radicals could increase the cellular life span (1,8). Minimizing these deleterious reactions by counteracting longevity determinant processes, such as DNA repair processes, free radical scavengers, detoxification processes, and decreased rates of development and differentiation, would reduce the degenerative rate of these processes and accordingly increase the life span of the organism. According to this model, repair and protective mechanisms have evolved in homeothermic organisms rather than senescent or ageing processes.

EVOLUTION OF BRAIN SIZE AND LONGEVITY

The evolution of homeothermy with its crucial reproductive innovations uniquely linked with metabolic energetics, also allowed increased diversity in growth rates and generation time (7, 14, 16, 18, 22). A decreased number of generations in a period of time and an extended life span, for example, would confer an advantage to a species in that it diminishes the propensity of DNA to incur changes in sexual recombination and reduces the overall opportunity for mutations to occur in the genome (10). In this sense, an extended life span can be considered a device utilized by a species to protect its genomic integrity. On the other hand, K strategies, which are characteristic of these stable conditions, allow the evolution of larger and more complex brains. As a result, the precision of the neural processes and the functional capacity of the nervous system will increase, and with that, the organism's ability to cope more adequately with specific problems related to food supply, predation, reproduction, physiological maintenance and homeostasis. The evolution of relative brain size, in other words, is an essential dynamic survival mechanism. Because of the continuing high energy demands of the brain, an evolutionary expansion of this organ has to go with the development of extensive, perhaps even new, maintenance systems which act to stabilize the brain's proper state of differentiation against the destabilizing effects of the pleiotropic by-products of energy metabolism. Thus the nerve cells in more encephalized and longer-lived species, such as some dolphins and primates including man, are probably inherently more stable in maintaining their cellular and molecular integrity in the presence of destabilizing insults than do low encephalized species with short life spans, such as rodents and insectivores. It might explain why the life span of postmitotic neurons in the human brain is about 15 times longer than that of rats, whereas their internal structure and physiological properties are basically the same. Whether or not this genetic program of repair and protective mechanisms can be activated by simply increasing the cellular activity, as Swaab suggests, remains hypothetical. However, if these "longevity-assurance genes" can be activated, it supports the view that natural selection acts on mechanisms for increasing the stability of the organism, instead of a genetic program that codes for age changes. In this respect, the study of life maintenance systems may be more productive than the current emphasis on programmed theories of ageing (12).

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Is the Pattern of Nerve Cell Loss in Ageing and Alzheimer's Disease a Real, or Only an Apparent, Selectivity?

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The pattern of neuronal loss from the brain in Alzheimer's disease (AD) is selective, not on the basis of neurotransmitter type, metabolic character or trophic dependence, but only in relationship to the anatomical connection of all affected cell types with the association cortex. The "selectivity" of the process of AD seems to lie with local factors within the cerebral cortex whose presence (or absence) links the processes that lead to the deposition of amyloid (A4) protein, to the neuritic response that results in the production and accumulation of abnormal tau proteins and which, ultimately, form the neurofibrillary tangle and bring about the demise of the neurone.

DR. SWAAB puts forward the view that ageing of the human nervous system carries with it an inbuilt vulnerability of certain neuronal types and that this may be mediated, in part, by an "under-usage" of such cells, consequent upon their suboptimal stimulation through a lack of various activity promoting factors. The preferential and additional (for age) loss of certain nerve cell types in Alzheimer's disease (AD) is considered to represent an extreme version of the same (kinds of) processes that dictate neuronal vulnerability during ageing alone. However, it is necessary to establish whether there are indeed specific patterns to the cell loss of ageing and AD and whether these overlap in any significant degree. If the answer to both these questions is affirmative, then it is reasonable to enquire as to the common basis underlying such patterns.

In "normal" human ageing a progressive loss of neurones from the cerebral cortex (1, 3, 4, 11, 24, 37), hippocampus (2, 24, 28, 32), substantia nigra (17,22), locus coeruleus (22, 27, 42), nucleus basalis of Meynert (18,23), cerebellar Purkinje cells (9), suprachiasmatic nucleus (35) and mammillary bodies (43) has been reported. By contrast, no such changes apparently occur in the dentate nucleus of the cerebellum (9), the cochlear (15), trochlear and abducens (40,41) cranial nuclei, the supraoptic and paraventricular nuclei of the hypothalamus (36) and the inferior olivary nuclei (29,30).

In AD there is a neurofibrillary degeneration and loss of the large pyramidal cells of the frontal and temporal neocortex (13, 24, 31, 38), the stellate cells of the entorhinal cortex (14), pyramidal neurones of CA1, CA4 and subiculum of the hippocampus (2, 24, 32), neurones of the amygdala (12,33), nucleus basalis of Meynert (18,22), parabrachial and pedunculopontine nuclei (6), medial thalamus (6), locus caeruleus (22, 39, 44), ventral tegmental area (6, 7, 25), dorsal raphe (6, 22, 44), suprachiasmatic nucleus (35) and from several lateral nuclei of the hypothalamus (33). Nerve cell types essentially (though not always entirely) spared include substantia nigra (6, 7, 22, 25), medial (33), supraoptic and paraventricular nuclei of the hypothalamus (36), lateral nuclei of the thalamus (6), mammillary bodies (33), dentate and Purkinje neurones (26) and olivary and pontine neurones (Mann, unpublished data).

Within vulnerable cell groups such as the noradrenergic locus coeruleus and the serotonergic raphe, a topography of cell loss is apparent (27,44), such that a preferential decimation of neurones occurs in the dorsal and rostromedial parts of the locus (27), and within the dorsal raphe rather than the nucleus centralis (44).

Comparison of these lists shows much overlap between the observed pattern of cell loss with ageing and that with AD, though there are notable differences (e.g., in ageing, there is a