PNAS Nexus, 2024, 3, pgae499
https://doi.org/10.1093/pnasnexus/pgae499
Advance access publication 3 December 2024
Research Report

Disagreement on foundational principles of biological aging

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Competing Interest: The authors declare no competing interests.
Received: June 27, 2024. **Accepted:** October 5, 2024

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Edited By Patrick Stover

Abstract

To gain insight into how researchers of aging perceive the process they study, we conducted a survey among experts in the field. While highlighting some common features of aging, the survey exposed broad disagreement on the foundational issues. What is aging? What causes it? When does it begin? What constitutes rejuvenation? Not only was there no consensus on these and other core questions, but none of the questions received a majority opinion—even regarding the need for consensus itself. Despite many researchers believing they understand aging, their understanding diverges considerably. Importantly, as different processes are labeled as "aging" by researchers, different experimental approaches are prioritized. The survey shed light on the need to better define which aging processes this field should target and what its goals are. It also allowed us to categorize contemporary views on aging and rejuvenation, revealing critical, yet largely unanswered, questions that appear disconnected from the current research focus. Finally, we discuss ways to address the disagreement, which we hope will ultimately aid progress in the field.

Significance Statement

This article highlights the lack of consensus among aging researchers on fundamental questions such as the definition, causes, and onset of aging as well as the nature of rejuvenation. Our survey revealed broad disagreement and no majority opinion on these issues, indicating diverse perceptions and approaches within the field. This disparity suggests a need for clearer definitions and goals to streamline research efforts. By classifying contemporary thinking and identifying critical unanswered questions, we propose ways to address these disagreements. Achieving a more unified understanding could support progress in aging research.

Survey on the foundational principles of aging

With major advances in medical practice in the past 200 years, common risk factors for mortality, such as smallpox, polio, or plague, were found to be preventable or curable (1–3). Although some current mortality risk factors, such as cancer or COVID-19, are not yet fully preventable, their mechanisms are well known, and treatments have been developed to effectively lower the fatality rate (4). In contrast, the most prevalent human mortality risk factor—aging—seems to still be hidden in the mist. While the field of aging has seen major advances, e.g. extending the lifespan of all major model organisms through genetic, pharmacological, and dietary interventions, there is no convincing evidence of the exact causes and mechanisms of aging, and no effective treatment proved to slow down or reverse the aging process in humans. Even the definitions of aging in the published literature are widely different and not easily reconcilable.

Understanding how scientists who study aging view this process could help bridge this gap and accelerate progress in the field. With this in mind, we conducted a survey on the most basic features of aging with the participants of the 2022 Systems Aging Gordon Research Conference. In designing questions (Supplemental Information), we benefited from an earlier survey (5). The survey did not cover age-related diseases and many other topics, focusing on the most fundamental issues. As the conference attendees were selected based on their professional standing in the field of aging and related areas, the group was deemed to be qualified to provide expert opinions on the topic. We obtained 103 responses (~20% of which were submitted anonymously). The respondents included 29.8% professors, 25% postdoctoral fellows,

22.1% graduate students, 13.5% industry professionals, and 9.6% representing other categories (a total of eight additional groups) (Fig. 1). These responses offered an opportunity to learn how scientists view the foundations of aging research.

How do you define aging?

Responses to this first question immediately exposed diverse views on the nature of aging. Word signature analysis (Fig. 2) and further text examination allowed us to cluster responses into 10 groups (Table S1). The most common response (~30%) was related to aging being the loss of function over time. Another popular definition involved the accumulation of damage and other detrimental changes over time. A third broad category was a multifactorial process of changes over time. Some scientists viewed aging as being a systemic decline, physical decline, or a decline in health with age. Additional categories were related to a shift from an ideal state, increased mortality and morbidity with age, a developmental stage, a program, or a loss of homeostasis.

Clearly, there was no consensus among respondents on how they define aging, with some stressing the phenotypic side of the process (i.e. considering diminished physiological characteristics such as function, health, physical activity, fitness), and others emphasizing potential causes (i.e. advocating for considering detrimental molecular changes such as damage, homeostasis, deviation from an ideal state) (Table S1). Some respondents pointed to any age-related changes (not necessarily negative changes), some to whole-organismal outcomes (mortality, morbidity), and some to programmatic features (aging program, developmental stage). Systemic and multifactorial features of aging were also frequently discussed regardless of whether these applied to cells, tissues, systems, or organisms.

This diversity of opinion is remarkable as these definitions of aging would be associated with different strategies of targeting the aging process. For example, in the period from 20 to 25 years of age, men do not show an increased mortality rate, whereas molecular features and biomarkers of aging, such as epigenetic aging clocks, show an increased predicted age, and the direction of functional changes during this period depends on which functions are measured. The responses further imply the lack of consensus on cell versus organismal aging.

What causes aging?

About 30% of responses noted damage and other deleterious changes as the cause of aging, and damage was also noted in several other answers (Fig. 2 and Table S2). Other responses could be clustered into the following categories: dysregulation, infidelity, molecular and systemic factors, evolutionary constraints, decline in repair, drift, and program. About 15% of respondents answered only with single words (e.g. time, entropy, age, living, causality, environment, etc.), and another 15% of responses could not be clearly classified at all. Six respondents noted that they do not know the answer to this question (it was the only question which received such responses). Several terms were also frequently mentioned: stochastics, environment, genetics, and programmed. Responses to this question highlight (i) a mild preference for the role of damage as the cause of aging; (ii) a very wide range of views on the causes of aging; and (iii) acknowledgement that we do not know the causes. As with the first question, the lack of consensus on the cause(s) of aging is also noteworthy as this factor would clearly point to different research directions and targeting strategies.

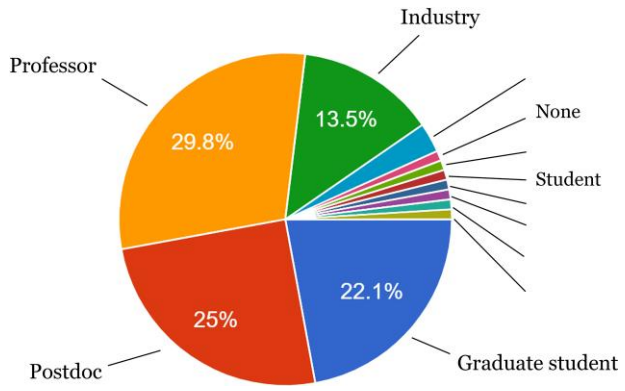

Fig. 1. Survey participants.

How do you define rejuvenation?

This question also received highly diverse answers (Fig. 2 and Table S3). One slightly more popular view was the broad category of a decrease in cumulative damage. Interestingly, responses considering rejuvenation as a gain of function were half as common as those classifying aging as a loss of function. Other common categories included a change to a younger state, a process opposite to aging, and the restoration of a healthy young state. Seven respondents thought that rejuvenation is a decrease in biological age (whereas an increase in biological age was not among the common answers to the question on how aging is defined). Additional response categories included a shift to a more optimal state, the reversal of deterioration, decreased morbidity and mortality, a reset of aging hallmarks, the restoration of homeostasis, reversal of the aging program, and repair. Similar to the responses defining aging, rejuvenation was viewed by different scientists from molecular, physiological, whole-organism, or other perspectives. While some respondents considered rejuvenation to be the direct opposite of aging, others commented on various distinct aspects of the two processes. The diversity of opinions on rejuvenation was even more dramatic than in the case of aging. Regardless of a formal definition, these responses raise the question of how the field can effectively move forward in the face of such broad disagreement.

What is the most important unanswered question in the field?

About a third of respondents noted that the most common unanswered question in the field concerns the fundamental nature of aging and rejuvenation (Fig. 2 and Table S4). While this aligns with the lack of consensus on these processes among researchers, it is surprising given the limited amount of ongoing research directly addressing this issue (except for reviews and theoretical studies). This may reflect the difficulty in designing experiments that directly tackle the fundamental nature of aging and rejuvenation. Interestingly, many respondents commented on the need to define aging and rejuvenation, yet they did not attempt to define these terms in the questions earlier of the survey.

Other popular topics related to longevity interventions (11 answers), rejuvenation/age reversal (10 answers), measuring aging (8 answers), embryonic and germline rejuvenation (6 answers), and mechanisms of aging (6 answers). Topics with 2–3 responses included radical lifespan extension, removal of damage, the

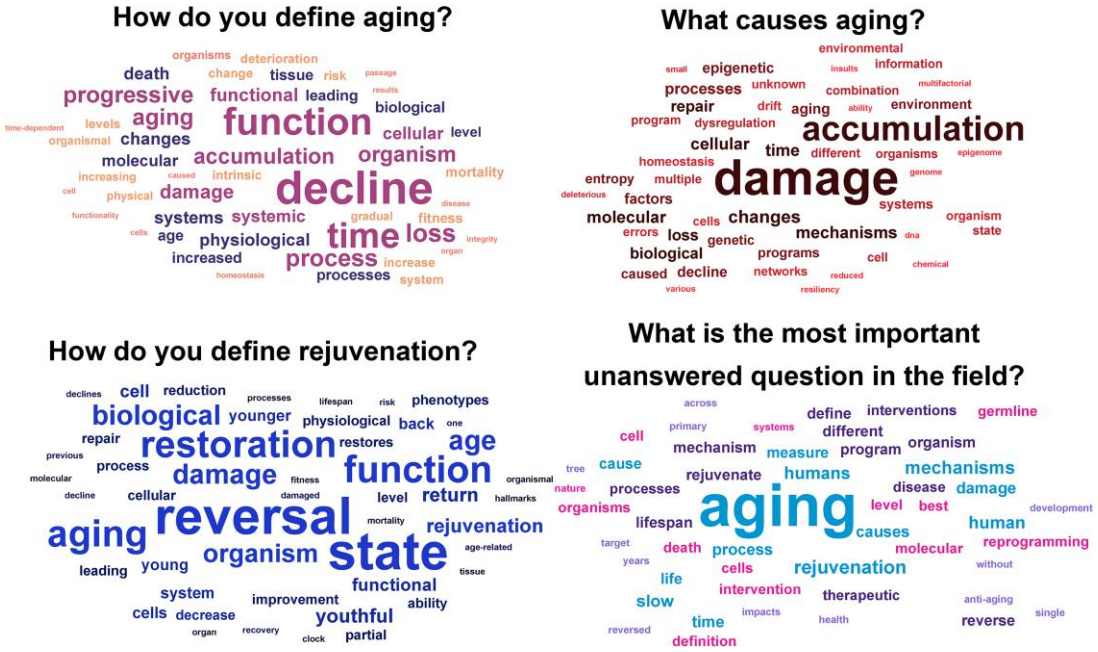

Fig. 2. Word clouds of responses to questions on foundational issues in the aging field.

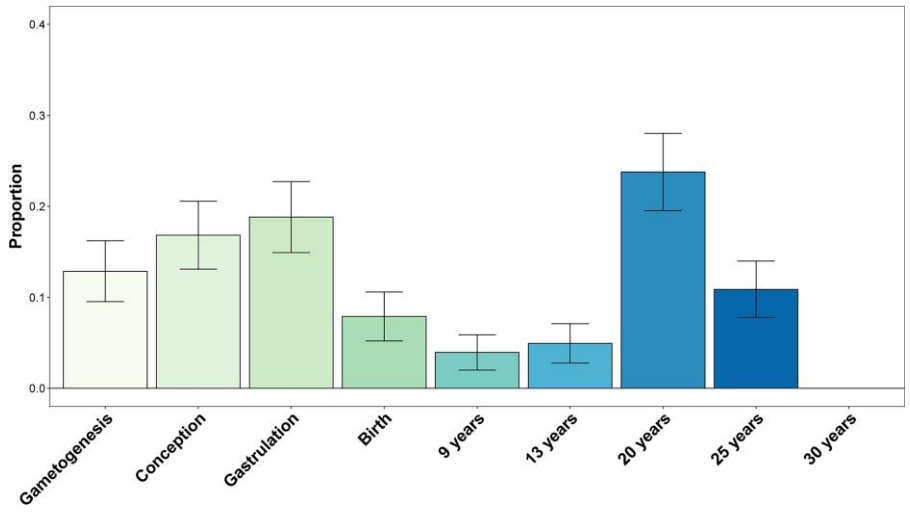

Fig. 3. "When does human aging begin?" There were nine response options given, with eight receiving responses and plotted as a proportion of one (nobody responded that aging begins at 30 years).

relationship between aging and development, aging program, aging trajectories, aging across species, and aging and disease. 13 responses could not be classified. As in the responses to other questions, opinions were highly diverse.

At what age does aging begin in humans?

We observed a great diversity of opinion on this question too. Conference attendees thought that aging begins at 20 years (22%), gastrulation (18%), conception (16.5%), gametogenesis (13%), 25 years (11%), birth (8%), 13 years (5%), and 9 years (4%) (Fig. 3). Nobody chose the only remaining option (30 years). Thus, multiple respondents chose each of the major milestones in development when (i) gametes are made from which a future organism emerges, (ii) organismal genome is formed (corresponds to fertilization), (iii) ground zero is reached (corresponds to the lowest biological age and formation of the germline and soma), (iv) an organism is born (zero calendar age), (v) minimal mortality is reached, (vi) puberty occurs, (vii) when development is largely completed, and (viii) maximal physical performance is observed.

This diversity of opinion probably reflects underlying divergent views on the nature of aging, as revealed by the question on what aging is. For example, evolutionary biologists often consider a decrease in the strength of natural selection as the beginning of aging, which may correspond to the onset of reproduction or completion of development. Other scientists, most notably demographers, consider an increased mortality rate as the defining feature of aging and therefore consider the point of lowest mortality as its start. Mortality rates are frequently analyzed using the Gompertz function, one of the most famous equations in aging

research. Both evolutionary and demographic perspectives treat the entire organism, as opposed to the sum of aging components of that organism, as the entity that ages. For example, even though during development individual cells show an increased level of damage and an increased predicted age based on aging biomarkers, these features would not qualify as aging in this line of thinking, as the organismal physical function increases during this period. Interestingly, the largest group of respondents placed the start of aging at or near the beginning of development (gametogenesis/conception/gastrulation). In this paradigm, aging and development run in parallel, and the sum of aging of individual components of an organism does reflect aging of that organism. This question and the considerations that go into answering it highlight the need to understand the nature of aging, as it is directly relevant to answering fundamental questions such as this.

Is aging a disease?

Responses to this question again revealed a clear difference of opinion (Fig. 4). The most popular answer was "neutral," followed by "agree" and "disagree," with "strongly agree" and "strongly disagree" following (but still represented by 10–20% each). Whether aging is a disease has been discussed and debated, and it was noted that one challenge in answering this question is how we define a disease (6–9).

Is it essential for the field to have a consensus definition of aging?

This is the only question where at least mild preference was observed for one answer (agree), although almost half of the answers corresponded to strongly disagree, disagree, and neutral (Fig. 4). Those who disagree with this statement often refer to the need for experimental progress that could then help refine definitions, whereas other respondents may think their views on aging are correct and therefore it is enough to advance the field even if there is no consensus on the issue. Some disagreeing respondents may also think that a mosaic of different definitions is just as good as a consensus, or even better.

The average lifespan in developed countries will be increased by 10 years or more in the next 20 years

Split opinion was observed in the responses to this question too (Fig. 4). Slightly more people were optimistic about the increase in average lifespan in the near future, although 28 scientists disagreed with this statement, and two strongly disagreed.

When a person has stopped smoking, their biological age (based on aging biomarkers) is decreased: This person is rejuvenated

This question showed a bimodal distribution of responses, with only 13 people being neutral (Fig. 4). Slightly more scientists disagreed with the statement than agreed with it. The answers largely reflected how respondents view/define aging and rejuvenation, and perhaps general views on the utility of aging biomarkers. The issues that distinguished opinions were whether aging is best represented by damage, whether rejuvenation is the decrease in biological age over artificially elevated conditions or baseline, and whether a temporary unhealthy state or transient increase in aging biomarkers result in bona fide changes in biological age. A useful follow-up question to consider is whether one can improve

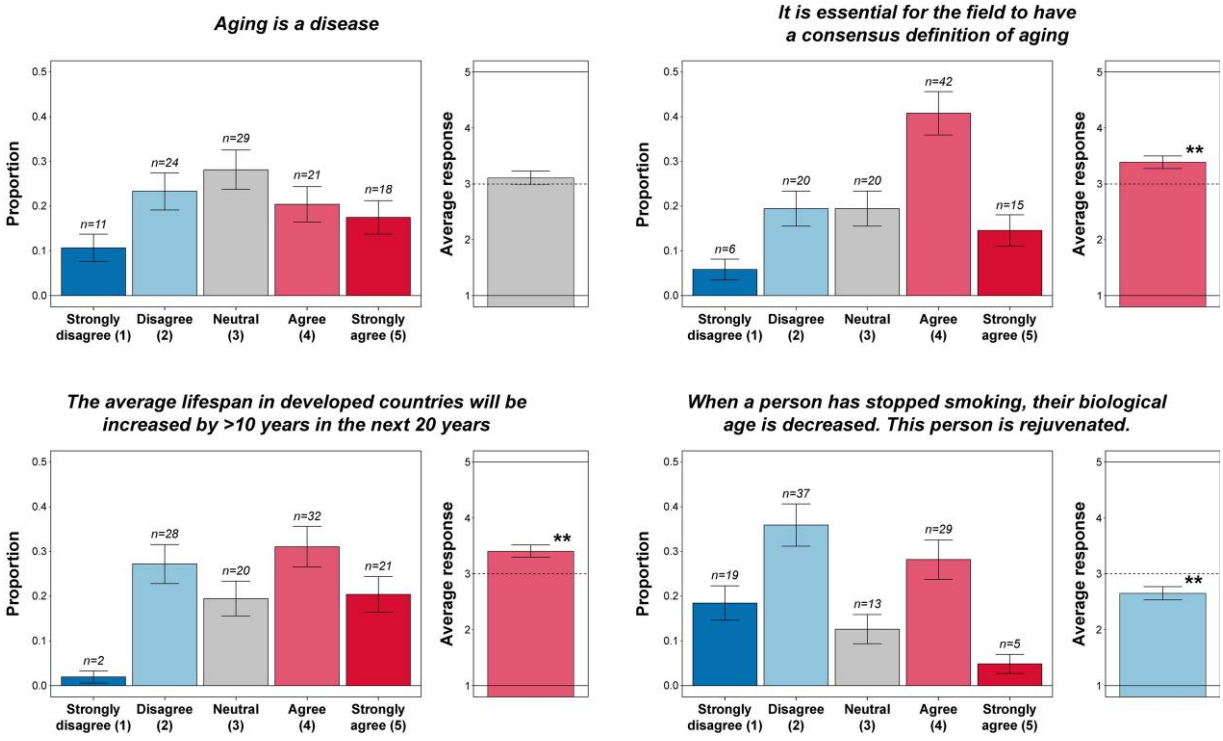

Fig. 4. Responses to questions. Each question (shown above the panel) could be answered with strongly disagree, disagree, neutral, agree, and strongly agree. Statistical significance of difference between average response and neutral opinion is reflected with asterisks. * P.adjusted < 0.05; ** P.adjusted < 0.01; *** P.adjusted < 0.001.

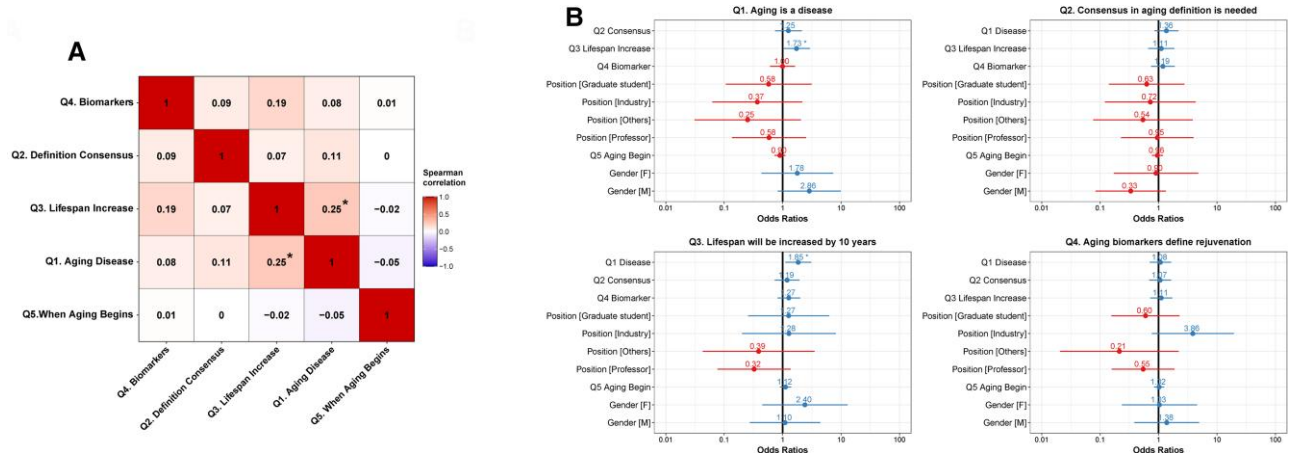

Fig. 5. Relationship between different responses and respondents' characteristics. A). Correlation between ordinal responses. B) Odds ratios. Odds ratios show how agreement with the statements is affected by other responses and by respondents' characteristics. The only significant association is between positively answering questions on whether aging is a disease and whether lifespan will increase by 10 years or more in the next 20 years.

something that is falling apart with rejuvenating it. For example, we could imagine rejuvenating a kidney versus replacing that organ. The system may be rejuvenated as a whole in both cases, whereas in one case the underlying part is not rejuvenated but replaced.

Relationship among responses

We analyzed the relationships between respondent's answers, examining whether particular responses were associated with other answers or with characteristics such as position type and gender (Fig. 5). The only significant association we found was between positively answering the question "Is aging a disease?" and agreeing with the statement "The average lifespan in developed countries will be increased by 10 years or more in the next 20 years." Also, professors were more likely to answer these two questions/statements negatively than graduate students and postdocs. No significant gender effects were observed.

Integrative analysis of the responses

Shared themes of thought on aging

Notwithstanding the broad disagreement revealed by this survey, the answers nevertheless show elements of shared thinking, with most respondents aligning on certain principles and features of aging, as well as on what aging is not. First, there is a general consensus that aging—however it is defined—exists, has identifiable causes and effects, and can be studied experimentally. These views may be compared with the idea that aging as a unified phenomenon does not exist (10). Second, most scientists agree that aging is inherently deleterious, involving the accumulation of harmful changes, damage, degeneration, and loss of function.

Third, aging is widely regarded as a process, with most respondents explicitly referring to it as such. It has certain characteristics, manifestations, a rate of progression, and outcomes—most notably, leading to death. Fourth, aging may be targeted, modulated, regulated, accelerated, and decelerated. Fifth, the aging process has a definable starting time or period within an organism's life. Sixth, rejuvenation is acknowledged as a real phenomenon (in that it can be defined), implying that aging can theoretically be reversed, not just slowed—though this does not imply feasibility. Seventh, a clear distinction exists between chronological age and biological age. These shared views on aging emerged indirectly from the responses, rather than as direct answers to the posed questions, and could serve as a common ground for building further consensus. Similar conclusions were drawn in another analysis of the field (11), suggesting that while consensus on the nature of aging remains elusive, there is still a common understanding of certain aspects. This shared ground could help shape future research priorities.

Broad disagreement on the foundational issues in the biology of aging

It is clear from the responses that aging remains an unsolved problem in biology. Scientists disagree over whether it is a universal property of life, whether it is pathological or normal, whether it is subject to natural selection, and whether it has a particular purpose (11). Interestingly, almost all respondents answered all questions, suggesting that they have a clear opinion on the subject. Yet, their responses were widely different. So, while most scientists think they understand the nature of aging, apparently their understanding differs.

It is also clear from the responses that scientists working in the aging field have mixed opinions on the most fundamental definitions and mechanisms in the biology of aging. In the whole survey, no question received more than 50% of common responses. When discussing the biology of aging with colleagues, we often assume we are talking about the same process, but clearly, we are not. Some of us consider aging to be a loss of function, some accumulation of damage, some an increase in mortality rate, etc. While these and other features often go hand in hand, they are fundamentally different and therefore may be targeted differently. If so, which approach would be most efficient? Although the sample size is relatively small, it is unlikely that the major conclusions we draw from the responses would dramatically change if another similar sized cohort of scientists in the field is examined.

It is apparent that this diverse opinion is largely due to a multifaceted definition of the word "aging" itself, as some scientists emphasize the causes and others the consequences of this process, and as such envision different targeting strategies. This is analogous to COVID-19, where some may stress the importance of targeting the underlying mechanisms, while others focus on ameliorating the phenotypes (Fig. 6). Therefore, we think it is

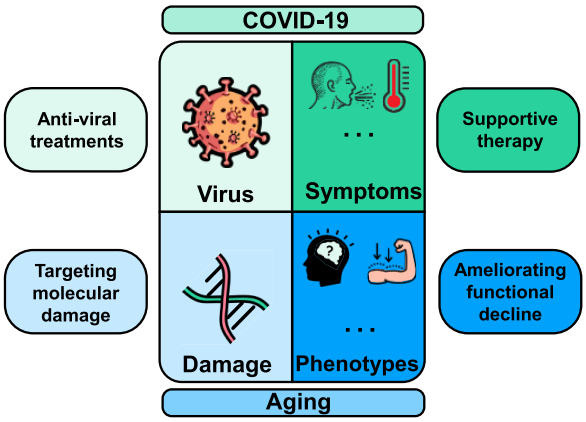

Fig. 6. Different views on the nature of aging. COVID-19 is shown for comparison. This disease is caused by SARS-COV-2, but its symptoms manifest phenotypically once the disease progresses. Accordingly, it may be targeted with antiviral approaches or with supportive therapy. Likewise, aging may be viewed as the accumulation of molecular damage and as functional decline, and it may accordingly be targeted by slowing damage accumulation or slowing phenotypic manifestations.

important to emphasize the need to distinguish various meanings of aging to ensure that scientists mean the same process when referring to aging and do not debate over the confusion with wording. It can be accomplished, for instance, by including the definitions of aging in published papers. Perhaps, new terms describing aging and its causes and consequences, molecular and phenotypic features, and damaging and adaptive nature may be defined to better fit the various features of aging.

A consequence of such divergent conceptions of aging is reflected in the great diversity of opinion on when organismal aging begins. Similar to COVID-19 with its stages of asymptomatic and phenotypic infection, can aging initially occur aphenotypically? Or must it involve phenotypic/physiological/functional decline? If development, where molecular damage already begins to accumulate, corresponds to the stage of aphenotypic aging, and the subsequent ages associated with functional decline correspond to the stage of phenotypic aging, which of these should be the prime targets for interventions? This is an example of the type of questions exposed by the survey. Perhaps, future studies may address it experimentally.

Our survey was intended to reveal what experts consider to be the essence of aging—that is, what aging actually is. In this regard, the essence of aging and the formal definition of aging are not necessarily the same thing. We think it may be easier to achieve a common understanding of the essence of aging as opposed to its formal definition. Interestingly, perhaps because of the difficulty of pinpointing the essence of aging or the apparent disconnect on this issue in the field, many scientists, both the survey respondents and scientists at large, attempt to replace causation with association, stating what aging is associated with rather than saying what aging is. Others try to bridge the features of aging to describe its essence. Moreover, it is not uncommon for the same scientists to define aging, especially when it is discussed in different contexts, as the accumulation of damage (12), functional decline (13), and increased mortality rate (14). There is also an attempt to consider two or more categories as a whole (e.g. damage and functional decline, or functional decline and mortality) or view a single category simultaneously as aging, a cause of aging, and a consequence of aging. For example, the survey received statements such as "aging is the functional decline caused by damage and characterized by increasing biological age," "aging is an accumulation in molecular damage which eventually contributes to increased risk of mortality," and "aging is damage accumulation and gradual decline of function performance" (Table S1). Many other scientists attempted to bridge aging features in the form of one feature immediately following from the other, e.g. "Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and vulnerability to death" (4). Yet another approach in the field is to avoid defining aging altogether (15). Although such noncommittal approaches may make statements on aging less wrong, they may lack explanatory power and causal inferences (16).

We also sought to understand how the field broadly understands the nature of aging, especially fundamental features that characterize aging as a biological process. Aging is often contrasted for biological organisms and mechanical objects and frequently considered at the interface of biological, chemical and physical realms. This is also reflected in the answers to the survey, although its focus was on biological aging. Another dimension that emerged is that aging is often viewed as a process at the level of whole organisms. However, parts of these organisms or even individual cells, when taken in isolation or placed in appropriate conditions (e.g. cell culture), are also viewed as aging systems. Thus, it is unclear whether various scientists consider aging to be an emergent property of a system or the sum of aging of its parts. If the former, then when should we consider an organism to be an organism, and if the latter, then what about aging of the components other than tissues and cells, e.g. organelles, suborganelle locales, biological liquids, extracellular materials, etc.? Should these components receive more focus in future aging studies?

Another feature that emerged from our analysis is the disconnection between mechanistic (molecular) and evolutionary models of aging. Although mechanistic models attempt to determine how organisms age, and evolutionary models determine why they age, these models also differ in treating individual organisms versus populations. Arguably, this gap has not closed since the emergence of dominant evolutionary models, i.e. mutation accumulation and antagonistic pleiotropy, and the initial attempts to bridge them in the form of the disposable soma theory (12, 17–19). Moreover, the evolutionary models or their interpretations have recently been questioned (20–22), e.g. suggesting that antagonistic pleiotropy is a general feature of life and not an emergent property that leads to aging.

Despite the importance of foundational issues in the biology of aging and the clear lack of consensus on these issues, little effort is being placed into directly addressing them. Moreover, there is a clear disconnect between what respondents think are the most important unanswered questions in the field and the ongoing research in the field. It is not necessarily because scientists are biased toward what they do. It is more likely that this is because these are very difficult questions to answer or to even design proper experiments and statistical treatments to address them. A part of the problem is also that most terms in the field are ill-defined, causing confusion due to different emphasis in different contexts and due to the variable use of the terms, including the term aging. For example, aging can be described as normal, normative, successful, healthy, pathological, premature, accelerated, etc., but what exactly all these terms mean is rarely discussed.

More generally, it is clear from the survey that in the most commonly referenced sequence of events—damage causes functional decline causes age-related disease causes mortality—different events are viewed as aging by different respondents. This may

present a critical impediment to developing the most effective strategies to target aging. Depending on what one considers the essence of aging (23), experimental strategies may be disconnected from aging and directed either to the causes of aging and other upstream events or to the consequences and associations of aging.

Outlook

The goal of our survey was to assess modern thinking about the foundational issues in the biology of aging among experts who study this process. Despite its surprising findings of wide disagreement, we consider it a step forward. By simply identifying and spelling out the issue, it may be enough to inspire creative thinking, conceive new experimental approaches, and uncover new practical leads in the field of aging.

Supplementary Material

Supplementary material is available at *PNAS Nexus* online.

Funding

There is no funding associated with this paper.

Data Availability

There are no primary research data underlying this work.

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