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Review

Changing course in ageing research: The Healthy Ageing Phenotype☆

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ABSTRACT

Ageing is often associated with the aged and the diseased, nevertheless ageing is a process that starts in-uterus and is characterised by a progressive functional loss but not necessarily by the presence of disease and poor quality of life. How to meander through life without crossing the confines of major chronic disease and cognitive and physical impairment remains one of the most relevant challenges for science and humankind. Delimiting that 'immaculate' trajectory – that we dub as the 'Healthy Ageing Phenotype' – and exploring solutions to help the population to stay or return to this trajectory should constitute the core focus of scientific research. Nevertheless, current efforts on ageing research are mainly focused on developing animal models to disentangle the human ageing process, and on age-related disorders often providing merely palliative solutions. Therefore, to identify alternative perspectives in ageing research, Unilever and the Medical Research Council (MRC) UK convened a Spark workshop entitled 'The Healthy Ageing Phenotype'. In this meeting, international specialists from complementary areas related to ageing research, gathered to find clear attributes and definitions of the 'Healthy Ageing Phenotype', to identify potential mechanisms and interventions to improve healthy life expectancy of the population; and to highlight areas within ageing research that should be prioritised in the future. General agreement was reached in recognising ageing research as a disaggregated field with little communication between basic, epidemiological and clinical areas of research and limited translation to society. A more holistic, multi-disciplinary approach emanating from a better understanding of healthy ageing trajectories and centred along human biological resilience, its maintenance and the reversibility from early deviations into pathological trajectories, is urgently required. Future research should concentrate on understanding the mechanisms that permit individuals to maintain optimal health when facing pathological hazards and on developing and assessing potential interventions that could aid to re-establish resilience when lost or guarantee its integrity if present. Furthermore it is fundamental that scientific findings are translated incessantly into clear messages delivered to governmental institutions, the industry and society in general.

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☆ Report from a Spark meeting, Amsterdam, May 2007.

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1. Introduction

"Prevention is better than cure"
Desiderius Erasmus (1466–1536)

The age distribution of the world's population is dramatically shifting; longevity continues to rise and there are steady improvements in healthcare, but there is not an accompanying increase in fertility rates [1,2]. In total, the global proportion of people aged above 60 years is expected to increase from 10% to 21% in the next 5 decades [3]. However, research into how to achieve healthy ageing and which life-time trajectories are associated with positive health and wellbeing in older age, is still relatively under-researched. Hence, to identify alternative perspectives in ageing research, Unilever and the Medical Research Council (MRC) of UK convened a Spark workshop entitled 'The Healthy Ageing Phenotype' [4]. Spark workshops are strategic meetings in which scientists from different disciplines and perspectives, share knowledge, build novel concepts, and assess options for future research activities. In this particular meeting, international specialists from complementary areas related to ageing research gathered to:

(i) find clear attributes and definitions of the 'Healthy Ageing Phenotype';
(ii) identify potential mechanisms and interventions to improve healthy life expectancy of the population;
(iii) highlight areas on ageing research that should be prioritised for the future.

2. The world is ageing

Global life expectancy in the last two centuries has been increasing linearly and does not appear to be approaching a plateau [2]. Longevity in best in class countries has risen by approximately 3 months per year for the past 170 years and average mean life expectancy is forecasted to be 96.4 years in 2050 [2]. Incessant progress in the prevention of mortality as a result of advances in income, hygiene, sanitation and infection control, nutrition, education, and medicine, is generally believed to account for the increases in longevity [2]. Concomitantly, fertility rates are falling, leading to an unprecedented shift in demographics [1–3]. Nevertheless, increases in life expectancy and in the proportion of individuals living longer do not necessarily translate into improvements of health and wellbeing [5,6]. Indeed, many countries, although experiencing steady increases in longevity, are suffering from stagnation of healthy life expectancy and a greater burden caused by chronic conditions and disability [5,6]. For example, in the UK between 1991 and 2001, life expectancy increased by 2.2 years but only 0.6 years were healthy years [5,7]. Disparities in life expectancy between the best and worst (electoral) wards in the U.K. exceed twenty years [8] and increasing healthy life expectancy across the world has been identified as a key objective for research [5,7].

3. The malleability of the ageing process

The recent history of human longevity demonstrates that the ageing process is malleable to a significant degree, but the extent of this has not yet been fully explored in humans as the majority of research on this area has been conducted in lower animal models (e.g., nematodes, flies) with a limited degree of extrapolation [4,9]. Ageing is a multi-factorial process and it is vital to understand the mechanisms associated with ageing and those that determine healthy life trajectories [10,11]. Aberrant gene expression, for example, is strongly involved in processes leading to the development of diseases that restrict lifespan and some have suggested that genetic factors may also underlie the ageing process itself [12,13]. However, the ageing process seems to occur at different rates in different tissues and appears to have a considerable stochastic element [11,14]. Although twin studies suggest that genotype explains roughly 25% of differences in life expectancy, the role of environmental and lifestyle factors (such as pollution, infections, stress, physical inactivity, psychological wellbeing, health infra-structure and financial security), combined with an element of chance, are also important and could account for the remaining variance [12,15,16]. It has been claimed that the influence of the environment is permanent and starts immediately after fecundation [17]. For example, several studies, have reported that the intrauterine environment has short-term influences on health outcomes as well as long-term influences on the development of diseases during adulthood [17–19]. Low birth weight and being born small for gestational age have also repeatedly been associated with development of diabetes, hypertension and cardiovascular disease (CVD) at middle age [17–19].

4. Yin and Yang: vulnerability and resilience

It is important to note that ageing over the lifecourse is not necessarily a steady decline from optimal physiological performance in early adulthood to poor functioning in late adulthood. To a large extent, remarkable physiological resilience in early stages of the ageing process reduces the negative effects of external stressors such as smoking, infections, psychological stress, sedentarianism and poor dietary habits and these stressors do not visibly induce morbidities at a young age. By resilience, we mean the capacity to maintain adequate function and structure at molecular and cellular levels by adapting or changing to specific challenges [20,21]. This process relies on the interaction of multiple mechanisms that aim to preserve physical and psychological stability and homeostasis to ensure that the individual remains outside the realms of disease. The integrity of these homeostatic mechanisms determines the deviation from normality; deviation can be generalised or tissue-specific and is not necessarily clinically manifested [20,21]. An adequate detection and measure of the level of resilience/vulnerability is key to identify the processes that lead from health to frailty and ultimately to the appearance of disease and death [20,21]. A further exploration of the nature of resilience and the how we can prevent permanent dysregulation would provide significant insights into the healthy ageing process.