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Origins as a Paradigm in the Sciences and in the Humanities

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Contents

Suresh I. S. Rattan

Origins of Ageing Mechanisms and Prospects for Anti-ageing Interventions

I. A Question of Life and Death

Sooner or later, all individuals die out. Although the apparent immortality of a population may overshadow the mortality of its individual members, the lifespan of an individual is not unlimited. Lifespan of organisms ranges from a few hours to hundreds of years, and a vast variety of life histories unfold before the ultimate cessation of life. In biological systems, three main categories of degeneration – rapid, negligible and gradual [1] – can explain most types of life histories that lead to the death of an individual. For example, rapid degeneration is common among species that die during or soon after reproduction. Such organisms generally undergo a single bout of reproduction during their life and are called semelparous, for example salmon fish. At the other end of the scale are organisms in which the rate of degeneration is imperceptible over very long periods and can be considered as undergoing negligible senescence. Various vascular plants, such as bristlecone pine and other conifers; invertebrates, such as lobsters; and vertebrates, such as rockfish and tortoise, belong to this category. The third category, found most commonly in animals, involves the growth and development of the organisms to adulthood and to a period of reproduction followed by gradual and progressive ageing and senescence culminating in death. Generally, species with repetitively reproducing (iteroparous) life histories experience ageing after completing a period of reproductive fitness. It is in this category of organisms, which includes human beings, that the phenomenon of progressive and intrinsic ageing is best manifested during the limited lifespan of the organism.

The main questions are, therefore: (i) what are the mechanisms of ageing and death? (ii) How did these mechanisms originate during evolution? (iii) Are these processes accessible to interventions aimed to delay ageing and thus to increase

1 Caleb E. Finch, *Longevity, Senescence, and the Genome* (Chicago: The University of Chicago Press, 1990).

the lifespan indefinitely? In order to answer these questions, it is important to understand certain basic principles of life processes, which also provide clues towards understanding what prevents these processes from functioning for ever.

II. Life and Homeodynamics

All living systems, in contrast to the non-living systems, have the intrinsic ability to respond, to counteract and to adapt to external and internal sources of disturbance. The traditional conceptual model to describe this property is *homeostasis*, which has dominated biology, physiology and medicine since 1930. However, tremendous advances made in our understanding of the processes of biological growth, development, maturation, and reproduction have led to the realization that homeostasis model as an explanation is seriously incomplete. The main reason for the incompleteness of the homeostasis model is its defining principle of 'stability through constancy', which does not take into account new avenues of thought opened up by cybernetics, control theory, catastrophe theory, chaos theory, information and interaction networks, which constitute the modern biology of complexity.

Since 1994, the term *homeodynamics*, introduced by F. E. Yates, has been increasingly used – though it has not yet fully succeeded in replacing homeostasis. [2] The concept of homeodynamics accounts for the fact that the internal milieu of complex biological systems is not permanently fixed, is not at equilibrium, and is a dynamic regulation and interaction among various levels of organization. Almost in parallel with the development of the concept of homeodynamics, another term, *allostasis*, coined and introduced by P. Sterling and J. Eyer in 1988, [3] has also gained recognition and use. According to the allostasis model, 'stability through change' is the most realistic situation for living biological systems. The model also takes into account characteristics such as reciprocal trade-offs between various cells, tissues and organs, accommodative sensing and prediction with respect to the severity of a potential stressor, and the final cost of making a response and readjustment to bring about the necessary change. Every act of allostasis adds to the *allostatic load* in terms of, for example, unrepaired molecular damage, reduced energy deposits and progressively less efficient or less stable structural and functional components. Ageing, senescence

2 Francis Eugene Yates, 'Order and Complexity in Dynamical Systems: Homeodynamics as a Generalized Mechanics for Biology', *Math. Comput. Model.*, 19 (1994), 49 – 74.

3 *Allostasis, Homeostasis, and the Costs of Adaptation*, ed. by Jay Schulkin (Cambridge: Cambridge University Press, 2004).

and death are the final manifestations of imperfect and unsuccessful homeodynamics.

The key biochemical and physiological pathways and processes of maintenance and repair that constitute the homeodynamic machinery of a living system are:

1) The multiple pathways of nuclear and mitochondrial DNA repair, including those for maintaining the accuracy of the information transfer from DNA to RNA to proteins, and those for the removal of spontaneous lesions in DNA.
2) The processes for sensing and responding to intra- and extra-cellular stressors, such as heat shock response, stress hormones, and ionic fluxes.
3) The pathways for protein repair, such as the renaturation of proteins by chaperones, and the enzymic reversal of the oxidation of amino acids.
4) The pathways for the removal and turnover of defective proteins by proteasomes and lysosomes.
5) The antioxidative and enzymic defences against reactive oxygen species.
6) The processes for the detoxification of harmful chemicals in the diet.
7) The cellular and humoral immune responses against pathogens and parasites, including massive apoptosis (programmed cell death) after the completion of the cellular immune response.
8) The processes of wound healing, blood clotting and tissue/organ regeneration including angiogenesis (blood vessel formation).

In addition to the main categories of pathways and processes constituting the homeodynamic machinery, some other physiological processes can also be included as components of homeodynamics. These processes include temperature control, the epigenetic stability of differentiated cells, and fat storage and energy utilization. Together all these processes give rise to a 'homeodynamic space' within which an individual operates and survives, and beyond which its chances of succumbing to diseases and death increase. At least theoretically, these homeodynamic processes, which are also referred to as the longevity-assurance processes, can work efficiently for ever, and an organism can be immortal – which obviously is not the case.

III. Homeodynamics and Longevity

The so-called longevity assurance processes assure longevity of an organism only in accordance with its evolutionary life history and for the duration required to fulfill its Darwinian purpose of life – reproduction and continuation of generations. In the context of the origin of mechanisms of ageing, it is incorrect to assume that ageing and limited lifespan of an individual had some purpose or

adaptive significance in terms of being advantageous for the species. In natural wild populations the probability of death by accidental causes, including disease and predation, is so high that there is never a significant number of long-lived individuals left that might require special mechanisms to terminate life for the sake of newly born individuals. Even if there were any life-terminating mechanisms that operated after a long period of survival, these would not be capable of resisting the spontaneous origin and evolution of non-ageing and immortal 'mutants', which in a given population would soon take over.

A more widely accepted view is that ageing occurs because natural selection is insufficient to prevent it, owing to its post-reproductive nature, or that senescence is a by-product of the expression of genes with early beneficial traits but deleterious and pleiotropic effects at later stages. Two major schools of thought (whose ideas are not mutually exclusive) in the non-adaptive theories of the evolution of ageing and lifespan are represented by *antagonistic pleiotropy*, [4] and the *disposable soma theory* based on Weismann's distinction between the soma and the germ line. [5] According to these theories, evolutionary forces have optimised conditions for efficient and successful reproduction either by (i) selecting for 'good' early genes that later have 'bad' effects, or (ii) selecting for efficient maintenance and repair of the germ cells at the cost of somatic maintenance. The disposable soma theory [6] considers the evolved life history and the structural and functional design of the organism to be the basis of the evolution of ageing.

Thus, evolutionary forces of natural selection have resulted in evolving mechanisms of maintenance that operate in concert with the complete structural (anatomical) and functional (physiological) design of the organism and assure the survival of the body until reproduction. This has been termed 'essential lifespan, ELS' [7] or 'warranty period'. [8] ELS can be considered as the 'natural lifespan of a species', and is distinct (and usually several-fold shorter) from the average lifespan for a cohort, and from the maximum lifespan observed for a single member of a species. For example, for humans, ELS is considered to be about 40 years; whereas at present the average lifespan in rich countries is between 80 and 85 years, and the maximum human lifespan recorded so far is 122 years, 5 months and 14 days!

4 Michael R. Rose, *Evolutionary Biology of Aging* (New York: Oxford University Press, 1991).
5 Thomas B. L. Kirkwood and Thomas Cremer, 'Cytogerontology since 1881: a Reappraisal of August Weismann and a Review of Modern Progress', *Hum. Genet.*, 60 (1982), 101 – 21.
6 Thomas B. L. Kirkwood, *Time of Our Lives* (London: Weidenfeld & Nicolson, 1999).
7 Suresh I. S. Rattan, 'Biogerontology: the Next Step', *Ann. N.Y. Acad. Sci.*, 908 (2000), 282 – 90.
8 Bruce A. Carnes, S. Jay Olshansky, and Douglas Grahn, 'Biological Evidence for Limits to the Duration of Life', *Biogerontology*, 4 (2003), 31 – 45.

IV. Biological Principles of Ageing: Present and Future Prospects

Biogerontology, the study of the biological basis of ageing, has so far gathered a large body of descriptive data about the age-related changes in organisms, organs, tissues, cells and macromolecules. These data clearly show that the progression and rate of ageing are highly variable in different species, in organisms within a species, in organs and tissues within an organism, in cell types within a tissue, in sub-cellular compartments within a cell type, and in macromolecules within a cell. Although these data imply that there are no universally applicable markers of ageing, three general principles of biological ageing can be derived. [9]

First, the evolutionary *life history principle* describes ageing as an emergent phenomenon taking place primarily in protected environments, which enable survival beyond the natural lifespan in the wild (discussed above). Therefore, from an evolutionary point of view, ELS is the canvas against which genetic selection and functional optimization unfold.

Second, the *non-genetic principle of ageing* specifies that ageing and longevity of an individual are not programmed in specific gerontogenes. Unlike development, which is a highly programmed and well-coordinated genetic process in the evolutionary life history of an organism, there is no genetic programme which determines the exact duration of survival of an organism. However, as regards the role of genes in ageing, there are some misunderstandings that need to be clarified. For example, a lack of specific gerontogenes according to the 'non-genetic principle' does not imply that no genes have any influence on survival, longevity and ageing. There is ample evidence from studies performed on yeast, fungi, nematodes, insects, rodents and humans that mutations in certain genes can either prolong or shorten the lifespan in various animals, and cause premature ageing syndromes in humans. [10] However, it is most important to realise that these genes did not specifically evolve to cause age-related accumulation of damage or to kill the organism. Since their involvement in influencing ageing and longevity is only indirect, they have been termed 'virtual gerontogenes', [11] or 'longevity genes'. [12] Studies on establishing an association

9 Suresh I. S. Rattan, 'The Science of Healthy Aging: Genes, Milieu, and Chance', *Ann N Y Acad Sci*, 1114 (2007), 1 – 10.

10 Huber Warner, 'Longevity Genes: from Primitive Organisms to Humans', *Mech. Age. Dev.*, 126 (2005), 235 – 42; George M. Martin, 'Genetic Modulation of Senescent Phenotypes in *Homo sapiens*', *Cell*, 120 (2005), 523 – 32; Maris Kuningas, Simon P. Mooijaart, Diana van Heemst, Bas J. Zwaan, P. Eline Slagboom, and Rudy G. J. Westendorp, 'Genes Encoding Longevity: from Model Organisms to Humans', *Aging Cell*, 7 (2008), 270 – 80.

11 Suresh I. S. Rattan, 'Gerontogenes: Real or Virtual?', *FASEB J.*, 9 (1995), 284 – 86; Id., 'Ageing, Gerontogenes, and Hormesis', *Ind. J. Exp. Biol*, 38 (2000), 1 – 5; Id., 'Theories of Biological Aging: Genes, Proteins and Free Radicals', *Free Rad. Res*, 40 (2006), 1230 – 38.

12 Huber Warner, 'Longevity Genes'.

between genes and longevity have reported that the genetic heritability of variance in lifespan is less than 35 %. [13] Several studies have reported an association between human longevity and single nucleotide polymorphisms (SNP) in a variety of genes in various biological pathways, including heat shock response, mitochondrial functions, immune response, cholesterol metabolism and others. [14] The complex processes of maintenance and repair involve hundreds of genes whose products and interactions give rise to a 'homeodynamic space', or 'buffering capacity', which is the ultimate determinant of an individual's chance and ability to survive and maintain a healthy state. [15]

The third principle of ageing derived from biogerontological studies is the *mechanistic principle*, which characterizes ageing as a progressive accumulation of molecular damage in nucleic acids, proteins and lipids. Since homeodynamic ability of a living system is primarily due to its maintenance and repair systems, the progressive failure of these processes is the biochemical basis of ageing and age-related diseases. [16] The future of biogerontological research lies in resolving the complex nature of gene-protein networks and the role of molecular damage and heterogeneity in the process of ageing.

V. From Understanding to Intervention: Anti-ageing or Healthy Ageing?

Once it is understood that ageing is an emergent phenotype due to the failure of homeodynamics, and is not due to the action of any harmful and death-causing mechanisms, our approach towards ageing interventions shifts from 'anti-ageing' to 'healthy ageing'. According to the three principles of ageing and longevity described above, ageing occurs in spite of the presence of complex pathways of maintenance, repair and defence, and that there is no 'enemy within' that causes it. All mechanisms and processes in the body have evolved to work towards its survival and maintenance of health, in accordance with the evolutionary history

13 Thomas E. Johnson, Kaare Christensen, and James W. Vaupel, 'The Quest for Genetic Determinants of Human Longevity: Challenges and Insights', *Nature Rev. Genet.*, 7 (2006), 436 – 48; Ripudaman Singh, Steen Kølvraa, and Suresh I. S. Rattan, 'Genetics of Longevity with Emphasis on the Relevance of HSP70 Genes', *Frontiers in Science*, 12 (2007), 4504 – 13.

14 'Genes Encoding Longevity'; 'Genetics of Longevity'; Beáta Bessenyei, Marietta Márka, Lázló Urbán, Margit Zeher, and Imre Semsei, 'Single Nucleotide Polymorphisms: Aging and Diseases', *Biogerontology*, 5 (2004), 291 – 300.

15 'Theories of Biological Aging'; Suresh I. S. Rattan, 'Increased Molecular Damage and Heterogeneity as the Basis of Aging', *Biol. Chem*, 389 (2008), 267 – 72.

16 'The Science of Healthy Aging'; 'Theories of Biological Aging'.

of the species. This viewpoint makes modulation of ageing different from the treatment of one or more specific diseases. [17]

As a biomedical issue, the biological process of ageing underlies all major human diseases, such as atherosclerosis, cancer, cardiovascular defects, cataract, diabetes, dementia, macular degeneration, neurodegeneration, osteoporosis and sarcopenia. Although the optimal treatment of every disease, irrespective of age, is a social and moral necessity, preventing the onset of age-related diseases by intervening in the basic process of ageing is the best solution for improving the quality of human life in old age.

In the case of a disease, such as a cancer of any specific kind, its therapy will, ideally, mean the removal and elimination of the cancer cells and restoration of the affected organ/tissue to its original disease-free state. If the same therapeutic approach is applied to 'treat' ageing, it raises a crucial question as to what the 'treatment' of ageing means, and to what original 'age-free' stage should one hope to be restored. Furthermore, the basic notion of 'disease' in clinical terms implies that it is only a proportion of the population that becomes inflicted with that condition. However, a condition such as ageing, which happens to all who survive longer than ELS, cannot be considered as a disease, and cannot be approached as such.

Another important implication of understanding ageing as the inefficiency and imperfections of homeodynamics is that the prospect of developing anti-ageing magic bullets must be abandoned. This also means abandoning enemy-oriented rhetoric, such as the 'war against ageing', 'defeating ageing', and 'conquering ageing'. Instead, interventions in ageing require a 'friend-oriented' approach and the use of a positive language such as maintaining health, achieving healthy ageing, successful ageing, and preserving the homeodynamics.

Ageing, diseases and eventual death are the consequences of imperfect homeodynamics. Ageing is characterized by a progressive shrinkage of the homeodynamic space, mainly due to stochastic occurrence and specific accumulation of molecular damage. [18] A shrinking homeodynamic space implies a declining buffering capacity and increased vulnerability, impaired functionality and increased chances of one or more diseases. While most anti-ageing approaches are targeted against the treatment of specific age-related diseases, and these are often more effective and immediate, they do not address the process of ageing itself. [19]

17 Suresh I. S. Rattan, 'Anti-ageing Strategies: Prevention or Therapy?', *EMBO Reports*, 6 (2005), S25-S29.

18 'Theories of Biological Aging'; 'Increased Molecular Damage and Heterogeneity as the Basis of Aging'.

19 Leonard Hayflick, 'Biological Aging Is No Longer an Unsolved Problem', *Ann. NY Acad. Sci*,

Therefore, rational anti-ageing strategies based on scientific evidence aim to slow down the ageing process by preventing and/or delaying physiological decline and regaining, to some extent, lost functional abilities. Such approaches may be either piecemeal (short term) or long term. For example, piecemeal interventions include organ replacement, stem cell injections, and external supplementations to regain youthful levels of hormones, enzymes and micronutrients. Although some of these therapies have demonstrated some clinical benefits in alleviating problems associated with severe deficiencies in old age, none of these piecemeal interventions really act on and modulate the ageing process itself. [20]

VI. A Formula for Eternal Youth?

Long term prevention or slowing down of ageing will require effective interventions to increase the homeodynamic space and to decrease the rate of its shrinkage due to accumulation of unrepaired molecular damage. Therefore, in order to modulate ageing and to achieve healthy old age and/or to achieve eternal youth, three main conditions need to be fulfilled, as represented by the formula $E = GMC^2$, discussed below. [21]

The first parameter *G* represents genes, which are the basis of survival, growth, development and ELS. If all the genes involved in creating the homeodynamic space, especially in the pathways of damage removal and repair, can be manipulated in such a way that their interactive accuracy and efficiency remains functional indefinitely, then the first requirement for eternal life is fulfilled. However, at present our knowledge about the numbers, variations, interactions and means of manipulating genetic networks is too meager to even conceptualize what may be possible to do in this respect.

The second parameter *M* represent milieu – the environment in which living systems operate and survive. The milieu in which genes and gene products function ranges from the intracellular molecular and ionic milieu to all other orders of organization including cellular, physiological, psychological, and societal. Almost all the ongoing work on ageing modulation and intervention at present is aimed at modifying the milieu either by replenishing those enzymes,

1100 (2007), 1 – 13; Id., 'Entropy Explains Aging, Genetic Determinism Explains Longevity, and Undefined Terminology Explains Misunderstanding Both', *PLoS Genet.*, 3 (2007), e220.

20 'Anti-ageing Strategies: Prevention or Therapy?'; 'Entropy Explains Aging, Genetic Determinism Explains Longevity, and Undefined Terminology Explains Misunderstanding Both'; S. J. Olshansky, Thomas T. Perls, 'New Developments in the Illegal Provision of Growth Hormone for 'Anti-aging' and Bodybuilding', *JAMA*, 299 (2008), 2792 – 94.

21 'The Science of Healthy Aging'.

hormones and other molecules such as antioxidants and micronutrients whose levels are reported to decrease during ageing, or by increasing the levels of such biochemicals through nutritional supplementation. Some of the main approaches include supplementation with hormones including growth hormone, dehydroepiandrosterone, melatonin and estrogen, and nutritional supplementation with synthetic and natural antioxidants in purified form or in extracts prepared from plant and animal sources. Claims for the benefits of intake of high doses of vitamins and various antioxidants and their supposed anti-ageing and life-prolonging effects have very little scientific evidence to back them. In contrast to this, nutritional modulation through caloric restriction (CR) has been shown to be an effective anti-ageing and longevity extending approach in rodents and monkeys. However, this is a highly debatable issue at present both in terms of the practicalities of defining CR and of applying CR in human beings in physiological and evolutionary contexts. [22]

Another promising area of milieu improvement for achieving healthy ageing and longevity is through stress-induced hormesis. [23] Hormesis in ageing is defined as the life supporting beneficial effects resulting from the cellular responses to single or multiple rounds of mild stress. [24] As discussed above, a critical component of the homeodynamic property of living systems is their capacity to respond to stress. In this context, the term stress is defined as a signal generated by any physical, chemical or biological factor (stressor), which in a living system initiates a series of events in order to counteract, adapt and survive. While successful and over-compensatory responses to low doses of stressors improve the overall homeodynamics of cells and organisms, incomplete or failed homeodynamic responses lead to damaging and harmful effects of stress, including death.

The paradigm for considering the applicability of hormesis in ageing intervention is the well documented beneficial effects of exercise, which at a biochemical level results in the production of potentially harmful substances such as free radicals, acids and aldehydes. [25] Mild stresses that have been reported to delay ageing and prolong longevity in various systems include temperature shock, irradiation, heavy metals, pro-oxidants, acetaldehyde, alcohols, hypergravity, exercise and food restriction. [26] Hormesis-like beneficial effects of

22 Eric Le Bourg and Suresh I. S. Rattan, 'Can Dietary Restriction Increase Longevity in All Species, Particularly in Human Beings? Introduction to a Debate Among Experts', *Biogerontology*, 7 (2006), 123 – 25.

23 Suresh I. S. Rattan, 'Hormesis in Aging', *Ageing Res. Rev.*, 7 (2008), 63 – 78.

24 Ibid., ivi.

25 'The Science of Healthy Aging'.

26 *Mild Stress and Healthy Aging: Applying Hormesis in Aging Research and Interventions*, ed. by Éric Le Bourg and Suresh I. S. Rattan (Dordrecht: Springer, The Netherlands, 2008).

chronic but mild under-nutrition have been reported for human beings. Furthermore, intermittent fasting has been reported to have beneficial effects on glucose metabolism and neuronal resistance to injury. Although at present there are only a few studies performed which utilize mild stress as a modulator of ageing and longevity, hormesis is a useful experimental approach in biogerontology. [27]

Several dietary components, such as vitamins, antioxidants, trace elements, minerals, ethanol, and even herbicides and pesticides have been shown to have typical hormetic dose response. All such compounds (natural or synthetic), which bring about biologically beneficial effects by acting through one or more pathways of maintenance and repair, and stress response, are termed as hormetins. [28] The hormetic effects of various vitamins and macro- and micro-minerals, including iron, iodine, fluorine, selenium and copper have also been reported. [29] Additionally, the effects of zinc also show a typical hormetic dose response, and its beneficial effects are achieved through alterations induced by stress response, in gene expression of various maintenance and repair pathways. [30] Components of various medicinal plants used frequently in the Chinese medicine and in the Indian Ayurvedic system of medicine are claimed to have anti-ageing effects, which appear to be achieved through hormetic pathways. Hormesis may also be an explanation for the health beneficial effects of numerous other foods and food components, such as garlic, Gingko, and other fruits and vegetables. [31] Understanding the hormetic and interactive mode of action of natural and processed foods is a challenging field of research, and has great potential in developing nutritional and other life style modifications for ageing intervention and therapies. For example, it may be possible to develop multi-hormetin formulations as healthy-ageing nutriceuticals whose mode of action is through hormetic pathways by mild stress-induced stimulation of homeodynamic processes.

The last factor for achieving eternal youth is the factor C in the formula $E = GMC^2$. While the G, genes, and M, milieu, components of the formula are being taken care of by various experimental approaches discussed above, the third factor C represents chance, which is the probability of stochastic events leading to a cascade of error-catastrophe in complex interacting systems. Recent de-

27 Ibid., ivi.

28 'The Science of Healthy Aging'; Rehab E. Ali, Suresh I. S. Rattan, 'Curcumin's Biphasic Hormetic Response on Proteasome Activity and Heat Shock Protein Synthesis in Human Keratinocytes', *Ann. NY Acad. Sci*, 1067 (2006), 394 – 99.

29 Dan P. Hayes, 'Nutritional Hormesis', *Eur J Clin Nutr*, 61 (2007), 147 – 59.

30 'The Science of Healthy Aging'.

31 'Nutritional Hormesis'; Carlos K. B. Ferrari, 'Functional Foods, Herbs and Neutraceuticals: towards Biochemical Mechanisms of Healthy Aging', *Biogerontology*, 5 (2004), 275 – 89.

velopments in our understanding of complex networks at all levels of organization, from molecular to societal and global networks, have highlighted the vulnerability of all strong and weak links. Furthermore, this realization of complex networks has reasserted the significance of chance events, which are not amenable to regulation and manipulation.

Thus, understanding the evolutionary basis for the origin of ageing mechanisms as being emergent due to the imperfections of survival mechanisms helps us to reclaim the control of our bodies' homeodynamics and health span. It also helps us to understand that from the nature's side there is neither a mechanism to kill us, nor is there any processes to make us immortal. Therefore, whereas the prospects for achieving healthy ageing and for extending health span are based in solid scientific footing, and will become more and more effective, the dreams of eternal youth are best left to thrive in the domain of the unscientific.

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