EMBO reports

introduction

The science of ageing and anti-ageing

Halldór Stefánsson

The dramatic rise in life expectancy that the industrial world has experienced throughout the twentieth century has made ageing, or rather, the quest for a prolonged and healthy lifespan, an important topic, in need of a cross-cultural, as well as historical, understanding. The main aim of the 2004 interdisciplinary EMBL/EMBO Science and Society conference on 'Time & Ageing—Mechanisms & Meanings', which constitutes the backdrop to this special issue of *EMBO reports*, was therefore to assess and analyse developments in those areas of the life sciences that focus specifically on the nature of 'time' and 'ageing'. We also wanted to pursue the wide range of meanings that result when basic science questions are projected into society and viewed by many as present-day manifestations of the relentless human proclivity to defy nature in the quest to prolong life and cheat death.

"All living organisms have time-measuring devices that affect their development, generation time, lifespan, and lifestyle" (Schibler, page S9). Beyond this apparent universality of physiological time, people perceive time and the passing of time in diverse ways, as mediated by their cultures (Helman, page S54). The value of 'long life' is thus, to a large extent, ascribed collectively, but differently in each time and place. On a global scale, 'population ageing'—the process by which older cohorts become relatively prominent in a given population—was one of the most distinctive demographic events that marked the twentieth century and will undoubtedly remain an important trend throughout this century (United Nations, 2001). Initially restricted to the more technologically developed countries, population ageing has recently become apparent in much of the developing world as well. In the near future, virtually all nations will face population ageing, although at varying levels of intensity and in different time frames.

Around the turn of the twentieth century, life expectancy was less than 50 years in most industrialized nations. At the turn of the twenty-first century, it had risen by about 50% to exceed the 75-year limit. This dramatic rise happened mostly as a result of improved hygiene practices, success in averting epidemics and infectious diseases and a sharp fall in infant mortality. Clearly, modern technology has had an important role in improving human health and enabling a greater number of people to survive into old age. Not only biomedical sciences, but also innovations such as clean water and sanitation, waste treatment and disposal, improved diet and antibiotics have given us considerable control over the infectious and parasitic diseases that have in the past taken countless lives, particularly those of children. As a result, chronic degenerative diseases—that very few people lived long enough to experience in the past—have replaced infectious and parasitic diseases as the primary cause of death in the wealthier parts of the world. But while this trend is being observed on a worldwide scale, life expectancy at birth remains conspicuously unequal, not only along the north–south axis, but also between social milieus in the 'affluent' parts of the world (Mauron, page S67).

Ageing refers to the various processes of wear and tear that affect us continuously. Even if people argue over what drives any or all of those processes, they all seem to agree on how they affect us: perceptibly as well as imperceptibly, they make us prone to falling apart. Not surprisingly, the search for remedies against the ageing process, and the study of human ageing itself, has a long history in numerous cultural traditions around the world. Traditional Chinese medicine has always maintained a keen interest in the arts of extending human lifespan and attaining immortality in the flesh. 'Fountain of youth' remedies abound in Chinese medicine, and legends of immortals living on mountaintops have been a constant in its folklore. Western science also has a long history of preoccupation with the arts of prolonging human lifespan (Gruman, 2003). One example of early proto-scientific attempts in the Western world to develop effective, systematic means of life extension is *Makrobiotik* by the German physician Christofer Hufeland (Hufeland, 1798), which contained advice about diet and lifestyle that the author recommended for prolonging life.

Gerontology, in the modern meaning of the term, did not take form until about a century later, when the French physician Jean Martin Charcot published his famous *Clinical Lectures on the Diseases of Old Age* (Charcot, 1881). It initiated gerontology as a study of the bodily changes and pathologies that accompany ageing. But if the late nineteenth century's medical gaze introduced systematic investigation of physiological and biological processes associated with senescence, it did not, however, put an end to the age-old quest for magical 'fountain of youth' potions, often disguised as scientific remedies for restoring youth and vitality. Ironically, around the time of Charcot's lectures, another respected French medical researcher, Charles Édouard Brown-Séquard, claimed that the consumption of extracts from crushed dog testicles would allow old men to regain their potency (Gosden, 1996).

The age-old quest for long life has arguably attained unprecedented heights in our era of marked population ageing, in which the pursuit of health and the relief of suffering have been prominently prioritized. Gruman's historical account (Gruman, 2003) shows how humans have always been fascinated by the quest for a radical extension of the length of life: "the more it changes, the more it stays the same." However, during most of documented history, this quest has been the purview of ascetics, poets and philosophers. In recent times, relative longevity has become a common good and, on the social scene, new players have arisen that cater to the specific needs and desires of the new 'immortals': the members of the present-day third and fourth age—the old and the very old. Another view of the historical process perceives it not as a linear progression, but more as entailing multiple deviations and occasional ruptures. Thus, Karin Knorr Cetina (page S76) postulates a growing polarization between two radically distinct mentalities and corresponding social practices. On the one hand, we have the familiar enlightenment worldview in which *Homo sapiens* figures as the measure of all things, and on the other hand, an emerging 'culture of life', which is the topic of Cetina's essay. According to Cetina, it is from this new cultural matrix that the anti-ageing projects of the present moment draw their ultimate significance.

The most visible aspect of this change is the success of the anti-ageing industry that caters to the needs of the elderly. Like alternative medicine, it owes much of its success to its fundamental, albeit ambiguous, relationship with science. This particular sector in consumer society is shrouded with an aura of science that is used for the promotion of a variety of goods. It thrives on symbolic uses of science, while passing over its requirements for experimental evidence, peer review and official regulations. The aura and the discourse of science are skilfully applied for product enhancement in response to a fast-growing demand from the ageing public (see McConnel & Turner, page S59).

The anti-ageing market is replete with products: yoghurt cures, enema regimens, cell injections, magnetic devices, skin creams, herbal elixirs, glandular extracts, hormonal therapies, vitamin supplements, fad diets and exercise programmes. They give us anti-oxidants to neutralize oxygen-free radicals; chelators to bind heavy metal ions such as copper and iron; dehydroepiandrosterone to rejuvenate the immune system, improve brain function and relieve stress; growth hormone to increase muscle mass and function; retinoic acid to decrease skin wrinkling, and many more. Recently, scientists have begun to object to what they see as excesses in the burgeoning business of 'false promises' and commercialization of science (Olshansky *et al*, 2002). These critics emphasize the distinction between the anti-ageing industry and the scientific field of 'biogerontology'. Biogerontology has grown into a subfield in biology in which researchers not only study the complex causes for the physiological failure to maintain homeostasis, but also the ways and means to slow down, arrest or even reverse degenerative processes in living organisms.

Consequently, three main paradigms or research orientations have been distinguished in biological research on ageing (Juengst *et al*, 2003): 'compressed morbidity', 'decelerated ageing' and 'arrested ageing'. Compressed morbidity refers to the most conventional of these research agendas. Its goal is to forestall all chronic ailments of old age by intervening in the underlying molecular processes. In this model, the ultimate goal is to seek increases in average human life expectancy, but not in maximum human lifespan. Realization of this paradigm should result in a society with many more old people who have active roles until their final, swiftly fatal, decline.

As a considerably more ambitious agenda, the decelerated ageing approach seeks to slow down the fundamental processes of ageing to the extent that average life expectancy and maximum lifespan are increased. Finally, the most radical of the three research approaches seeks to 'cure' ageing. The goal of arrested ageing is to continually restore vitality and bodily function by removing the damage that is inevitably caused by metabolic processes.

The rationale and the methods for obtaining compressed morbidity are non-controversial in the research community. Those who adhere to either of the other two paradigms may regard it as overly conservative, but in no way objectionable. Moreover, all members of the public who are open to the idea that science can be used to improve the human condition easily support the compressed morbidity agenda. Hence, a substantial amount of publicly funded basic research has been carried out and is being planned in the USA, Japan and Europe.

A number of essays in this special issue therefore address the questions of how time is embodied and how it results in 'ageing' of the organism. They point to how these processes can be studied scientifically. Life is a form of metabolism with potentially damaging side effects, and those side effects accumulate in our bodies over time. Many of these changes become pathogenic, and, together, they drive the ageing process that makes us frail and eventually kills us. The first part of this special issue of *EMBO reports* therefore contains a comprehensive representation of how life scientists now study the nature of these changes, and the possible means to counter the damage caused by ageing.

Adherents of the arrested ageing approach wish to take the potential of life extension to its logical conclusion. If nihilists used to complain that "life is a disease with death as its only cure", it now seems that more and more people seriously propose turning this depressing slogan around, claiming that physical ageing is basically a curable disease. In their view, what is needed to overcome the ill effects of ageing and to fulfil the promises of science is a change in mindset among decision-makers and members of the public (de Grey, page S49; Caplan, page S72). But not everyone is happy with such a radical programme for biogerontology, for various reasons, which is reflected in the second part of this issue.

Critics see several problems inherent to life-extension visions and projects. For instance, if "adding days to life, rather than life to days" was the outcome, this would be counterproductive for the individual 'beneficiaries' of such new technologies, as well as for society as a whole (Bruce, page S63). The use of human frailty for commercial exploitation is also singled out as a deplorable characteristic of the present-day anti-ageing medicines and market (McConnel & Turner, page S59). Many critics have also raised fundamental objections to biotechnological life-extension projects, because their realization would inevitably result in further inequalities between the haves and the have-nots: the life of the poor would remain 'short and brutish', while the rich could look forward to an extended enjoyment of their

privileges (Mauron, page S67; Bruce, page S63; McConnel & Turner, page S59).

From the essays in this issue of *EMBO reports*, we can learn how the biological impact of time applies both to cyclical and to linear mechanisms, which together translate into the complex processes of physical ageing. It can be assumed that enhanced understanding of basic biology will bring the dimension of time and ageing to the forefront of our appreciation of health and disease. Social and ethical concerns notwithstanding, knowledge and technologies that grow out of biological research in this area are likely to have a radical impact on the quality and possibly the extent of human lifespan in the future.

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Halldór Stefánsson heads the Science & Society programme at the European Molecular Biology Laboratory in Heidelberg, Germany.
E-mail: halldor.stefansson@embl-heidelberg.de

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