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CHALLENGING AGING: THE ANTI-SENESCENCE EFFECTS OF HORMESIS, ENVIRONMENTAL ENRICHMENT, AND INFORMATION EXPOSURE

VOLUME 1

Marios Kyriazis

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Frontiers in Aging Science

Volume 1

Challenging Aging The Anti-senescence Effects of Hormesis, Environmental Enrichment and Information Exposure

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Frontiers in Aging Sciences

Challenging Ageing : The Anti-senescence Effects of Hormesis, Environmental Enrichment and Information Exposure

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Biography

Marios Kyriazis qualified as a medical doctor (MD) from the University of Rome, Italy, and after preclinical work in the USA he worked as a clinician in acute medicine in Cyprus, and the UK. He subsequently qualified as a Gerontologist with interest in the biology of ageing and became a Chartered Member of the academic organisation 'Royal Society of Biology' in the UK. He also has a post-graduate qualification in Geriatric Medicine from the Royal College of Physicians of London. Other appointments include Member of the Board of Trustees at the Mediterranean Graduate School of Applied Social Cognition, affiliate researcher at the Evolution, Complexity and Cognition Group, University of Brussels, and a Ronin Research Scholar.

Currently, he works with the ELPIs Foundation for Indefinite Lifespans, a serious endeavour to study the elimination of age-related degeneration. The research is focused on transdisciplinary models and explores common principles between biology, complexity sciences, evolution, cybernetics, neurosciences, and techno-cultural elements. Areas of interest include robustness and degeneracy in organic systems, fragility and redundancy, repair processes (including self-repair), hormesis and environmental enrichment in ageing, and prolonged survival of somatic cells.

Dr. Kyriazis is a member of several editorial boards including the Elsevier Editorial System, Rejuvenation Research, The Biologist, World Journal of Translational Medicine, Peptides journal, the European Journal of Clinical Nutrition etc. He is also a Member of many age-related organisations, committees and advisory boards. He has a portfolio of over 1000 articles, papers and lectures in the field of healthy ageing.

FOREWORD

Life is a constant struggle between the intrinsic and extrinsic challenges and the ability to counteract, defend and adapt to those challenges. This is a highly dynamic process. However, beyond the evolutionarily required "essential lifespan" (ELS), a progressive failure of homeodynamics is the fate of life, manifested in ageing and eventual death. How to prevent or slow down this failure, or how to enhance our functionality and survival, is the challenge of ageing.

Comprehensive scientific studies over the past five decades have led to the conclusion that the traditional disease-orientated biomedical model of ageing needs to be abandoned for a wholistic concept. This is because there are no specific gerontogenes or any master controller molecule(s) that cause ageing and which can be counteracted one at a time. Maintaining health, and any possible extension of lifespan, require whole-body interventions. One such approach is the phenomenon of mild stress-induced hormesis, which is the subject matter of this book.

Hormesis, hormetins and hormetics are, respectively, the phenomenon, the agents and the science of bi-phasic dose response to stressors. This is a scientific and evidence-based approach. Marios Kyriazis' book, which also includes a contribution from another author, deals with this subject of scientific and wholistic hormesis in a most comprehensive and accessible manner.

Hormesis works. Stress of choice is good for health. Food, physical activity and psycho-social engagement are the three pillars of health. These can be personalised and optimised by using the three principles of hormesis: pleasure, moderation and variety. This book helps in opening several new practical possibilities in this regard.

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PREFACE

This Series on 'Frontiers in Aging Science' aims to exploit the method of online sharing of information, and will examine in detail several important models, hypotheses, theories and other notions (including Blue Skies Research) which may help us elucidate the intricacies of the ageing process. The first such eBook will examine the role of challenges. These are interventions that provoke action (a protective response) from the organism. This response is mediated by the up-regulation of protective cellular mechanisms that diminish the effect of age-related degeneration in humans.

Several authors have suggested that the process of biological ageing is associated with loss of information, disruption of homeostasis, and a reduction of functional and physiological complexity. As time-related damage accumulates, and the processes of repair become progressively less able to deal with this damage, organisms begin to experience dysfunction, degeneration and chronic clinical diseases, eventually leading to death. One possible way of remediating this loss of complexity is to increase exposure to relevant and meaningful information which can, through various mechanisms, up-regulate functional and structural complexity with a consequent improvement in function. This basic premise (that age-related loss of complexity may be counteracted by exposure to stimulation and information) has been studied in a variety of levels and under many different guises. One way of increasing information exposure is through mild and repeated challenges or mild stress, *i.e.* hormesis. In medicine and biology hormesis is defined as 'an adaptive response of cells and organisms to a moderate, intermittent, challenge'.

Hormesis describes phenomena where there is a low dose stimulation, high dose inhibition, and it suggests that nutritional, physical, mental and chemical challenges, if appropriately timed, may result in mild damage to the organism which up-regulates repair mechanisms. In crude terms it can be said that during the process of repairing this damage, any coincidental age-related damage is also repaired. A similar concept is that of Environmental Enrichment where experimental animals are exposed to an enriched environment with regards to visual, auditory and habitat augmentation. The majority of experiments confirm that an enriched and stimulating environment (an 'information-rich' habitat) has several positive effects on health, specifically on brain and immune function. These concepts are presented in Chapters 1-3.

In Chapters 4 and 5 there is a discussion about the biological mechanisms of information exposure, and how the impact of new information and challenges may result in the reallocation of resources from the germ line to the soma. This is important because it may underlie a hitherto dormant mechanism that may lead to radical reduction of age-related degeneration. In Chapter 6 I analyse further the relationships between information,

challenges, human evolution and possible biological changes, building upon the previous discussion. In Chapter 7, Atanu Chatterjee from the Indian Institute of Technology analyses certain significant concepts which are crucial in our understanding of life generally and the human body in particular. He provides a grounding and a framework for expanding our notions of hormesis and stimulation, from a general domain to the specific case of human ageing. He explains notions such as complexity in living systems, energy distribution and entropy, which form the foundation of our efforts to devise ways that maximise information exposure that increases our biological complexity.

Finally, in chapter 8 I expand the scope of the discussion and aim to examine ways we can become better participants within an increasingly technological environment. The overall aim is to examine ways whereby humans, in a modern context, can harness the power of challenging information, and use it to up-regulate their functional complexity (both in the biological and in the social sense). As a result, damage repair becomes maximised, the risk of dysfunction diminishes and the incidence and prevalence of age-related degeneration and disease is kept to a minimum or even totally eliminated.

Our methodology is conceptually different from many existing approaches which depend on physical, pharmacological, genetic or cellular methods and other disruptive technologies for defying ageing. Despite discussing several drugs or compounds acting as hormetic agents, the essential characteristic of our methodology is that it is based less on physical items and more on environmental abstract, virtual and cognitive elements (see Figure below).

The title of the book reflects this: Ageing is seen as a challenging problem but, at the same time, it may be overcome by exposure to challenges (situations that incite biological action) which may be clinically useful. The book is targeted at gerontologists, anti-ageing physicians and clinicians, medical students, and university students (in gerontology, biology, complexity sciences, evolution). The slant is a blend of graduate/postgraduate level, providing an in-depth analysis and discussion of the main concepts (hormesis, environment, information, human evolution, biology of ageing) and a synthesis of these as applied to defying age degeneration. It will be valuable to those pursuing a medical or biological career, as well as others interested in human ageing.

Master Figure. This explains the relationship, influences and feedback loops between the concepts of hormesis, environmental enrichment and social effects upon somatic and germ line biology. The intention is to show that external challenges have an impact on somatic repair mechanisms and thus may help improve repair of age-related degeneration, resulting in prolongation of healthy lifespan. The reader is requested to revisit this figure after reading the entire book and review the interconnections of the different components. This will give a much clearer idea of the overall concept I tried to describe in this book.

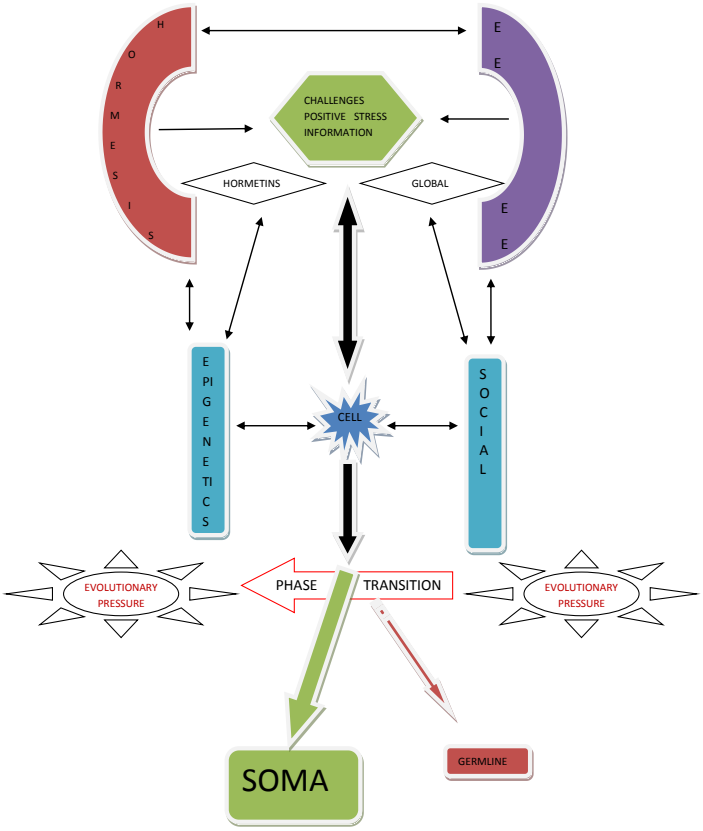

Fig. (1). Schematic representation of the relationship between the different concepts discussed in this book. The concept of hormesis is based on challenges, positive stress and information exposure. It influences (partly through Hormetins) both directly and indirectly (through epigenetic mechanisms) the cell. (The concept of the 'cell' is better described as a 'somatic agent' which includes cells, molecules, genetic material and anything else that makes a human, with the exception of germline material). Environmental enrichment (EE) is also based on challenges, positive stress and information, and through both local and global mechanisms (such as the Global Brain, smart cities, Ambient Intelligence) also has an effect on the 'cell'. This effect is modulated by social and cultural factors. The enormous evolutionary pressure placed upon the 'cell' results in a phase transition which shifts the priority of repair resource allocation from the germline to the soma, resulting in reduced or absent age-related functional decline.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

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I would like to thank the contributors and reviewers of this project for their input, discussions and inspiration. Suresh Rattan for acting as a compass in the entire field of biogerontology generally, and for his contributions to the hormesis research specifically. Ed Calabrese and Mark Mattson, for providing the sources of a substantial amount of research mentioned in the book. Francis Heylighen and the members of the Evolution Complexity and Cognition group at the University of Brussels, for horizon-expanding discussions, arguments and inspiration in developing concepts such as the Global Brain, Complex adaptive system behaviour, evolution and cybernetics.

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CHAPTER 1

Hormesis and Adaptation

Abstract: Our biological response to external challenges frequently obeys hormetic principles. During the phenomenon of hormesis, mild stressful challenges may up-regulate defence and repair pathways, with a subsequent overall improvement in function. It is important to highlight that hormesis is a dose-response, non-linear phenomenon, meaning that a low dose of a stressor can result in benefit whereas a higher dose may result in damage. Hormesis is invoked when the challenge is of sufficient magnitude and appropriate quality as to satisfy the definition of 'novelty'. Routine and monotony do not, as a rule, invoke a hormetic response. In this chapter I will discuss certain characteristics of hormesis as applied to humans, and examine several situations whereby an adequately-timed stimulus may be of practical health benefit. The assessment and response to the new challenge leads to adaptation and thus, eventually, improvement of function within a particular environment (the environment where the challenges have originated from). In this way, there is a direct link between external challenging information and internal physical or biological changes. This link will be explored in detail, both in this chapter and in other chapters of this book.

Keywords: Adaptation, Cellular networks, Exploratory behaviour, Homeodynamic space, Hormesis, Non-linearity, Novelty, Physical challenges, Power law, Stress response, Stressor, Stimulation.

SOME DEFINITIONS

Agent = An entity that acts on its environment.

Stress = Any sudden, unforeseen perturbation of a system, when the system itself does not have the resources to deal with the change, *i.e.* it cannot, or has not have the time to, adapt to the perturbation.

Stressful event = A perturbation of a system, a challenge, a stimulus that incites the system to act.

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Challenge = The term refers to a softer situation where, following a stressful event the system has both the time and the capability to adapt, *i.e.* change in response to the perturbation. So, strictly, stress and challenge are not equivalent, but mild/positive stress (as opposed to chronic, intense stress) can be seen as the equivalent of a 'Challenge'. Here, a challenge is defined as a situation that potentially carries biological value for an organism, so that the organism is inclined to act. A challenge provokes action because it represents a situation in which not acting will lead to an overall lower fitness than acting.

Adaptation = When the system or the agent undergoes a structural or functional rearrangement in order to accommodate the new information carried by the challenging event.

Hormesis = A biphasic dose response to an environmental challenge, characterized by a low dose stimulation (benefit) and a high dose inhibition (damage).

Indefinite and Infinite Lifespans An **indefinite** lifespan is a lifespan without a pre-determined end, and it denotes the virtual elimination of the mortality rate as a function of age (the elimination of age-related functional decline). In other words, the incidence of involuntary death caused by ageing tends to zero. Death can still ensue through other means such as accidents, injuries, infections, starvation and so on. An **infinite** lifespan on the other hand, is equivalent to true immortality and the total abolition of death from any cause (however idealistic this may be).

Ageing (in humans) = Time-related dysfunction.

Evolution = The adaptation to changes in the environment, so that survival continues.

Fitness = Good function within a specific environment.

INTRODUCTION

Although hormesis is a term applicable to a wide range of situations [1] in this book I discuss hormesis with particular relevance to humans. Hormesis is a

phenomenon characterised by a non-linear, 'U'-shaped, 'low-dose activation, high-dose inhibition' principle. In other words, a low dose of a stimulus can positively challenge the organism and result in health benefits, whereas an excessive, suboptimal, or prolonged exposure can result in damage and disease [2]. In a wider sense, the concept is based on repeated mild exposure to new information, a sustained (but not excessive) state of 'novelty' which resets homoeostatic mechanisms.

In order to use the correct terminology, it is necessary to clarify that there are different terms describing diverse hormetic effects. For example, a previous exposure to mild stress (a low dose of a hormetic agent) protects the organism against a larger, stressful dose later on. This is called 'Conditioning Hormesis' and it bestows a protective effect against future stresses [3]. A different type of hormesis is 'Post-exposure Conditioning Hormesis', when an organism who is subjected to a high, toxic level of stress may experience improvements when it is subsequently exposed again to low doses of the same stressor. For the purposes of this book, while we use the term 'hormesis' we, on the whole, refer in fact to the Conditioning Hormesis aspect of the concept.

The hormetic response is triggered by encounters with any physical, chemical, biological, mental or other challenges, which may disturb the cellular or organismic homeostatic mechanisms [4] (Fig. **1**). Although hormetic effects have been studied extensively at cellular level, and not so much at the level of the entire organism, it is legitimate to assume that effects at higher levels are real and valid [5].

Hormesis, through functionally diverse stressors, may trigger several mechanisms of lifespan extension such as disruption of the Insulin-like Growth Factor-1 (IGF-1) signalling pathway, up-regulation of immunity, proteostasis and oxidative stress response [7]. A basic characteristic of a hormetic event is **novelty of information**. Here, novelty is defined as 'the quality of being new, original, or unusual', and this includes both unfamiliarity and unconventionality. Novelty is also associated with creativity, innovation and imagination. These are essential characteristics because, as I will discuss in other chapters, a worldview which encompasses creativity, innovation and imagination is more likely to lead to a

CHAPTER 2

Vitagenes and Hormetins: The Pills of Hormesis

Abstract: In the previous chapter I discussed the physiological basis of hormesis and given examples of how certain practical actions can have a hormetic benefit upon our health. Here I will examine examples of oral drugs, compounds or supplements which may exhibit a hormetic effect. These compounds are called hormetins and many of these act on vitagenes, genes which encode transcription factors that are necessary for maintaining health. Thus, I explore a direct link between **information** carried by chemical compounds, and **physiological modulation**, with resulting health improvement. Some of these hormetins are pluripotent agents, exhibiting benefits at multiple levels and tissues. Other compounds are mimics of hormetic physical actions such as calorie restriction and exercise. I will also discuss the phenomenon of xenohormesis, *i.e.* hormetic gains experienced by humans through hormetins which originate from a different species. The discussion here complements both the concept of hormesis and that of Environmental Enrichment which will be discussed in the next chapter, and the aim is to provide a comprehensive approach ensuring a better understanding of hormetic mechanisms in a wider sense.

Keywords: Adaptation, Calorie restriction mimetics, Exercise mimetics, Vitagene, Hormesis, Hormetic pathways, Hormetin, Inter-individual variations, Sex mimetics, Xenohormesis.

INTRODUCTION

Hormesis affects many age-related processes [1 - 3]. However, the physiological mechanisms of the hormetic action itself may also be mimicked by certain chemical compounds (such as the active ingredients [4] extracted from the roots of the Chinese herb Sanchi (*Panax notoginseng*) for example), which act to up-regulate signalling and other pathways sharing the same physiological mechanisms as the hormetic intervention itself [5, 6]. These agents are called hormetins [7]. Hormetins may act upon vitagenes [8], a group of genes which are

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involved, through a complex mechanism, in maintaining the health of cells during ageing. Vitagenes encode proteins (such as Heat Shock Proteins –Hsp) which are normally expressed after a stressful episode, and also encode the sirtuin protein system which is involved in ageing [9, 10] (Fig. **1**).

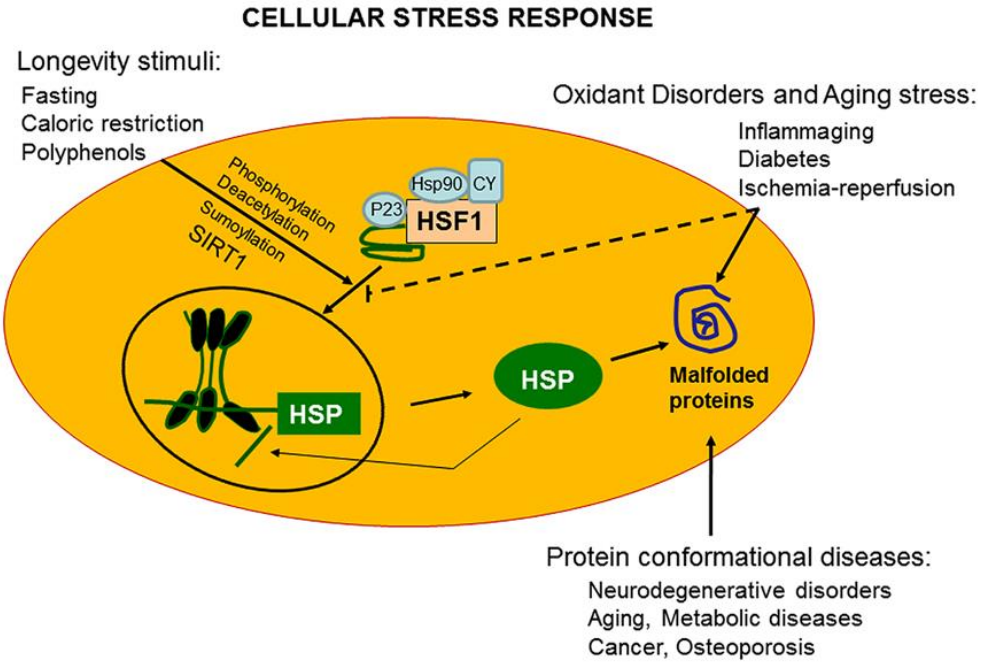

Fig. (1). Vitagenes and the pathway of cellular stress response. Misfolded proteins cumulating in response to proteotoxic stresses trigger the cellular stress response. Hsps that are normally bound to HSF1, maintaining it in a repressed state before stress, are titrated away by damaged or misfolded proteins with resulting HSF-1 activation. Multi-step activation of HSF1 involves post-translational modifications, such as hyperphosphorylation, deacetylation, or sumoylation... Nutritional anti-oxidants, are able to activate vitagenes, such as heme oxygenase, Hsp70, thioredoxin reductase and sirtuins which represent an integrated system for cellular stress tolerance. Activation of vitagene system, with up-regulation of HO-1, thioredoxin, GSH, and sirtuin, results in reduction of pro-oxidant conditions. During inflammaging, including aged-associated pathologies, such as Alzheimer's disease and osteoporosis, a gradual decline in potency of the heat shock response occur and this may prevent repair of protein damage, leading to degeneration and cell death of critical parenchymal cells. Image and text credit from [11].

The concept of hormetins shares common frontiers with that of calorie restriction, in the sense that many mechanisms involved are similar or shared. This suggests that it is possible to choose a range of compounds or treatments which have pluripotent effects for a maximum overall benefit.

It is known that high amounts of polyphenols found in the Mediterranean diet act along hormetic pathways and regulate stress resistance. Pathways involved include those that inhibit mTOR (mechanical Target of Rapamycin) and those which modulate FOXO (Forkhead box O genes) [12]. This indicates that compounds which influence stress resistance (hormetins) may have actions similar to mTOR inhibitors or to other mimetics (discussed below).

Inter-Individual Variations

Before I discuss some of these hormetins I must highlight that there is considerable inter (and even intra-)-individual variation in the response to stress. Individuals who have similar phenotypes at rest may react differently when exposed to a stressful challenge. This concept is very important in the entire discussion about hormesis and hormetic lifestyle [13]. The implication of this is that there is still a lot to learn about the hormetic mechanisms, which could be expressed differently, even in the same individuals under different conditions. The long-time hormesis authority Edward Calabrese [14] quotes:

> *A principal concern in assessing the effects of drugs on humans is that of inter-individual variation. Numerous factors are known that contribute to such variation, including age, familial background, gender, nutritional status, the presence of pre-existing disease, amongst other factors. Using the hormesis database we ... identified a substantial number of experimental settings in which hormesis had been studied in individuals or closely related strains of organisms which differed in susceptibility to toxic agents. In these evaluations we compared responses where the range in susceptibility varied* ***from less than 10 fold to well in excess of 100 fold.*** *Of particular note was that the hormetic response was generally independent of susceptibility, with hormetic responses occurring in subjects ranging from high to low susceptibility. Likewise, the quantitative features of the hormetic dose–response are independent of susceptibility. In about 20% of the cases, it appeared that the lack of an hormetic response in a susceptible strain or subgroup was related to its*

CHAPTER 3

Environmental Enrichment: General Concepts and Research

Abstract: The environment plays a huge role both during ageing and in relation to the phenomenon of hormesis. In this chapter I discuss the impact of any stressful stimuli or challenges originating from our environment, and expand the concept of hormesis to take into account the environment in a wider sense. An enriched environment is taken to mean an 'information-rich' habitat, including the immediate surroundings of an organism. In the case of humans, these surroundings include not only the physical aspects such as towns, natural landscapes and weather, but also social and virtual elements such as online environments and digital relationships. The discussion lays the foundations for understanding how enriched environments act as vehicles of information which lead to biological modifications. These biological modifications may then participate in a novel evolutionary event, which is the emergence of techno-culture, an amalgam of biology and technology. It would be unthinkable to consider human ageing without referring to these new technological developments. Speculative elements such the notion of the 'noeme' (a biological- digital entity), empirical research, emerging research and other concepts are discussed within a mutually-influencing landscape, with the emphasis being on the biology of human ageing

Keywords: Cognition, Epigenetics, Environmental enrichment, Gut microbiota, Indefinite lifespan, Internet, Molecular pathological epidemiology, Natural environment, Noeme, Rejuvenation, r-k model, Social enrichment, Technoculture.

INTRODUCTION

We know that plasticity of the nervous system, and specifically of the synapses, neurogenesis, and general neuronal health, is subjected to external influences, including an intervention which is formally called Environmental Enrichment (EE) [1, 2]. **EE implies being exposed to an information-rich environment**

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which augments the organism's physical and social functions (for example [3]). Such an environment can modulate concentrations of several neuroactive compounds such as glutamate, GABA, dopamine, acetylcholine and others [4].The result of this stimulation is a hormetic effect, whereby mild external challenges (hormetic stresses) up-regulate the function of neural and other elements [5].

There are many studies confirming that EE is a useful strategy in maintaining brain health [6, 7], but research on whether EE has widespread effects on other aspects of physical health is not as widely available. One may argue that a well-functioning brain cannot exist in a badly-functioning body, and thus it can be extrapolated that if EE positively affects the brain it must, somehow, also affect the health of the rest of the body.

What is an Enriched Environment?

An enriched environment is one that consists of substantial amounts of data or information which is meaningful and useful to the organism (*i.e.* non-trivial): - the information entices the organism to respond to the stimulus in order to adapt to it. An information-rich environment may be one that it is richly natural (*i.e.* containing an abundant variety of trees, plants and wildlife [8]). Or it may be a structurally striking city, a stimulating neighbourhood (both socially and architecturally) or an evocative virtual environment (online games or stimuli). Exposure to such an environment affects not only mood, vitality and cognition, but it also provokes distinct biological changes [9] including changes in dopamine and in other neurontransmitters, and modifies several genetic elements. For example, one well-studied gene that has been directly implicated in environmental change is the dopamine receptor gene D4 (DRD4 gene) and its various alleles/polymorphisms. This mediates challenges originating from the environment, and results in distinct phenotypes. It can predict longevity [10] and it is also influenced by the season of birth [11] which supports the notion that the environment may directly affect genetic inheritance.

Natural landscapes may improve other neuronal 'feel-good' factors and result in mental well-being and optimism for the future. This depends on the degree, value and weight of the information carried by the environment [12]. Although in a natural environment one is exposed to a combination of visual, auditory and other

stimulation, the health benefits may be experienced even if one is exposed to just one type of stimulation. Pati *et al.* [13] have shown that patients who are exposed to a simulated natural environment (ceiling-mounted photographic sky compositions, in a hospital setting) experience a significant improvement in patient outcomes, with lowering of the blood pressure, a reduced need for medication, reduction of anxiety and stress, and improved environmental satisfaction. This indicates that stimulating even one of the senses can still result in biological/physiological changes as long as the value of information remains relevant, and is able to provoke an adaptive response.

On the other hand, it is also known that modern societies are slowly moving away from nature and espouse a more virtual/artificial setting. The definition of 'natural' is crucial in this discussion. **Natural is an environment which is not made or caused by humans**. This is important because I will later discuss how our environment is becoming more technological and less natural, although one may argue that it is natural for humans to develop (and live in) technological environments.

It was shown that time spent watching television, playing video games or internet use is inversely proportional to hours spent in raw nature [14]. This is characteristic of our modern techno-cultural milieu and it is not necessarily adverse to health, as it is also known that computer use can have health benefits, and it is associated with increased longevity (Fig. **1**).

Being cognitively stimulated in a virtual setting is shown to have several health benefits. For instance, playing online action video games (AVGs) affects the plasticity of sensorimotor regions in the grey matter, and improves connectivity between neurons, particularly those involved in attention and experience [16]. These cognitive benefits of interaction with technology are not specific to action video games, but other active online experiences may also improve cognition. Use of general video games for one hour a day improves spatial memory, cognitive control and complex verbal span [17]. General use of the internet has been studied in a variety of settings and initial results show health promoting effects, including an increase in life expectancy, as discussed in Fig. (**1**) but although there is correlation, the causation is still unclear. A study in Taiwan found that internet

CHAPTER 4

Epigenetic Regulation and Adaptation to Stimuli

Abstract: Changes and variations to physiological traits which are caused by environmental factors are studied by the science of epigenetics. This sub-section of genetics describes alterations in transcription which may result in different phenotypes depending on the influence of the environment. The study of epigenetic mechanisms is very relevant in ageing and, in particular, in situations involving external challenges and exposure to novel information. In this chapter, I will discuss some elements related to epigenetic regulation as applied to situations where humans are exposed to 'positive challenges' which aim to up-regulate somatic repair mechanisms. The role of epigenetic factors, including non-coding RNAs (such as microRNAs) will also be discussed in the context of an information-rich environment. In addition, I will explore certain principles (such as the Condition-Action rule) which are relevant to the operation of the adaptation mechanisms, and some mechanisms which govern the process of information assimilation by the cell. The underlying theme, which will also be explored in the following chapters, is the consideration of mechanisms that may result in reallocation of repair resources from the germ line back to the soma. Overall, the aim is to highlight factors, processes and principles which depend on the environment and may be involved in human health improvement.

Keywords: Adaptation, Condition-Action rule, Environmental challenges, Epigenetic landscape, Epigenetic regulation External stimulation, Germ line repair, Information, MicroRNAs, Soma-germ line conflict.

INTRODUCTION

Adaptive phenotypic plasticity is an important factor in human evolution. There is considerable evidence suggesting that the environment influences the plasticity of the phenotype [1] and that there exist precise, if hitherto not very well studied, mechanisms, which respond to stimulating changes in the environment, in an attempt to adapt to the stimulus [2]. This adaptation to a stimulus is very relevant

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in the study of age-related pathology and in the evolution of ageing in general. It is also relevant in the context of hormesis and stress response processes. Increasingly, research shows that the environment is crucial in determining prolonged healthy longevity [3]. In human terms, the 'environment' is an abstract notion of an amalgam of physical and virtual surroundings, interactions with modern society, and techno-cultural elements. It is, in other words, a highly 'information-rich' milieu. It is worth noting at this point that I define information as 'a meaningful set of data or patterns which influence the formation or transformation of other data or patterns, in order to reduce uncertainty and help achieve a goal' [4] (Fig. **1**).

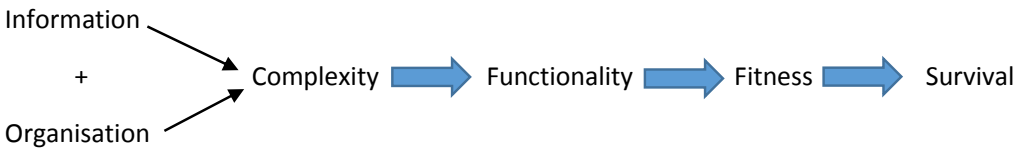

Fig. (1). The impact of information upon survival. Information (plus organisation) [5] increases complexity and this increases functionality [6]. This improves fitness and thus survival [7]. Any increase in internal fitness requires the formation of new links and the strengthening of the interconnectedness between its nodes *i.e.* increased complexity, thus increased fitness and increased survival. The definition of **fitness** is 'good function within a specified environment'.

Ashby's law of Requisite Variety [8] suggests that less predictable environments (where we don't know what will happen next, *i.e.* those environments that are more challenging) require more complexity of function in order to survive in that specific environment. As our technological environment is now increasing in complexity and becomes more 'information-rich', we too need to adapt to these changes in order to function efficiently and survive. Our technology and evolving culture are driving us to continually adapt and change, in a perpetual attempt to become better able to deal with new challenges. However, there has to be a balance both with respect to the amount of stimulation and with regards to an optimum level of unpredictability. If this balance is disturbed for significant periods of time, then overexposure to information will result in loss of function. This is a 'dose-response' phenomenon, *i.e.* a hormetic effect. The concept of 'information fatigue' becomes increasingly more relevant in a society which is inundated in information.

In addition, as our environment is constantly changing, (and recently, changing at an ever-accelerating manner [9]) we need to adapt to these changes quite fast. This must depend on intentional evolutionary actions executed through technology rather than the much slower Darwinian natural selection processes [10]. There is simply not enough time for us to continue relying on natural selection, when new disruptive and global technologies appear so quickly. Epigenetic factors mediate between the genome and the environment, and play an important role in this respect, allowing for rapid changes in protein expression which may be applied almost immediately when needed. Of course, there are other factors which may initiate and achieve rapid biological and physiological adaptations, but the epigenetic ones are the most relevant.

Epigenetic Regulation in Ageing

There is an increasing body of research which highlights the role of epigenetic changes in age-related degeneration [11]. Epigenetic changes such as chromatin remodelling and DNA methylation can modify the phenotype and play a modulating role in senescence and age-disease. One of the reasons for this, is based on the fact that epigenetic processes can regulate mechanisms necessary for development [12]. Ageing has been interpreted by several authors as a continual and disproportionate operation of basic developmental processes, which eventually lead to time-related malfunction [13, 14]. Therefore, a corrective regulation of this defective process could lead to the control of at least some ageing mechanisms. In addition, it is known that there could be 'molecular brakes' which restrict the plasticity of adult cells in certain types of neurons [15]. These and other epigenetic mechanisms may lead to stabilisation and delayed expression of any brake factors and thus account for seamless and rapid plasticity of the cell. The fact that several of these factors are found in the flexible and adaptable extracellular space makes it more likely that epigenetic control would be more effective compared to 'hard-wired' genetic intracellular mechanisms.

Epigenetic Changes and Hormesis: The Epigenetic Landscape

Referring to the complexity of gene regulatory networks and to the effect of the environment, Huang [16] remarked:

CHAPTER 5

A 'War of Trade-offs' Between the Soma and the Germ Line

Abstract: In nature there is always a fierce competition for resources. This is particularly relevant during the process of ageing, where there is canalisation of repair resources; these tend to flow from the somatic tissue towards the germ line, in order to assure the survival of the species. In the early periods of phylogenetic development there was a time when repair of germ line cells became more efficient compared to the repair of somatic cells. The level of somatic repair became just sufficient to ensure that the organism reached sexual maturity. We are now looking for evidence that this could be changing, that we may be witnessing a **phase transition** from effective germ line repair to an effective somatic repair. Here, I consider mechanisms of fidelity-preservation which may be present in the germ line, and examine the possibility that these may be made to operate upon somatic cells instead. Mechanisms which safeguard the reliability of germ line repair and ensure robustness/resilience in the germ line may also (or instead) be applicable upon somatic material (cells, molecules, and other factors) and safeguard a continually-effective repair of this somatic material. Relentless hormetic challenges from the environment guarantee that the flow of information remains operational and it persistently fuels the ability to repair the soma. Apart from germ line cells, some unicellular organisms such as certain bacteria maintain their ability for ongoing repairs (at least for some considerable time, albeit not indefinitely), a fact that indicates that, in principle, senescence is not unavoidable. Thus the ability to repair and maintain somatic organic material within biological systems is not entirely lost.

Keywords: Apoptosis, Environment, Germ line, Germ line to soma cross-talk, Indispensable soma hypothesis, Immortalisation, MicroRNAs, Somatic repairs, Trade-offs, Transposons.

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INTRODUCTION

In this chapter, I will discuss, review and speculate on matters relating to how exposure to information (in humans) may lead to a situation whereby ageing as a process may be significantly downgraded (or even virtually eliminated, at least in some sections of humanity). This is particularly relevant if we accept that ageing is programmed, when we could conceivably stop the programme as mentioned in the Condition-Action rule previously. However, the discussion is also relevant if ageing is stochastic, when random damage causes dysfunction. This is because the discussion accounts for repair of age-related damage, even when this damage is random. Some initial concepts have already been discussed in the previous chapter but I will continue addressing this matter from a variety of angles. In this chapter and throughout the book, I define human ageing simply as 'time-related dysfunction'. This accounts for the fact that ageing is a process dependent on the passage of time, and it is only of interest to humans because it results in loss of function (and consequently, chronic degenerative disease and death). This concept is important because it places the discussion, not only on a biological basis but also on a clinical, everyday life basis.

This argument, and most of the concepts found in this book, is based upon certain simple evolutionary principles. It is indisputable that the widespread tendency in nature is towards continual survival and good function. When a **mildly** stressful (*i.e.* not excessive or prolonged) event happens, such as famine or starvation, the reproductive priorities in humans are down-graded [1]. The crucial question to ask here is 'why does this happen?' Again, it is undeniable, in my view, that the answer is this: When life is immediately in danger, there is a 'hard-wired' tendency in natural principles to protect the organism as a priority, and allocate to this process whatever resources are necessary for effective repair and maintenance. This may mean a reduced priority for reproductive resources. There are species that will hold off on reproduction, or send embryos into diapause, during hard times, such as the honey bee, or the roe deer for instance. What is relevant here is that, although this does not mean that the organism lives longer, at least there is strong evidence that organisms can reallocate resources from reproduction to tissue maintenance. There exist definite trade-offs between somatic maintenance and reproduction [2], but when somatic elements need repair

resources, the first initial objective (*i.e.* the 'default' option) is to allocate these to the soma. If the danger continues, or if the environment is risky and there is an increased likelihood of the organism dying early, then nature switches to 'option B', the second best option for ensuring survival, which involves the withholding of somatic repair resources and the reallocation of these to the germ line [3]. The point of this argument is to show that the tendency to survive as a discrete organism is **innate and present now** in all of us, and it is the first priority of most biological processes. Ageing and reproduction are merely secondary processes 'developed' by natural principles in order to assure survival, only as an ancillary, reserve mechanism. The above concepts should be taken within the definition I give to the term 'evolution'. For me, evolution means 'the adaptation to changes in the environment, in order to continue survival'.

In the co-evolution of the repair mechanisms employed by somatic and germ line cells, there was a certain antagonism, whereby germ line elements have succeeded in modifying the opponent's (somatic) control systems (for instance [4]). Despite several countermeasures deployed by somatic cells in order to acquire sufficient repair resources, there was a relatively rapid divergence of the functionality of the control and regulation systems, resulting in the immortality of the germ line with the mortality of the soma [5]. It is possible to study the basic theoretical mechanisms involved in such co-evolutionary setting, and consider ways to modify or interfere with the processes, in a way that favours the soma instead of the germ line. This may lead to methods which study a fitness landscape where somatic repair mechanisms can evolve rapidly [6]. In this respect, Smelick and Ahmed [7] have suggested that the germ line can antagonise the ageing of somatic cells, and that it may be possible that defects in the mechanisms operating during immortalisation of germ line cells may provide useful repair resources to somatic cells. Germ cells achieve continuous repair and fidelity of replication by ensuring that they maintain robustness - the redundancy that counteracts the effects of random damage. Evolution drives the balance of the appropriate trade-offs between robustness and maintenance resources. The trade-offs between survival of the somatic cells and reproduction could be due to factors such as:

a. The impossibility to maintain all processes within the body indefinitely, due to lack of repair resources (the notion of 'Clashing demands' in physiology: because

CHAPTER 6

Another Dimension: 'Zooming Out'

Abstract: The quest to find effective therapies aimed at chronic age-related degeneration has deep and wide ramifications. It is not sufficient to examine physical or pharmacological interventions which may have an impact on the process. Instead, we also need to consider more profound evolutionary principles which underpin the process of ageing. One example is the principle of degeneracy which may be useful in explaining how we may attain similar functions by using different structures. Another example is hysteresis, which examines dependence on already established conditions - a crucial obstacle we need to overcome in the quest to diminish chronic degeneration. This chapter will be an exploration of certain evolutionary and philosophical principles, such as a contemplation of the meaning of life, which complement the biological and medical ones. Concepts relating to resilience, complexity and self-organisation, as well as a discussion of certain cybernetic principles (such as path-dependency and nudging), all taken together will provide a suitable and realistic framework for achieving our aim: to manipulate nature in a way that diminishes the impact of age-related degeneration, and reduces mortality as a function of age.

Keywords: Boundary, Complexity, Degeneracy, Health, Homoeodynamic space, Hysteresis, Life, Lifestyle, Nudging, Path dependency, Resilience, Resilient interface, Stigmergy.

INTRODUCTION

In order to place the general discussion of this book into a broader framework, it is necessary to reflect on some concepts which hitherto have not been considered with due vigour by gerontologists (Fig. **1**).

These concepts have nevertheless, direct and significant relevance upon the ageing process. The question whether there is an ultimate 'aim' or 'purpose' in evolution has tormented the greatest minds ever lived. In order to simplify the

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matter, and also in order to fashion the concept into something relevant to this book, I posit that:

1. Nature has a general tendency to 'life'. Evolution is biased towards increasing fitness in order to ensure survival.
2. But, in humans this tendency has reached another level. Human creativity has evolved into something that it is clearly over and above what is needed to ensure mere survival.

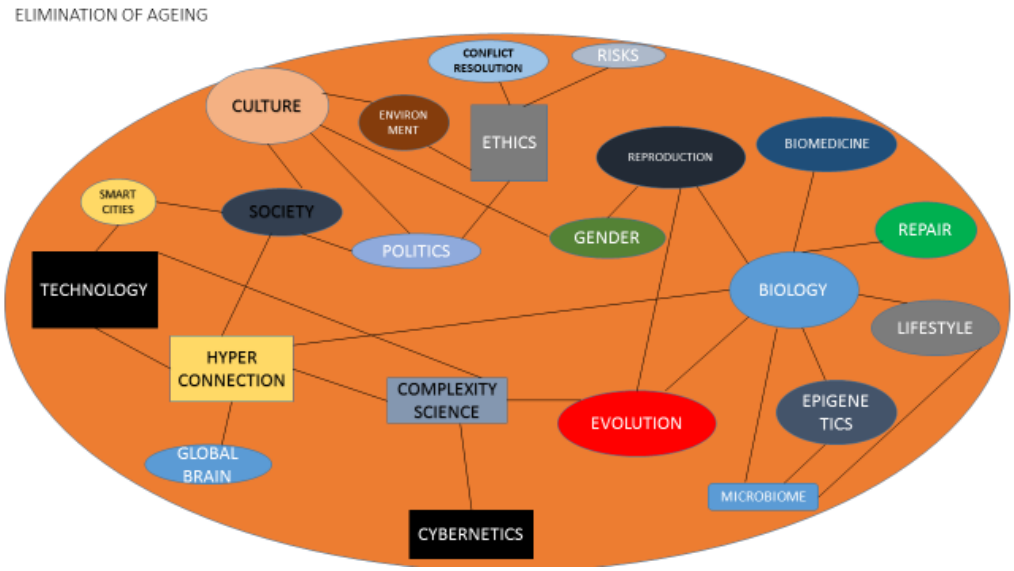

Fig. (1). A wider picture of ageing. In order to devise methodologies which may help us eliminate age-related degeneration, we need to see a bigger picture, and consider ageing as a mechanism which is being influenced by many diverse concepts. The disciplines of biology or medicine are not enough. We need to study societal and environmental aspects, complexity principles, human evolution, ethics and politics and a generally much wider approach.

This creative impulse has been identified by some philosophers as the effort to 'transform darkness into light' [1]. It is in other words, a quest, to continually reach a stage which is better compared to the previous one. Organic agents and humans in particular, are merely instruments of nature, existing only in order to enhance this fundamentally-driven process of continual evolution. These agents are then discarded, exchanged for new ones (new individuals, new societies, new

cultures) in perpetuity. Each participating organism contributes a small part in the entire process, and then it perishes. There is nothing in this scenario to suggest that the duration of this presence must be short. In fact it can be as short or as long as necessary in order to facilitate and enhance the adaptive capabilities of the entire mechanism of continual evolution.

The view put forward in this book is not merely to just improve our health in order to increase our survival. No. It is to improve our health which will lead to our prolonged survival, in order to achieve a superior stage of evolution, and so fulfil the innate creative impulse of humanity (Figs. **2** and **3**).

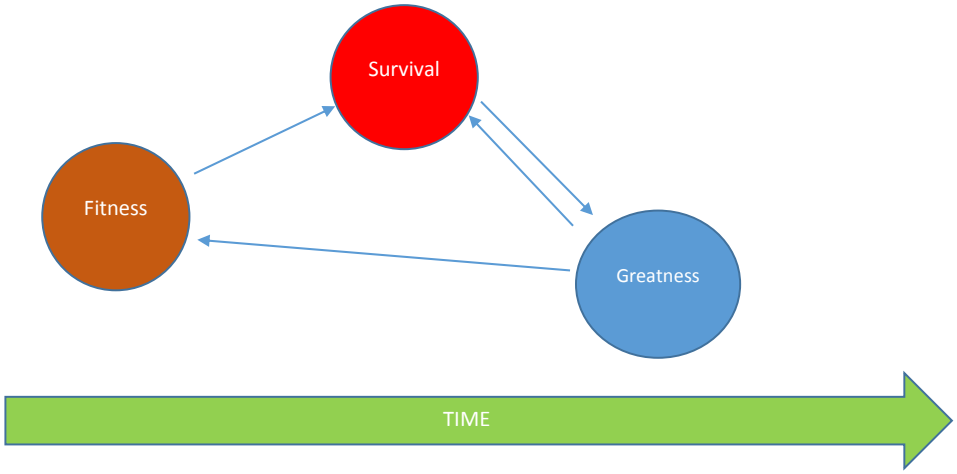

Fig. (2). Human destiny over time. In this example, 'fitness' is literal *i.e.* 'being fit', appropriate and suitable for one's environment. 'Greatness' (intellectual creativity) is defined as: 'the continual quest to reach a stage which is better compared to the previous one'. Being fit increases the chances of long life, which improves the chances of achieving a higher stage of evolution. This, in turn, helps to increase fitness and further improves survival, in a continual manner. This process is fuelled by the continual input of meaningful, organised information (as in Fig. **3**).

Living systems are defined by their ability to contain high level of information [2]. Any far-from- equilibrium systems (such as living humans) have high entropy generation, and the way to maintain a stable entropic state is to achieve an extreme level of information content [3]. Frieden and Gatenby [3] quote:

CHAPTER 7

Energy, Entropy and Complexity: Thermodynamic and Information-Theoretic Perspectives on Ageing

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Abstract: The human body is a complex system. It has a natural ability to grow and develop over time, as well as adapt to the frequent changes in the surroundings. The complexity associated with it and the various processes it undergoes lie in its structure and functionality. Complex chemical reactions play a central role in the evolution of structure and organization of this complex adaptive system, which are inherently directed along the paths of maximum entropy production. Entropy production causes a system to degrade itself by the gradual consumption of free-energy to a more thermodynamically-stable state. However, the human body, and open systems in general, have a tendency to preserve or increase order and complexity with time. This phenomenon of spontaneous appearance of order is known as self-organization. Thus, the human body has a structure and several underlying functions that give rise to organization. Simultaneously, it prevents the destruction of this state of organization by self-organizing itself with time. In the following chapter, we will look into the details of (self) organization from a physical and an information perspective, in order to see the relationship between complexity and the growth in organization of a system with time. Further, understanding the concept of (self) organization from a functional perspective is also important as it will allow us to relate metabolic reaction-sets to structural symmetry, metabolites to interacting nodes, and mapping these interactions into complex networks. Finally, our aim will be to relate ageing to the loss of energy, information, organization and functionality of the human body with time.

Keywords: Complexity, Dissipative Systems, Principle of Least Action, Second Law of Thermodynamics.

INTRODUCTION

The human body, its structure and functionality have always been a topic of

extreme interest in the scientific community. The structural complexity exhibited by the human body has always intrigued mankind. How do small entities such as the cell, metabolites and protein molecules, which are invisible to the naked eye, amalgamate to form bigger molecules, tissues and organs is a very interesting question. In general, the concept of life is fascinating. One of the most important scientific accounts on this fascinating subject can be found in Schrödinger's book which dealt with the definition of life. In this book, which was based on a course of public lectures that he had delivered in 1943, he had focused primarily on one important question: "*How can the events in space and time which take place within the spatial boundary of a living organism be accounted for by physics and chemistry?*" [1].

In this book, he speculated about an 'aperiodic crystal' that contained the genetic information in its configuration. Although the existence of DNA was established back in 1863, its specific purpose in reproduction still remained a mystery. By 1903 people thought that chromosomes were the heredity units but it wasn't until 1933 that Jean Brachet showed that the chromosomes were composed of DNA. By 1944 there was experimental evidence for DNA being the heredity material. The ideas presented by Schrödinger in his book provided an early theoretical description of how the storage of genetic information would work [2]. Although there are accounts of ideas on the physical basis of life even before Schrödinger, such as Muller's article on "Variation due to change in the individual gene", Schrödinger's approach to the problem is particularly interesting[1]. Primarily, Schrödinger did not discriminate between the processes occurring outside the cell with those occurring inside. Secondly, his treatment of the problem was based on the fundamental laws of physics or from the first principles [4, 5]. He identified the field of thermodynamics and statistical mechanics to provide himself with an answer. The Second Law of Thermodynamics is a powerful tool in the hands of a physicist [6 - 11]. Schrödinger observed that the purpose of life is to increase the complexity and the information content in a living being, whereas, we being surrounded by the Second Law should observe just the opposite. This led him to coin the term, *negative entropy* or *negentropy* – the entropy that a living system exports into the surroundings in order to keep its entropy low, which he corrected in the later editions by stating that life feeds on free energy [1]. The other

interesting observation that Schrödinger made was that most physical laws at macro scales are a result of chaos at the finer levels. This realization of Schrödinger's is what we know as the phenomenon of self-organization [12, 13]. Thus, Schrödinger in his explanation of life provided us with two important insights – his formulation of life as a thermodynamic process and his observation on the appearance of global order from local fluctuations. Both the observations lead us to visualize the human body as a complex adaptive system [12, 14].

The domain of Complex Adaptive Systems (CAS) is a relatively new field when compared to its counterparts, such as classical thermodynamics or statistical mechanics. CAS are macroscopically complex, made up of numerous interacting finer entities, and are adaptive to the fluctuations in the surrounding environment. Typical examples of CAS include the human body, the cell, the stock exchange, the ant colony, *etc*. It is observed that the property of these systems as a whole differ from each of their individual agents, which is contrary to the usual stance of classical physics. These systems are adaptive and complex, yet they lack a central coordination. The entities that make up a CAS often follow simple rules to interact with each other. In Fig. (**1**), we can observe that the left extremity of the bell-curve is occupied by causal-Newtonian physics, according to which, the path of each interacting particle in a system is deterministic. In the extreme right of the bell-curve in Fig. (**1**), we observe dis-ordered complexity arising due to stochasticity in the system. In the middle of the curve, lies ordered complexity, such as the cell or the human body, which although complex have structure and organization. In ant colonies, for example, the only mode of interaction between the ants is through the pheromone trail that an ant leaves while foraging for food. The simple idea of 'following the trail' leads ants to find the shortest path in the real world between the colony and the food source [16]. Also, in the organizational hierarchy of the ant colony, there does not exist any central control, rather the control between various agents is distributed, and the above simple rule gives rise to a global coordination in the entire colony. Interestingly, the numerous interactions and distributed coordination makes the system robust to perturbations in the surroundings [12]. Similar to the above example of an ant colony is the human body, the brain or one of the smallest building units of the human body, the cell. All of these are made of finer entities which interact with each other,

CHAPTER 8

Engagement with a Technological Environment for Ongoing Homoeostasis Maintenance

Abstract: Emerging empirical and theoretical thinking about human ageing places considerable value upon the role of the environment as a major factor which can promote prolonged healthy longevity. Our contemporary, 'information-rich' environment is taken to mean not merely the actual physical surroundings of a person but it is also considered in a more abstract sense, to denote cultural, societal and technological influences. This modern environment is far from being static or stable. In fact, it is continually changing in an exponential manner, necessitating constant adaptive responses on behalf of our developmental and evolutionary mechanisms. In the previous chapters we have presented our views about these adaptive responses and mechanisms. Here, I will describe in some more detail these and related mechanisms of how a continual, balanced and meaningful exposure to a stimulating environment, including exposure to 'information-that-requires-action' (but NOT trivial information), has direct or indirect repercussions on several factors (mostly epigenetic) which may then act to prolong healthy longevity. Information gained from our environment acts as a hormetic stimulus which up-regulates biological responses and feedback loops, eventually leading to improved repair of age-related damage. The consequence of this up-regulated information-processing systems may influence resource allocation and redress the imbalance between somatic cell *versus* germ-line cell repairs. This can eventually have evolutionary consequences resulting in the drastic reduction of age-related disease and degeneration.

Keywords: Ambient intelligence, Cognition, Complexity, Germ line repair, Human evolution, Information, Phase transition, Physical exercise, Smart cities, Techno-culture.

INTRODUCTION

The discussion here builds upon elements examined in previous chapters, and

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attempts to elaborate on some more details and mechanisms involved. I will revisit several of these elements and present arguments that support my general hypothesis: that **a worldview based upon purposeful and focused integration with technology which hermetically challenges our cognition, may initiate a shift in evolutionary priorities, resulting in a virtually total elimination of age-related dysfunction**. Here, I must make clear that, in my view, evolution is not a totally random process, as it generally has a tendency towards survival. I define the term 'evolution' as 'the adaptation to changes in the environment so that survival continues'. Therefore, life's 'priorities' are geared towards ensuring survival by any means (such as reproduction for instance). It may be possible to modify the thrust of evolution, and shift the emphasis from the survival of the species to the survival of the individual. Although one of the most obvious possible mechanisms of this appears to be the soma to germ line reassignment of repair resources, there could be other mechanisms, perhaps equally as important. However, in this book I am not going to speculate any further about other mechanisms, and will concentrate on the somatic *vs* germ line argument.

I argued elsewhere that ageing is accompanied by loss of information and complexity *i.e.* increased entropy over time [1] (Box **1**). This loss is rooted in the suboptimal conditions caused by the uneven distribution of resources favouring the survival of the germ line *versus* somatic repair. The rate of somatic repair tends to become progressively compromised as a function of age, resulting in accumulation of damaged biological material that reduces organisation and functionality [2] *i.e.* reduced information content, reduced complexity and thus reduced survival.

If it is assumed that the above concepts are, on the whole, valid, then one may ask the question: Can we intervene in any way in order to accelerate or modify this process? In this book we have proposed and discussed interventions and environmental challenges which increase the information load of the individual and may result in up-regulation of essential repair processes, resulting in clinical benefits. At this point I must re-iterate that a 'Challenge' is a situation that potentially carries biological value for an organism, so that the organism is inclined to act. A challenge provokes action because it represents a situation in which not acting will lead to an overall lower fitness than acting.

Box 1. Three essential elements (or assumptions) need to be considered in the case of human ageing:

1. During human evolution, there is a general tendency to attain higher levels of functional complexity [3],
2. The process of ageing is accompanied by a general loss of this functional complexity [4], and
3. By increasing complexity (either artificially, through information or challenges, or through any other means) age-related dysfunction is minimised [1, 5].

Environmental Enrichment: Speculations, Inferences and the Phase Transition

While the health benefits of Environmental Enrichment (EE) have been well studied, it is not clear what impact an enriched environment has on prolonging healthy lifespan, and certainly it is not clear if EE can prolong human lifespan well beyond the current maximum limit (approximately 115-120 years). I have already discussed some initial facts concerning these mechanisms in the previous chapters. Here, an attempt will be made to further clarify some possible mechanisms involved in this respect, particularly with regards to examining whether EE (and thus information) can have any effects on reducing age-related dysfunction and thus prolong human lifespan beyond the current maximum limits.

In order to place the discussion within a wider framework, I will revisit the general concept of phase transition. A phase transition is a profound structural re-organisation of a system, when there is a large change in resource availability for maintenance [6]. Sudden, rapid-acceleration phase transitions are associated with emergence, mutations, breakthroughs and development of autocatalytic systems which disrupt the status quo and result in new situations which may improve fitness and survival [7]. The study of such threshold dynamics gives interesting insights into plausible mechanisms for artificial manipulation of the process. In order for a phase transition to take place it is necessary to have increased complexity, increased exposure to new challenges and a reduction of available

Appendix

PART 1. COGNITIVE AGEING QUESTIONNAIRE

Although not scientifically validated, this is a general-purpose questionnaire that can be used in the clinic or at home, aiming to evaluate certain aspects of cognition in ageing. The questions cover a wide spectrum of ordinary, everyday activities and reflect an element of hormetic stimulation and challenging cognitive behavior. The concept of *power law* (frequent mild activities, occasional moderate ones and rare intense ones) is also reflected. This can be used as a tool to inform the user about the value of cognitive challenges, and the role of hormesis in daily life. Part 2 of the Appendix is then about examples of activities one can participate in, so that to try and improve cognitive and physical functions, thus providing a practical guide to complement the questionnaire.

Cognitive Ageing Questionnaire

PLEASE TICK ONE

1. Do you watch (listen to) the news on TV (radio)?

1. regularly
2. frequently
3. occasionally
4. never

2. Do you believe that you will be able to develop new skills when you are much older?

1. yes
2. maybe
3. I don't know
4. no

3. Do you have to remember many tasks or events during your day?

1. all the time
2. frequently
3. occasionally
4. no

4. Do you get bored with ordinary routine?

1. yes, I like a change
2. sometimes
3. don't know/undecided
4. no, I love everyday routine

5. Are you satisfied with your job (or with not working)?

1. not at all
2. not sure
3. sometimes
4. yes, I am satisfied

6. Do you have to think creatively and use your brain during your day?

1. yes, all the time
2. frequently
3. occasionally
4. no, almost never

7. During the past two years how frequently have you been to intellectually stimulating courses (*e.g.* evening or weekend courses, part-time home study)?

1. regularly
2. frequently
3. sometimes
4. never

8. How frequently do you read science, art, philosophy, or other serious books (or online)?

1. every day
2. two or three times every week
3. two or three times every month
4. almost never

9. Do you find that your memory is getting worse as you get older?

1. definitely
2. somewhat
3. not sure

4. no

10. Do you believe that your intelligence is frequently letting you down?

1. yes
2. sometimes
3. not sure
4. no

11. Do you keep yourself informed of the latest developments in science, fashion, politics or world affairs?

1. yes, every day
2. frequently
3. sometimes
4. no, almost never

12. Do you daydream about positive life events (either past or future)?

1. regularly
2. frequently
3. sometimes
4. never

13. Are you happy with the way you are stimulated intellectually during your day?

1. yes
2. frequently
3. sometimes
4. no, too much or too little stimulated

14. In general, do you believe that people's memory seriously gets worse as they grow old?

1. yes
2. frequently
3. I don't know
4. no

15. a) Does intelligence worsen with age? Yes No

1. Does learning ability decline with age? Yes No

2. Do you believe that there is nothing you can do about memory loss? Yes No
3. Do you specifically avoid using your brain in order to avoid wear and tear? Yes No

16. Do you do crosswords, puzzles, memory exercises, brain training or using the internet to keep you cognitively stimulated?

1. yes, daily
2. once or twice every week
3. once or twice every month
4. no, almost never

17. Do you feel uneasy when having to handle new equipment (video recorder, computer, a new app *etc*.)?

1. yes
2. sometimes
3. not sure/no opinion
4. no, I look forward to the challenge

18. Are you unable to make decisions easily?

1. yes, I am
2. sometimes
3. not sure
4. no, on the contrary

19. Do you fall behind with your schedule at work or at home?

1. almost never
2. sometimes
3. many times
4. all the time

20. How much time do you set aside for you hobbies?

1. every day
2. about twice a week
3. about once or twice a month
4. none at all

21. Do you feel depressed, lonely or unhappy?

1. all the time
2. frequently
3. occasionally
4. almost never

22. a) Do you usually sleep well? Yes No

b) Is your appetite usually good? Yes No

c) Do you frequently feel like crying? Yes No

d) Have you given up hope? Yes No

Now check your score. Award yourself the points corresponding to your answers:

1. a)0 b)2 c)8 d)10
2. a)0 b)2 c)8 d)10
3. a)0 b)2 c)3 d)10
4. a)0 b)3 c)8 d)10
5. a)10 b)8 c)7 d)0
6. a)0 b)2 c)8 d)10
7. a)0 b)2 c)8 d)10
8. a)0 b)3 c)6 d)10
9. a)10 b)5 c)4 d)0
10. a)10 b)8 c)3 d)0
11. a)0 b)3 c)8 d)10
12. a)0 b)2 c)8 d)10
13. a)0 b)6 c)8 d)10
14. a)10 b)7 c)3 d)0
15. a) yes = 8 no = 0, b) yes = 8 no = 0, c) yes = 10 no = 0, d) yes = 10 no = 0
16. a)0 b)2 c)5 d)10
17. a)0 b)3 c)6 d)10
18. a)10 b)7 c)6 d)0
19. a)0 b)3 c)7 d)10
20. a)0 b)3 c)7 d)10
21. a)10 b)8 c)5 d)0
22. a) yes = 0 no = 5, b) yes = 0 no = 6, c) yes = 8 no = 0, d) yes = 10 no = 0

The lower the score, the more likely it is that your cognitive function and is healthy. You should make a record of your score and then retake the questionnaire at regular intervals, for example every six months. You can then compare your score with the original and see whether your mental attitude or cognition are improving. A persistently low score indicates that your brain and mental attitude are healthy.

COMMENTS ON THE ANSWERS

1. Keeping yourself informed about the national and international situation implies that you have a certain interest in the world around you which keeps the brain nicely stimulated. Do make a point of watching the news and then, if possible, discuss these with a neighbour or friend. Also spend some time online exploring new concepts, and sharing information which makes others act on it.

2. Given the right help and assistance, even very old people can learn computing and develop many other skills. Memory and mental faculties should be exercised but, as everything in life, this should be within reason, should not be excessive or prolonged. Rather, frequent light mental exercises could be mixed with less frequent moderate ones.

3. Day to day and hour to hour memory (short term memory) is important and needs to be exercised. If you are not using your memory frequently it may deteriorate later on in life. Try remembering some commonly used telephone numbers instead of writing them down.

4 and 5. Being satisfied with your everyday life is the basis of happiness. If you are not happy with your routine you now will also feel unhappy later on in life. However, this does not mean that you should sit back and enjoy what you have. You also need to seek new adventures, new situations and explore new ideas, in a way it makes you feel comfortable.

6. All faculties of our brain need to be exercised. Research suggests that a brain which is stimulated and challenged regularly will perform well even in very old age. Stimulating activities can be:

- thinking how to reposition the furniture in your sitting room
- writing a letter to your local paper on an issue
- learning how to use your local library, or a new computer

7. Studying keeps the brain active and disciplined. It also makes you feel better, particularly at the end when you receive the qualification. There are hundreds of courses for all abilities. Ask at your local library or adult education department, or explore hundreds of free courses online.

8. Reading books shows an interest in learning new things which in itself keeps the brain

active. It also means that in later life you will have something to do (*i.e.* read books), therefore boredom will be less likely. It is never too late to start reading stimulating books regularly.

9. Memory may worsen with age, more so if it is not exercised regularly. A certain degree of memory loss is normal. If you think that your memory is getting seriously worse you should see your doctor for evaluation.

10. If you do not believe in yourself then your chances of brain problems later in life will increase. If your brain is letting you down, why not exercise it? It may also be possible to consider oral supplements which may help you achieve a state of positive stress. These are called 'hormetins'. Ask a suitably qualified health practitioner for details.

11. By keeping yourself informed you maintain the brain active and stimulated. You will also get information about new anti-ageing treatments which you may find useful in maintaining your health.

12. It is wrong to think that day-dreaming about past events is damaging. People of any age need to think and review their lives constantly. This is particularly true in later life. Reminiscence therapy helps people put their lives in perspective and improves their current role in life. Day-dreaming about future events increases motivation and well-being. Also, meditation and mindfulness exercises are essential in improving several health aspects of your brain.

13. Intellectual stimulation during the day keeps your brain in good form. However, over-stimulation can cause too much strain, headaches and other unnecessary discomfort. When you are satisfied that you have had enough then it is time to stop for the day.

14. An older person may use different ways of dealing with a mental problem than a younger person but this is not abnormal. In some cases, Alzheimer's disease is the cause of mental impairment but this is a disease and not necessarily a normal ageing event. "Senility" is not an inevitable part of ageing.

15. The brain does not slow down appreciably but it uses different techniques to deal with problems. Properly performed IQ studies show that intelligence does not decline significantly in healthy elderly people. With proper training healthy elderly people may be able to maintain good cognitive functions for many years.

16. If you use your brain by doing activities like chess, puzzles, writing *etc.*, you may reduce the chances of brain failure in later life. Brain stimulating activities need not be very hard, an easy crossword will do. Activities which put a lot of pressure on the brain may cause

unnecessary strain. However, always remember that, for best results, you need to perform frequent light mental activities, some moderate ones and rarely, some heavy ones.

17. It is often difficult to handle technical equipment, and unfamiliarity makes matters worse. However, you should try and keep up with technological advances which make life easier. The challenge of dealing with a new situation is a great way to stimulate your brain.

18. Taking a quick decision shows a sharp mind willing to take some risk. People who manage to carry these qualities with them into older age are fortunate. Those who don't, should exercise them. If however, you have been a slow decision maker throughout life, it will be very difficult to change.

19. The way you work reflects many aspects of your intellect and personality. Falling behind with everyday routine might mean a less organised approach to life which can cause trouble and confusion later on. Try to work in a way that looks chaotic and irregular but has underlying order and intent. This means you deliberately do irregular activities in order to achieve your aim, but this irregularity is planned and controlled. You should not act in a disorganized way but do well-controlled and varied activities.

20. Setting aside time for your hobbies is one of the most important steps to take in order to avoid stress. It also indicates that you have your priorities right, you care about yourself and therefore you keep yourself well.

21 and 22. These questions test for depression, which can present as memory loss. Treatment for depression is not always difficult and the results can be spectacular. If you think you are depressed see your doctor for treatment.

23. Physical exercise and a low cholesterol diet may improve blood flow to the brain. A family history of atherosclerosis (thickening of the arteries) may indicate an increased risk of brain failure. There are several nutrients and compounds which may help, if taken with medical supervision.

24. Recent research shows that low education is associated with an increased risk of Alzheimer's dementia. It is never too late to exercise the brain and try to prevent any further deterioration.

PART 2. EXAMPLES OF PRACTICAL COGNITIVE AND HORMETIC CHALLENGES

My colleagues and I have been using these exercises and advice for the general public for several decades. The intention is to place some aspects of the discussion from this book into a

practical, simple framework and make it easy for people to use in their everyday life. The concepts of hormesis, environmental enrichment, power law, and positive challenges are incorporated in all of these exercises. One possible way these mental, social and spiritual challenges exert their hormetic benefits could be *via* the up-regulation of nerve growth factors and receptor-ligand interactions, increasing responsiveness of neural stem cells, and bolstering other neuroprotective elements such as reducing neuronal apoptosis or down-regulating the expression of amyloid alpha and synuclein. Another theoretically possible mode of action could be the induction of ultra-low secretion of glutamate or other neurotoxins/neurotransmitters, which have a protective hormetic effect on the brain. Population studies have confirmed that a combination of external stimulation such as activities of daily living (ADL), attendance at religious events, physical exercise and solitary leisure activities are associated with a reduced mortality in old age, whereas greater social networks and social engagements are associated with a reduced cognitive decline in elderly individuals.

Advice for the Public

Below are some examples of easy-to-perform practical cognitive and other exercises which can help improve the flow of information in your brain and achieve a state of positive stress. If you don't find an exercise stimulating enough (or if it is not 'stressful') then try to increase the difficulty by adding more complicated and challenging activities. If you feel pleasantly stimulated after the exercise then it means that you have achieved a suitable state of positive stress. Also if you do that particular activity every day anyway, then try to do something different that you don't do every day. The activity has to be varied and challenging for you. It should not create prolonged feelings of discomfort. Any type of stimulation, such as physical, mental, social, sensual and spiritual should be used, in order to keep your body and mind agile and energetic.

HORMETIC-TYPE CHALLENGES

NB. The order of how these exercises are presented has deliberately been diversified. The grouping together of similar activities (all nutritional together, all social together *etc.*) is, in itself, not hormetic!

Examples of physical stimulation

Day 1: Do 30 minutes tai chi in the morning and 20 minutes ballroom dancing in the evening
Day 2. Go for a 20 minute brisk walk, and then do 15 minutes yoga
Day 3. Play football or other ball games for 30 minutes in the afternoon

Day 4. No exercise, just follow everyday routine
Day 5. Try a new sport such as horse-riding, fencing or rowing
Day 6. To the park for 20-25 minutes of tree/stone or other weight lifting
Day 7. Aerobics for 20 minutes, followed by a new/unusual exercise (chi kung, twerking, lifting logs)
Day 8. No exercise

Varied socialisation. During a seven day period, you may want to consider the following plan

1st day: volunteer at your local charity or community centre
2nd day: litter picking with local scouts group
3rd day: no social activities, perhaps don't talk to, or interact with, anybody
4rd day: work with your local or national political party
5th day: online work, explore the internet, chat to friends through social media
6th day: physically visit relatives or friends. Try to make a new friend
7th day: light work with social media

Examples of unusual physical activities:

1. Try painting or drawing, even if you have never done it before (particularly then!)
2. On certain days or times, walk around your house completely naked (if children *etc.* allow it)
3. Choose a controversial subject and argue the side opposite to your own opinion
4. Listen to strange or weird music, or music you don't usually listen to
5. Tune into a foreign language radio station and try to guess the general meaning of the programme
6. For about 5-10 minutes, read a magazine holding it upside down. To make the exercise more difficult, hold it upside down in front of a mirror and read from the mirror image
7. Lie on the floor for 10 minutes and examine your surroundings from this unusual view point
8. Blindfold yourself and try to continue your usual activities in the house (if safe)
9. Read a magazine or newspaper that you do not usually read. Check out a weird website

More difficult exercises. Think about, and devise, exercises based on the concept of 'doing two/three demanding things at once'

For example: write down simple arithmetic (*e.g.* Addition: 2+2=4, 2+4= *etc.*) while someone is reading a story to you (then, remember and discuss the story)

Or: listen to music while surfing the internet AND using a grip exerciser on the other hand

Or: play table tennis while listening to the news AND arguing the side opposite to your own opinion

Or: use your non-dominant hand to write a good paragraph, while blindfolded (and chatting about something else)

Eat according to the season. We are used to eating the same foodstuffs regularly. But our innate biological patterns obey seasonal rhythms which we need to rediscover. Try to explore new and unusual foodstuffs and choose products which are in season, according to the month of the year: Blueberries, fish, tomatoes, sage and fennel for the summer, *etc*.

This introduces an element of irregularity and complexity in our food patterns that mimics nature. Also try to alternate your meals and include unusual items such as exotic fruit, game, or nuts.

Clock-less days. Rely on your natural timetable rather than clocks or watches. Set aside a day (maybe a Sunday) and prepare from the night before. Hide all watches, clocks *etc*. Wake up when you wake up, eat when you are hungry, and sleep when you are tired. This makes your body and brain able to deal with new situations and challenges, whilst trying to guess the natural time for you.

Technology-free days. You can try this activity on rare occasions, perhaps every six weeks.

Imagine that you live in the 16th century when electricity or gas have not been discovered. Try to live your life without using **any** modern facilities whatsoever.

EXAMPLE:

Don't use electric razor or toothbrush

Don't use electricity/gas to make cup of coffee or cook breakfast/lunch

Don't use telephone, TV, radio, computer *etc*.

Don't use anything that was not present in the 16th century

Instead:

Read a book, write a letter, chat to other people

Do some gardening, go fishing or go for a swim

Use your imagination to discover new games (with dice, cards or paper)

This exercise will make you think hard to identify items or services which you normally take for granted. It will then force your brain to develop alternative strategies for coping. The brain will be constantly on the lookout for any actions which are prohibited, and therefore it will keep continuously stimulated.

Stop the exercise when you feel that it is becoming quite uncomfortable to continue.

Sense imagery To help consolidate memory information already stored in your brain the technique of 'sense imagery' is used.

* Recall a face that you know really well. Then spend a few minutes thinking about the particular characteristics of that face and try to recreate the face in your mind. Instead of using a face you may think of:

1. A well-known scenery such as your house, your garden or your neighbourhood
2. Geometrical shapes like triangles, spheres, pyramids, stars
3. Tones of voices such as the voice of a well-known person. On this occasion you should really make an effort to feel the tone. Other hearing mental images are: a familiar voice calling you by your name, the shouts of the traders in the market, the noise of an airplane.
   - Try to recall in your mind the smell of some common objects such as your soap, your house, and others such as freshly cut grass, the smell of cooked eggs and bacon, surgical spirit *etc*.
   - Tastes. Can you recall, in turn, the taste of: bread, ketchup, salt, sugar, beer, vinegar?

Examples of social and spiritual stimulation

- Don’t accept easy answers or explanations. Always look for the real reason behind each event or situation
- Strengthen your social bonds, friendships and family ties
- Take an active part in your society, by volunteering or by doing charity work
- Explore other religions
- Explore aspects of your own religion which you have not considered in the past
- Learn new methods of mediation
- Always look for new ideas, and then try to implement them

A cognitive exercise. Use your non-dominant hand to draw one of the following, upside-down.

A smiley face

A sad face

The numbers 5 and 7

Then: a clock (remember, upside down!). When you finish, turn it round. It should have the numbers in the correct sequence, evenly-spaced and correctly drawn. Try it again until you get it right.

This is a good example of beneficial brain stress. You make your brain work at different levels. First, by using your non-dominant hand (new neural pathways are stimulated). Second, by drawing upside down (your brain processes unusual visual inputs). Third, by trying to get the drawing evenly balanced (developing new judgment capabilities).

An example of nutritional stimulation. Apart from a calorie restricted regime which is not currently recommended in everyday situations, another nutritional stimulation is this:

If you are taking vitamins, herbals or nutritional supplements it may be better to try and take these at irregular intervals instead of taking the same dose every day at a regular time.

For instance, on one day you could take your vitamin E in the morning, your vitamin C before lunch, your co-enzyme Q10 tablets in the afternoon and your glucosamine in the evening. Next day take only two of the above together and one at night, missing one out. The following day do not take anything. The day after take one of the above at lunchtime and the three others in the afternoon. And so on. You should only do this under expert supervision.

CONCLUSION

By following a carefully planned but irregular and apparently haphazard lifestyle, you increase the amount of meaningful stimulation to your body and mind, therefore lending a hand in maintaining the complex biological reserves of your body. This may help you ward off ageing and disability. Although, to an untrained observer, may appear chaotic, it should in fact be planned very carefully with logic behind each step.

Using a combination of suitable medication with lifestyle measures can go a long way in helping you defeat some signs of ageing. What matters is you. If you feel satisfied with a particular nutrient or drug, if you enjoy your lifestyle and if you are content with your plan of action, then so be it. You only have a short time left on this earth and you should make the most of it.

But also remember that you can influence that time, up to a certain point. Choose wisely, and you will increase it both in quality and in quantity. Choose poorly, and you will make it even shorter.

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