What if there’s no such thing as “aging”?

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ABSTRACT

Are diseases caused by aging? What are the mechanisms of aging? Do all species age? These hotly debated questions revolve around a unitary definition of aging. Because we use the word “aging” so frequently, both colloquially and scientifically, we rarely pause to consider whether this word maps to an underlying biological phenomenon, or whether it is simply a grab-bag of diverse phenomena linked more by our mental associations than by any underlying biology. Here, we consider how the presence of the colloquial word “aging” generates a cognitive bias towards supposing there is a unitary biological phenomenon. We ask what kind of evidence would support or refute that idea, and subsequently show clear evidence at multiple levels that aging is not a unitary phenomenon. In particular, the known aging pathways lead to heterogeneous outputs, not a single coordinated phenomenon. From levels ranging from cellular/molecular to clinical to demographic to evolutionary, we show how the supposition that aging is a unitary phenomenon can mislead and distract us from asking the best questions. For major sub-disciplines of aging biology, we show how going beyond the notion of unitary aging can hone the paradigm and help advance the pace of discovery.

1. Introduction

Some 23 years ago, Peto and Doll (1997) argued that aging is not a biological phenomenon. Their argument – that there are not necessarily common mechanisms underlying the major aging-related chronic diseases, such as cancer, but rather a suite of individual disease processes synchronized via natural selection – would surely find little favor today. Common mechanisms, including inflamm-aging, mitochondrial dysfunction, and cellular senescence, are now thought to be well established (Kennedy et al., 2014; López-Otín et al., 2013). In retrospect, the argument seems ignorant of aging mechanisms. Here, we argue that Peto and Doll were right, but for the wrong reasons: that our more detailed knowledge of aging mechanisms is increasingly showing that there is no unitary phenomenon usefully summarized with this word.

What is aging? This question, at the heart of our field, has received a great deal of attention, and many definitions, implicit or explicit, have been proposed (Comfort, 1979; Gladyshev, 2016; Kuo et al., 2020; Rose et al., 2012; Shefferson et al., 2017). (Here, we use the term “aging,” though all our arguments equally apply to the term “senescence,” which is favored by some (e.g. Shefferson et al., 2017).) A coherent definition is even essential for the field: there are intensive efforts to measure aging, to slow aging, and to treat aging, and it will be impossible to know if they are succeeding without a clear definition of the subject of our research. Is it accumulation of molecular damage? Is it loss of function with increasing age? Is it increases in mortality (or decreases in reproductive rate) with age? Underlying the discussion to date is an assumption so basic it goes unnoticed: that there is an underlying biological phenomenon of aging. We have a word for aging, and therefore we assume that science will accommodate us, providing a phenomenon to match our word. And in a colloquial sense this is certainly the case: no one can doubt that we see ourselves, our relatives, and our friends age. But is this colloquial usage scientifically justified? Is there really a “thing” or a phenomenon we can call aging? We argue here that our understanding of the biology is now sufficient to say definitively that this is not the case, that from a scientific perspective there is no such thing as aging, but rather a collection of disparate phenomena and mechanisms – sometimes interacting with each other – that relate in one way or another to our colloquial sense of the word. Accordingly, our desire to find a single reality of aging has created a great deal of confusion in the field.

We are well aware that not all researchers in our field will like our thesis here: our identity as “aging researchers” is tightly wrapped around the notion that there is a phenomenon of aging. However, we do not

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believe there is a need to feel any existential threat from this idea, which is in some sense a natural extension of the multi-factorial hallmarks/pillars framework (though not an inevitable one – see below). Rather, we think that being more careful about our underlying assumptions, and how they do or do not conform to biological reality, can only make us better researchers. The field of aging research can still exist, but with a more nuanced understanding that we are not studying a single biological phenomenon, but an assortment of loosely related processes that we find convenient to lump together.

2. Linguistics, the definition of categories, and the word “aging”

Linguists have long recognized that mental classifications, which can vary across cultures, are reflected in vocabulary, and that the presence of words in a vocabulary creates the perception that reality is organized in line with lexical ontology (Goddard and Wierzbicka, 2013; Hussein, 2012; Kay and Kempton, 1984). For example, in Japanese, water does not exist. What Westerners would call water, the Japanese divide into oyu (warm-to-hot water) and mizu (water-that-is-not-hot). You take a bath in oyu and use it to make tea. Mizu fills the oceans and is refreshing to drink when it’s hot out. Japanese scientists certainly do acknowledge that there is a single chemical structure, H₂O, that is shared by both oyu and mizu, and everyone knows that there’s a bit of ambiguity when you put some mizu on the stove and start to boil it. But for a Japanese person in her daily life, there’s no such thing as water (in our sense), and all H₂O encountered gets mentally classified as oyu or mizu.

Conversely, in Japanese there are neither rats nor mice, only nezumi, a single word that covers mouse-and-rat-like rodents. Here, science would seem to side a bit more with the Japanese: while there are two distinct genera of the muridae family that describe mice and rats, Mus and Rattus respectively, they are relatively closely related, and there are many other rodents that most people would classify as a mouse or a rat that are relatively distantly related to both genera, enough so that Wikipedia has an entire section on “Types of animals known as mice” (https://en.wikipedia.org/wiki/Mouse#Types_of_animals_known_as_mice). Yet English speakers who are not mammologists will nonetheless immediately classify any relevant rodent as a mouse or a rat, despite the fact that neither is a real biological category.

In the cases of both water (oyu/mizu) and rodents (nezumi), science has provided clear answers as to the underlying reality, and colloquial uses of the relevant terms can coexist with the technical understanding with a minimum of tension or confusion. In the case of aging, the scientific consensus on the underlying reality is still evolving and fast moving. The subject is substantially more complex than water chemistry or rodent phylogeny, and there are not (to our knowledge) major linguistic differences for translations of “aging” across languages/cultures. Perhaps for these reasons, we still use the words “aging” and “senescence” as if these corresponded to a single underlying reality, a single phenomenon to be understood. While some definitions of aging might be able to englobe a wide array of these phenomena (e.g., “inexorable declines in organismal function associated increasing chronological age”), this doesn’t mean they describe a useful scientific concept. As we make clear below, the attempt to arrive at a general definition does more harm than good.

Accordingly, we are not arguing that the term “aging” should never be used. It will certainly continue to be used colloquially, and it may be useful to retain it to describe our field, or in certain situations when the very broad set of phenomena is really of some interest. But we believe scientists should move away from the term, particularly when they are only referring to a subset of the phenomena in question. For example, when we mean “damage accumulation,” we should say this rather than “aging.” Likewise, when we mean age-associated increase in mortality risk, we should find a term such as “demographic aging” or “Gompertzian mortality patterns.”

Below, we show why aging is not a single phenomenon, we show how the use of a single term has led to confusion about the underlying reality in a number of subfields, and then discuss the implications.

3. What would it mean for aging to exist?

Philosophers have debated whether there is an objective reality that is knowable by humans independent of cultural and psychological biases (Boghossian, 2010). The enterprise of science assumes that there is, but this does not imply that science is free from psychological and cultural biases (Boghossian, 2010). We wish to argue that the concept of “aging” does not have an existence independent of such biases, and that it may in fact be misleading us into missing key aspects of the underlying biology that might indeed be understood free of such biases. In order to make that argument, we first need to establish what it would mean for aging to exist as a single, objective phenomenon, what we refer to as a “unitary phenomenon.”

Some 20–30 years ago, many researchers in the biology of aging believed aging was due to a single mechanistic process, such as oxidative stress (Harman, 1956), inflammation (Franceschi et al., 2000), or telomeres (Levy et al., 1992). Currently, views have changed substantially, with the emergence of a near-consensus that aging is multifactorial and heterogeneous (Taffett, 2003), as described by the hallmarks (López-Otín et al., 2013) and pillars (Kennedy et al., 2014) frameworks, among others. Indeed, it could be argued that much of the field already agrees with our core thesis, having largely accepted the framework of the hallmarks/pillars, though few of the researchers that accept that framework would likely be willing to state that “there is no such thing as aging.” However, even if aging is multifactorial and heterogeneous, it could still be considered a unitary phenomenon if any of the following applied:

1. There were a single upstream mechanistic cause, universally present wherever aging is considered to exist.
2. There were a single gene or pathway that exerted exclusive control over aging, wherever aging is considered to exist.
3. The heterogeneous/multifactorial mix were identical across all species considered to age, and absent in those that do not.
4. There were a uniform demographic signature across all species considered to age, and absent in those that do not.
5. A number of genes or pathways had evolved specifically to jointly adjust aging in a coordinated fashion, in the evolutionarily teleological sense.

4. Biological reasons to believe aging is not a unitary phenomenon

While our linguistic argument is, to our knowledge, novel, our biological argument is not. Many authors have remarked on the heterogeneity of aging in different ways (e.g. Franceschi et al., 2017a; Mitnitski et al., 2017; Rattan, 2008). Medvedev (1990), in reviewing more than 300 theories of aging, stated:

“It is obvious now that the expectation that a really unified, or a single ‘main cause’, theory of ageing would eventually emerge is not realistic. Many theories co-exist because they do not contradict each other, or because they try to explain different and independent forms of senescence.”

Similarly, many more recent papers, notably the hallmarks/pillars framework, highlight the multi-factorial nature of aging (Kennedy et al., 2014; Kirkwood, 2005; López-Otin et al., 2013). For example, Rattan (2006) integrates many of the known mechanisms into a multi-level model of homeodynamic loss in aging. Gladyshev (2016) argues that aging can be considered as the accumulation of the deleterium – the set of “cumulative, deleterious age-related changes.” In some sense we cannot disagree, and the scientific substance of Gladyshev’s arguments is excellent, but the definition is in the end circular: it is essentially a
concession that the biological nature of these deleterious processes is too heterogeneous to be defined by any biological common features, mechanisms, or control switches. Whether it is the hallmarks/pillars, the deleteriome, or some other multi-factorial framework, the question then is whether this means that there is no such thing as biological aging.

To answer this, we should evaluate the five propositions above. Several can be excluded summarily, or nearly so. For #1, it seems highly unlikely (though not impossible) that so many biologists working so hard for so long have missed a single upstream cause that would neatly unify our field. For #2, multiple genes and pathways have been identified that interact to influence aging-related processes (Bitto et al., 2015). For #3, it is clear that the mix of mechanisms varies dramatically across species (Cohen, 2017).

The fourth proposition is not so easily excluded. In fact, there is a reasonable argument to be made that aging could be defined as an exponential increase in age-specific mortality. Substantial work has gone into showing how aging-like demographic patterns can be simulated (e.g. Gavrilov and Gavrilova, 2001), or emerge from simple underlying processes (Karin et al., 2019). Nonetheless, an increasing number of studies are publishing demographic data for a wide array of species across the tree of life, and these data are showing that the demographics of age-specific mortality are highly heterogeneous (Baudisch et al., 2013; Jones et al., 2014; Shefferson et al., 2017). Even among species that show increases in mortality with age, the increase is not necessarily exponential, and not necessarily smooth. While this might be explained by appropriate models of upstream processes (Le Cunff et al., 2014), the resulting demography is still heterogeneous. Accordingly, by all indications, either there is not a stable emergent demographic process that could be labeled aging, or the definition of which species “age” would need to be restricted to the point where the word would lose most correspondence to our intuitive sense of it.

The fifth proposition is the most problematic and will be treated in detail. Our increasing knowledge of the aging process, genetically and mechanistically, allows us to build a model of how different aging pathways integrate signals. The starting point is to consider that almost all biological regulation occurs in the context of the complex systems formed by biological networks, either (a) to structure development, or (b) to maintain homeostasis/allostasis, in the broad sense of allowing an organism to develop and to adjust appropriately to its internal and external conditions (Cohen et al., 2012). (Here we use “homeostasis” in this broad sense, well aware that it is not static, and can be predictive as well as reactive (Sterling, 2020).) Accordingly, aging pathways such as IGF signaling and sirtuins also almost certainly evolved to have roles in maintenance of homeostasis (though also with roles in development,

![A model of how pathways thought to influence aging integrate information.](image)

Fig. 1. A model of how pathways thought to influence aging integrate information. On the left are various signals from the internal and external environment. In the center are known aging pathways. Obviously, they influence each other, though this is not shown. On the right are outputs – downstream targets. Many of the potential links are well-documented, though others remain hypothetical. Crucially, this model permits differential and flexible adjustment of the outputs.
which we will not consider here).

Martin (1997), expanded on by Partridge and Gems (2002), proposed the model of public versus private aging mechanisms, in which the conserved signaling pathways (IGF, sirtuins, etc.) are upstream regulators of multiple downstream processes. Each species could thus have its own set of aging mechanisms, but the conserved pathways are the upstream regulators adjusting aging rate. This is much like the vertebrate and arthropod eyes, which evolved independently but are nonetheless controlled during development by an orthologous gene (PAX-6) that likely controlled development of a light-sensitive patch of cells in a common ancestor (Gehring, 1996). The underlying assumption is that there are trade-offs modulated by the public aging pathways: for example, that either species or individuals might wish to accelerate aging in order to increase reproduction, and thereby maximize fitness.

The public/private mechanism distinction maps nicely on the “bowtie” model of regulation that has emerged from complex systems theory (Csete and Doyle, 2004), subsequently applied to immune aging by Franceschi and colleagues (Cevenini et al., 2008; Franceschi et al., 2018; Tieri et al., 2010). Applied to aging pathways, the bowtie model suggests that multiple input signals converge on a limited number of aging pathways, which then integrate this signal and use it to adjust a number of downstream mechanisms. Fig. 1 shows a schematic of the bowtie model; while simplified in terms of the network structure and hierarchical relationships of some elements, this schematic preserves the key elements of how information is processed. This elegant model would appear at first glance to support the public/private distinction, and thus to support the fifth proposition above, suggesting that aging is a suite of downstream mechanisms, specific to a given species, that are coordinated by the signaling pathways to produce a coherent aging process.

However, closer inspection in fact suggests the opposite. The structure shown in Fig. 1, though not identical, bears a remarkable resemblance to neural networks, both real networks of neural connections and the statistical tool derived from them (Fig. 2A), which might be more precisely termed a cybernetic network (Wiener, 1948). More specifically, they resemble a type of neural network known as autoencoders (Fig. 2B). In all cases, the structure can be understood as a framework for processing information, and there is a reason for the apparent convergence: just like in other areas of convergent evolution, this particular structure is highly efficient at performing its task. The presence of multiple pathways ensures (a) that an error in one pathway will have a modest impact on the overall result of the regulatory pathways, generating robustness; (b) that diverse information can be synthesized in a flexible way to generate a globally optimized metabolic response; and (c) that multiple downstream targets can be optimized simultaneously and differentially as a function of multiple upstream input signals.

This last point is the key one here: from an information theory perspective, the structure of the regulatory network in Fig. 1 implies that it evolved to differentially regulate the downstream targets, not to make them converge on a single coordinated signal of aging. Aging as a unitary phenomenon via proposition #5 above would require convergent, not differential, regulation of the outputs. The key difference between Fig. 1 and Fig. 2A is that Fig. 1 has many outputs, whereas Fig. 2A has only two. If aging were a unitary phenomenon, we should in fact expect a single output, or a network with a single bottleneck node: a clear pathway controlling aging, from which all downstream regulation would emanate. But our knowledge of these pathways implies that this is not the case. Another important point: The concept of artificial neural networks can be extrapolated to multiple hidden layers, in which case they become “deep neural networks” (Putin et al., 2016). These deep neural networks often outperform standard neural networks in prediction. The feedback loops among the known aging pathways in fact suggest that they are closer to a deep neural network than a simple neural network, again supporting the argument that this structure evolved because it represents a near-optimal information processing strategy.

Differential regulation, as implied by network structure, indeed makes sense. Why should an organism want to perfectly coordinate all mechanisms related to aging? For example, two major aspects of mammalian aging are sarcopenia and immunosenescence. It is easy to imagine scenarios in which organisms would wish to adjust the relative rates of these processes: in a low-pathogen but physically demanding environment, it might be advantageous to accelerate immunosenescence and decelerate sarcopenia, and vice versa. So why constrain regulation to a single global target of “aging” when the components might be fine-tuned? Beyond the structure shown in Fig. 1, this is supported by simulations of multiple trade-off currencies (Cohen et al., 2017), which are implicit in the regulatory structure.

One of the most striking features of Fig. 1 is the large percentage of potential links that have already been identified, supporting the inference of simultaneous, differential fine-tuning of the “output” parameters. As attractive as the public/private model is (and certainly it contains at least a grain of truth), it has an important weakness, namely that it supposes that regulating aging is a core function for which signaling pathways would have evolved and been conserved. Yet aging

Fig. 2. A. An artificial neural network, as represented on the Wikipedia page of that name as of May 17, 2020. B. A sparse autoencoder, as shown in (Ng, 2011). Note the similarity to Fig. 1.
(in the cellular/molecular mechanistic sense) is not a core fitness component such as survival or reproduction, and it is unlikely that aging would be a primary target of selection. As soon as we abandon the concept of aging as a unitary phenomenon, Fig. 1 makes perfect sense as a way for organisms to fine-tune a number of processes that are related to resource use, stress, and investment in repair and in now vs. future. Accordingly, we argue that there is now good reason to believe that aging is not a unitary phenomenon. And if we are correct, the implications are broad: an anti-aging intervention via the core signaling pathways that purported to have a general effect on the downstream mechanisms might in fact be having differential effects on the mechanisms, and/or effects that vary depending on environment. Biomarkers of one hallmark might be contradicted by those of others (even supposing that the hallmarks are likely to have positive feedback loops with each other). Indeed, there are now multiple studies showing that various metrics of the aging process are largely uncorrelated with each other (Belsky et al., 2016; Kabacik et al., 2018; Li et al., 2015; Vetter et al., 2019). Below, we explore a number of the implications of our contention at different biological levels.

5. Areas where the concept of unitary aging creates confusion

5.1. Aging as biology or demography?

There has been substantial discussion on whether and to what extent mortality patterns can be considered a proxy for aging biology (Burger and Missov, 2016; Kizina et al., 2019; Stroustrup et al., 2016; Yashin et al., 2002). In different sub-disciplines, this subject is treated very differently. Demographers and biodemographers often tend to assume that mortality patterns in themselves can be studied as variation in aging, though some researchers have questioned how well such “demographic aging” might parallel “physiological or biological aging” (Burger and Missov, 2016). Demographers would tend to define aging as an increase in mortality rates (or decrease in reproductive rates) with age, though it has been noted that these demographic patterns can arise due to factors unassociated with biological aging. For example, in plant populations, developmental stages can determine mortality rates more than age or any biological aging process (Caswell and Salguero-Gómez, 2013); if for some non-biological reason (such as exposure of trees to lightning strikes), older developmental stages experience higher mortality rates, this could generate demographic aging patterns in the absence of any biological aging process.

 Likewise, Caenorhabditis elegans raised at temperatures that kill all individuals within a half day (less than 1/20 normal lifespan) still show aging-like demography, though presumably they are not being killed by normal aging mechanisms at these timescales (Stroustrup et al., 2016). Invertebrate models of aging such as C. elegans and Drosophila melanogaster often have underdetermined causes of death (Johnson, 2003), and the physiological and functional aspects of aging were for a long time less well characterized (Jacobson et al., 2010). Accordingly, many curves were and still are a common tool for evaluating the aging process in nematode worms and fruit flies (Rose, 2001; Stroustrup et al., 2016). The assumption again is that there is an underlying physiological process or processes that are translated relatively directly into mortality rates;

 In this context, our tendency to use the word “aging” to group both demographic and physiological processes leads to substantial confusion. Compare the following two hypotheses for clarity: (1) Demographic aging processes are a reflection of underlying biological aging processes, and (2) Exponential increases in mortality rates with age are determined in large part by the accumulation of macromolecular damage.

5.2. Identifying the mechanisms of aging

 If aging is a unitary phenomenon, it has underlying mechanisms. Twenty years ago, many researchers were debating individual mechanisms; now, there is a broad consensus that aging is multifactorial, with interactions among a variety of mechanisms (Franceschini et al., 2018). But what are the mechanisms of aging? Many researchers today agree that the “hallmarks” or “pillars” of aging do a good job describing the key mechanisms (Kennedy et al., 2014; López-Otín et al., 2013). However, there are several problems with this assertion: (1) Such lists tend to change over time, sometimes dramatically, as knowledge advances. The current “Hallmarks of Cancer” are quite different from the original list (Hanahan and Weinberg, 2011, 2000), and oxidative stress is not now considered a hallmark of aging (Hekimi et al., 2011), though it certainly would have been twenty years ago. (2) The list is restricted to cellular and molecular mechanisms, but there are clearly mechanisms that operate at other hierarchical levels of biology. For example, psychological stress through the hypothalamo-pituitary axis (HPA) appears to accelerate aging (defined either functionally or biochemically) (Seeman et al., 2001; Szanton et al., 2009), and should thus be considered a mechanism, particularly as it is upstream of the known molecular pathways. Perturbed sleep or circadian cycles also appear to accelerate the aging process (Bushey et al., 2010; Kojima et al., 2000). Likewise, tooth wear in mammals and wing wear in insects seem to fit nearly every definition of an aging mechanism, but are processes that are determined at the tissue/organ level. There are undoubtedly numerous other aging mechanisms that occur at higher levels of biological organization, but we have not been looking for them and thus we have not catalogued them well. (3) The hallmarks of aging were designed to apply to mammals, and indeed some of them, such as intercellular communication, could not possibly apply in yeast or bacteria, which are known to age. The list therefore does little to clarify species-specific or taxon-specific mechanisms, of which there are many.

 The attempt to achieve a list of “mechanisms of aging” is of course predicated on the assumption that aging is a unitary phenomenon, and that there is thus a particular meaning to a list of its mechanisms. But what if the mechanisms are an odd assortment of particularities that share little more than their effect on age-specific mortality? Some might begin early in life, some late in life. Some might be present in just one species, others in all living organisms (Cohen, 2017). Some might have large effects, others small effects, or their effects might vary across species and environmental conditions. As is the case with the hallmarks and pillars, any list of mechanisms will thus tend to focus on mechanisms that apply across many species, probably with an anthropocentric bias. In this sense, the search for such a list probably leads us to underestimate the complexity of aging and obscures the true nature of the phenomena in question. It forces us to either exclude a mechanism such as tooth wear, or to try to integrate it with cellular/molecular mechanisms that are unrelated in every relevant way. In contrast, if we view the assortment of mechanisms as a biological grab-bag, we will intuitively be more flexible in adjusting the list of considered mechanisms to the context of a given study. For example, if we want to decompose mortality patterns based on the contributions of different mechanisms, we may want to consider mechanisms that are less canonical but key for the species in question, or we may want to consider a nearly exhaustive list; on the other hand, when considering the evolutionary conservation of molecular pathways, more particular mechanisms could naturally and comfortably be excluded. This flexibility is hard to achieve if we have in mind that there is some canonical list of mechanisms that are linked as parts of a unitary process known as “aging.”

5.3. Confusion between signaling pathways and physiological mechanisms

 If aging is a distinct process, the presence of conserved signaling pathways that regulate aging (sirtuins, mTOR, insulin and IGF signaling, etc. (Bitto et al., 2015)) implies that physiological and biochemical mechanisms, such as the hallmarks, are downstream of these genetic pathways and directly under their control (Fig. 1). While there is certainly some support for this, the picture is clearly more nuanced. For
example, mechanisms at higher levels of biological organization (HPA activation, perturbed sleep cycles, wing damage in insects, etc.) are unlikely to be directly controlled by the conserved signaling pathways. Likewise, there are clearly feedback loops among the mechanisms (e.g. impacts of inflammation on cellular senescence and vice versa (Freund et al., 2010)) that can proceed at least somewhat independently of the conserved pathways. By abandoning the idea that aging is a distinct process, such nuances make much more sense. The conserved signaling pathways were generally identified because mutations in key genes prolonged lifespan in model organisms, not because they impact the mechanisms (Guarente and Kenyon, 2000; Kenyon et al., 1993). Indeed, the best way to see these pathways is as conserved mechanisms to integrate environmental information on conditions in order to optimize decisions related to reproduction, repair and maintenance, etc. (Fig. 1).

There is no need to relate this concept to “aging.” Increasing maintenance may have the consequence of helping the organism survive until conditions are better, but this is not necessarily synonymous with slowing aging. Is C. elegans entering a dauer stage a slowing of aging, or some other physiological state? What about states of hibernation and torpor in mammals? Might there be cases where surviving until the next reproductive opportunity could actually imply a faster subsequent decline, and if so does this mean that aging was slowed and then accelerated? These questions are more terminological than substantive, and they can be avoided by abandoning the concept of aging as a unitary phenomenon.

5.4. Discussions on when aging begins

When does aging begin? At parental gamete formation, conception, birth, sexual maturity, or later in life? At the moment when mortality is lowest, often between birth and sexual maturity? Answering this question requires defining aging as either a physiological or demographic phenomenon, and these two give different answers, as recently shown (Kinzina et al., 2019). Furthermore, even physiological definitions would likely give discordant answers. DNA damage accumulation likely starts at parental gamete formation. Epigenetic changes are also likely to start before birth (Horvath, 2013). Meaningful impacts of cellular senescence, however, are primarily later in life. Some answers may be based on evolutionary expectations such as “essential lifespan” (Rattan, 2006). Such discordant answers to the question are only problematic because we expect a single answer; by seeing the diverse processes and mechanisms as separate rather than as facets of aging, we can easily answer that each starts at a different point in the life course, as makes sense.

5.5. Which species, if any, don’t age?

Examples of organisms that appear not to age have been known for a long time. Finch (Finch, 1990) termed this negligible senescence, and gave several examples. More recently, theoretical work from Vaupel, Baudisch, and colleagues has explained how this can occur demographically (Baudisch, 2005; Vaupel et al., 2004), and the collection of lifetables from species across the tree of life appears to show that negligible senescence is not rare or exceptional, but is actually quite common across the tree of life (mammals and birds excepted) (Jones et al., 2014; Salgueiro-Gomez et al., 2016, 2015). But what does it mean that a Greenland Shark (Somniosus microcephalus) can likely live in excess of 400 years (Nielsen et al., 2016), or the ocean quahog Arctica islandica upwards of 500 (Butler et al., 2013)? Is this a lack of aging, or a very slow pace of life? Are the same biochemical and cellular processes that happen in other species happening in them too? There are many important avenues for research here, and many outstanding questions, but the concept of aging as a unitary phenomenon is likely to do more harm than good. Hydra (Hydra vulgaris), desert tortoises (Gopherus agassizi), and naked mole rats (Heterocephalus glaber) are all exceptionally long-lived, but demographically, evolutionarily, and physiologically, they are unlikely to have much else in common in relation to aging. For example, some demographic definitions of aging define declining mortality rates with age as “negative senescence” and then attempt to classify organisms as having negative, positive, or negligible senescence (Jones et al., 2014; Vaupel et al., 2004); however, examination of the mortality curves reveal marked heterogeneity in the forms. A species such as a tree that shows dramatic declines in mortality as it grows larger is not showing negative senescence in any way that would be of interest in terms of understanding sub-organismal processes related to deterioration with age, or their evolution. The demographic patterns reflect an amalgam of underlying processes – physiological, social, cohort effects, competition/predation, population-specific effects, etc. Sometimes one or another may dominate, and all may be of interest, but by searching for “aging” or “senescence” specifically, we often miss the nuances created by the amalgam. Why not simply accept that there is no generalized answer to whether or not they age, and what that would mean or look like? From a comparative perspective, we can rather evaluate one at a time the roles of conserved signaling pathways, known damage accumulation mechanisms, demographics, etc. From a natural history perspective, we can attempt to integrate the physiology, ecology, and demographics of each species to achieve a global understanding of what leads to their particular life histories.

5.6. Aging in modern humans, versus as a general phenomenon

Obviously, most aging researchers are particularly interested in human aging, and studies on model organisms are often justified based on what they might teach us about human aging. But human aging is peculiar in a number of ways. Relative to other mammals, we have an exceptional longevity for our body size. Furthermore, our modern lifestyle means that most aging-related causes of death are due to diseases that were probably rare or absent in our ancestors (diabetes, heart disease, cancer, neurodegenerative diseases, etc. (Capasso, 2005; Fox, 2018; Gurven et al., 2016)). To what extent is what we observe in modern humans aging, versus other pathologies? What is the relationship between aging as a basic biological process and aging-related diseases in humans? Any organism, taken out of the environment for which it is adapted, might show a range of pathologies reflecting the mismatch between the genetics and environment, and these pathologies might shorten lifespan. Is this aging? Once again, all these questions can only be asked if we think that aging is a unitary phenomenon. Without this concept, we could simply characterize how our modern environment affects the risk of each disease, as well as study conserved mechanisms (e.g. inflammation, the mTOR pathway) that could interact with disease risk, and perhaps contribute to shared risk for multiple diseases.

6. Implications for Geroscience and the anti-aging movement

The Geroscience approach – i.e., using interventions in the aging process to combat multiple chronic diseases simultaneously (Kennedy et al., 2014) – is certainly impacted by the paradigm shift we propose. There is substantial disagreement within the field of aging biology and among the public as to whether aging is a disease and whether it should be treated as such (Calimprort et al., 2019; Cohen et al., 2020; Fulpol et al., 2019; Rattan, 2014). Our argument at least superficially appears to render the discussion moot – if there is no unitary phenomenon, it is not possible to intervene in “aging,” and there is nothing to treat or classify as a disease.

However, this response is a bit simplistic. Many of the proposed “anti-aging” therapies target only a subset of known aging processes, but nonetheless may have the potential to impact the risk of multiple chronic diseases, whether or not we call them “anti-aging therapies.” For example, under our perspective, we would argue that metformin is not an “anti-aging” drug (Justice et al., 2018), but rather a “counter-modern-lifestyle drug” that combats some of the metabolic consequences of sedentariness, over-nutrition, and minimal exposure to
pathogens, within a subset of individuals that will respond favorably. Understanding who will respond favorably, and how to identify them, will be important for a safe deployment of its “anti-aging” applications, given that it would not be to treat an acute condition for which short-term improvements could be measured.

This example is telling: suggesting that there is no such thing as biological aging is not a brake on research, but helps fine-tune the question. If metformin is “anti-aging” and we all age, everyone could take it and expect to slow aging. However, if metformin makes specific modulations to the signaling pathways in Fig. 1 with a diverse set of impacts on the outputs, a careful understanding of who it affects how is necessary before proceeding. In this sense, abandoning the notion of a unitary aging process may be necessary for the safe deployment of multi-disease therapies, and may save the Geroscience movement the profound embarrassment and setbacks that could come from an overly broad application. Of course, there are also implications for the regulatory framework around drug approval. We would argue that the drug approval question is much broader than whether aging is classified as a disease: the US Food and Drug Administration, and other similar agencies, need to carefully consider whether to approve pharmacological interventions to broadly maintain or restore homeodynamics within an individual, regardless of the impact on specific diseases. As our understanding of health as the maintenance of this kind of homeodynamic equilibrium gains steam (Cohen, 2016; Rattan, 2006; Sterling, 2020), this kind of question will be increasingly important, as will the question of whether/how pharmacological approaches can be safely applied in this context.

7. Recommendations and conclusions

Here we have argued that the concept of aging does not reflect any underlying biological reality, and has in fact hindered progress in our field. Aging is not like development, nor like a clear pathological process such as Type-II diabetes, and our attempts to treat it as such explain why we have had so much difficulty arriving at a common language and definitions, and at integrating across different perspectives, including ecological, evolutionary, molecular, genetic, mechanistic, epidemiological, demographic, and clinical. We are aware that many colleagues are already considering the heterogeneity of the aging process from different angles (Franceschi et al., 2017b; Jones et al., 2014; Kuo et al., 2020; Rattan, 2008), and thus that our biological arguments already have achieved some degree of acceptance. We nonetheless contend that this acceptance is far from universal, and that the linguistic confusion is a big part of the reason. We advocate for a flexible and gradual abandonment of the concept of aging in a formal sense so as to facilitate a more nuanced and detailed understanding of the highly heterogeneous processes that affect health and mortality risk as we age. This does not mean we can never use the words “aging” or “senescence,” but rather that we should do so with careful, clear, context-specific definitions, and an overarching awareness that there is no generalized phenomenon of “aging.” In this sense, we distinguish between the possibility of using a facultative definition of aging and whether that definition corresponds to an underlying reality, as shown in Fig. 3. For example, under some circumstances, it might be reasonable to define aging facultatively as “the ensemble of functional and health-related declines with age in modern humans that we might like to alleviate through interventions.” This definition explicitly recognizes that it doesn’t approach some universal reality – it limits itself to modern humans, a scenario like Fig. 3D. Here, we are explicitly concerned with distinguishing between the scenarios in Fig. 3A and 3B: does the underlying reality correspond to our linguistic category. This is done while acknowledging that some ways of defining the linguistic categories might be useful even if they are not objectively true.

Nonetheless, we believe that even facultative definitions are dangerous: we have often seen that a very circumscribed definition of aging in one paragraph is followed by a much less circumscribed application of the concept, showing how profoundly our linguistic categories influence our thinking. This will not be easy, given our identity as “aging researchers” and the depth with which the concept is anchored in our field and in the culture more broadly. Nonetheless, the biological arguments against aging as a unitary phenomenon are clear-cut, and the advantages to the field both numerous and important. Indeed, as the
field moves toward potential anti-aging therapies, large numbers of human lives may depend on fully knowing what we are measuring and what the risks are of getting it wrong.

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