



# Osteoarthritis: An example of phenoptosis through autonomic dysfunction?

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**Summary** Phenoptosis, the programmed death of organisms akin to cellular apoptosis, constitutes a type of Darwinian selection that enhances inclusive fitness. It provides a means by which senescent and pre-senescent members can self-terminate if they have incurred sufficient cumulative stress such that their continued survival detracts from inclusive fitness. Sepsis, vascular disease, menopause, cancer, and aging all represent examples of phenoptosis at work. We previously proposed that feed-forward autonomic dysfunction fundamentally drives phenoptosis in all its guises. Accordingly, we now postulate that osteoarthritis defines a type of biomechanical phenoptosis, mediated by feed-forward autonomic dysfunction, and manifested through joint destruction associated with fitness disadvantages. Biomechanical capability plays a significant role in evolutionary fitness, and sustained joint insults such as immobility or undue biomechanical stress may serve as proxies for inferior fitness. By both hindering an individual's ability to compete for energy and increasing that individual's vulnerability to predation, feed-forward joint destruction may facilitate adaptive phenoptosis among impaired or senile members. Empirical data suggests that contrary to common belief, heavy joint use does not necessarily cause osteoarthritis, whereas immobility and neuropathy can predispose to the condition. From a Darwinian perspective, another process mediated by sympathetic activity, the alarm cry of attacked prey, simultaneously promotes the escape of kin while attracting predators and scavengers. By effectively enabling the martyrdom of biomechanically-challenged individuals, osteoarthritis may serve to optimize system energy efficiency in a similar fashion. This framework may generalize to other situations where regenerative capacity dissipates in conjunction with maturation, typically leading to fibrosis. By allowing environmental pressure to sort the phenotypes, imperfect repair mechanisms may accelerate adaptation and optimize long-term inclusive fitness for all individuals. As the basis of competition shifts from biomechanical to cognitive skills, and as novel triggers for physical stress emerge, osteoarthritis may now represent a modern maladaptation.

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## Hypothesis

Osteoarthritis constitutes a disease where joint cartilage erodes, accompanied by changes in adja-

cent bone and variable degrees of inflammation and thickening of the surrounding soft tissue. It can develop either as a secondary process due to some form of antecedent insult, typically trauma [1], or as a primary process with no known inciting event [2]. Its incidence and prevalence increase with age, and represents a significant source of morbidity [3]. Theories for the mecha-

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nistic basis of osteoarthritis have ranged from chronic trauma to joint misalignment [4–8]. The teleologic basis of osteoarthritis remains unknown, but proposed paradigms generally focus on the notion of a maladaptive biomechanical epiphenomenon related to chronic insults associated with aging.

We hypothesize that osteoarthritis may represent a biomechanical mechanism of adaptive phenoptosis, the programmed death of organisms akin to cellular apoptosis that enhances inclusive fitness.

## Phenoptosis

### Phenoptosis and inclusive fitness

Why joints enter a cycle of destruction rather than one of regeneration remains unclear. While the temptation exists to ascribe the phenomenon to a lack of selection pressure, ontologic and paleopathologic data suggest otherwise. The ability to regenerate cartilage has been observed in nature, particularly early development, so a lack of effective biologic programs does not furnish a satisfying explanation [9,10]. The fossil record also suggests that osteoarthritis represents an ancient condition, dating at least to the Mesozoic era, and seen in many diverse species [11,12]. That osteoarthritis might represent a programmed adaptive process remains unexplored.

Phenoptosis, the programmed death of organisms akin to cellular apoptosis, constitutes a type of Darwinian selection that enhances inclusive fitness [13,14]. It also supports the central tenets of group selection [15]. Phenoptosis provides a means by which senescent and pre-senescent members can self-terminate if they have incurred sufficient cumulative stress such that their continued survival detracts from inclusive fitness.

Phenoptosis appears to occur throughout the full range of organismal complexity. Sporulation of *Bacillus subtilis* causes lysis of the parent cell. In plants, normally long-lived species such as bamboo die after production of seeds. Phenoptosis includes the sacrificial offering of the male body to the female during the mating of redback spiders or praying mantids, since the male contributes resources directly to its offspring. Phenoptosis also encompasses sudden post-reproductive death in salmonids and marsupials, as well as the cessation of feeding by the female octopus following birth of its progeny, since the parents indirectly transfer the food chain to their offspring. Sepsis, vascular disease, menopause,

cancer, and aging all represent examples of phenoptosis at work. We previously posited that feed-forward autonomic dysfunction may fundamentally participate in all mechanisms of phenoptosis [16].

### Osteoarthritis as a systemic condition

Emerging evidence suggests that osteoarthritis may represent a systemic phenomenon rather than a local response [17,18]. Furthermore, examination of skeletons in the paleopathologic record suggests that osteoarthritis may affect a broader range of joints than those for which symptoms typically manifest [17,19]. Indeed, poor correlation frequently exists between the severity of symptoms and the degree of joint damage witnessed on radiologic examination in humans [20–22]. Moreover, autopsies have found articular lesions in individuals who otherwise showed no evidence of disease [23]. In individuals immobilized for extended periods or afflicted with neuropathy, limbs develop changes in cartilage indistinguishable from those found in osteoarthritis [24–27]. Recent data suggests that sympathetic bias may play a critical multifactorial role in the pathogenesis of osteoarthritis [28,29]. The observation that osteoarthritis may be a systemic phenomenon, rather than a local one caused by the accumulation of chronic biomechanical insults alone, hints at the possibility that the condition may arise as a functionary of a larger adaptive process. That osteoarthritis may involve sympathetic bias, a common pathway seen in other mechanisms of phenoptosis [30], only provides further support for this proposition.

Extant disease models exist for autonomic dysfunction and its potential role in promoting osteoarthritis. In Charcot's arthropathy, or neuropathic joint syndrome, individuals who experience denervation to a particular joint secondary to diabetes or traumatic nerve damage develop changes similar to that found in osteoarthritis [31]. Most notably, autonomic dysreflexia has been shown to predispose to this finding [32]. Lesions similar to those found in osteoarthritis also occur in patients with familial dysautonomia [33]. Additional evidence for the potential role of autonomic dysfunction comes from the condition known as reflex sympathetic dystrophy. In this case, known autonomic derangement secondary to trauma causes remodeling of local soft tissue and bone, indicating that alterations in autonomic innervation can produce such changes by itself. Similar mechanisms may also operate in the case of increased bone resorption in sepsis [34].

## Osteoarthritis as a mechanism of phenoptosis

Biomechanical skills play a significant role in evolutionary fitness; and immobility, biomechanical stress, or other manifestations of chronic joint dysfunction may serve as proxies for inferior fitness. By hindering the ability to compete for energy and increasing vulnerability to predation, osteoarthritis may represent feed-forward joint destruction that facilitates predation of impaired or senile members. While the impaired ability to compete in the energy landscape may appear to reduce fitness, the elimination of that individual may paradoxically increase inclusive fitness. For instance, such behavior may protect related kin from predation or enhance the ability to compete for food. As a behavioral example of the former, many species exhibit an alarm cry when attacked by predators [35]. The alarm call of the attacked prey not only promotes the escape of kin, it also attracts additional predators. Certain fish such as fathead minnows will release chemicals that function in a similar fashion [36]. As an example of the latter, injured canids are removed from hunting packs and are left to fend for themselves. The reduced energy effort of prey and predators alike may optimize the system energy efficiency and evolutionary fitness for all involved. The alarm call represents yet another potential mechanism of phenoptosis mediated by sympathetic activity [30]. By enabling the martyrdom of biomechanically-challenged individuals, osteoarthritis may serve to optimize system energy efficiency in a similar fashion.

However, modern humans have substantially remodeled their own environment such that the basis of competition has shifted from the physical to the cognitive arena. Fitness has come to increasingly depend on intelligence rather than biomechanical prowess. The profile and extent of biomechanical activity has concomitantly undergone significant change. Nonetheless, the factory settings of our body may reflect adaptive needs of a bygone era, such that the alterations of modern biomechanical activity may trigger joint dysfunctions in a maladaptive fashion. Many modern biomechanical functions, postures, and exercise regimens are non-ergonomic and can produce unnatural joint stresses, instability, and alignment, all of which converge to promote osteoarthritis. Other behavioral and physiologic triggers of systemic sympathetic bias, including aging itself, [37] may contribute to the systemic pathophysiology of osteoarthritis.

## Implications

### Orthopedic mechanisms of phenoptosis

In this paper, we examined the possibility that orthopedic dysfunction may represent another manifestation of autonomic dysfunction as phenoptosis. Cartilage defects and joint injury may function as sensors of biomechanical stress and poor orthopedic fitness for prevailing environmental conditions. The low prevalence of osteoarthritis manifesting in particular joints, such as the ankle, may reflect both the adaptive features of particular joints to accommodate ongoing trauma and the lack of information utility for signals emanating from such sites because of the high noise component. This lack of information utility may also explain why bony changes in certain locations such as bunions on the medial aspects of the feet exert minimal impact on physiology. Ultimately, however, osteoarthritis may represent a centrally-initiated mechanism by which age-related autonomic dysfunction can promote phenoptosis even when antecedent joint injury has not occurred.

Bony fractures represent another form of common orthopedic insult. Fractures not only impair biomechanical functions such as mobility, but also incite a fierce pain response with sequential violation of the periosteum and marrow. Both responses may contribute to phenoptosis by enhancing the likelihood of successful predation. Of course, not all individuals with fractures necessarily succumb, and in time, most fractures will heal, as if individuals who survive the momentary disadvantage undergo an endorsement of their compensatory prowess. This tactical validation of the individual may become superseded by the strategic imperative of the group, as fractures heal poorly in older individuals, often producing iterative system failures that lead to rapid demise [38–42]. The orthopedic example may extend to other physiologic responses that tend to limit or inhibit function, such as scar formation in response to soft tissue and organ injury. The tendency for fibrotic responses to occur later in life suggests the superimposition of a strategic imperative. Age-related decline in DNA repair mechanisms with aging may represent a similar phenomenon at a cellular scale. The decline of skeletal muscle mass, bone mineralization, and sensory functions such as hearing and vision begins at the onset of adulthood and likely contributes to vulnerability to predators [43–45].

## Common pathways of phenoptosis

For more than a century, a debate has raged as to whether death constitutes an intentional ontogenetic program, the so-called Wallace–Weissman hypothesis, or the passive result of an inexorable accumulation of defects. By accounting for benefits to kin, the former assertion becomes more plausible [46–48]. The inability to identify definable discreet mechanistic pathways for programmed death has provided a major source for criticism of this theory. Although evolutionary dynamics and pluralism may both contribute to the Darwinian value of phenoptosis, intuitive appeal persists in the notion of an oligarchy of functional hubs underpinning the many proximate mechanisms of phenoptosis. Indeed, given its processes' central roles in apoptosis, the mitochondrion may represent an ideal candidate to serve as one such hub on the level of the organelle [43]. The induction of cellular damage by reactive oxygen species has been noted to be a mechanism of self-termination that encompasses all scales of biology [43,49,50]. However, we believe that identification of hubs that operate on the level of systems as opposed to that of subcellular components may afford greater potential utility for modification and correction. Endocrine pathways, particularly those involving reproduction and circadian rhythms, have already been implicated in this regard [43,51–54].

In a series of articles published in this journal, we proposed that the autonomic system serves as a fundamental common pathway that regulates a host of seemingly disparate mechanisms that culminate in death, including menopause, cancer, sepsis, vascular disease, sudden cardiac death, organ failure, renal failure, and aging [37,55–59]. Under varying conditions of stress, autonomic dysfunctions may arise on an acute and chronic basis, producing secondary sequelae that eventually prove fatal. Autonomic dysfunction also provides an opportunity to model behavioral mechanisms of self-termination such as the cry response during traumatic injury.

Although the compendium of named medical diseases appears extensive, these diseases manifest through an abbreviated roster of symptoms, and, most notably, the autonomic system participates in all of them. While research has largely focused on the complexity of disease, autonomic dysfunction with respect to phenoptosis may provide yet another example of cellular automata where apparent complexity constitutes an emergent property of simple underlying rules [60].

Although unknown at this point, autonomic dysfunction could ostensibly arise through a number of mechanisms, including timed immolation of a central regulator (apoptosis of the suprachiasmatic nucleus), autocatalysis of autonomic regulatory loops, and/or retraction of hegemonic control over end-organs [37].

What we term autonomic dysfunction may merit consideration as a function unto itself—as opposed to something which constitutes a disease state, it may simply represent a process invoked under a particular set of circumstances—that where a specific individual has persisted beyond its ability to contribute to group fitness. The autonomic nervous system serves to amplify those physiologic perturbations that signal this lack of utility, and those changes, thus amplified, may cause sufficient interference with overall physiologic function so as to produce the demise of the organism in question. Joint changes may constitute one such set of perturbations which sympathetic overdrive then magnifies into full-blown osteoarthritic sequelae and effective phenoptosis.

## Opportunities for reprogramming

The recognition that death may represent a programmable process implies that the option may exist to rewrite its code and thereby extend life. Modern medicine has largely focused on error correction, but as attention shifts from individual diseases to the central hubs of phenoptosis, the possibility of reprogramming the existing human lifecycle will increasingly lie within reach. Many examples of reprogramming behavior exist in nature. For example, cells will trigger apoptosis, or programmed cell death, in response to metabolic stress or viral infection. Cells also routinely exhibit the capacity to reprogram themselves and escape their apoptotic fate—witness the millions of new cancer patients a year. Cancer cells fail to achieve immortality largely due to the inhospitable nature of their host. Aspiring cancer cells adopt a myriad of different strategies for reprogramming themselves so as to avoid apoptosis, suggesting both the relevance of convergent evolution and the potential robustness of any approach to reprogramming the human life cycle. Ironically, cancer, the scourge of humanity and a major contributor to phenoptosis, may hold the keys to human longevity.

Whether multicellular organisms have both the potential and the motivation to intrinsically reprogram their lifecycles remains unclear. However, with identification of central hubs of phenoptosis

and development of methods for reprogramming, the potential for external intervention appears significant. We believe that the autonomic nervous system defines a central hub of phenoptosis and that appropriate treatment of autonomic dysfunction—many of whose manifestations display characteristics of a nefarious feed-forward cycle—can produce substantial remodeling of the human life-cycle. Appropriate neuromodulation via pharmacologic, behavioral, and device-based routes should afford opportunities to extend life. Creating artificial contexts that simulate the systemic conditions of youth have already shown promise [61], and may offer additional strategies to restore function and sustain existence.

### Post-Darwinian era

When viewed from the perspective of systems, death enables the efficient acquisition of useful traits serially over generations. Individuals devote their lives to sampling the environment for innovations that can enhance fitness, and sexual or asexual reproduction generates newer models that incorporate such innovations. The progenitors recycle themselves by returning themselves through the local ecosystem and thus avoid competing with their successors. Darwinian forces of variation and natural selection govern this iterative process.

When biochemical systems such as genes, proteins, and other biomolecules encoded advantageous traits, Darwinian evolution ruled the day. However, in the post-Darwinian era, memes, or ideas, have increasingly displaced biochemical codes as the basis of fitness advantage. Unlike genes, memes cost little to acquire or distribute, both vertically across generations in either direction, or horizontally to peers. Memes, like biochemical codes, constitute embodiments of energy, such that erasure of an idea releases energy [62]. In this context, phenoptosis has become a vestigial process. Memes do not require life-death recycling for processing and accumulation. Indeed, they would undergo far more efficient assimilation if the potential existed for longitudinal acquisition within a single individual.

As both ideas and the humans who translate and realize them persist to an increasing degree, the rate of innovation may accelerate. The experience of the last two centuries provides evidence for this trend, as the twin forces of health care and general prosperity have propelled each other iteratively in a virtuous cycle. Appropriate healthcare consumption has contributed to lifespan gains and prosperity. Over the past century, those who made many of the major discoveries and inventions that con-

tributed to prosperity did so at ages which may not have been reached without the expansion of health and lifespan. As for concerns regarding indefinite lifespan causing systemic stress secondary to overpopulation and overconsumption of resources, empirical evidence suggests that with the extension of lifespan comes delay of reproduction and decreased replacement rate beneath of unity. The finite period of female fertility may represent a natural control system that anticipates the coming era of indefinite lifespan.

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