Endogenous parasitism: a biological process with implications for senescence.

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Received 16 February 1995, 4 August 1995

ABSTRACT: This paper presents arguments in support of a basic biological process of within-organism selection which is given the name of endogenous parasitism. It is suggested that endogenous parasitism may have a role in senescence. Lineages such as epithelial cells, mitochondria, or gene sequences may experience large numbers of replications within the lifespan of the organism. Such reproducing entities will give rise to random variants (e.g. genetic mutations). Each generation of variants will be subjected to selection by the somatic environment such that subsequent generations are progressively enriched by the most adaptive variants. Adaptive variants would tend to be those that demonstrated the most 'selfish' behaviour, and favoured the reproductive interests of their own lineage over their 'somatic duties' and the interests of organismal integrity. Replicating lineages will evolve towards a quasi-parasitic exploitation of the organismal environment, with the consequence of a progressive and inevitable decline in organismal integrity leading to senescence. Due to endogenous parasitism, the organism can be conceptualised as an entity which will progressively self-destruct from the moment of its formation.

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Introduction

Multicellular organisms are composites. Individuals are composed of cells capable of division and variation. Within eukaryotic cells are organelles, also capable of reproduction and variation, and within organelles and nuclei are gene sequences which may have these capabilities. Buss, 1987.

If you have things that are reproducing their kind; if there are sometimes random variations, nevertheless, in the offspring; if such variations can be inherited; if some such variations can sometimes confer an advantage on their owners; if there is competition between the reproducing entities - if there is an overproduction so that not all will be able to survive to produce offspring themselves - then these entities will get better at reproducing their kind. Nature acts as a selective breeder in these circumstances; the stock cannot help but improve. Cairns-Smith, 1990.

Individual organisms are formed of components with the potential for competition. Throughout the evolutionary history of an organism, interactions between components have been selected to enable development and benefit reproduction. But natural selection operating within the organism throughout its life span can also 'improve the stock' of those components which behave as reproducing entities (Cairns-Smith, 1990) by favouring those variants which most effectively exploit their somatic environment. Such 'improvement' would be expected to proceed in the direction of an increase in 'selfish' behaviour (Dawkins, 1989) until the replicating lineages become *de facto* parasitic upon the 'host' organism. In this paper I will suggest the term *endogenous parasitism* for a process by which replicating somatic lineages evolve away from co-operation and towards exploitation. This process is to the detriment of the individual organism and, given sufficient time to operate, would constitute an inevitable cause of senescence.

Inherited disharmony

Organismal integrity is predicated upon the continued subordination of component parts to the goals of the organism. Yet there is an inherited and intrinsic potential for disharmony between the organism and its constituents (Buss, 1987; Tauber and Chernyak, 1991; Tauber, 1994; Maynard Smith & Szathmary, 1995). This potential disharmony has arisen throughout phylogeny because evolution involves a hierarchical process of integration and co-ordination of constituent parts incorporated from ancestors. To maintain life there is a need for active harmonisation at every level of organisation: for instance, elements of the genome may be of viral origin, mitochondria were probably autonomous life forms which entered into a symbiotic relationship with primitive cells, and the differentiated cells typical of multicellular organisms are descendants of totipotent free-living cells (Cosmides and Tooby, 1981; Buss, 1987). The processes by which organismal integration (and, by implication, health) are created and maintained have been termed 'salutogenic' - a name coined by Antonovsky to contrast with the 'pathogenic' processes and events which cause disease (Charlton, 1994; Charlton, in press).

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Evolutionary Theory 11: 119-124 (January, 1996)
The editors thank N.W. Blackstone, E.J. Klekowski, and another referee for help in evaluating this paper.

The condition of integration imposed on a state of inherited disharmony is an aspect of the phenomenon which has been labelled 'the paradox of the organism' (Dawkins, 1990). This points up the conflict of interest between the self-replicative goals of subordinate parts (in this case 'selfish' genes; Dawkins, 1989) and the whole organism. The same argument applies at other levels of biological organisation. Natural selection operates on different units of selection - such as self-replicating molecules, gene sequences, organelles and cell lineages as well as the individual organism (Cosmides and Tooby, 1981) - and all of these units would be expected to act 'selfishly' in Dawkins' sense of the word . The 'paradox' is that self-interested genes will nevertheless collaborate in constructing highly elaborate organisms as 'vehicles' for containing and reproducing themselves. Organisms demonstrate surprising complexity and mutual inter-dependency given that the genes responsible for building and maintaining them are in competition.

The solution to this paradox is that the organism is necessary to all the genes, because the organism forms the only common route into future generations (Dawkins, 1990). The many selfish genes which comprise the genome are united by their joint interest in perpetuating the integrity of the organism, in so far as the gametes are the sole vector for transmission to organismal descendants. On its own, and without the assistance of its phenotypic vehicle, a given gene cannot (or cannot optimally) reach further 'hosts'; therefore the gene must work with other genes to build and maintain an organism, such that the maximum number of further copies of itself will be produced. The necessary degree of co-operation is achieved through orchestration of appropriate developmental sequences and the hierarchical imposition of harmony by organism-wide integrative systems which have been selected-for throughout the organism's evolutionary history (Buss, 1987; Tauber, 1994; Maynard Smith & Szathmary, 1995).

Mechanism of endogenous parasitism

Multicellular organisms commence life as a single cell which divides by mitosis to produce a clone of initially homogenous cells. However, some cell lineages undergo vast numbers of mitotic divisions during development and throughout the adult lifespan. Examples include many of the covering and lining epithelial tissues, or the haemopoetic stem cells. Random genetic mutations in such lineages will give rise to new genetic variants. The most adaptive mutations will be selected by the somatic environment and will differentially be favoured in succeeding generations. Therefore, although the organism commences existence as a somatic clone, throughout life it will increasingly become a *chimera* composed of the original zygotic genome plus newly evolved lineages (Buss, 1987).

Whatever integrative mechanisms have evolved to maintain harmony between cell lineages (synchronised developmental sequences, genetic programmes, immune, nervous and hormonal systems, inter-cellular signalling etc.) will themselves constitute the environment within which selection of adaptive variants will proceed. Organisms which invest heavily in these 'salutogenic' mechanisms will be able to postpone the onset of senescence for longer than organisms which do not invest so heavily. But given the finite repertoire of any organismal integrative mechanism, it seems inevitable that, assuming sufficient mitotic divisions, replicating lineages will eventually evolve to elude surveillance, resist suppression and subvert organismal integration - lineages will adapt to exploit their environment rather than to support it. The process would also apply to other reproducing entities which form organismal components, such as gene sequences, or replicating organelles containing their own genes, such as mitochondria.

For instance, it might be speculated that genes coding for surface marker antigens would tend to evolve in the direction of eluding immune or other cell recognition systems; endocrine suppression of cell division would be avoided by selection favouring those cells with the lowest concentration of hormone receptors; cellular variants would tend be selected which lacked the capacity to respond to inter-cellular signals for apoptosis (and thereby avoid programmed death); and mitochondrial DNA deletions which promoted replication of the organelles at the cost of diminished capacity for oxidative phosphorylation would increase in frequency. The above phenomena (and several others) have been suggested as mechanisms of senescence and are compatible with endogenous parasitism (Strehler, 1977; Timiras, 1983; Finch, 1990; Rose, 1991; Wallace, 1992; Raff, 1992; Martin, 1993). However, these potential phenomena of senescence are usually interpreted as the consequences of accumulated random errors, and therefore of mutations which are (on average) fitness-reducing for the lineage. By contrast, endogenous parasitism would predict that the reproductive fitness of some lineages would progressively *increase* with age to cause the accumulation of more adaptive phenotypic variants, even as their functional capability and contribution to organismal integration would decrease. This prediction is empirically testable.

Perhaps the most convincing instance of endogenous parasitism, and one which demonstrates this adaptation of a lineage, is neoplasia. Current models of cancer-generation and tumour-progression emphasise exactly the kind of within-organism natural selection for selfish phenotypes that is described by the more general phenomenon of endogenous parasitism (Varmus & Weinberg, 1993; Alberts *et al*, 1994). Endogenous parasitism must take account of the prediction that the great majority of random mutations will tend to be deleterious or lethal (Dawkins, 1982). This means that mutations will typically be adaptation-removing. Yet apparently adaptive mutations are seen in neoplasia, for instance those of genes coding for replication (oncogenes). In addition, mutations are also seen in genes coding for

suppression of replication of neighbouring cells (tumour-suppresser genes). Tumour progression may therefore be a combination of removal of constraints, together with evolution of adaptations as a consequence of natural selection.

There is no paradox involved here. The deleterious nature of random mutation will tend to remove the 'higher order' cellular adaptations to multicellularity; whether these be responsivity to inhibition, or synthesis of an inhibitory substance - the manufacture of which is energy-consuming. In either case, mutation allows the cell to escape the costs of a 'somatic duty' and selfishly improve its reproductive fitness. Because multicellularity is a positive adaptation (Buss, 1987; Maynard Smith & Szathmary, 1995), both random damage and adaptive change will tend to be in the direction of impaired integration and organismal disharmony.

Analogy with parasitism

The process of an organism being overwhelmed by endogenous parasitism of its component parts is analogous to the process by which an aging organism is overwhelmed by exogenous parasites. It has been suggested that parasites - a term which includes pathogens such as bacteria and viruses - are the main force of mortality in all but the smallest animals and those in the least hospitable of habitats (Hamilton, 1980; Ridley, 1993).

The suggestion is that, in most circumstances, most organisms are most likely to be killed by parasites. The reason is that parasites are able to out-evolve their hosts because they are usually more numerous, shorter-lived, and multiply more rapidly. A parasite will typically reproduce orders of magnitude more often than its host over a given time span. Within-host selection may occur in the lifespan of the host, when selection can operate on the parasite but not the host (Ridley, 1993; Bell, 1993). Host and parasite are therefore engaged in an 'arms race' of co-evolution (Van Valen, 1973). The host organism may start its lifespan with advantages such as an immune system; but no matter how sophisticated, this system will have a limited potential range of anti-parasite adaptations. Rapid replication means that a parasite can evolve in such a way that it eventually overcomes its host's defences. This is an arms race in which the odds become progressively stacked in favour of the parasite with time. The phenomenon of endogenous parasitism suggests that very similar arguments apply to replicating somatic lineages: in 'competition' with the organism the faster-replicating lineages would be expected to undergo an adaptation akin to 'within-host' selection.

The analogy between endogenous parasitism and exogenous parasitism goes further, in that somatic lineages will progressively evolve in the direction of overtly parasitic behaviour. Somatic components have a variety of functions, ways in which they serve the purposes of organismal reproduction, all of which constitute costs to their own lineages (Buss, 1987). Somatic lineages are forced to bear these costs by the mechanisms which impose co-operation and organismal integration; but any evolved somatic variants which enhance replication and avoid the costs of 'somatic duties' will have a selective advantage over their neighbours. Organismal components will tend to evolve into 'free riders' which exploit the advantages of an intra-organismal environment without paying the price of contributing to organismal upkeep. An extreme scenario occurs when somatic components actually harm or kill the organism as a consequence of pursuing their own 'selfish' replicative goal of maximising the frequency of their lineal descendants (as in the case of malignant tumours).

Clearly, the existence of organisms as such is predicated upon mechanisms having evolved for controlling free-riding and exploitation throughout development, and at least until the time for organismal reproduction. Equally clearly these 'salutogenic' integrative mechanisms (Charlton, 1994; Charlton, in press) will become less effective over the lifespan of the organism, given the existence of natural selection among replicating components in the face of a fixed repertoire of integrative responses. The phenomenon of free-riding would be expected to increase throughout the lifespan of an individual, just as organisms tend to carry an increasing parasite load with age (Ridley, 1993). There is a further analogy with progressively increasing parasite infestation as a proposed mechanism of senescence (Bell, 1993). The accumulation of free-riding elements would reduce effective co-operation and induce homeostatic dysregulation, impair organismal efforts to mount an integrated adaptive response to external environmental challenges, impose a drain on organismal vigour by its exploitation of the somatic environment, and may (e.g. by the development of malignancy) itself constitute an internal environmental challenge to organismal survival.

However, a crucial difference between endogenous parasitism and exogenous parasitism is that selfishly adapted variants are capable of transmission only to their own lineal descendants within the host organism, and within the lifespan of the host; new hosts cannot be 'infected'. (Unless - of course - the replicating component evolves to form a true (exogenous) parasite - as may for example have occurred with some viral gene sequences; Buss, 1987.) The process of endogenous parasitism must therefore start afresh with each new generation of the host organism, and exploitative adaptation in somatic lineages would typically be host-specific.

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Senescence

Endogenous parasitism may be seen as a potential mechanism of senescence; one which would be unavoidable given sufficient lifespan to operate. If organismal existence is predicated upon the ability of its integrative systems to enforce co-operation, then the finite capacity of the organism to achieve integration must eventually be overwhelmed by the open-ended evolutionary capacity of the somatic components. The process seems inevitable in a qualitative sense; but is not necessarily quantitatively important in any given instance.

For instance, the mortality rate of many organisms under 'natural' conditions may be so great that there is no opportunity for endogenous parasitism to occur to any significant extent. The rate of replication of lineages may, in these circumstances, be too low to allow significant numbers of heritable divisions during the lifespan. In other words, an organism may be killed by predator, exogenous parasite, hardship or accident before any of its components have had the opportunity to undergo parasitic adaptation.

The validity of my argument in favour of the *inevitability* of senescence due to endogenous parasitism is dependent upon how senescence is defined. Although senescence is an organism-level phenomenon (often defined as a progressive increase in mortality rate with age); I suggest that organismal individuality must ultimately be assumed to inhere in genotype rather than phenotype, and therefore that senescence must operate at the level of genes.

The problem is to differentiate between an organism and a colony of organisms. In order to be considered non-senescent, an organism should - I suggest - be capable of maintaining its original genetic endowment on an indefinite basis. In this sense, the commonly cited instances of supposed 'immortality' in organisms (eg. those listed in Rose, 1991) can more plausibly be interpreted as the mere persistence of a physical form by a colony of genetically heterogeneous components. In other words, this kind of 'immortality' may be of the nature of persistence of a species rather than the persistence of an individual. Endurance of physical form may be made possible by non-integrative mechanisms: for example, certain long-persisting plant phenotypes may be relatively resistant to the ill effects of endogenous parasitism due to their rigid cell walls which could enable sequestration of potentially 'parasitic' variants (Buss, 1987; Finch, 1990).

An important distinction between the phenomenon of endogenous parasitism and most other evolutionary theories which purport to explain senescence is that endogenous parasitism postulates a *quasi-purposive* mechanism (i.e. natural selection) as the cause of senescence. Most other theories see senescence as caused by random, entropic mechanisms (Rose, 1991). Current theories of senescence usually favour an explanation in terms of progressively reducing selection pressure on the organism with time, and stress the diminishing reproductive returns and high maintenance costs of *not* aging - senescence is seen to be due to the *lack* of natural selection among those of post-reproductive age (Rose, 1991; Bell 1993). Such theories emphasise the tendency of organisms to accumulate random damage of various kinds (whether chemical, genetic, mechanical, or whatever; Strehler, 1977; Comfort, 1979; Timiras, 1988; Finch 1990). Reduced selection pressure on the organism with time *allows* senescence to occur, because older organisms have already reproduced the bulk of their offspring, and further survival would carry little advantage (Kirkwood & Holliday, 1979; Kirkwood and Cremer, 1982; Rose, 1991). The longer the lifespan, the smaller becomes the marginal benefit of producing more offspring.

This general view sees senescence as a non-purposive accumulation of random errors; an entropic process which might, in principle, be preventable, repairable or reversible; but which is not prevented in the natural state because any advantage of an extended lifespan for increasing gene frequency in future generations is outweighed by prohibitively expensive 'maintenance' costs in terms of surveillance and repair. In effect, the reproductive benefits of adding extra increments of increased lifespan are progressively diluted because each incremental unit constitutes a diminishing proportion of lifespan, while the maintenance costs of each extra incremental unit remain constant. For instance, 'somatic mutation' theory sees senescence being due to an accumulation of random genetic mutations in the soma; which is, in any case, 'disposable' after reproduction has already occurred (Kirkwood & Holliday, 1979; Kirkwood and Cremer, 1982).

Endogenous parasitism takes a different view by emphasising that somatic mutations will themselves be subject to selection pressure from the integrative mechanisms of the organism, and the least adaptive mutations will be culled preferentially in each generation. There will not only be an accumulation of *random* mutations, but also (or instead) a progressive enrichment of the soma by *adaptive* mutations: mutations which have been selected on the basis of reproductive success: i.e. their capacity to escape integrative mechanisms or shed somatic duties. Senescence due to endogenous parasitism would eventually occur *even if* non-senescence did happen to be of selective advantage to the organism. The integrative mechanisms that hold the organism together cannot do so indefinitely in the face of progressively increasing competition between replicating components.

If somatic mutation posits that a disposable soma is 'allowed' progressively to accumulate random entropic damage as a consequence of declining selection pressure on the organism with age; then endogenous parasitism suggests an alternative explanation for senescence in terms of an *increasing force of selection* on the organism caused by progressive evolution of its component parts towards autonomy. Increased force of selection is due to the biotic environment becoming more hostile (Bell, 1993) - endogenous parasitism means that the environment *within* an organism would deteriorate progressively due to increasing levels of free-riding, parasitism and exploitative behaviour among component parts such as somatic cell lineages, mitochondria or gene sequences. Due to the inevitability of this process, senescence is not preventable, even in principle, by organismal mechanisms (although the potential for repair by an external agency remains a theoretical possibility).

Conclusion

Endogenous parasitism is not being suggested as the rate-determining mechanism of senescence, but as implying that senescence and eventual death is inevitable in any organism with replicating somatic components *given sufficient time.* In other words, the organism is an entity which will progressively (although perhaps very slowly) self-destruct from the moment of its formation. This description does not, of course, rule out other mechanisms of senescence. Indeed, endogenous parasitism might, for instance, be expected to interact synergystically with the random accumulation of genetic damage to salutogenic systems.

Endogenous parasitism describes a process which would eventually lead to senescence; a 'purposive' mechanism driven by the adaptive evolution of replicating component lineages. This view of senescence is in line with the current emphasis on competitive co-evolution and 'Red Queen' mechanisms (rather than the external environment, or random events) as the main constraint operating on living systems (Van Valen, 1973; Ridley, 1993); as well as the idea that health is an active process which requires to be maintained against endemic forces of disintegration (Charlton, 1994; Charlton, in press). The suggestion is that the most important restriction on one living thing is another living (or at least replicating) thing. Typically, organisms are killed by reproducing and evolving competitors, rather than by the blind workings of physical nature.

Although I have argued that, in principle, it seems likely that instances of endogenous parasitism should be observable in long-lived organisms such as the human, there is - unsurprisingly - currently little specific evidence that this phenomenon is a cause of senescence. However, experimental evidence to test this theory is unlikely to emerge unless it is sought; and the main purpose of this paper is to provide a stimulus, framework and rationale for such experiments.

Endogenous parasitism is suggested as a basic biological process: that tendency of replicating organismal components to evolve 'parasitic' adaptations during the lifespan of their 'host' organism. The process is progressive and ends in terminal dysregulation. By this argument, primary cancers are merely the tip of an iceberg: the most visible aspect of a much more widespread process. Endogenous parasitism implies that senescence may be delayed but cannot be permanently prevented; and organismal immortality is precluded.

Acknowledgements: I am very grateful to Matt Ridley, Tim Horder, Jonathan Rees, Laurence Hurst, Dorian Pritchard, Adam S Wilkins and three referees from *Evolutionary Theory* for their help in preparing this paper.

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