1 GENERAL INTRODUCTION

Ageing and senescence

As humans grow older, the structures and functions of their bodies deteriorate. As a consequence, their risks of disability, disease, and death increase. It is an omen of the various confusions and controversies existing in the research on this process that the process itself has no universally accepted designation.

In line with renowned gerontologists, we distinguish between ageing and senescence.[1-5] Ageing refers to the mere passage of time. It encompasses all changes that occur in the body during time, whether their effects are detrimental, beneficial, or negligible. The progress of ageing is indicated by one's chronological age, which can be easily deduced from a birth registry. Senescence is part of ageing. It refers to the deterioration of the body's structures and functions and encompasses specifically the detrimental changes that appear with ageing. The progress of senescence is indicated by one's biological age, although it is still elusive how one's biological age can be precisely determined.[6-10]

Apart from senescence, ageing is accompanied by changes that are beneficial to the body's structures and functions. Such changes take place in a programmed order early in life as growth and development, are brought about by the body as regeneration when it repairs its damaged parts, for example during the healing of a fractured bone,[11] and can be effectuated by medical interventions, like the replacement of stem cells, which is called rejuvenation.[12] Ageing is also accompanied by changes that are, as far as we know, neither detrimental nor beneficial to the body. A classic example is the greying of hair. These changes are simply spoken of as age-related changes.[13]

Some researchers are accustomed to denote the senescence of cells in particular as senescence and to denote the senescence of individuals or populations as ageing.[14-18] However, as will be substantiated hereafter, there is no reason to fundamentally separate cellular senescence from senescence of individuals or populations.

Senescence at different levels

Senescence is generally attributed to an accumulation of random damage to the human body.[14,19-22] During life, the body is exposed to a wide variety of intrinsic stressors from within the body and extrinsic stressors from without the body. Examples of intrinsic stressors include DNA replication errors, spontaneous chemical reactions, and metabolic waste products. Examples of extrinsic stressors include pathogens, radiation, and mechanical forces. A stressor may at any moment damage the body's structure and function. In the case of sufficient damage, death may follow. In other cases, damage repair mechanisms, with which the body's cells and tissues are equipped, are activated. Some of the acquired damage can be repaired fully by these mechanisms, after which the body will have regenerated and recovered. Some damage can be repaired only partly or not at all, will irreversibly remain, and become apparent as dysfunction, disability, or disease. If a stressor affects the damage repair mechanisms, the accumulation of further damage is accelerated.

Alternative theories attribute senescence to other processes than the accumulation of random damage. A noteworthy theory, which is discussed in more detail in Chapter 5 of this thesis,[23] proposes that senescence may be the result of persistent developmental processes.[24,25] Nonetheless, these theories too acknowledge that the damaging effects of such processes are crucial in the causation of senescence.[23-26]

As schematically shown in Figure 1.1, the accumulation of damage occurs in the body at different levels of complexity. Stressors may damage the structure and function of a molecular component of a cell, an entire cell, an organ or tissue, or the body as a whole. Much research is devoted to the mechanisms of senescence at the molecular-cellular level.[17,27,28] Important roles have been attributed to DNA damage,[29-33] the effects of metabolic waste products such as reactive oxygen species,[34-37] the various forms of dysfunction that are observed in senescent cells,[27,38] the accumulation of senescent cells in tissues,[15,18,27,39] and chronic smouldering inflammation called inflammageing.[40]

The effects of damage acquired at lower levels seep through to higher levels of complexity in the body.[20,21,24,28,41] Molecular damage underlies cellular senescence.[17,27,38] Senescent cells secrete numerous signalling factors that induce senescence of other cells[17,27,38] and systemic symptoms of senescence, such as chronic smouldering inflammation.[42] Cellular senescence causes dysfunction and disease of tissues, such as impaired wound healing, cancer, and cardiovascular disease.[16,43-45] Molec-

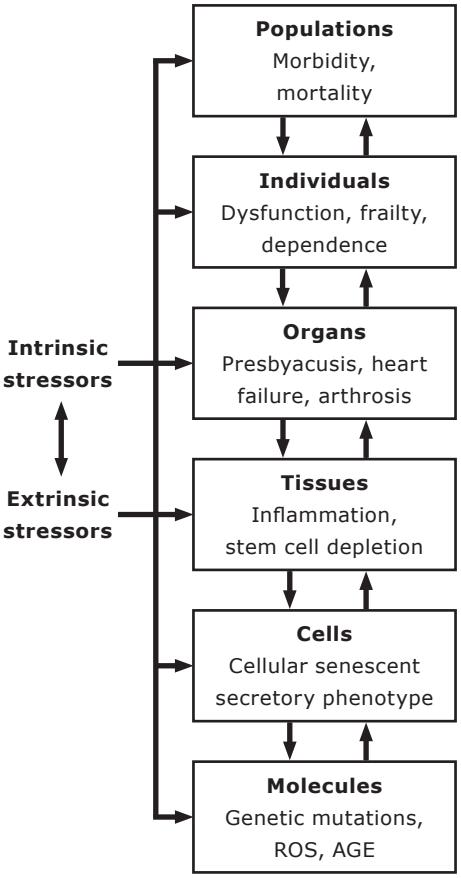

Figure 1.1 • Schematic overview of the accumulation of damage at different levels in the body during senescence. Intrinsic and extrinsic stressors, in interaction, damage the human body at different levels of complexity. The damage at the lower levels seeps through to the higher levels. The damage at the higher levels probably also drips down to the lower levels. ROS: reactive oxygen species. AGE: advanced glycation end products.

ular and cellular senescence are the basis of disorders characterised by similar clinical features of accelerated senescence.[46] The accumulation of damage in the body's structures and functions and the development of disabilities and diseases culminate in an increasing risk of death.[2,19,20,24,41,47-49]

Measuring senescence at the population level

As senescence manifests at different levels, it follows that it can be measured at different levels. For example, it can be measured at the molecular-cellular level through DNA lesions and cell cycle arrests, at the level of tissues and organs through inflammation and vascular calcification, and at the level of the body as a whole through instability and physical disability. In this thesis, we measure senescence in human populations. At the population level, senescence is defined as an increase in the risks of dysfunction, disease, and death with increasing chronological age.[2,19,47,50,51] A constant risk of death during ageing marks the absence of senescence.[52,53]

Knowledge of senescence can be obtained by studying molecules, cells, individuals, but also populations. These approaches are fundamentally different, but yield equally valuable and complementary insights. Observing and comparing populations with different characteristics is especially relevant in order to understand how the course of senescence can vary, what determinants account for this variation, and what preventive measures can ameliorate the senescence process.[54,55]

Aims of this thesis

In Part I of this thesis we investigate how a population's senescence can be measured through the increase in mortality with age. In Part II of this thesis we investigate how senescence can be measured through the increase in morbidity in a non-western population and thus be compared with the senescence process in western populations. A more detailed introduction to each research question is given at the opening of each part of this thesis.

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