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If ageing is a disease, then life is also a disease

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ABSTRACT: Ageing is distinct from a disease. Sound arguments have been adduced to explain that senescence cannot be understood as a pathological process. Nevertheless, this distinction is believed to be artificial (Holliday 1995), and other eminent researchers argue that the senescence-pathology dichotomy is also misleading. Recently, it has been suggested that ageing should be classified as a complex pathological syndrome or a 'pre-disease' that is treatable. Proponents of this new paradigm argue that: (i) modern evolutionary theory predicts that 'although organismal senescence is not an adaptation, it is genetically programmed', (ii) 'insofar as it is genetically determined, organismal senescence is a form of genetic disease' (Janac et al. 2017) and (iii) 'ageing is something very much like a genetic disease: it is a set of pathologies resulting from the action of pleiotropic gene mutations' (Gems 2015). Also new generations of researchers, free of these traditional shackles, come with the belief that it is time to classify ageing as a disease, as the distinction between normal dysfunction and abnormal dysfunction is not completely clear and should be abandoned. Although they marshal their arguments in a convincing manner, persuasive counterarguments can be mounted. Here, the senescence-pathology dichotomy is critically discussed. A deeper analysis of this subject reveals the underlying problem of undefined terminology in science.

KEY WORDS: ageing, disease, health, homeostasis, medical terminology, nosology, senescence

Introduction

Traditionally, biological ageing was understood as a physiological process that is distinct from a pathology (Hayflick 2003, 2004, 2007, 2016; Rattan 2014, 2016). Nevertheless, it was generally accepted that this distinction is 'artificial' (Holliday 1995) and it can be abandoned if need be (Izaks and Westendorp 2003). Nowadays, researchers interpret ageing as a set of cumulative, universal, progressive, intrinsic and deleterious (CUPID) changes that occur over time (Ark-

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ing 2019) because of the gradual failure of maintenance mechanisms (Kirkwood 2005; Cohen 2016), leading to an increasing risk of illness and death. Interestingly, the same factors that can be described as ageing-modulating drugs and pro-longevity interventions can reduce the risk of cancer and selected age-related diseases (Sikora et al. 2010; Wilken et al. 2011; Kumar et al. 2016; Gurău et al. 2018; Gómez-Linton et al. 2019; Zhao et al. 2020). Given that ageing is due to molecular damage, there is likely to be considerable overlap between the underlying causative pathways of ageing and age-related pathologies (Kirkwood 2011; López-Otín et al. 2013). Therefore, more and more researchers are convinced that the distinction between senescence and age-related pathologies is not only artificial but also elusive (Bulterijs et al. 2015; Gems 2015; Stambler 2015, 2017; Janac et al. 2017). Although they marshal their arguments well, persuasive counterarguments can be mounted. Here, the traditional distinction between ageing and disease is critically discussed. A deeper analysis of this subject reveals the underlying problem of undefined terminology in science. Moreover, the way how these processes are defined, described and treated is far-reaching and has further consequences (Faragher 2015; Stambler 2017; Chmielewski 2020a, 2020b).

Traditional paradigm: ageing is distinct from pathology

It has long been argued that ageing is distinguishable from a pathological process. Unlike any disease or pathology, age changes: (1) are universal and occur in every individual that lives longer than the essential lifespan (ELS), (2) can be observed in all sexually reproducing animals, (3) have the same molecular basis or aetiology, i.e. the accumulation of molecular and cellular damage that results from the gradual failure of maintenance mechanisms that are unwarranted in the long run (Rattan 2014; Hayflick 2016; Chmielewski 2017, 2018, 2019, 2020a)

The fundamental cause of ageing is a failure of natural selection that is caused either by declining strength of natural selection or pleiotropic constraints (Chmielewski 2019, 2020b), whereas the fundamental cause of any pathological process is a disruption of the normal structure and/or function or 'any abnormality of bodily structure or function' (Bulterijs et al. 2015). From an evolutionary perspective, ageing has nothing to do with the molecular biology of the eukaryotic cell, as this dynamic and emergent metaphenomenon originates in the difficulty in maintaining homeostasis in complex biological systems (Kirkwood 2005; Cohen 2016).

Signs (objective characteristics, e.g. blue lips in hypoxia) and symptoms (subjective characteristics, e.g. dyspnoea) of any disease can be described as 'abnormal dysfunction'. Are age changes 'abnormal'? If so, what is normal? The phenotype of an 18-year-old person? Does ageing consist in 'abnormalities'? From a medical standpoint, the distinction between 'normal dysfunction' and 'abnormal dysfunction' occurring in organ systems is not completely clear as any type of dysfunction is always undesirable. Therefore, some biogerontologists suggest that: 'The distinction between so-called natural ageing and the pathologies that are common in old people is artificial. What we see is an increasing likelihood of many diseases in individuals as they age' (Holliday 1995). According to

some researchers and scholars, ageing *sensu stricto* does not exist, as only accumulation of pathologies over time in the body can be observed and studied, and these CUPID changes are collectively referred to as senescence (Izaks and Westendorp 2003; Blagosklonny 2006; Arking 2019). Therefore, it would be more natural to describe biological ageing as the root of age-related diseases or a complex pathological syndrome (David Gems), a 'super-disease' (Cynthia Kenyon) or a 'pre-disease' (Mikhail Blagosklonny). Nevertheless, it is questionable whether ageing *sensu stricto* does not exist. If normal, not to mention healthy or successful, ageing is a fact, then this traditional distinction should be pursued. From a biological standpoint, ageing is *prima facie* quite different from a disease, and it is definitely too broad to be understood as any type of pathology that is easily treatable with pharmaceuticals (Hayflick 2003, 2004, 2007, 2016; Carnes et al. 2008, 2013; Rattan 2014, 2018, 2019; Gavrilov and Gavrilova 2017; Chmielewski 2017, 2018, 2019, 2020a, 2020b).

New paradigm: the senescence-pathology dichotomy is artificial and false

Some researchers have recently suggested that biological ageing should be classified as a disease (Bulterijs et al. 2015; Gems 2015; Stambler 2015, 2017; Janac et al. 2017) or a 'pre-disease' (Blagosklonny 2018) that is 'easily treatable'. This view harks back to older but controversial models (Dilman 1988). The following arguments have been presented to explain why senescence can be understood as something similar to a disorder in its broadest sense: (1) in biology and medicine, it is not completely clear what is 'normal' and what is 'abnormal' as it changes over time, (2) the modern definition of disease covers age changes and senescence, (3) the distinction between ageing and disease is artificial, as only accumulation of pathologies over time in the body can be observed and (4) it will be advantageous to classify ageing as a disease, as more funds for ageing research will be available, and ageing-modulating drugs and pro-longevity interventions will be better tested and safer (cf. Bulterijs et al. 2015).

Let us consider their first argument: what is 'normal' and what is 'pathological' is influenced by historical context. For example, osteoporosis, isolated systolic hypertension, cataract, neurodegeneration, such as Alzheimer's disease and so forth, have long been described as natural processes, which was a serious mistake because these pathologies should be prevented, diagnosed and treated. Classifying 'drapetomania' or human sexual behaviour that is different from biblical patterns as mental disorders was non-ethical and criminal conduct (Bulterijs et al. 2015). Nevertheless, it is clear why osteoporosis, cataract, hypertension, Alzheimer's disease etc. should be classified as pathologies, whereas it remains unclear why age changes should be described as 'abnormality'.

This also refers to the second argument, i.e. the broad definition of disease. From a theoretical standpoint, this would require that some adults undergo senescence, whereas the majority of humans are 'normal' and they do not age, which is obviously false. Moreover, when some phenomenon is described as a disease in medicine, then its causes are extremely important for the understanding of the aetiology of a given pathological

process. What is the aetiology of ageing? It can be understood as a consequence of natural selection (Kirkwood and Holliday 1986) and a side-effect of metabolism (Rattan 2016). To eliminate ageing, much less 'disposable' bodies and different types of evolution, development and metabolism are required. Unlike Hydra the immortal (Austad 2009), the human body is disposable and is not time proof. Although it is possible that the pace of ageing can be modulated to some extent, the claim that humans will be supercentenarians soon thanks to drugs and medical interventionsis seem naive and unrealistic (Hayflick 2003, 2003, 2007, 2016; Carnes et al. 2008, 2013; Holliday 2009; Rattan 2019; Chmielewski2019, 2020b). Although the distinction between senescence and pathology can be artificial, as Robin Holliday suggested, it also depends on terminology and context. In particular, if ageing *sensu stricto* is not an illusion but a real stochastic process, as many researchers believe, then this distinction makes sense and should be pursued.

Solving the problem of rival paradigms in biogerontology

The concept of healthneeds to be explored. Who is healthy and who is ill? Health is a dynamic process that varies with changes in interactions between an organism and the internal and external environments. As shown in Fig. 1, the structural and physiological integrity of the body (*y*-axis)undergoes constant changes that can be plotted over time (*x*-axis). First, small changes can be observed as the biological system is constantly striving for the optimal physiological integrity, and it is close to the optimum ('healthy').Every now and then, harmful factors, e.g. pathogens, toxins, vitamin deficiencies etc., act upon the organism and they produce an answer in it. This is a response to stresses. If these factors are strong enough or if they constitute a long-standing condition, e.g. lack of physical activity, an unhealthy diet or a stressful lifestyle, they can cause a disease. A disease can be defined as a disruption of the normal structure and function of the body or 'any abnormality of bodily structure or function' (Bulterijs et al. 2015) that interrupts or modifies the performance of the vital functions, is typically manifested by signs and symptoms, can be diagnosed and is often treatable.

Drugs or medical interventions (black arrows) can counteract these effects in many different ways. For example, they can help eliminate the parasite or the pathogen from the body or they can correct, modify or restore physiological functions by exerting a metabolic, phar-

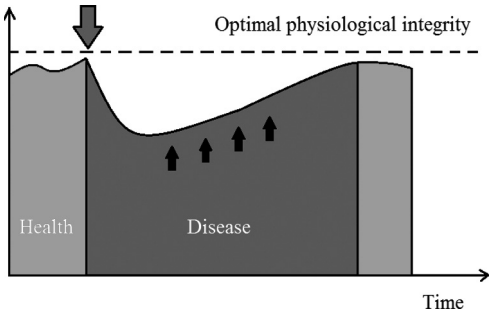

Fig. 1. Health *versus* disease. The large arrow denotes a harmful factor, e.g. a pathogen, a toxin, lack of vitamins etc., that is strong enough to cause a disease. Drugs (black arrows) can counteract these effects in many different ways. Nevertheless, they cannot stop, reverse or effectively postpone ageing so the body remains continuously in good health because this would require a different type of action, e.g. all functions should be alleviated and all damage should be repaired, which is unrealistic (see text for details)

macological or immunological action. Nevertheless, drugs cannot enhance the homeostatic capabilities so the body remains continuously in good health (i.e. very close to the optimum, dashed line) because this would require a different type of action, e.g. all functions should be alleviated and all damage should be repaired, which is unrealistic (Hayflick 2003, 2004, 2007; Cohen 2016; Rattan 2019; Chmielewski 2019, 2020b).

Furthermore, it is important to understand that drugs do not make us healthy. They just affect the chemical and/or biological factors to help overcome the disease. The idea that they can help overcome age changes in the body, i.e. a stochastic process that results from the escalating loss of molecular fidelity, remains scientifically ungrounded (Carnes et al. 2008, 2013; Rattan 2018, 2019; Chmielewski 2020b). Firstly, any medical intervention is risky. For example, removal of dysfunctional mitochondria from the body can be very risky, not to mention elongation of telomeres and chemical changes to DNA. Secondly, even relatively safe drugs, such as aspirin and metformin, have side-effects. Thirdly, there are limitations of reductionist and disease-oriented approaches to human ageing (Chmielewski 2020b), so all claims that ageing is 'easily treatable'are over-hyped and naive. Lastly, the claim that some chemical factors, such as natural compounds or repurposed drugs, or biological processes are only good or only bad is misleading. In biology, the general answer to everything is: 'It depends' on time, dosage etc. Let us consider cellular senescence. This is an important process that can help protect the body against cancer as senescent cells do not divide anymore (Sikora et al. 2018).At the same time, cellular senescence promotes cancer (Rodier and Campisi 2011). Similarly, autophagy can help maintain cellular homeostasis in healthy cells as it prevents genomic instability (Bergaminiet al. 2007; Lorin et al. 2013; Barbosa et al. 2019). On the other hand, it plays an important role in cancer progression and it appears to support tumour development (Guan et al. 2013; Pan et al. 2013). Should autophagy be induced chemically (e.g. by metformin)? Should we take more curcumin, resveratrol, aspirin and so forth? Should we fast? Well, it depends on: (1) who is taking these compounds, (2) when, (3) how much, (4) how long etc. Furthermore, it is highly questionable whether interventions founded on reductionist premises and disease-oriented approaches to ageing will succeed (Hayflick 2003, 2004, 2007; Rattan 2019; Chmielewski 2019, 2020a, 2020b).

When we do not feel well, we go to the doctor. The diagnosis is: everything is fine, the tests are within the normal range, there is no need to panic. The concept of 'health' is similar to the concept of 'wellbeing'. But can health be measured objectively and quantitatively? As Professor David Gems (2015) suggests, our science and medicine remain in the dark ages. It is theoretically possible to check every organ in the body and to perform more sophisticated tests, thereby increasing the credibility of the diagnosis. Nonetheless, it is also possible that our science and medicine are well developed, and the health can never be objectively measured. Such assessment would require a unit of health, and all diseases should have specific and characteristic signs. In fact, many diseases develop silently, which diminishes the chances of an early diagnosis (Strzelec et al. 2018).

In current biogerontology, different researchers have different opinions. There is marked disagreement on the most fundamental questions in the field (Chmielewski 2020b). Some researchers are convinced that ageing is 'an inherent biological programme by which the maximal lifespan of each species of the animal kingdom is time restricted and to a large extent predetermined' (Declerck and VandenBerghe 2018). Other authors have come to similar conclusions (Lenart and Bienertová-Vašků 2017; Lenart et al. 2018), although this implies that the modern understanding of evolutionary theory, but especially the selfish gene theory and standard population genetics, are specious and wrong. Any genetic programme for ageing must be susceptible to inactivation and elimination, assuming that metabolism is possible without this 'programme', as the same genes that control metabolism are involved in ageing, and the same maintenance mechanisms that sustain life generate damage, self-debris and toxins that can contribute to senescence (Bartke et al. 2002). Other eminent researchers assert that modern evolutionary theory teaches us that 'although organismal senescence is not an adaptation, it is genetically programmed' and 'insofar as it is genetically determined, organismal senescence is a form of genetic disease' (Janac et al. 2017). All these authors are affiliated to University College London. At the same time, 'it is generally accepted that the idea that ageing is programmed is wrong' (Kowald and Kirkwood 2016). How to solve these contradictions?

From a linguistic perspective, the word 'ageing' means 'the process of getting older', so biochemists and geneticists believe that 'from the moment of conception, we begin to age' (Bocklandt et al. 2011). Is this ageing programmed? In biology, growth, development and maturation can never be understood as ageing because it does not make any sense (Kaczmarek and Szwed 1997; Rattan 2014, 2016; Chmielewski 2017, 2018, 2019; Kaczmarek and Wolański 2018), and there is a difference between ageing and senescence (Bonsall et al. 2006). When biologists and biogerontologists speak about ageing, they usually think about senescence. These examples can be mounted (cf. Gems 2015). Therefore, a clear, precise and worldwide accepted terminology is a must. Researchers are sure that ageing is programmed or that it cannot be programmed, but we do not know what ageing really is and what ageing really does. Similarly, there is no precise definition of programmes in biology. Is it a general timetable or an order of things that happen over time, a defined phenomenon that results from other programmed and non-programmed processes or a set of biological factors and biochemical pathways that act *inadvertently* (a quasi-programme) or *purposefully* (a programme) to eliminate older individuals from a given population?

Similarly, the distinction between senescence and pathology is either valid or not, depending on terminology and context. Some authors try to avoid this context, and they argue that biological ageing is a 'physiologic/pathologic process' (Stallone et al. 2018) or that ageing is 'neither a disease nor a non-disease' as it 'combines all age-related diseases and their preclinical forms' (Gladyshev and Gladyshev 2016). Other researchers come to the conclusion that ageing *sensu stricto* does not exist, as only accumulation of pathologies over time can be observed (Izaks and Westendorp 2003; Blagosklonny 2006). If this is the case, then

there is no real difference between senescence and pathology, and the former can be understood as a 'super-syndrome' or a 'pre-disease'. Yet it is questionable whether real ageing does not exist and whether we do not have to age. In our view, if ageing is a disease, then life is also a disease. In fact, disease can affect people at any age, and many people are struggling with diseases. Age is a major risk factor that makes us more vulnerable to many pathologies but ageing does not give rise to all diseases (Carnes et al. 2008). Therefore, the title *Has aging ever been considered healthy?* can be rephrased as follows: *If we do not feel well, are we really healthy?* Probably not, but this would mean that an old medical joke is true: 'There are no healthy people, only those who have not been diagnosed yet' (cf. Fig. 1, the optimum is higher than the observed level of physiological integrity). Nonetheless, the claim that millions of years of evolution can be easily changed by a 'fasting' pill, a 'happiness' pill or an 'anti-ageing' (this term is a misnomer, cf. Hayflick 2004) pill is not only naive and precarious (Rattan 2019) but also arrogant (Holliday 2009).

Conclusions

The relationship between ageing and age-related pathologies constitutes one of the trickier questions in biology and medicine. To answer the question: 'Is ageing/senescence a disease/pathology?', a clear, logical, precise and generally accepted terminology should be developed. Both modern evolutionary theory and medical practice teach us that 'anti-ageing' interventions founded on reductionist premises or disease-oriented approaches are unlikely to succeed, as biological ageing has evolved as an emergent metaphenomenon that originates in the difficulty in maintaining homeostasis in complex biological systems. Organismal senescence cannot be stopped or reversed. It can only be modulated to some extent. Therefore, only holistic interventions and evidence-based strategies might be useful in postponing ageing and preventing age-related diseases.

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