

Biogerontology

Healthy ageing, but what is health?

--Manuscript Draft--

Manuscript Number:	BGEN-D-13-00066
Full Title:	Healthy ageing, but what is health?
Article Type:	S.I. : ECB2013
Section/Category:	Opinion
Keywords:	aging; anti-aging; longevity; stress; homeostasis; homeodynamics; hormetics, hormetin
Corresponding Author:	Suresh Rattan, PhD, DSc. Aarhus University Aarhus, DENMARK
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Aarhus University
Corresponding Author's Secondary Institution:	
First Author:	Suresh Rattan, PhD, DSc.
First Author Secondary Information:	
Order of Authors:	Suresh Rattan, PhD, DSc.
Order of Authors Secondary Information:	
Abstract:	Ageing occurs in spite of complex pathways of maintenance and repair. There is no "enemy within" having the specific evolution-selected function to cause ageing and death. This understanding of ageing should transform our approach towards interventions from therapeutic "anti-ageing" to maintaining health. But what is health? In pragmatic terms, health is a state of adequate physical and mental independence in activities of daily living. The concept of homeodynamic space can be useful to identify a set of measurable, evidence-based and demonstratable parameters of health, robustness and resilience at various levels ranging from genetic and metabolic networks to overall functionality and quality of life. Age-related health problems for which there are no clear-cut causative agents, except the complex process of ageing, may be better tackled by focusing on health mechanisms and their maintenance, rather than disease management and treatment. Continuing the disease-oriented research approaches are economically, socially and psychologically unsustainable as compared with health-oriented and preventive strategies, such as hormesis. Supporting health-oriented research is an urgent need of the time.

OPINION

Healthy ageing, but what is health?

Suresh I. S. Rattan

Laboratory of Cellular Ageing, Department of Molecular Biology and Genetics, Aarhus University, Denmark.

Address for communication

Dr. Suresh Rattan

Department of Molecular Biology and Genetics,

University of Aarhus,

Gustav Wieds Vej 10

DK8000 Aarhus C

Denmark

Phone: +45 8942 5034; Fax: +45 8612 3178; Email: rattan@mb.au.dk

Running title: What is health

Abstract

Ageing occurs in spite of complex pathways of maintenance and repair. There is no “enemy within” having the specific evolution-selected function to cause ageing and death. This understanding of ageing should transform our approach towards interventions from therapeutic “anti-ageing” to maintaining health. But what is health? In pragmatic terms, health is a state of adequate physical and mental independence in activities of daily living. The concept of homeodynamic space can be useful to identify a set of measurable, evidence-based and demonstratable parameters of health, robustness and resilience at various levels

ranging from genetic and metabolic networks to overall functionality and quality of life. Age-related health problems for which there are no clear-cut causative agents, except the complex process of ageing, may be better tackled by focusing on health mechanisms and their maintenance, rather than disease management and treatment. Continuing the disease-oriented research approaches are economically, socially and psychologically unsustainable as compared with health-oriented and preventive strategies, such as hormesis. Supporting health-oriented research is an urgent need of the time.

Keywords: *longevity; stress; homeostasis; homeodynamics; hormetics, hormetin*

We want to maintain or even enhance health; and we wish to achieve healthy ageing. But what exactly is health? Even the WHO's definition of health as "*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*" is incomplete, vague, and does not clarify what is meant by "wellbeing" in definitive terms. Furthermore, although everyone talks about health - there are ministries, faculties and departments of health – most of the biomedical research is dominated and supported by disease-directed thinking. This gives little understanding as to what is health, what determines health and how one maintains health and avoids the emergence of diseases in the first place. Therefore, a major change in thinking, approach and strategy is required to understand health, maintain health, improve the quality of life, extend the health-span and enhance public- and social-health (Contrada and Baum 2011; Farrelly 2012; Shelton 2013). A lack of scholarly, serious and interdisciplinary health discussion has allowed the mushrooming of numerous self-proclaimed health-specialists and health-gurus, which has created a lot of confusion, muddled thinking, and irrational, impractical and even harmful interventional strategies [Holliday 2009; Le Bourg, 2013 #7235].

If ageing is understood as an emergent phenotype due to the failure of homeodynamics, and not due to the action of any specific harmful and death-causing mechanisms (Rattan 2012b), it transforms our approach towards ageing interventions from "anti-ageing" to "healthy ageing". Ageing occurs in spite of the presence of complex pathways of maintenance, repair and defence, and there is no "enemy within". This viewpoint makes modulation of ageing different from the treatment of one or more age-related diseases. 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” etc. 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. As a biomedical issue, the biological process of ageing underlies all major diseases, and 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 approach for achieving healthy ageing and extending the health-span.

Health, homeodynamics and ageing

Health and survival of an organism is a dynamic tug between the occurrence of damage and the processes of maintenance and repair (Holliday 2007; Rattan 2012b). The traditional conceptual model to describe this characteristic has been the so-called homeostasis. However, deeper understanding of the processes of biological growth, development, maturation, reproduction and ageing have led to the realization that the term homeostasis, which means “stability through constancy”, fails to incorporate dynamic themes and processes, including interacting networks and complexity in biological systems. Therefore, the term homeodynamics (Yates 1994) has replaced homeostasis to account 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. All these processes and their interactions give rise to a homeodynamic space, which may also be considered as the “survival ability” or “the “buffering capacity” of a biological system, and is the ultimate determinant of an individual’s health, and the ability to survive and maintain a healthy state (Carnes 2011; Rattan 2007; Rattan 2012b).

All apparently normal organisms are born with certain extent of homeodynamic space, but with a significant zone of vulnerability in early stages of life. The homeodynamic space undergoes expansion during growth, development and maturation, with a concurrent decrease in the vulnerability zone. The extent of homeodynamic space achieved by an individual depends both on genetic factors including polymorphisms, and on pre-natal and early-life epigenetic factors, including nutrition, infections, mental stimulation and physical activity. At the species level, biological evolutionary processes have optimised homeodynamics only for a limited period of time termed as the essential lifespan (ELS) (Carnes 2011; Rattan 2012b), which is required for successful reproduction. However, survival beyond ELS is accompanied

by a progressive shrinkage of the homeodynamic space, which is the basis of frailty, ageing, age-related diseases and eventual death. The main three characteristics of homeodynamic space are: (1) damage control; (2) stress response (SR); and (3) constant remodelling and adaptation (Demirovic and Rattan 2013; Rattan 2012b). Importantly, these three characteristics of health and homeodynamics can be studied at the level of biology, psychology and sociology.

Ageing is the progressive shrinkage of the homeodynamic space (Rattan 2012b). At the biological level, survival of an organism is a constant struggle between the occurrence of biochemical damage and the mechanisms of maintenance and repair. A large number of molecular, cellular and physiological pathways and their networks determine survival and longevity (Budovsky et al. 2007; Tacutu et al. 2010). At the molecular level, the theories of the mechanisms of ageing are mostly centered on the accumulation of molecular damage (Rattan 2006; Rattan 2008b). Recently some other views, such as a continuous and unregulated growth leading to a kind of quasi-programme of ageing, have also been put forward, which also include the molecular and metabolic disfunctioning (Blagosklonny 2012).

The two other components of the homeodynamic space are the stress response (SR) and constant remodelling and adaptation (Franceschi et al. 2000). All age-related changes, such as reduced hormone levels and remodelled immune profiles, may not be harmful, and may be a sign of adaptation. Similarly, the consequences of stress can be either harmful or beneficial depending on the intensity, duration and frequency of the stress, and on the price paid in terms of energy utilisation and other metabolic disturbances. But the most important aspect of SR is that it is not monotonic with respect to the dose of the stressor, rather it is almost always characterized by a nonlinear biphasic relationship, termed hormesis (Calabrese et al. 2007). Hormesis in ageing is defined as the life supporting beneficial effects resulting from the cellular responses to single or multiple rounds of mild stress (Rattan 2004; Rattan 2008a; Rattan 2008c; Rattan and Demirovic 2009). Exercise, temperature, radiation, and numerous components of the food, such as flavonoids, polyphenols, and other micronutrients have been shown to be hormesis-inducing agents, termed hormetins (Rattan 2012a).

Subjective and objective measures of health

Health is often described either in the context of the absence of one or more diseases or as a vague concept of wellbeing, without having any objective measures for that. Although some parameters of frailty have been proposed (Fulop et al. 2010; Hubbard and Woodhouse 2010; Montesanto et al. 2010), direct measures of health largely remain undefined. Since one of the

crucial aspects of health is the functionality, health could be defined as a state of COMPLETE physical and mental independence in activities of daily living, but this is an ideal state, which perhaps no one can have. Therefore, being healthy, in a practical term, means having ADEQUATE physical and mental independence in activities of daily living, which will vary widely but can be established objectively. However, the so-called “quality of life” as a measure of health is mainly a subjective notion shaped by culture, surroundings and other psycho-social factors.

The above pragmatic definition of health as a state of having adequate physical and mental independence in activities of daily living requires identifying a set of measurable parameters at the most fundamental level of biological organization. Analyzing the components of the homeodynamic space can be an objective way to quantify health at the level of cells, tissues and the body. The following three lines of investigation may be useful to develop evidence-based and demonstratable markers of health:

1. Establishing immediate and delayed stress response profiles of cells, organisms and humans at different ages (Demirovic and Rattan 2013). This will also include developing methods for measuring resilience and robustness, in terms of biological and psychological parameters of wellness and wellbeing, respectively (Kriete 2013).
2. Developing methods for measuring the limits of health at the individual level. Relationship between stress tolerance, recovery, survival, innate immune response and longevity could be studied at different levels and ages, using a variety of systems and making use of the most comprehensive longitudinal studies examining health-related genetic and non-genetic processes (Yashin et al. 2013). Furthermore, converting multidimensional information about the number of determinants of health at different levels to a single number expressing the biological age or the size of the homeodynamic space could be achieved by applying bioinformatics and mathematical modelling (Budovsky et al. 2007; Mitnitski et al. 2007; Tacutu et al. 2010).
3. Developing physiological and psychological criteria and methods to monitor health improvement (as measured by health markers discussed above) by physical, nutritional or other interventions, including hormesis (Rattan 2012a; Rattan 2004; Rattan 2008a; Rattan 2008c; Rattan and Demirovic 2009).

The rationale and the perspective

The scientific rationale for the need of understanding and defining health is the present crisis

in dealing with lifestyle diseases. The traditional biomedical approach of disease-directed treatments has now come face-to-face with the big challenge of how to deal with physical, mental and social health issues where there are no clear-cut causative agents or “enemies” (such as germs, bacteria, viruses, pollutants etc). With increased life expectancy and rapidly changing demographic structures, major conditions such as ageing, metabolic disorders, depression, dementia, osteoporosis, sarcopenia, incontinence, malnutrition, and several types of cancers are now known to be due to the generalised processes of life and their interactive networks.

Another important socio-political reason for the need of having such health-oriented thoughts, in contrast to the disease-oriented views, is the realisation that continuing the disease-oriented approach to health is scientifically and socio-economic-politically not compatible with the highly desirable future of global health and sustainability. Several prospective analyses have shown that the prevalent disease-management or disease-treatment approaches are economically, socially and psychologically unsustainable as compared with health-oriented and preventive strategies (Carnes 2011; Carnes et al. 2012; Olshansky et al. 2011).

Although various ongoing discourses on health catch on to some reality, it is important to find out how these various discourses may be interrelated as regards their interests, concerns, problems and needs (Faragher 2009; Fulop et al. 2010; Gems and Partridge 2013; Mitnitski et al. 2007; Phelan et al. 2004). That would further clarify as to how health is an important issue and how we can do something about it. Disease-management or disease-treatment approaches are economically, socially and psychologically unsustainable as compared with health-oriented and preventive strategies. We cannot continue with the “more of the same approach” in matters of individual, social and public health.

Acknowledgement

Laboratory of Cellular Ageing is financially partially supported by a research grant from LVMH Recherche, Saint Jean de Braye, France.

References

Blagosklonny, MV (2012) Cell cycle arrest is not yet senescence, which is not just cell cycle arrest: terminology for TOR-driven aging. *Aging* (Albany NY) 4:159-165

- Budovsky, A, Abramovich, A, Cohen, RM, Chalifa-Caspi, V, Fraifeld, VE (2007) Longevity network: construction and implications. *Mech Ageing Dev* 128:117-124
- Calabrese, EJ, Bachmann, KA, Bailer, AJ, Bolger, PM, et al. (2007) Biological stress response terminology: integrating the concepts of adaptive response and preconditioning stress within a hormetic dose-response framework. *Toxicol. Appl. Pharmacol.* 222:122-128
- Carnes, BA (2011) What is lifespan regulation and why does it exist? *Biogerontology* 12:367-374
- Carnes, BA, Olshansky, SJ, Hayflick, L (2012) Can human biology allow most of us to become centenarians? *J Gerontol A Biol Sci Med Sci*
- Contrada, RJ, Baum, A, Eds. (2011) *Handbook of stress science: psychology, biology, and health*. New York, Springer.
- Demirovic, D, Rattan, SI (2013) Establishing cellular stress response profiles as biomarkers of homeodynamics, health and hormesis. *Exp Gerontol* 48:94-98
- Faragher, RG (2009) What could advances in the biology of ageing mean for the quality of later life? *Quality in Ageing* 10:30-38
- Farrelly, C (2012) 'Positive biology' as a new paradigm for the medical sciences. Focusing on people who live long, happy, healthy lives might hold the key to improving human well-being. *EMBO Rep* 13:186-188
- Franceschi, C, Valensin, S, Bonafè, M, Paolisso, G, Yashin, AI, Monti, D, De Benedictis, G (2000) The network and the remodeling theories of aging: historical background and new perspectives. *Exp. Gerontol.* 35:879-896
- Fulop, T, Larbi, A, Witkowski, JM, McElhaney, J, Loeb, M, Mitnitski, A, Pawelec, G (2010) Aging, frailty and age-related diseases. *Biogerontology* 11:547-563
- Gems, D, Partridge, L (2013) Genetics of longevity in model organisms: debates and paradigm shifts. *Annu Rev Physiol* 75:621-644
- Holliday, R (2007) *Ageing: the paradox of life*. Dordrecht, The Netherlands., Springer.
- Holliday, R (2009) The extreme arrogance of anti-aging medicine. *Biogerontology* 10:223-228
- Hubbard, RE, Woodhouse, KW (2010) Frailty, inflammation and the elderly. *Biogerontology* 11:635-641
- Kriete, A (2013) Robustness and aging - a systems-level perspective. *Biosystems*, 112:37-48

- Mitnitski, A, Song, X, Rockwood, K (2007) Improvement and decline in health status from late middle age: modeling age-related changes in deficit accumulation. *Exp. Gerontol.* 42:1109-1115
- Montesanto, A, Lagani, V, Martino, C, Dato, S, et al. (2010) A novel, population-specific approach to define frailty. *Age* 32:385-395
- Olshansky, SJ, Biggs, S, Achenbaum, WA, Davison, GC, et al. (2011) The global agenda council on the ageing society: policy principles. *Global Policy* 2:97-105
- Phelan, EA, Anderson, LA, LaCroix, AZ, Larson, EB (2004) Older adults' views of "successful aging"--how do they compare with researchers' definitions? *J Am Geriatr Soc* 52:211-216
- Rattan, SI (2012a) Rationale and methods of discovering hormetins as drugs for healthy ageing. *Expert Opin Drug Discov* 7:439-448
- Rattan, SIS (2004) Aging, anti-aging, and hormesis. *Mech. Age. Dev.* 125:285-289
- Rattan, SIS (2006) Theories of biological aging: genes, proteins and free radicals. *Free Rad. Res.* 40:1230-1238
- Rattan, SIS (2007) Homeostasis, homeodynamics, and aging. In: *Encyclopedia of Gerontology*. Birren, J. UK, Elsevier Inc.: 696-699.
- Rattan, SIS (2008a) Hormesis in aging. *Ageing Res. Rev.* 7:63-78
- Rattan, SIS (2008b) Increased molecular damage and heterogeneity as the basis of aging. *Biol. Chem.* 389:267-272
- Rattan, SIS (2008c) Principles and practice of hormetic treatment of aging and age-related diseases. *Hum. Exp. Toxicol.* 27:151-157
- Rattan, SIS (2012b) Biogerontology: from here to where? The Lord Cohen Medal Lecture-2011. *Biogerontology* 13:83-91
- Rattan, SIS, Demirovic, D (2009) Hormesis and aging. In: *Hormesis: a revolution in biology, toxicology and medicine*. Mattson, MP, Calabrese, E. (Eds) New York, Springer: 153-175.
- Shelton, JD (2013) Ensuring health in universal health coverage. *Nature* 493:453
- Tacutu, R, Budovsky, A, Fraifeld, VE (2010) The NetAge database: a compendium of networks for longevity, age-related diseases and associated processes. *Biogerontology* 11:513-522
- Yashin, AI, Arbeev, KG, Wu, D, Arbeeva, LS, Kulminski, A, Akushevich, I, Culminskaya, I, Stallard, E, Ukraintseva, SV (2013) How lifespan associated genes modulate aging changes: lessons from analysis of longitudinal data. *Front Genet* 4:3

Yates, FE (1994) Order and complexity in dynamical systems: homeodynamics as a generalized mechanics for biology. *Math. Comput. Model.* 19:49-74