

The changing understanding of ageing

Part 1: Evaluating ageing theories and studies

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Summary

This is the first of three discussions on emerging views of ageing, its derivation, and ageing-related diseases. To offer a context for the series, this first report briefly reviews several major early and recent theoretical debates. Arguments for and against several well-known ageing theories are presented for their veterinary relevance, including mutation, pleiotropy, reproduction-longevity trade-offs, oxygen metabolism and ageing as a genomically programmed product of natural selection. Additionally, the author presents commonly encountered problems when reading to interpret laboratory and population studies of ageing, offering busy clinicians a perspective on evaluating complex papers that analyse ageing-related data. Included among these problems are categorising intrinsic and extrinsic diseases, contrasts between laboratory-based and population-based observations, over-generalising research outcomes, short-term and long-term studies, and theoretical treatises. Central ideas of these discussions include why post-reproductive life span is relatively common among animals, the nature of age-related diseases relative to stochastic or programmed origins and the disease-related implications.

Keywords

Ageing, Disease, Diet, Evolution, Programmed ageing, Reproduction.

L'evoluzione del concetto di invecchiamento

Parte 1: Valutazione delle teorie e degli studi sull'invecchiamento

Riassunto

Questa è la prima di tre discussioni su teorie emergenti, origine e malattie relative all'invecchiamento. Questo primo contributo presenta una breve rassegna di diversi dibattiti teorici fondamentali, datati e recenti, utili a contestualizzare la discussione. Vengono presentate argomentazioni pro e contro numerose teorie sull'invecchiamento in base alla loro rilevanza in campo veterinario, incluse la mutazione, la pleiotropia, i compromessi tra riproduzione e longevità, il metabolismo dell'ossigeno e l'invecchiamento interpretato come prodotto genomicamente programmato della selezione naturale. L'autore discute i problemi frequenti relativi all'interpretazione dei referti di laboratorio e degli studi di popolazione sull'invecchiamento, offrendo ai clinici impegnati nella ricerca una prospettiva per la valutazione di studi complessi sull'argomento. Queste problematiche comprendono la categorizzazione delle malattie intrinseche ed estrinseche, le differenze tra le osservazioni di laboratorio e quelle basate sulle popolazioni, l'ipergeneralizzazione dei risultati delle ricerche, studi a breve e lungo termine e postulati teorici. Le discussioni sono incentrate sul perché la vita post-riproduttiva sia un fenomeno relativamente normale negli animali, sulla natura delle malattie correlate all'età rispetto alle origini

stocastiche o programmate e sulle implicazioni delle malattie.

Parole chiave

Alimenti, Evoluzione, Invecchiamento, Malattia, Riproduzione.

Prologue

After two years of refining my theoretical ideas about ageing and working towards bringing emerging information to the veterinary profession in disease-related terms, a three-article series is presented in this issue of *Veterinaria Italiana*.

My primary purposes are to stimulate thought, facilitate the understanding of emerging knowledge on ageing biology and provide a context to help busy clinicians and academicians view increasingly complex papers in this area.

I purposefully avoided disease catalogues and also avoided my own prior publications: both could be distracting from the different goals that I have now.

Specifically and importantly, these manuscripts present my own view of the evolutionary biology of ageing, as extended to encompass diseases of senescence in a way that has not been done previously, insofar as I am aware. These views are, however, aligned with emerging views of other researchers. The field itself remains controversial in many respects.

Introduction

Challenge to scientific convention invites a more or less sequential series of events that progress through controversy, new ideas, new research questions and new studies. Ultimate emergence of an expanded and clarified view is the desired result. This series of three discussions describes challenge to some ageing-related conventions, looking at selected older and recent reports in the context of a newly emerging perspective. I suggest also, as have others, how 'diseases of ageing' might be reconsidered (*not* re-concluded). My intent is neither to provide a critical review nor a comprehensive summary, but rather, it is

thought towards understanding the science of ageing. I begin simply by asking, 'How shall we think about ageing and where shall we start?'

What causes ageing?

It does not seem appropriate to respond with a list of known age-related biological changes or diseases, as this description is incomplete within and across species. Ageing theory continues to be debated along established and newer lines of thinking. In reality, overlap and even some interdependence are evident among the various theories. Given the impressive diversity of nature, perhaps no theory should be regarded as completely correct or incorrect at this time. Rather, we should consider that all of them may describe nature at some level.

Early theory

Early ageing theories tended to focus on the relationship between fecundity and energy distribution, either directly or indirectly. This considerable literature has been reviewed recently (33, 37). The following discussion of theories is paraphrased in part from these writings.

Antagonistic pleiotropy (50) and disposable soma (24) are variants of the concept of genetic trade-offs, proposing the following:

- early fecundity (early maturity, including growth and development) can be costly to longevity because the same genes that contribute positively to early development may contribute negatively to senescence (antagonism), or that
- resources are allotted preferentially to reproduction over repair when energy is limiting (disposable soma) (37)

Antagonistic pleiotropy

Changes in the immediate environment(s) in which genes operate represent one possible interpretation of early-late pleiotropic differences and effects on fitness (7). However, early-late pleiotropic linking, in context of fecundity-longevity trade-offs, leads to some difficulty when costs of some life-extending mutations are examined closely. Longo and colleagues (33) summarise *daf-2* gene (insulin-

like receptor) life-extending mutations in the tiny nematode *Caenorhabditis elegans*, where the evident costs involve the ability to resist starvation (21). The *daf-2* mutant data suggest that not all longevity trade-offs necessarily need to involve reproduction and, consequently, that some theoretical modification may be needed. The fact that *daf-2* homologue genes and their effects have been conserved broadly as stress response mechanisms is of great importance to the understanding of the stress-related aspects of mammalian ageing.

Pike and colleagues have reported elegant studies of carotenoid influence on sexual strategy in stickleback fish (*Gasterophilus aculeatus*). Males that produce greater carotenoid-dependent social displays are more attractive as mates. Concurrently, greater longevity is conferred, in addition to better antioxidant capability to resist parasites and stress. However, during carotenoid limitation, males attempt to maintain sexual display at the expense of other carotenoid functions, with a resulting shorter life span. Surprisingly, in pair-wise breeding trials, females preferred mates with greater chance of surviving the breeding season, suggesting a female ability to differentiate male carotenoid status (42). Thus, longevity-fecundity selection reflects short-term 'attempted selection' on male reproductive success, but with a longevity effect that appears to be under the influence of mate selection by females. This example illustrates the complexities of natural selection and the importance of well-designed experiments. Simple cause-effect relationships are more likely to be exceptions rather than the rule.

Disposable soma

According to the disposable soma theory, unrepaired damage over a lifetime is manifest clinically as either neutral (wrinkling, greying) or negative (precipitous lean mass loss, overt diseases) ageing phenotypes. This occurs because natural selection has optimised allocation of always limited energy resources between development and longevity (25). The allocation process would favour early puberty in unsheltered populations. Indeed, trade-offs involving lowered fertility or slower growth

can be observed in many long-surviving mutant organisms (32).

On the other hand, a significant challenge for disposable soma is a very large set of observations over the past seven to eight decades that have demonstrated the role of energy restriction (diet restriction, calorie restriction) in extending longevity across many vertebrate and invertebrate species. The energy restriction-longevity response, while not wholly universal in terms of species or diseases, nonetheless pervades the overwhelming majority of studies.

The argument has been made that energy restriction studies are simply a return to 'wild-type' feeding that aligns more closely with evolved organism needs. Weindruch and Walford have pointed out a key flaw in that argument with respect to reproduction. Wild-type feeding does not delay puberty (such a delay would be disastrous for unsheltered populations), whereas delayed puberty is observed with diet (energy) restriction (49).

Most studies on diet restriction have not included breeding trials, and whether uniformly delayed puberty represents a consistent reproductive 'cost' remains an open question. The theoretical problem occurs if natural selection uniformly has defaulted to reproductive efficiency or resting life phases in response to limited resources. Increased longevity and significant post-reproductive life span in an energy-restricted model would contradict that theoretical model. Heininger has written an exhaustive and important review of the germ-soma conflict in the biology of ageing, to which we shall return in the second and third reports in this series (16, 17).

A directly relevant challenge has been expressed by Carnes and Olshansky (7). In order for deleterious genes or gene-related processes to express themselves in advanced life, advanced life first must be present. Theories that depend on late expression of deleterious phenotypes will probably not explain independently the lengthy post-reproductive life span of many species. Additionally, age-related senescence appears

to be uncommon in the wild, compared to laboratory settings or to populations outside the laboratory that are sheltered in some way (7). The theoretical problem is that sheltering modifies the environment and therefore possibly also epigenetic influences that are subject to natural selection in both sheltered and unsheltered populations.

Mutation accumulation

Mutation accumulation proposes that declining impact of natural selection due to chronological decline in fertility allows mutations to accumulate in a genome because there is no strong selection against them (10, 35). In the case of mutation accumulation, the link between reproduction (fertility) and ageing is less direct. The outcome is expressed as phenotypic diseases of ageing, mediated by effects of stochastically altered genes. Mutation accumulation, like antagonistic pleiotropy and disposable soma, does not consider the possibility of purposefully selected genetic programming for ageing.

Part of the problem with the mutation accumulation theory is that life-extending single gene mutations (point mutations) have been identified in multiple species, such as *C. elegans*, yeast, fruit flies and mice (37). Clearly, then, mutations have 'options' to be negative, neutral, or positive. For example, a mouse insulin-like growth factor (IGF-1) receptor gene was evaluated by deleting one or both copies from the genome. Deletion of both alleles had a negative impact on size and development, but single deletion resulted in life span extension without evident developmental cost (18).

In other studies, genes involving apoptosis in mice (36) and guanosine triphosphate-binding regulatory protein in fruit flies (29) similarly have been shown to extend life span without obvious cost. One might argue that costs could be occult at the present state of knowledge, but this question can be resolved by further research (37). Given the small amount of experimental support and the significant challenges posed by newer research, mutation accumulation does not presently occupy a prominent position in ageing theory.

Theoretical problems

There are other problems for pleiotropic and mutational theories of ageing, as we presently understand them. One is that portions of genomes may have differential susceptibility to damage (6, 31). Damage to DNA from random causes may not be random in effect (7). For example, it has been suggested that the cellular damage responses (DNA repair) may be selective to genes undergoing active transcription (6).

At the population level, the observation that death rates actually decline in very elderly humans is directly contrary to the idea of life-shortening mutations that accumulate with time (41). Furthermore, this cannot be regarded as a uniquely human-associated population trait. The same decline in age-specific mortality rate has been observed in *Drosophila* (8), which lies a long evolutionary distance from *Homo*. The opposing argument, that these changes in death rates merely reflect individual genetic robustness in a population, is inconsistent with the way in which we understand both mutation accumulation and pleiotropy. Considered together, the observations suggest that ageing mechanisms probably do not act primarily via deleterious pleiotropy and mutations. That said, the observations also do not independently refute these early theories.

Opposing fecundity-linked ageing theory, experimental support for longevity pathways that are independent of growth and development can be seen in similar metabolic pathways across very different species (22). Prominent among these pathways is insulin/IGF-1 signalling. In *C. elegans*, the pathway regulates life span and a diapause (dauer) phase that is triggered by food limitation and crowding (12). In yeast, protein kinase homologues of the insulin/IGF-1 system regulate growth, sporulation and longevity, largely in response to environmental stimuli (30). In *Drosophila*, an insulin/IGF-1 pathway regulates body size, and heterozygotes for two different mutations in the insulin/IGF-1 pathway are very long lived (48). Very recently, about one-half of the variability in

size among domestic dog breeds (*Canis familiaris*) was shown to result from the action of a single IGF-1 allele, with greater IGF-1 production favouring greater size (47). In the latter instance, defining relationships to longevity requires additional study. I will return to these ideas in the third paper of this series, where I will note that IGF-1 pathways may also play a role in some ageing-related diseases.

The examples of insulin/IGF-1 and homologous signalling indicate broadly conserved processes, over long evolutionary distance. As such, they are compelling evidence for programming relative to ageing. The question to be explored in the second and third papers of this series is whether this programming is:

- secondary and consequent to other actions of natural selection, or
- a primary and purposeful outcome of natural selection.

If programming is not a secondary outcome of other selected traits, the existence of purposeful ageing programmes would be damaging for the historical ageing theories (37).

As theoretical research continues, some important questions arise from the studies that we have examined. Many scientists are now asking these questions in various ways:

- Is interdependence of fecundity and longevity fixed in the genome of some species and not others? Where do species and strains that are frequent subjects of laboratory studies fall along the biological continuum of ageing research? This seems an important question because of the growing body of evidence that earlier theories of causes for senescence are at the least incomplete
- Do various evolutionary theories of ageing describe phenomena that actually reflect even more fundamental natural processes that are not yet fully understood? This question is important because of the growing body of evidence demonstrating that the chemistry and biology of ageing are complex, interwoven and are still being elaborated.

Further considering this point, the most effective ageing intervention identified to date is diet restriction that affects a wide variety of biochemical processes across many vertebrate and invertebrate species, usually extending life span in the presence of limited energy. The energy restriction phenomenon supports conservation of multiple and basic biological stress response capacities and begs the questions of why and how these processes evolved in, or into, the context of post-reproductive life span. Most interesting is that increased longevity and repair (disease postponing in more complex diet-restricted subjects), are also inconsistent with population and species survival as defined by unmodified historical senescence theory.

Free radicals (mitochondrial ageing)

Very extensive literature exists on oxygen metabolism, free radical formation and ageing. The accepted theory is that ageing is accelerated because of damage done to cells, subcellular organelles and metabolic pathways by active metabolically generated oxygen radicals (reactive oxygen species: ROS) (4, 15). At the same time, age-related decline of damage protection and repair mechanisms shift the balance to favour cell death (2, 39).

However, there remain significant arguments in the free radicals arena. Some examples will illustrate the current opposing views. Favouring the free radicals ideas are studies such as that performed by Honda and colleagues, who showed that high- and low-oxygen environments shortened and lengthened the *C. elegans* life span, respectively (19). Additionally, the *C. elegans* life span was longer when cellular respiratory pathways were suppressed experimentally with small interfering RNA, if the nematode was exposed to this manipulation during development. This observation also implies existence of response programming because the effect extended well beyond the time of the intervention (9, 27).

However, other studies have yielded different perspectives (3). One fascinating study involves the naked mole rat (genus:

Heterocephalus) which lives well over two decades. This species, despite a very long mean life span for a rodent, has normally high levels of evident oxidative damage, detectable both in tissues and molecular systems (1, 13). In other studies, antioxidant pharmacology that collectively included alpha tocopherol, alpha-lipoic acid, and co-enzyme Q10, did not further extend life span of mice when caloric intake was controlled (i.e. in a diet restriction model) (26, 38).

The idea that oxidative processes cause cellular damage and influence ageing is not in dispute. However, it has been suggested and supported that assigning the exact role that oxygen-related damage pathways play in ageing is premature, even at this late date (33).

Programmed longevity, altruism and population selectionism

I have pointed out that conserved ageing-related metabolic pathways argue for genetic programming, but do not independently explain why they evolved or define their influence on subsequent evolution. Longo and colleagues point out that possessing stress-response programming would allow simpler organisms, such as yeast and invertebrates, to enter static modes during times of deprivation, while more complex organisms would be able to down-regulate critical metabolic pathways (33). The afore-mentioned insulin-glucose-IGF-1 pathway is just one example of a stress response that is conserved in species-aligned forms in yeast, nematode, fruit fly, mouse and humans (33).

Across wide evolutionary distances and across phylogeny, the modest stress of diet restriction has extended longevity, probably by favourable modulation of many metabolic pathways. In addition, the onset of species- and strain-specific late life diseases is postponed or prevented (34). As a result, stress response and longevity are coupled in what has become known as hormesis. Hormesis states that 'modest environmental stresses frequently enhance the average life span in a population' (33). Programmed ageing might be viewed as a hormesis-like state. Ageing is

related to the population through the proposition that individuals age less from stochastic causes or trade-offs than by actions of specifically evolved stress-response programming that benefits closely related group members (33). Earlier death of some population members would avail more resources to support survival of longer-lived mutants or individuals that are suited better to an existing environment. These advantages would act to help prevent local extinctions from total population decimation (33).

If natural selection operates at more than one level, then group or population selection to preserve underlying favourable physiological mechanisms should be evident, but the idea has been subject to debate. Hamilton observed nearly a half-century ago that 'the possibility of the evolution of characters benefitting descendants more remote than immediate offspring has often been noticed' (14). Hamilton suggested that opportunities for self-sacrifice to benefit more distant descendants likely are less common than opportunities to benefit same-generation relatives (14). Alternatively, Shanahan (45) suggests that altruism does not necessarily require the death of the altruistic individual(s). The individual's role may be confined to greater risk-taking that could result in the survival of the altruist. Shanahan's example is well-stated: individual birds may take self-exposing risk by warning the flock of approaching danger, so that all depart at once and thus share risk and benefit. Thus, concerns about the nature of 'self-sacrifice' can be modified by a taking a slightly different view of altruistic 'behaviours' (45). Therefore, the possibility that evolved altruistic behaviours do function to support continued population stability must be recognised.

The more fundamental argument, however, is whether apparently social implications of evolutionary change are:

- a collective result of individual competitive successes in using limited resources, or
- reflections of natural selection at multiple levels, including population structure (45).

It seems to me that a useful direction for this research would be to define more precisely the

fundamental genetic and epigenetic nature of an altruistic response and to further elucidate the critical network of biochemical pathways that modulate sensory triggering mechanisms relative to altruism.

I find three thoughts interesting about population selectionism, as follows:

- one might observe that it is species that must survive, not individuals, and that species survival cannot occur independently of some type of population structure, whether local or disseminated
- both individual and group aspects of population survival may occur simultaneously in a selection process; the mechanisms may or may not be the same
- if ageing is a product of natural selection rather than simply residuals of a fecundity-longevity trade-off, this would imply that it has an independent function (37).

Evaluating ageing-related studies

Once we understand that single ageing theory cannot be concluded as being completely correct or completely incorrect at present, we must accept that honest differences of opinion or views of data dictate the need for additional research. It is my view that prospectively designed, well-controlled, longitudinal studies (same subjects over a defined period of time) offer the best approaches. However, the length of time required and the expense can be significant barriers. Retrospective longitudinal studies are possible also (5), but often they are not supported by rigorously constructed data collection and analysis, with adequate controls drawn randomly from the same population.

On account of barriers to longitudinal studies in veterinary medicine especially, many ageing studies are cross-sectional. Cross-sectional ageing studies usually evaluate a spectrum of ages simultaneously and each subject appears only once. Cross-sectional studies can be conducted prospectively or with retrospective data (5). Where prospective approaches are not possible, retrospective cross-sectional studies are best approached with data that are more likely to have been collected reliably and are at

least theoretically less complicated by influential variables that can be lost to view with the passage of years (5). Cross-sectional studies might be designed in various ways, each with advantages and disadvantages that investigators should identify in publications.

Extrinsic and intrinsic disorders

When studying diseases, whether of extrinsic or intrinsic origin, one must consider the time differential between biological presence and clinical signs. Extrinsic diseases are those that originate outside the body (7, 40). Examples include infections with discernable or variable incubation periods; toxicities with brief or protracted elapsed time between exposure and symptoms; or climate-, trauma-, or catastrophe-mediated morbidity and mortality. With many extrinsic problems, one may observe dose-dependency and relationships between biological and clinical disease may be elusive.

With respect to ageing and intrinsically mediated diseases, the problems of biological and clinical onset are even more universal. In clinical settings, screening tests must first be recommended (and agreed to) and then must be sufficiently sensitive for early detection. All clinicians are familiar with diseases that may be present long before even subtle clinical signs are evident. Examples might include pancreatic carcinoma, bronchiogenic carcinoma, hemangiosarcoma, osteoarthritis, renal failure, or some types of liver disease, but in reality a very long list could be constructed. When the prior history of a patient is not available or does not exist, early recognition of occult problems can be extremely difficult. As a consequence, diseases may be considered to be intrinsic if the underlying extrinsic cause goes unrecognised.

The ability to segregate intrinsic and extrinsically mediated morbidity and mortality is a very important design aspect of ageing studies. Both may represent legitimate targets for data analysis, but the hypothesis of the study will dictate how each grouping is considered.

Species-specificity in ageing: laboratory and free-living populations

Scientists tend to study non-human vertebrate ageing in laboratories, even though members of subject species rarely survive into senescence in the wild. These laboratory studies should not be placed aside because of this fact. They hold twofold importance to practicing clinicians, namely:

- they allow understanding of metabolic pathways and genetic programmes that are involved with ageing and diseases of ageing
- they offer a knowledge base to support evaluations of preventive and therapeutic measures for individuals or groups of patients.

An important lesson from studies of diet restriction models is that cross-species extrapolations of *specific* outcomes should be discouraged, despite the overall robustness of the response. Phenotypic effects (diseases or pathways that are influenced) may differ among species, or the same metabolic pathways may serve different purposes. However, the lesson provides for several guidelines that might be considered when evaluating ageing studies, in particular:

- exercise caution about accepting life span interpretations of studies when life span is not included in experimental designs
- post-intervention survival of serious diseases is an entirely different matter from restricted-energy survival models that are largely about prevention
- because of the broad nature of influences that diet restriction exerts on metabolism, it is very likely that multiple and perhaps interacting modulations are involved in the longevity and disease-mitigation responses (20); influencing one or some of these pathways in a sub-life span model does not independently guarantee increased life span or quality of life
- strain- and species-specific details in the diet restriction model remind us of the variety of potential responses available to the cell, organ, and organism.

Generalising outcomes

A disease-related question that pertains to the diet restriction and ageing model is whether all species or diseases respond. The answer is that there are some animals and diseases that do not respond according to expectations. In a landmark early study, Ross found that diet restriction of rodents did not influence urinary bladder papilloma, fibroma, fibrosarcoma and some carcinomas (especially endocrine carcinomas) (44).

Differential influence of diet restriction on ageing of the same strain can be observed. In a study of Fischer 344 rats, diet restriction delayed both pituitary adenoma and leukaemia, but in differing degrees in the same animals (46). In a study of physiological and molecular responses to diet restriction, locomotor activity, body temperature, plasma leptin, white and brown adipose, and hypothalamic neuropeptide YY₁ receptor (anti-thermogenic) activity varied among three important laboratory rodent strains (11). The significance of this particular study is that the three inbred strains are progenitors of many other strains that are suited and used for a variety of chromosome and trait mapping studies. Thus, genetic background is important to experimentation strategies, and to the interpretation of results.

Another common problem with interpreting studies of ageing (and other things) in populations is the tendency to imply (authors) or draw (readers) conclusions of cause and effect when the experimental design more logically facilitates inference to identify avenues for further documenting research. As with all research, the alert reader will ask whether the methods used, and the control populations, were structured sufficiently well to support the conclusions.

Long-term studies

Interpretation of long-term, controlled laboratory experiments can sometimes take surprising turns. Consider the *Drosophila* longevity-fecundity experiment (43) that now spans several hundred generations of selection

for longevity (summarised recently by Mitteldorf) (37). Two strains of fruit fly, derived originally from the same stock, are termed 'B' (control) and 'O' (selected for longevity). In both groups, eggs laid after transfer to each new environment are harvested to become the next generation. B strain flies appear to have adapted physiologically and behaviourally to lay eggs soon after recovery from anaesthesia and transfer (perhaps an unintended adaptation), while O strain eggs have been selected only from the longest living flies.

Earlier in the experiment, the results aligned with the tenets of the antagonistic pleiotropy ageing theory, in that O flies began to live steadily longer, at the evident cost of early fecundity (43). However, after several hundred generations, still-increasing O strain longevity was accompanied by increasing fecundity (28). The debate centres on the interpretation of these observations. Briefly, the investigators have the position that the rise in O strain fecundity is not uncoupling of fecundity and longevity, but rather a genotype-by-environment (epigenetic) effect that resulted at least partly from non-fixed resources (28). The opposing argument is that the observations indicate the presence of 'longevity' genes that do not couple with fecundity, thus challenging the antagonistic pleiotropy theory (37).

As a logical extension of these challenges, Mitteldorf observes that, if fecundity is under strong positive selection pressure in nature, then wild-type optimisation of fecundity by natural selection may have failed at least partly, in light of the O strain outcome (37). Thus, many of our previous assumptions on ageing could be reconsidered, especially the longstanding tenet that ageing is purely stochastic.

Do theoretical perspectives contribute to clinical understanding of ageing?

Post-reproductive life span: the 'ageing' phase of life

Long-held evolutionary theory attributes post-reproductive life span to corollary effects of

natural selection for increasing fitness (37). However, the puzzle clearly is more complicated than that. For example, post-reproductive life span with purpose would be understandable in human terms, perhaps as an adaptation to grouped existence and evolution of social behaviours in early hominids. The problem is that this idea does not explain that fact that post-reproductive life span extends far beyond 'higher' mammals, even to include 'lowly' nematodes. In fact, post-reproductive life span is not at all unusual in animals. In a broad context, these observations conflict with evolutionary theory that ties competition for limited resources to fecundity. It may be that reproduction favouring optimum fitness is not the 'only goal' of natural selection (37).

Why does post-reproductive life span exist? There are several possibilities. A social context certainly cannot be dismissed as one possibility (37). Predation, trauma, climate, social structure and local competition for resources, all tend to limit widespread senescence in free-living animals. These observations might argue in favour of selection for reproductive fitness as the explanation for post-reproductive life span. If the organisms were better adapted to begin with, greater post-reproductive longevity might simply reflect that fitness. While this idea does not align well with some ageing theory, neither should it be dismissed prematurely.

Diseases of late life could align with the increased overall fitness argument if we characterise them as the result of eventual failure of fitness. That is, biologically imposed limitations to life span are suggested by the disposable soma, with germ line perpetuation of species integrity being the mechanism for passing on fitness through reproduction (an otherwise disposable soma being the residual) (16, 17). Under the disposable soma idea, the implication for physicians and veterinary clinicians is that at least some diseases of late life are inevitable but nonetheless secondary consequences of these evolutionary events. In my view, the difficulty here is the genetic and biochemical complexity of 'disposability' and of many late life diseases. Natural selection, as we understand it, typically does not invest

substantial energy in death. Ageing-related observations made by clinicians will be a valuable database as research proceeds to appropriately modify the disposable soma theory. That is, the understanding of specific diseases of late life needs to be expanded greatly.

Heininger proposes characterising the process as a germ-soma *conflict* that intimately involves stress at the metabolic level (16, 17), but evidently does not need to imply disposability in an obligate sense. There are good arguments that do not readily characterise post-reproductive life span as a collection of biological residuals. If population stability could be achieved by the theoretical effects described in the preceding paragraphs, the outcome would be more limited occurrence of ageing and chronic senescent diseases. As a result, there would be little need for genetic programming to extend post-reproductive life span. The argument is circular until we identify ageing-related genetic programmes that function independently of theoretical constraints. Fortunately, there are many such observations (23) that lead us to examine the

question of their interpretation in the next two papers.

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