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Aging – Molecular aspects

Kalluri Subba Rao

Department of Biochemistry, University of Hyderabad, Hyderabad 500 134, India

DUE to the rapid strides of progress in medicine and health care practices, the average human life span has been on the increase during the past 100 years. Consequently, there has been a steady rise in that fraction of the population which is above 60 years. For example, it is estimated that today there are about 60 million persons in India who are above 60 years of age. If the present trend continues, it is expected to touch the 100 million figure soon after the turn of the century. The

picture is more alarming in the case of developed countries like USA, if one considers the percentage of population above 60 years.

How old age is viewed in a society is a cultural issue. How an organism becomes old is a biological question. However, deterioration in mental function is both a biological as well as a sociological issue. The study of the aging phenomenon is termed as *gerontology*. If the study emphasizes on the brain or the central nervous

system (CNS), then it become neurogerontology. It appears that human beings are the only creatures on the earth who are haunted by being conscious of their imminent mortality. It is also clear that death can occur at any age through a fatal accident or through failure of a vital physiological function. Mortality, on the other hand, can also merely be an end point of a physiological process called aging or senescence – characterized by deterioration of all physiological activities, including the mental capacity, and increased proneness to infection and disease, thus making this section of the population dependent on the rest of the society. It is this second aspect that has attracted the attention of scientists as well as administrators to explore the possibility whether through appropriate research 'healthy aging' can be achieved so that aging population could actually be converted into an asset to the society rather than being a liability. Indeed, the US government, realizing this need, had started a separate Institute for aging research, The National Institute on Aging, more than 15 years ago!

International status

The real support to gerontological research has come only during the last 30 years, mostly because of the advent of molecular biology, which provided tools to look at the various physiological processes at the molecular level. Thus, a great volume of literature on the possible mechanisms behind the process of aging has already accumulated. Several theories have been proposed on the basis of experimental observations as well as through intuition.

Many reviews have appeared in the recent times to summarize all the information available, as also to evaluate critically the various theories of aging. Some of these emphasize the genetic factors as determinants of the process, while the others give importance to random accumulation of damage such as that caused by mutations, errors and free radicals, in addition to the genetic component¹⁻⁸.

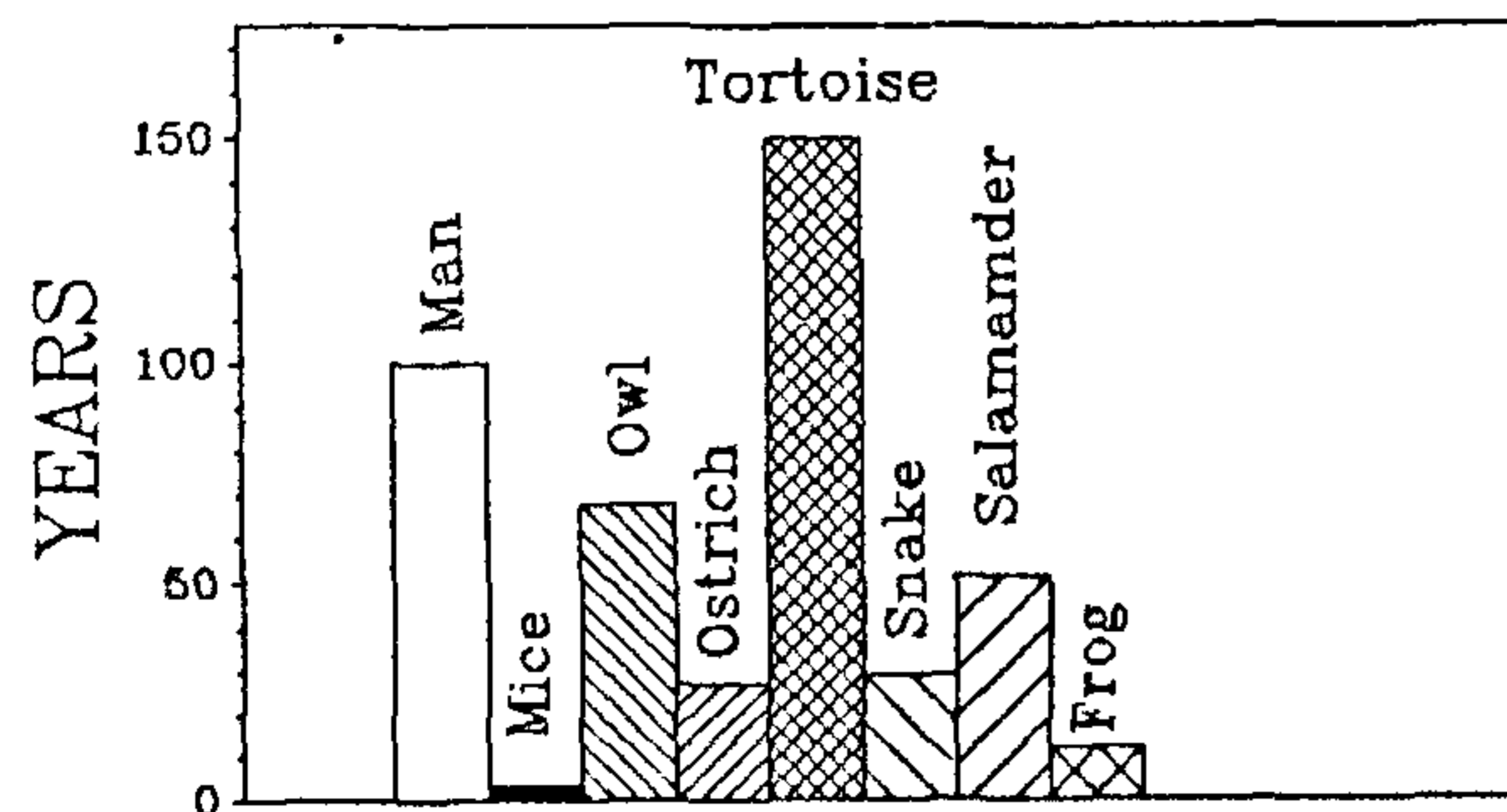


Figure 1. Maximum life span of different species. Note the difference between man and mice – both mammals

As a result of extensive research activity all over the world during the past 20 years to understand the phenomenon of aging, the following major conclusion has emerged:

The process of aging is genetically programmed, involving changes in gene expression

This conclusion is based on a multitude of experimental observations on the following lines:

1. Different species have different maximum life spans but for a given species the maximum life span appears to be fixed (Figure 1). For example, in humans the maximum life span that could be achieved may be taken as 100 years. However, it must be noted that all the individuals do not reach this maximum point due to a variety of factors. Thus, the average life span of humans is generally considered to be around 70–75 years in the western countries, while in India it is about 59 at present.

2. There is a curious link between the reproductive phase and the onset of the aging process, both phases exhibiting a temporal relationship – no matter what the actual length of life span is in a given species⁵.

3. There is considerable evidence that genetic damage (DNA damage) accumulates with age and the mechanisms to repair such a damage are not efficient enough in old age⁹⁻¹³.

4. Since DNA damage and its repair show a correlation with the aging process, it is postulated that neuronal cells, being post-mitotic, offer a good model system to study this correlation¹⁴.

5. DNA repair is a discrete process and does not occur in a homogeneous fashion throughout the genome. Genes which are transcriptionally active undergo repair in a preferential manner. Also, DNA repair occurs selectively in the transcribed strand of a gene. However, in neuronal type of cells, both the strands of active gene are repaired with equal efficiency¹⁵.

6. A number of human syndromes where premature aging is seen are found in nature. In some of these disorders neurodegeneration and defective DNA repair are also seen (Table 1)^{12,16,17}. Thus, aging is a multigene-dependent phenomenon.

7. Some genes responsible for senescence, DNA repair as well as certain neurodegenerative disorders in humans are discovered now¹⁸⁻²¹.

8. It is possible to correct some defects found in the above-mentioned syndromes either by somatic hybridization or through microinjections of appropriate factors^{22,23}.

9. Manipulations that could lead to decreased oxidative damage to DNA have been found to prolong the longevity in experimental animals^{24,25}.

10. There is hope that by suitable genetic and dietary intervention, the aging process could be modulated and,

Table 1. Genetic disorders that show signs of elevated genomic (DNA) damage/premature aging/neurodegeneration

Disorder	Symptoms		
	Genomic damage	Neuro-degeneration	Premature aging
Ataxia telangiectasia (Louis-Bar syndrome)	+	+	+
Cockayne's syndrome	+	+	+
Down's syndrome	+	+	+
Xeroderma pigmentosum	+	+	-
Huntington's disease	+	+	-
Parkinson's disease	+	+	-
Alzheimer's diseases	+	+	-
Friedrich's ataxia	+	+	-
Amyotrophic lateral sclerosis	+	+	-
Familial dysautonomia	+	+	-
Usher's syndrome	+	+	-
Bloom's syndrome	+	-	-
Fanconi's anaemia	+	-	-
Werner's syndrome	+	-	+
Progeria (Hutchinson-Gilford's syndrome)	?	-	+
Turner's syndrome	-	-	+

Information reproduced from ref. 7.

more importantly, debilitating aspects of old age could be eliminated.

National scene

Although there exist several groups in India working on diverse aspects of aging, there are only a couple of centres working actively on the molecular aspects of aging – the group at the Zoology Department of Banaras Hindu University, headed by Prof. M. S. Kanungo, and the other group at School of Life Sciences, University of Hyderabad, headed by the author. The third group is also coming up at Cancer Research Institute, Bombay, the leader being Dr. V. S. Lalitha.

The group at Banaras Hindu University believes that aging is due to sequential activation of some genes with simultaneous repression of others at about the time of reproductive phase of the animal. Their extensive studies during the past several years have shown that transcription decreases during old age and this is primarily due to the highly condensed chromatin structure in the brain and other tissues. Using different molecular biological techniques, these workers have come to the same conclusion time and again²⁶⁻²⁸.

The molecular neurobiology group at Hyderabad has been concentrating mainly on examining the accumulation of age-related DNA damage and its repair in rat brain cells. This is the only group in the country which studies aging process exclusively in the brain cells and at the DNA level⁷. The results obtained so far demonstrate that DNA damage (single- and double-strand breaks) definitely accrues in rat brain neurons

with age^{13,29}. It is also shown that, in spite of the increased single-strand breaks, the DNA from an old brain exists in a more compact state, resulting in decreased transcriptional efficiency, particularly the one catalysed by RNA polymerase II³⁰.

It is also shown by the Hyderabad group that isolated neuronal cells in culture offer an excellent model system to examine DNA repair at different ages. It was found that while the neurons from an old brain retain the same basic DNA repair potential (both excision and mismatch repair) as that of the adult neurons, their capacity to respond to a mutagenic challenge like UV light is limited. It is postulated that it is this limitation to cope up with the ever-increasing DNA damage that may be responsible for aging and death in the brain³⁰. Studies are in progress to measure the precise DNA damage that accumulates and also the level of various enzyme/protein factors that are required for the repair of such damage.

Dr. Lalitha's group at Bombay is isolating certain neurotrophic factors elaborated by cancerous cells. It is their aim to characterize these factors and to see whether these factors could be utilized to stimulate quiescent brain cells to grow and divide. This aspect has long-range implications of therapeutic potential, including neuronal transplantation.

Neurogerontology

Neurogerontology is gaining enormous attention of the gerontologists all over the world for two reasons. Firstly, it is clear now (partly because of the work done at Hyderabad) that neuronal cells offer an ideal model for studying age-dependent changes at the DNA level. Secondly, one of the most dreadful and incapacitating consequences of aging is the deterioration of mental function. Several neurological debilities develop occasionally during old age, thus making that part of the life miserable and despicable. Therefore, the subject of age-dependent neuronal degeneration has become one of the topmost thrust areas for research. Indeed, the nineties have been declared as 'The decade of the brain'.

There is no doubt that India should not lag behind in wresting an initiative in an important area like molecular gerontology, particularly because there already exist some groups making active contributions to the area with international recognition. This Indian lead must not be lost.

It is imperative that future research in this field must utilize all the biochemical and molecular biological tools available today. Also important is the fact that this research must be directed at examining the specific genes and their products that become active in the post-reproductive phase of the life span. Accumulation of a particular type of DNA damage and its repair must be

studied in a specific gene. The available technology makes such studies possible. Similar studies can be carried out in various age-dependent neurodegenerative conditions whenever such material is available, in order to pinpoint precisely the genetic defect in such disorders and to launch therapeutic measures at the genetic level or through transplantation of normal cells into the brain area.

Since the chromosomal localization of a number of genes has been established and also cDNA probes are becoming available for many genes, it should be possible to study in a specific gene the conformational state, the damage that is present and the repair of that damage.

What is needed, however, is the establishment of appropriate infrastructural facilities and continued encouragement by agencies like DST and DBT to places where such work is already initiated and there lies promise for meaningful achievements.

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Concept formation

Marcus Devanandan

Department of Neurological Sciences, Christian Medical College, Vellore 632 004, India

In general, a concept is an abstract idea. The Oxford English dictionary also defines it as a rough draft of an idea. In the context of our essay, let us define our concept as an abstract understanding of the external environment and of the development of the manner in which we should react to this environment.

Concept as defined above will encompass several parameters:

1. Abstract analysis of a theoretical situation.
2. Sensory inputs regarding the external environment.
3. Processing and consciously interpreting this sensory information.

4. Storage of this information.
5. Abstract organization of the required motor response.
6. Generation of the motor response and correction of any errors that may be present.

Abstract analysis of a theoretical situation can be a very real part of our understanding of the environment and of the development of the manner of our reaction to it. This is because prior experience enables us to imagine a theoretical situation. We can endow this theoretical situation with the physical properties that we expect it to possess and formulate the necessary reactions. Even if a