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Ageing and physiological functions

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Ageing and physiological functions

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SUMMARY

In youth, most physiological functions have generous spare capacity. Even in health, however, increasing age is characterized by progressive erosion of these 'safety margins'. Examples include the decline of bone mass (towards a threshold for likelihood of fracture), of glomerular filtration rate (towards a threshold for susceptibility to clinical renal failure), of renal tubular function (towards a threshold for clinically important susceptibility to dehydration), of hepatic function (towards a threshold for accumulation following conventional 'young adult' doses of common medications), or of lower limb explosive power (towards thresholds for impaired functional mobility).

Increasing age is also characterized by a rising prevalence of chronic pathologies, complicating attempts to determine the rate or the mechanism of the age-related decline in a physiological function. Nevertheless, it is clear that in many organs the loss of function is largely attributable to the loss of functioning cells, even in the absence of overt disease. This apparently fundamental aspect of ageing remains poorly understood.

1. INTRODUCTION

In adulthood, increasing age is accompanied by a progressive decline in the function of most physiological systems. This may not be immediately apparent, the individual living successfully without testing the function of any system to its limit. All the time, however, the limits are narrowing; the safety margins between maximal function and critical threshold levels of function, generous in youth, are being eroded (figure 1).

Some authors have drawn a distinction between an individual's chronological age and their 'physiological' (or 'biological' or 'functional') age, arguing that the latter might be more meaningful than the former. Nevertheless, it is questionable whether physiological age is any more real or valid a concept than chronological age (Costa & McCrae 1977). Chronological age may be nothing more than 'a grid for recording the passage of time within which events (commonly called ageing) occur' (Shock 1980). But physiological age is also a dubious concept. For example it seems to imply that all physiological systems in an individual 'age' at the same rate.

It seems better to think in terms of the absolute value of the function of each system. This has the advantage that it becomes possible to relate each value to a critical 'threshold' value for each function below which the individual will suffer, or become at risk of suffering, a catastrophic event. Examples include the decline of bone mass (towards a threshold for likelihood of fracture), of glomerular filtration rate (towards a threshold for susceptibility to clinical renal failure), or of lower limb explosive power (towards a series of thresholds for aspects of independent everyday mobility).

Another concept that has been widely taught is that ageing is characterized by impaired homeostasis. Whilst true, this tends to narrow thinking to only the unconscious, 'vegetative' functions, such as control of temperature, acid–base balance, blood pressure. It tends to obscure the fact that the loss of spare capacity affects all systems, voluntary and involuntary, lowering the ceiling of the individual's ability to respond to any environmental or situational challenge. To talk of impaired homeostasis also tends to focus attention on control mechanisms rather than on the effectors themselves. Both are important, the latter usually but the former only sometimes (e.g. the role of thirst in water homeostasis (Phillips *et al.* 1984), or the central nervous control of thermal homeostasis (Collins 1992)).

In 1866, at the Salpêtrière Hospital in Paris, Charcot (1881) launched a series of 24 lectures on 'Senile and chronic diseases', based on his experiences with the hospital's population of 2500 elderly and/or chronically disabled women. Many of his comments would sound very familiar to a modern geriatrician. He argued for 'the importance of a special study of the diseases of old age' and for 'the importance to be attached to measures of alleviation when it is impossible to cure'. Of particular relevance to this paper is his unifying view of the changes of ageing as 'a general atrophy of the individual', 'an atrophic process, which exerts its action not only on the voluntary muscles and on the various parts of the skeleton, but also on most of the visceral organs'. Whilst this paper will acknowledge some qualitative changes in physiological functions with increasing age, it will emphasize the central importance of the effect of the age-related loss of tissue in the physiological effectors, taking their function below important threshold

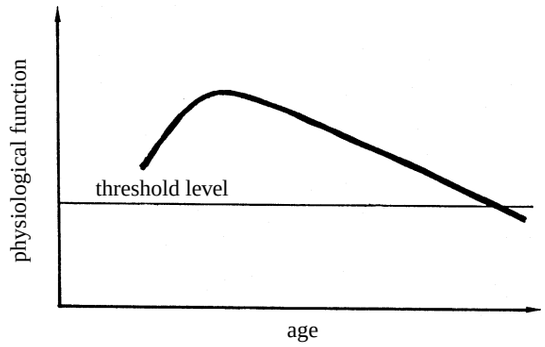

Figure 1. Diagrammatic pattern of change of physiological functions with increasing age, reaching a clinically or functionally important threshold in old age. Reproduced with permission from Young *et al.* (1994).

values. This will be illustrated largely by the age-related shrinkage of the voluntary muscles and the consequences for everyday physical performance but will also include comments on skeletal and visceral 'atrophies'.

2. MUSCULAR CACHEXIA OF AGEING

Cross-sectional comparisons of people of different ages indicate that the loss of muscle ('muscular cachexia' or 'sarcopenia' (figure 2)) begins in middle age, proceeds at approximately 1% per year and impairs all aspects of muscle function. Much of the loss is due to an apparently obligatory loss of muscle fibres (Lexell *et al.* 1983, 1988; Faulkner *et al.* 1990). This is associated with postmortem evidence of fewer anterior horn cells in the lumbosacral cord (Tomlinson & Irving 1977) and electromyographic evidence of larger but fewer motor units (Campbell *et al.* 1973; Doherty & Brown 1993; Doherty *et al.* 1993), suggesting that it probably results from a slowly progressive and incompletely compensated denervation (Young 1988; Lexell & Downham 1991).

The loss of muscle fibres may also be due to impaired regeneration of muscle after damage, especially as elderly animals regenerate muscle fibres less effectively (Carlson & Faulkner 1989; Brooks & Faulkner 1990). Indeed, if muscle cells exert a retrograde trophic effect on their motor neurons, the impairment of regeneration could be the primary defect, causing the loss of motor neurons, not resulting from it.

The age-related decline in performance of elite veteran sportsmen (Meltzer 1994; Moore 1975) suggests that the loss of muscle fibres is inevitable and largely unrelated to habitual activity. Atrophy of surviving muscle fibres, however, is variable (Lexell & Taylor 1991; Green 1986), perhaps reflecting individual variation in habitual activity (Klitgaard *et al.* 1990; Aniansson *et al.* 1992).

(*a*) *The functions of muscle*

(i) *Strength, power and related functional ability*

Across the age range 65–89, even highly selected, healthy men and women have differences in strength which imply 'losses' of some 1–2% (of a 77-year-old's value) per year (Skelton *et al.* 1994). Although most of the weakness is directly attributable to the reduced muscle mass, older muscle may also be weak for its size; possible reasons for this are discussed elsewhere (Harridge & Young 1997). Even more extreme weakness is common amongst elderly patients, as a result of both an even greater degree of cachexia and a more pronounced weakness per cross-sectional area of muscle (S. K. Phillips, D. Levy, A. Yeo, R. C. Woledge, S. A. Bruce, F. C. Martin and A. Young, unpublished data).

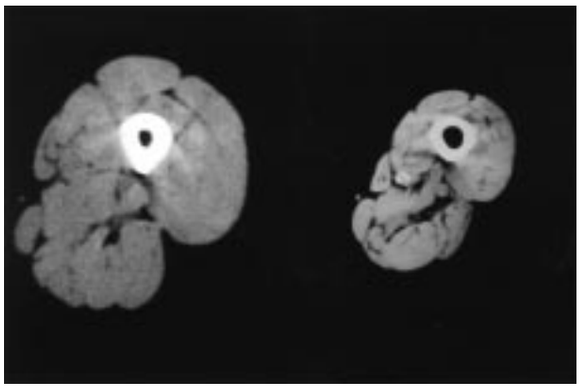

Figure 2. Cross-sectional images at mid-thigh (by computed tomography) from a healthy woman in her twenties and a healthy woman in her eighties, to the same magnification. Reproduced with permission from Young (1996).

Healthy elderly people have age-associated differences in explosive power which are even greater than the differences in strength (Skelton *et al.* 1994; Young 1992). Similarly, when comparing elderly patients with their healthy contemporaries, the difference in explosive power is much greater than the difference in strength.

The age-related loss of muscle is not accompanied by an equivalent loss of fat; the loss of strength is greater than the loss of body weight. Therefore, the frail elderly person is not only weak but, when moving their body weight, their weakness is such that they must use a slower contraction. As a result, deficits in power are even greater than deficits in strength. The greater the resistance against which power must be developed, the greater the 'extra' loss of explosive power. For example, the maximal plantar flexor power of a 70-year-old man might be only some 20% less than that of a young man when developed against a 10 Nm torque, but would be some 90% less than that of the young man when developed against a 70 Nm torque (figure 3) (Harridge & Young 1997). This has important implications for gait.

For completeness, it should be noted that the reduction in explosive power can be aggravated further by a reduction in the intrinsic 'speed' of the muscle, as a result of cooling (Young 1992; Davies & Young 1983; Faulkner *et al.* 1990; Skelton *et al.* 1992) (e.g. in those elderly people who are immobile, thin and living in poorly heated accommodation), and as a result of a change in the isoforms of myosin expressed in older human muscle (discussed elsewhere (Harridge & Young 1997)).

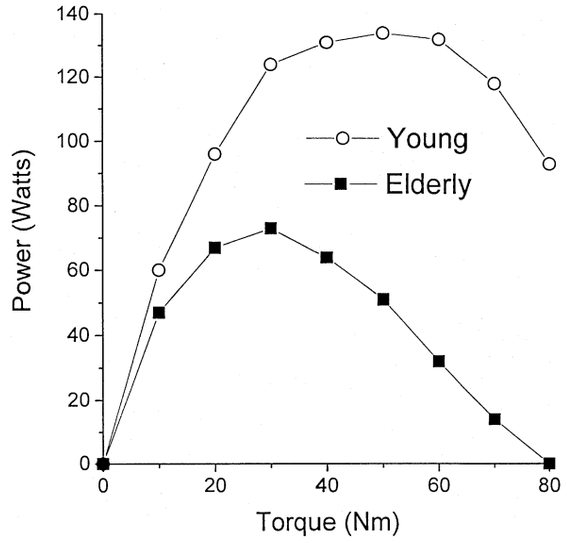

Figure 3. Power/torque curves for the plantar flexors of young and elderly men. Data derived, by interpolation, from measurements of torque and instantaneous power recorded at 25 degrees of plantar flexion in relation to the angular velocity of rotation of the ankle joint. Reproduced with permission from Harridge & Young (1997).

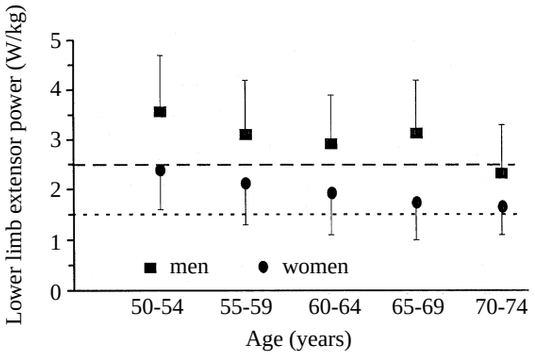

Figure 4. Lower limb explosive power (expressed as a power/weight ratio) of a representative sample ($N = 864$) of men and women aged 50–74 (data from the 1990 Allied Dunbar National Fitness Survey of England), compared with the threshold values required to be confident of being able to mount different heights of step (dashed line, 50 cm step; dotted line, 30 cm step) without using the hands (Levy *et al.* 1994). Bars show ± s.d. Reproduced with permission from Skelton *et al.* (1998).

For wild animals, the age-related loss of explosive power has fatal consequences, through starvation or slaughter, for hunter and hunted alike. For humans, the consequences for health occur later; when sufficiently severe, the loss of explosive power interferes with everyday functional abilities. This is especially so for women, as women have a lower power/weight ratio than men of the same age. A young person's power includes a generous safety margin but large numbers of healthy elderly women have power below, or near to, functionally important thresholds and so have lost, or are in danger of losing, the ability to perform some important everyday tasks. For example, in the English National Fitness Survey (Skelton *et al.* 1998), nearly half of all women (but 15% of men) aged 70–74 had a power/weight ratio below 1.5 W kg^{-1} (figure 4), the least value to be confident of being able to mount a 30 cm step without using the hands (Levy *et al.* 1994). The gender difference in power/weight ratio (figure 4) helps explain the lower step heights achievable by healthy elderly women (Skelton *et al.* 1994), the greater prevalence of disability and of falls amongst elderly women than amongst elderly men and the age-related decline in the percentage of elderly women using public transport on their own (Anonymous 1992; Young *et al.* 1994).

(ii) *Aerobic exercise and aerobic functional ability*

Maximal aerobic power (maximal oxygen uptake, $\dot{V}_{O_2\,max}$) also declines with increasing age (some 10% per decade). Although partly due to a reduced cardiovascular responsiveness to beta-adrenergic stimulation, the decline in $V_{O_2\,max}$ is probably also a consequence of the diminishing total muscle mass (Fleg & Lakatta 1988). The decline in this aspect of muscle function, especially when combined with the effects of disease, also limits the ability to perform some everyday activities. Many elderly people (especially women) need only a small further decline in $V_{O_2\,max}$ to render some everyday activities either impossible or so dependent on anaerobic metabolism as to be unpleasant to perform (Young 1986). For example, in the English National Fitness Survey, 80% of women (but 35% of men) aged 70–74 had an aerobic power/weight ratio below 25 ml kg^{-1} min^{-1}. This implies that they are probably unable to walk comfortably at three miles per hour, since the oxygen consumption required would probably be greater than 50% of their maximum. (For argument and data, see Skelton *et al.* (1997).)

(iii) *Other functions of muscle*

Sarcopenia also impairs other important functions of muscle (Parry-Billings *et al.* 1992), as a dynamic, metabolic store (e.g. for the control of blood glucose levels or as a source of materials and fuels for tissue repair and immune competence), as a vital source of heat and as protective padding (protecting the skeleton in a fall). The elderly person's reduced muscle mass means smaller safety margins when faced with the metabolic demands of surgery or severe illness. If the acute event is severe or prolonged, their greatly diminished muscle mass may no longer be adequate as a source of materials for tissue repair and cellular fuels for immune competence and, of course, as the means to functional mobility.

(*b*) *Improvable*

Just like the Olympic athlete, the elderly person must perform, frequently and consistently, at the very limit of their physical ability. The 85-year-old can therefore benefit from the study of athletic training methods and ergogenic aids. Randomized, controlled trials have confirmed that octogenarian muscle remains responsive to progressive resistance training (Fiatarone *et al.* 1994;

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Skelton *et al.* 1995). The improvements in strength are equivalent to 15–20 years 'rejuvenation' and, when combined with rehearsal, will improve selected functional abilities (Skelton & McLaughlin 1996).

Up to at least 70 years of age, a 10–20% improvement in maximal oxygen uptake can be expected from endurance training (equivalent to perhaps 10–20 years' 'rejuvenation') (Greig & Young 1992). At all ages, endurance training will make submaximal aerobic activities easier to perform, reducing the heart rate response to submaximal exercise (K. Malbut-Shennan, S. Dinan and A.Y., unpublished data).

Since strength, explosive power, aerobic power and the metabolic functions of muscle are all dependent on muscle mass, the anabolic effects of resistance exercise may be an important link between muscle function and health. Even aged muscle retains the ability to increase in size in response to resistance exercise training (Sipilä & Suominen 1995; McCartney *et al.* 1995; Häkkinen & Häkkinen 1996). This muscle growth occurs by hypertrophy of surviving fibres. Aged muscle fibres' capacity for hypertrophy in response to strength training seems similar to that of younger muscle fibres (Aniansson *et al.* 1984; Charette *et al.* 1991; Roman *et al.* 1993), but direct comparisons are difficult. An important factor in the hypertrophic response may be the local production of a muscle-specific isoform of insulin-like growth factor-1 (IGF-1), termed mechano-growth factor (MGF) (Yang *et al.* 1996). It is not known what effect ageing has on the ability of muscle fibres to produce MGF or to respond to it.

Some support for the possibility that aged fibres might have a reduced hypertrophic response comes from studies of muscles weakened by previous poliomyelitis. Like ageing, polio results in the loss of anterior horn cells and of motor units, with an increase in the number of muscle fibres in the surviving motor units. Many of the remaining muscle fibres, however, show a greater degree of hypertrophy than is seen in the muscles of active, healthy elderly people (Grimby *et al.* 1994). Potentially anabolic interventions worthy of evaluation for the very frail patient include anabolic drugs (e.g. growth hormone, anabolic steroids, β-agonists), patterned electrical stimulation and passive stretch of selected muscles. It is not known, however, if any of these can achieve any more than strength-training (Yarasheski *et al.* 1992, 1995).

Despite the fact that strength-training may provoke valuable hypertrophy of remaining muscle fibres, and despite the fact that this may help preserve muscle function, there is no reason to suppose that there is any change in the underlying, progressive, age-associated reduction in the number of muscle fibres.

3. BONE CACHEXIA OF AGEING

Osteoporosis is bone atrophy. It may occur 'prematurely' but also occurs as part of 'normal' ageing. The involutional osteoporosis of ageing results in thin cortical bone and sparse trabecular bone. In women, a lower peak bone mass in young adulthood and the accelerated rate of loss of bone for several years after the menopause mean that osteoporosis is much more severe than in men of the same age (Riggs & Melton 1992).

(*a*) *Bone function*

The primary function of bone is structural and includes the ability to withstand the challenge of an impact without loss of integrity. Fracture as a result of a trivial impact implies failure of bone function. Until this happens, osteoporosis has no effect on the affected individual. This can be considered in terms of a fracture threshold value for bone mass (Morgan 1983).

Women reach fracture threshold values of bone mass much younger than men. Nagant de Deuxchaisnes (1983) argues that, in the distal radius, the trabecular fracture threshold is reached at about age 60–65 in women (on average) but possibly not until after 90 years of age in men. Similarly, vertebral trabecular bone volume falls so fast that vertebral bodies are at risk of crush fractures in white women in their sixties and have occurred in about half of those in their eighties. The loss of cortical bone follows a somewhat different time course from the loss of trabecular bone but is still much more pronounced in postmenopausal women. At mid-shaft in the radius, the loss of cortical bone is such that women again reach an 'at risk' fracture threshold in their sixties. (For argument and references see Nagant de Deuxchaisnes (1983).)

4. RENAL CACHEXIA OF AGEING

There is a progressive loss of renal tissue with increasing age, even in the apparent absence of hypertension, diabetes or frank renal disease. There is a loss of functioning glomeruli and a reduction in the area of effective filtering surface in the surviving glomeruli (Rowe 1980). A qualitative change, over and above the loss of renal mass, is that the renal blood flow per gram of tissue falls progressively from about age 40.

(*a*) *Renal function*

The progressive decline in glomerular filtration rate is perhaps the most important functional expression of the loss of glomerular tissue. It is not immediately apparent, however, as it has no effect on the plasma concentrations of urea or creatinine because the youthful renal safety margin is so wide (and partly because of the falling rate of endogenous creatinine production, secondary to the declining muscle mass). This conceals the older person's increasing vulnerability to overdose with renally excreted drugs and to frank renal failure (e.g. secondary to dehydration or hypotension).

Salt retention and water retention, other important renal functions, are also both increasingly impaired with increasing age. Again, however, the deterioration remains concealed until the organ system is challenged (Rowe *et al.* 1976). In an elderly individual, a clinically significant failure of response can occur in response to an otherwise modest homeostatic challenge. Cross-sectional data suggest that the deterioration in salt and

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water-retaining ability proceeds at a different rate from the deterioration in creatinine clearance (Rowe *et al.* 1976). Nevertheless, it is probably also a result of the loss of functioning nephrons, the loss of reabsorbing ability being related to the loss of structurally intact tubule cells rather than the loss of glomerular integrity (Greenfeld *et al.* 1997).

5. HEPATIC CACHEXIA OF AGEING

Increasing age also brings a substantial fall in liver volume, due to a reduced number of liver cells and associated with an equivalent or perhaps slightly greater decline in liver blood flow (Woodhouse & James 1992). The age-associated decrement in hepatic clearance of many circulating drugs owes more to the reduced size of the liver (and its reduced blood flow) than to changes in the specific activities of drug-metabolizing enzymes (Woodhouse & James 1992). This clinically important impairment of hepatic function can be addressed in terms of 'threshold' values for the amount of functioning liver tissue that must be present to avoid a clinically significant risk of toxic accumulation following 'conventional' doses of commonly prescribed drugs.

6. AGEING, 'NORMALITY' AND THE CELLULAR BASIS OF CACHEXIA

Ageism in research is not only 'politically incorrect'. It is also scientifically incorrect. The exclusion of older patients from clinical trials of treatments for conditions whose prevalence is greatest in old age is an obvious example. Less obvious but no less misleading is the stereotyping effect of the expression 'the elderly', fostering the misconception of homogeneity after 65. In contrast, there are considerable differences between elderly individuals. Indeed, Sir Douglas Black (Black 1995) described 'old people' as 'infinitely varied in their needs and characteristics'. The considerable heterogeneity of those aged 65+ is the result of the broad age range, encompassing substantial on-going age-related deterioration, inter-individual differences in the rate of deterioration and a rising prevalence of chronic diseases. Some elderly people have exceedingly limited physical abilities: others are capable of performances that are better than those of many young adults.

Subject selection is thus a crucial issue in any gerontological study. Some investigations will require subjects who are representative of their contemporaries, with a typical complement of chronic disorders and medication. Other studies might attempt to identify the effects of what Busse & Maddox (1985) termed 'primary ageing', i.e. the features of ageing that 'would inevitably exhibit universally even in an optimally benign environment'. Such a study would require highly selected subjects who, although atypical, are 'normal', i.e. who are free of disease, free of risk factors for subclinical disease and free of medication. Rowe (1976) applied this approach to the selection of subjects for studies of renal function. The SENIEUR protocol (Ligthart *et al.* 1990) was developed to identify healthy subjects for immunogerontological studies. We have suggested exclusion criteria for studies of the effects of 'primary ageing' on exercise performance (Greig *et al.* 1994) and have drawn attention to the fact that the results obtained are different when the exclusion criteria are only slightly less demanding (Skelton *et al.* 1997). For studies of 'normal' swallowing in old age, Davies and her colleagues (1995) not only excluded people with symptomatic or diagnosed disease, they also excluded those with risk factors for cerebrovascular disease. To study age-related changes in cardiac output, Lakatta's group sought to exclude the effects of even subclinical ischaemic heart disease, e.g. excluding subjects with abnormalities on stress thallium scintigraphy (Rodeheffer *et al.* 1984). One can go further still and concentrate on age-related changes in the physical performance of elite veteran athletes (Ericsson 1990).

Even with rigid subject selection, it seems clear that functioning cells are lost from many organs as the individual ages. This loss, and differences between individuals and between organs in the rates of loss, remain unexplained. It is not clear whether the senescent loss of cells has the same molecular basis whatever the tissue but at least part of the explanation seems likely to lie with the progressive shortening of telomeric DNA. In addition, the apparent inevitability of cell loss with increasing age rather suggests the kind of 'programming' normally associated with apoptotic cell loss but any such link remains speculative. Perhaps the cachexia of ageing is the biological price which must be paid to have effective tumour suppression mechanisms, such as the loss of telomerase activity and apoptosis, providing protection from events more immediately lethal to the organism than the gradual loss of cells with ageing.

It is not even clear if a distinction between 'ageing' and diseases associated with old age is valid. (In osteoporosis, for example, the boundary between ageing and disease is especially indistinct.) Holliday (1995) has argued that ageing and disease may both be expressions of failure of the same cell-maintenance mechanisms. The diversity of the end results could be readily explained if different diseases represent failure of these mechanisms in varying combinations. In such a model, the loss of tissue with increasing age but without the stigmata of 'disease' would be merely the result of a particular combination of failures of cell maintenance mechanisms.

This is not to belittle the value of studies which concentrate on healthy subjects, defined according to strict criteria for 'health' and excluding those whose characteristics might more likely be the result of pathology. This approach remains informative, particularly to provide a standard ('successful ageing') against which to judge results from patients, even if its validity depends on the existence of an unvalidated putative entity of 'pure ageing'.

I have argued that ageing is associated with a loss of cells from many different organs, resulting in impairments of function of a severity that imposes clinically or biologically important limits on the ability to respond adequately to commonplace challenges. I have argued that the loss of safety margins in effector

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function may be more important than impairments in homeostatic control mechanisms. The underlying age-related cell loss may be a consequence of processes that are otherwise beneficial to the organism. As a result, putative interventions to slow the process may carry the risk of the loss of repression of harmful cellular processes, notably carcinogenesis.

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