The interface between ageing and health in man

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Introduction

Every organ of the human body undergoes change during the course of the ageing process. At the cellular and molecular levels these changes involve the accumulation of a wide range of pathophysiological modifications which eventually interfere with normal functions and with homeostasis. The upshot is a progressive rise in the incidence and prevalence of age-associated diseases, increasing frailty and a rising age-specific death rate. Not all change is deleterious, however, and some organs retain considerable powers of adaptation and functional reserve, even among centenarians. The process of ageing is also variable, to the extent that genetically identical individuals (monozygotic twins, or inbred laboratory animals) may age in different ways.

The interface between the 'normal' ageing process and disease in old age is therefore hard to define [1-3]. In some instances, the boundary between what is normal and what is pathological remains controversial. In the case of Alzheimer's disease (AD), for example, the brains of apparently healthy old people may be found at autopsy to show extensive amyloid plaques and neurofibrillary tangles—the characteristic lesions of AD [4]. Indeed, the accumulation of such lesions is probably a universal correlate of the ageing process, even though it does not always result in dementia. Age changes in teeth are another example: all teeth accumulate structural damage (abrasion and microfractures of the enamel) with the passage of time. Such wear is clearly part of 'normal' ageing, but what about periodontal disease resulting perhaps partly from a reduced cell division rate of senescent gum fibroblasts?

In this paper we address the interface between ageing and health (and its converse, disease) using the specific example of the immune system. The immune system is an excellent model with which to consider this question because, on the one hand, it plays a key role in the maintenance of health, while on the other hand, it undergoes important modifications with age, some of which are associated with increased incidence of disease. Failure of the immune system to protect against pathogens results in infectious disease, failure to recognize and destroy aberrant host cells may result in cancer, and the mistaken identification of host cells and proteins as 'non-self' may result in autoimmune disease. The increase in the incidence and prevalence of these conditions with age may therefore arise partly from extrinsic causes, merely reflecting the passage of time, but they may also result from intrinsic immunosenescence, in other words from the impact of ageing on the immune system itself.

The ageing process—its nature and causes

The ageing process is a 'normal' part of the life history of our species. Individuals grow, reach reproductive maturity, and enter a long period of adult life during which the level of health is generally very high. But beginning in the fifth, sixth or seventh decades of life, i.e. in the 40s, 50s and 60s, a number of changes become apparent, leading progressively and inexorably to an increase in frailty, decline in vigour, and finally to death. In this respect, we are like a great many other animal species which also exhibit this phenomenon known as 'senescence' [5, 6].

Although it was once thought that ageing was programmed, like development, perhaps for the 'good of the species' to prevent overcrowding, it is now seen that this idea cannot be right [7]. Mortality in wild populations is usually so great that individuals rarely live long enough to show clear signs of senescence and, in any case, for ageing to have arisen in this way would have required that group selection for advantage to the species or group was stronger than selection at the level of the individual for the
advantages of a longer life, which is highly unlikely. Instead, the underlying reason why ageing evolved is thought to be that the force of natural selection—that is, its ability to discriminate between alternative genotypes—progressively weakens with advancing age, leaving the way open for mutations to accumulate that have deleterious effects on late survival [8, 9].

Another important factor contributing to evolution of ageing is that for an organism to live a long time requires significant investments throughout life in a wide range of somatic maintenance and repair functions, all of which consume energy [10, 11]. There is no evolutionary advantage to be gained from such major investments in the long-term durability of the soma when mortality from extrinsic causes will sooner or later cause death. The greater priority is to invest in reproduction. This is the basis of the 'disposable soma' theory of ageing, which suggests that senescence results from limited investment in the maintenance of the soma [12-14].

The evolutionary theories, in particular the disposable soma theory, give insights into the genes and mechanisms that influence ageing [10]. The genes are predicted to be those that regulate key mechanisms of somatic cell maintenance, such as DNA repair, antioxidants, and the orderly synthesis and turnover of proteins and subcellular organelles like the mitochondria. Also important will be genes that regulate cellular processes such as the immune system, mechanisms responsible for cell proliferation and turnover, and those that maintain the integrity of higher level functions such as the neuroendocrine network. The general picture of the action of ageing on the body is one in which the process is driven by a gradual accumulation of random molecular faults, resulting eventually in a growing fraction of cells within organs and tissues failing to function as they should. In other words, 'normal' ageing—that is, the accumulation of faults that evade the maintenance and repair systems of the soma—leads to a progressive increase in abnormality—that is, departures from the normal ontogenetic body plan.

A long-standing debate in ageing research has concerned the relative importance of programmed events versus the kinds of stochastic damage just considered [15]. The absence of evolutionary support for the idea that ageing is programmed as an overall process to terminate the life of an organism weakens the case for programme theories at the mechanistic level. Nevertheless, it is known that programmed cell death (apoptosis) is essential in development and the maintenance of many tissues, and it appears that active genetic controls on DNA synthesis and cell division play a part in the limited cell proliferation of fibroblast cultures that are commonly used as a model of cell ageing. It is difficult to sustain the argument that apoptosis or programmed cell ageing are primary causes for the ageing of the organism, but it is quite possible that they contribute, perhaps extensively, to senescence as secondary consequence of a stochastic damage to cells. For instance, a cell that is normally prevented from apoptosis by a signal from outside will die if the ability to receive and transduce the signal appropriately is compromised by damage. Such a process could even be adaptive if it serves to bring about the suicide and replacement of a defective cell. Taken to an extreme, one could imagine a scenario where active cell death is the major, outward sign of senescence, while stochastic damage is the pervasive, underlying cause.

The development of senescent changes in the various organs of the body over similar time scales is often seen as evidence for the existence of a central pacemaker or clock that regulates the overall process of ageing. The case for a central clock is weakened, however, by the evolutionary arguments that point to the gradual loosening, and eventual disappearance, of genetic control over the late stages of the lifespan. The synchronicity of ageing changes in different organs is more satisfactorily explained by the fact that, in so far as selection works against the occurrence of senescence in the wild, any organ that consistently failed before the others would be subject to selection to improve its durability. On the other hand, any organ that failed long after the others would be 'over-engineered' and the resources invested in the maintenance and durability of this organ would be trimmed by natural selection, bringing its rate of senescence into line with that of other organs.

For all organs it is to be expected that selection will have favoured the evolution of a measure of 'reserve capacity', such that most organs remain in reasonably good condition at the time when the organism dies a natural death. As noted earlier, natural death usually results from extrinsic causes rather than from intrinsic senescence. Humans are unusual in that our rapid social and cultural evolution has led to greatly increased life expectancy, resulting in the situation where we now live long enough to erode the reserve capacities of our organs to an unprecedented extent.

The immune system and ageing
Infectious disease is the major cause of death in the elderly; thus the immune system occupies a crucial position at the interface between ageing and disease [16]. This role is further strengthened by the likelihood that immune responses play a role in defence against neoplasia, while altered/misdirected immunity leads to autoimmune disease. Thus the immune system can both protect against and be the cause of disease. It is the reduced efficacy of the former, together with an increased frequency of the latter, that characterizes the ageing process in the immune system.

An effective immune response requires interaction
between antigen-specific lymphocytes and the antigen-nonspecific accessory cells [17]. Thus, while foreign pathogens are recognized by and stimulate the effector functions of lymphocytes—the antibody-secreting B cells, cytotoxic CD8 T cells and cytokine secreting CD4 (with a minority of CD8) T cells—accessory cells such as dendritic cells (DC) are required for the processing and presentation of antigen to T lymphocytes in the initiation phase of an immune response, follicular dendritic cells (FDC) play a crucial role in the development of B cell memory, and effector cells such as macrophages, eosinophils, neutrophils, mast cells and NK cells are recruited to mediate the destruction of infected targets. Interplay between these cell populations is controlled by the expression of cell surface interaction molecules and secreted cytokines and chemokines.

**Generalized impairment**

The immune system undergoes a generalized impairment of function with increasing age, although the progression of such impairment differs greatly between individuals, suggestive of both genetic and environmental influences. Such changes can therefore be considered as comparable with those seen in other body components and no special case need be made for the immune system.

Elderly people (and other mammalian species studied, such as mice and rats) show an age-related decline in protective immunity to natural infections and to vaccination. Experimental analysis has revealed a wide range of molecular and cellular changes associated with increasing age, although which of these represent primary rather than secondary alterations is not known. Such changes include loss of expression of the costimulatory molecule CD28 from CD8 T cells, loss of CD7 and CD27 from CD4 T cells, and a failure to upregulate CD40L upon T cell activation [18–20]. Lymphocyte intracellular signalling pathways are also affected, with reduced activity of MAP kinases, calcium mobilization, PLCγ1, the nuclear transcription factors AP-1 and NF-AT, and differential expression/translocation of protein kinase C isoforms [21–25]. Accessory cell function may also decline with age; for example, both DC and FDC become less efficient in antigen presentation to T cells and B cells, respectively, while cytokine production by macrophages is altered [26, 27].

**Environmental shaping**

It is important to distinguish the alterations discussed above from those that have developed and accumulated during an individual's lifetime as a result of their microbial microenvironment. Ageing is accompanied by an increase in the proportion of memory T cells reflecting microbial experience, and a loss of naive cells—due in part to their activation and conversion to memory status, but also to a declining input of fresh naive cells from the progressively involuting thymus [28, 29]. This shift results in expansion of an oligoclonal T population, and changes in cytokine profiles in response to infection such as a reduction in interleukin (IL)-2-producing cells (typical of naive T,0 cells) and an increase in cells secreting γ-interferon and IL-4 (typical of memory T,1 and T,2 helper T cells) [31, 32]. Equivalent changes have been reported for B cell populations.

**Special features**

The above aspects of immunosenescence can be considered as comparable with the age-related changes that occur in other body components as a result of the generalized ageing process and environmental moulding. However, there are two major ways in which the antigen-specific cells of the immune system differ from other cell systems and which have an impact upon the ageing process. The first of these concerns replicative senescence.

The major function of a T or B lymphocyte is the recognition and destruction of foreign invading pathogens. In order to cope with the potential range of infectious microbes that an individual may encounter, the mechanism for lymphocyte generation is designed to create a vast diversity of cells each with a unique receptor for antigen—thus mammals have the potential to create ~10^10 different specificities. However, the corollary to this is that the number of cells bearing an antigen receptor of a given specificity will be very small. Thus clonal expansion in response to antigen is a prerequisite for an effective immune response.

Cell division is known to be associated with DNA damage, in particular the shortening of telomeres—leading to replicative senescence, exit from cell cycle and, ultimately, apoptotic cell death. Does this mean that clonal expansion renders lymphocytes particularly susceptible to replicative senescence? Probably not, since such a process is not inevitable—as evidenced by normal germ cells and malignant transformed cells where the production of the telomerase enzyme protects against telomere loss. Recent studies have shown that telomerase activity is detectable after antigen-activation of lymphocytes, perhaps reflecting an evolutionary adaptation to protect these crucial cells from DNA loss and to extend their replicative lifespan [33]. Nevertheless, the system is not absolute, and ultimately telomere shortening and senescence do occur, as seen in the 'clonal exhaustion' that can occur as a result of chronic infection [34]. Interestingly, other cells whose normal function requires cell division are similarly protected, for example the haemopoietic stem cells that give rise to all the lymphocytes and accessory cells involved in immune responses [33].

The second respect in which the immune system
for T cells, the positive selection of those that see antigens in the context of self major histocompatibility complex (MHC) [35, 36]. Such selection results in the elimination of ~95% of T cells during development within the thymus and ~75% of B cells within the bone marrow. Lymphocyte development is therefore a very energy-expensive process.

We have previously argued that the unique and dramatic involution that commences at as early as 6 months of age in the human thymus represents an evolutionary adaptation whereby the high cost of T cell production has been balanced against the requirement for generation of new T cells after the initial establishment and antigen-driven selection/expansion of the peripheral lymphocyte pool [28]. The lower cost of B cell production together with the propensity for microbes to alter the molecules seen by B cells during an immune response may explain the much less marked reduction in bone marrow lymphopoiesis—indeed some of the reduction seen may be secondary to the progressive loss of the thymus [37-39]. However, the product of evolution seen today reflects environmental conditions that were experienced by mankind long ago. Our current improved living conditions, permitting many more individuals to enjoy an extended lifespan, coupled to social changes that increase interactions and expose individuals to new pathogens throughout their life, have revealed the limitations of this early-onset progressive shutdown of lymphocyte production.

**Immunosenescence and disease**

What, then, are the links between immunosenescence and disease? Clearly the corollary to a generalized reduction in key immune parameters—such as a reduced efficiency of antigen presentation, of the response of lymphocytes to antigen and of the mediation of effector functions to destroy infectious organisms—may lead to increased susceptibility to infectious disease with age. Moreover, the shift from naïve to memory cells (resulting from clonal expansion and maturation of lymphocytes in response to previous antigen experience), coupled with a reduced output of new, and therefore naïve, lymphocytes (affecting in particular the T cell lineage) will create a situation where although the immune response to recall antigens is relatively unimpaired, responses to new antigens/vaccines may be much less effective. This, again, would lead to an increased susceptibility to infectious disease with age [16, 26-29].

Can susceptibility to some non-infectious diseases also be attributed to a declining immune system? Cancers are a major cause of death and show an increased frequency with increased age. A major part of this is likely to reflect the multistep nature of malignancy, where time is required to accumulate the necessary underlying defects. However, immunosenescence may also be a contributing factor. This has been highlighted in studies of renal transplant patients where immunosuppression is associated with an increased risk of almost all forms of cancer, in particular those with a known viral aetiology [40]. The overall increased risk for all tumours was found to be 3.4 times, ranging from only 1.1 times for breast cancer up to >1000 times for Kaposi's sarcoma. Thus the immune system may provide protection against cancer, but whether this involves more than its role in combating infectious disease is at present not clear.

A disease caused by the immune system itself is autoimmunity; however, immunosenescence *per se* may not be an important controlling factor in this. While the incidence of autoimmunity shows in general an increased incidence with age, the distribution for each individual disease follows a bell-shaped curve with the mean age of onset differing according to the specific disease, and there are likely to be both genetic and environmental influences on disease susceptibility. It has been suggested that autoimmunity might involve abnormal T cell development in the thymus (thymic abnormalities have been seen in certain autoimmune diseases such as myasthenia gravis), but in general the presence of the thymus seems to be protective presumably due to its role in tolerance induction and the generation of regulatory T cells [41, 42]. Thus the development of autoimmunity is more likely to be a problem of factors such as exposure to pathogens (which might be cross-reactive with self antigen), an individual's genetic predisposition (MHC to respond to a particular antigen peptide and the time taken for pathogenesis to give overt disease, rather than to ageing of the immune system.

Finally, there are some small compensations to immunosenescence; for example, the risk of transplant failure due to immunological rejection is reduced with increasing age, although unfortunately the risk of other problems such as sepsis increases [43]!

**Conclusions**

The interface between ageing and health in man is a grey area, in more senses than one. The major challenge is to understand the underlying biological mechanisms of ageing and how these contribute to the pathogenesis of age-related diseases. If it is correct to regard the ageing process as one that is driven primarily by the accumulation of random damage in the cells and tissues of the body, then it becomes relatively easy to explain the general increase in
variability of the aged phenotype. However, this increase in variability begs important questions about the validity of drawing firm distinctions between normal ageing and disease. Ultimately, it will be through the understanding of the cellular and molecular mechanisms of ageing, and the complex genetic bases of these processes, that the interface will become clearer. The immune system is an excellent exemplar of the intrinsic complexity and challenge of defining this interface, in particular as regards the impact of ageing on a system that relies on cell proliferation and cell–cell interactions for its normal functions.

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References


