Reflections on aging research from within the National Institute on Aging

The NIA (part of the NIH) is one of the leading funders of aging and age-related disease research worldwide. Last fall, *Nature Aging* spoke to Luigi Ferrucci, its Scientific Director since 2011, to get his thoughts on the field and learn about the institute's agenda and future plans for intramural and extramural aging research.

■ **My first question is short but of central importance. What is your definition of aging and when does aging start?**

This is a really interesting question, and, of course, my answer is going to be subjective. What is aging for me, and how do I conceptualize aging throughout my research? Aging is the ratio between damage accumulation and compensatory mechanisms. If you think about it, damage accumulation occurs constantly in our biology and physiology. We have DNA damage and protein misfolding, we have organelle deterioration, and so on. But over millions of years we have developed mechanisms that allow us to repair this damage. And when we cannot repair it, we can replace these molecules and these organelles; we throw away the protein, we eliminate the DNA, and we create new DNA, new protein, new organelles, and so on. The ratio between damage accumulation and compensatory mechanisms gives us the rate of aging. Because of this conceptualization, to me, aging starts at conception. I think there is a very strong and evolutionary conserved developmental mechanism for compensation of damage inscribed in our DNA that is so redundant and so well maintained that we don't see aging at the beginning of life. Early programs that build the soma strongly and fully compensate for the accumulation of damage. But this same accumulation also occurs in the molecules that take care of the damage, and so slowly and progressively, this compensation becomes less effective, more and more damage escapes from compensatory control, and, phenotypically, this manifests as aging.

■ **We know that chronological age is one of the biggest risk factors for many common chronic diseases. Some in the field believe that aging itself is a disease, yet regulatory institutions like the Food and Drug Administration (FDA) and the World Health Organization (WHO) do not recognize aging as a disease. Where is**

Credit: Image courtesy of the Buck Institute

the boundary between healthy aging and disease?

Because I study aging, I think you can predict my answer. Sixty years ago, Nathan Shock created the Baltimore Longitudinal Study of Aging, and his idea was that we needed to dissociate aging from disease, because only at that point would we know what disease is and how to treat patients. There was an interest in trying to understand aging so that we could ignore it, because there was nothing that we could do about it. And then, as researchers started to look at aging and began searching for the point of dissociation between aging and disease, they found that it was much more difficult than expected. As our technologies became more developed and sophisticated, the boundaries between aging and diseases continued to blur. The risk factor paradigm started with cardiovascular and cancer epidemiology; the basic idea is that if you wait a certain amount of time, risk factors will trigger a disease. People initially thought that there was some specificity between risk factors and diseases, but over time we have discovered that this specificity

was not really there. Exercise and physical activity can reduce the risk of developing cardiovascular diseases, cancers, pulmonary diseases, sarcopenia, and so on. Smoking increases the risk of developing these diseases, too. You can say the same thing for many different risk factors that are being considered. Cancer and cardiovascular disease, the two major causes of mortality, share many of the same risk factors. Think about obesity: it's associated with most chronic diseases that you can think of. And so there has been a shift in how we have considered aging, from something that we needed to account for and eliminate by statistical adjustment to a causal factor in disease. And I think that it makes a lot of sense. This explains why aging is a much stronger risk factor for dementia than carrying an *APOE4* allele. This shift in thinking is important because it places aging at the forefront of medicine. Now, if this is true, understanding aging provides the strongest chance to prevent chronic diseases and expand healthspan. This shift creates incredible opportunities, and even private companies have started to become interested in studying aging.

And you mentioned the FDA. I remember that many years before I came to the National Institutes of Health (NIH), I started talking about sarcopenia at the European Medicines Agency when it was still called EMEA, the agency that was regulating clinical trials in Europe many years ago. I went to London to represent a drug company to try to get approval for a trial that had walking speed and frailty as outcomes. When I showed the first slide introducing our outcomes, I was shot down. They didn't even allow me to present what I wanted to present because they said: "this is not a disease. Becoming frail is natural in humans. Do you want to go against nature? You can't really go against that. Everybody will eventually develop that. We cannot treat everybody." And, of course, many things have changed since then, but it is still difficult because for thousands of years, medicine has been conceptualized around diseases that develop in specific organs. There is still a lot of resistance, but I think that it is fading now. The experience in designing the Targeting Aging with Metformin (TAME) trial (<https://www.afar.org/tame-trial>), for instance, demonstrates that regulatory agencies are starting to seriously consider the validity of trials looking at multimorbidity and to recognize the need to develop biomarkers that capture biological aging. I think that over time we will overcome this resistance.

I just want to add one more thing that's really important. People don't realize, especially physicians, that when we talk about biological aging, it's something that is occurring before the development of a disease, before the phenotypes are manifesting. And that's why it's so important to measure it. We can measure it in individuals that are apparently healthy, identify those that are on accelerated aging trajectory and intervene at the time when those compensatory mechanisms are still there.

■ **The biology of aging is still a relatively young field, but it has grown tremendously over the last two or three decades. Can you highlight for our readers what, in your opinion, are some of the most influential and important discoveries in aging research over the last 20 years?**

First of all, I think that the discoveries that are the most relevant and most likely to translate to clinical applications are those for which we have developed technologies that can provide accurate and quantitative measurements of relevant variables in humans. And of the hallmarks of aging that everyone features in every slide of every

presentation, 90% have only been described in mice. We don't know whether these results would be true in humans. I'll give you a couple of examples: does intestinal permeability increase with aging in humans? We have absolutely no evidence. Do we know whether senescence contributes to wound healing in humans? We have no idea.

There are a few discoveries that have emerged and are leading the way. Steve Horvath's idea and demonstration that there is an epigenetic clock, for instance, has transformed the field. I think that it's important because it demonstrates that the aging process is not stochastic. The epigenetic clock shows us that there is a temporal line of events that track the aging process. This discovery represented a change in perspective. New epigenetic clocks, like PhenoAge and GrimAge, are very close to clinical translation. This also gets us closer to the biological mechanisms. Instead of just predicting age, we may be able to identify new targets that are suitable for intervention. This is about understanding how our experiences and the environment modify the epigenome as an adaptive process, and how this adaptation influences aging trajectories is the future. I think the second major discovery has to be cellular senescence. The finding that cellular senescence plays a role in aging was incredible. I think that we now all realize how important this was. Following on the pioneering work of Judy Campisi, Darren Baker's landmark study showing that many aging phenotypes in mice are delayed when you eliminate senescent cells was mind-blowing because it tied aging to a specific type of cellular alteration. Senescent cells are very unstable and metabolically challenged, but in spite of this they don't undergo apoptosis because part of the senescent program blocks this process. The idea that simply removing this block using small molecules would eliminate the senescent cells; I think it was genius. And these principles are already applied in the clinic with trials on senolytics in humans.

So, I think those are the two discoveries that are the closest to clinical translation and that I am most enthusiastic about. I think the role of mitochondria is next, because it makes a lot of sense. If you want to repair something, you need energy. Everything depends on the availability of energy, and so understanding the progressive decline of mitochondrial function with aging is really key. I should also mention autophagy, but we need to be able to measure it in a high-throughput manner, and in people, at the same time as other biomarkers, such as circulating proteins, to understand the underlying mechanisms. I think the advent of proteomics in plasma may allow

us to capture some of the mechanisms of aging biology and increase the chance of translational applications.

"Translation will not occur without a common language and collaborations across disciplines"

■ **Aging research can be divided into a diverse set of research areas covering a variety of disciplines, ranging from the core biology of aging to age-related diseases in model organisms and in the clinic, and the study of aging populations in a public health and socioeconomic context. How do you see those different disciplines interacting at present and in the future?**

I think this is almost a mantra for me. There should be interactions. If we don't interact, we will not make the discoveries that we need to make. When I reorganized my institute, I created labs where people who perform neuroimaging in dementia talk to people who perform teeny, tiny measurements of neurophysiology in isolated neurons. I live in a branch where, working on the same project, there is a pure biochemist who designs new molecules to manipulate cholinergic function in the brain, there is Rafa De Cabo who is carrying out a longitudinal study in mice, and I'm leading a longitudinal study in humans. When I started these kinds of collaborations, people thought I was crazy. And I can assure you that when you start putting such a diverse set of people together on common projects and gathering them in lab meetings, they refuse to talk to each other. But over time, they develop a common language and start seeing opportunities or become curious. The biologist will say "what are the real-world consequences of what I'm studying? Is this really related to health?" And then there are also opportunities for reverse translation. You can do the best translation and then go back to the lab. I do this all the time. In the Genetic and Epigenetic Signatures of Translational Aging Laboratory Testing (GESTALT) study (<https://bit.ly/3mb8vaA>), for instance, I am looking at high-throughput data, but I am at the point where I think that what I'm observing and the hypotheses I'm making can no longer be studied in humans, so I have to go back to animal models and see whether what I'm thinking really works or not. This is simply because manipulations that can be done in animal models cannot be done in humans. The same thing is happening in Rafa's group. They are making

some observations in mice but now want to know whether these observations also apply to humans or not. We must learn to speak a common language. I think this is absolutely fundamental. Translation will not occur without a common language and collaborations across disciplines.

■ **You obtained your medical degree and Board Certification in Geriatrics in the early 1980s. What motivated you to specialize in geriatrics early in your career and to continue to study aging ever since? Any advice for medical students contemplating a career in geriatrics?**

I became interested in aging when I was 16 years old. It is a long story, but somebody convinced me that a revolution in the world was occurring because of the aging of the population and that nobody was really paying attention to it, that the people who will become older had already been born, and that this will change society, healthcare, social security, everything, but that we were not preparing for it. I was told “if you really want to do something important for the world, you need to study aging”. So, I studied medicine, I specialized in geriatrics and obtained a PhD in the biology and pathophysiology of aging. And I worked as a geriatrician, in the trenches. I saw thousands of patients. So, I did that for a while, but I also realized that the work that we were doing was almost hopeless. We were gaining a little, adjusting some of the damage, doing some rehabilitation, and then we would see the patients with multimorbidity and disabilities coming back to the clinic three months later, having completely lost whatever they had gained with so much effort. I started thinking that I needed more tools to tackle the effect of aging and disease. The first thing I did was visit the London School of Hygiene & Tropical Medicine for a month, where I talked to epidemiologists. That’s when I really started to think that it was important to carry out more research. But at the time, aging research was not popular. Aging was really the Cinderella of science. Talking to people like Richard Peto and Geoffrey Rose really motivated me to study aging more. I went back to Italy and I did a lot of epidemiological studies. After doing epidemiology for a while, I started thinking: yes, I’m observing, describing, but that’s not enough. If I want to do more, I need to understand more, I need to look at mechanisms. So, I went through the best transition in my career. I started talking to scientists working on the basic mechanisms of aging and thinking about how such science could be used to inform our studies in humans. Looking at the past, I was not

alone: many epidemiologists were going through the same transformation, in part driven by the emergence of the new ‘omics’ technologies. Now I still work mostly in humans, but more and more I have become focused on mechanisms. The biology of aging is so beautiful that when you make a discovery, it just really fills your heart. What I can say to the people that are starting to study aging now is that I think we are on the verge of a revolution, that the science of aging is maturing and becoming a medical science, and a discipline that every doctor will have to be competent in to practice high-level medicine. There’s never been a more appropriate moment to dedicate oneself to older adults. It has an important societal role, the emerging science is incredible and opportunities for new treatments are here. There is an aging population, the need is upon us. So, if you could take me back 40 years, knowing what I know now, I’d go into geriatrics again, for sure.

“The biology of aging is so beautiful that when you make a discovery, it just really fills your heart”

■ **Why are epidemiological studies, like the Baltimore Longitudinal Study of Aging (BLSA), so important for understanding the aging process and the promotion of healthy aging?**

In a way, the BLSA tracks the history of the science of aging. Nathan Shock created the BLSA concept in 1958, and, as I said earlier, his idea was to dissociate aging from disease. At that time, he contributed a small article in a local journal where he asked “what can we do to delay the effect of aging?” And he wrote something like this: “don’t smoke. Smoke two, three cigarettes a day and not more. I think that eating has nothing to do with aging, so don’t try not to eat too much, because that doesn’t really do anything, and you should take some vitamins.”; It was complete bogus. Nathan Shock created the foundations of modern research on aging through a visionary intuition at a time when information on the aging process was very limited and, in many cases, not based on robust scientific evidence. But when you look back at those times, it is clear that the ‘children’ of Nathan Shock have come a long way. We’ve been talking about the extraordinary opportunities afforded by the science of aging, but we already know that if you avoid smoking, exercise regularly, avoid becoming overweight and

treat hypertension and cholesterol, you can increase your life expectancy and health expectancy by 10 years. That, to me, is incredible. Most people don’t exercise and have sedentary lifestyles. That’s a shame, because if they did exercise regularly, they would be healthier and live longer, much longer. But to go back to the BLSA, when the study started, not everybody was getting the same measurements, and so when they were trying to do large analyses on multiple variables, they couldn’t compare one person with another. So, when I came to NIA, the BLSA was in slight disarray. The breadth of information collected was incredible — for example, it had the largest collection of longitudinal glucose tolerance test results and of anthropometrics — but all this information was disorganized. I thought that we needed to connect the phenotypes of aging with functional measurements, and I think that this had led to many successes from different perspectives, including biological, physiological and psychological. As the geroscience initiative started, we also realized that in order to study aging, we needed to look early. We needed to study healthy, non-disabled individuals, and this required transforming the study to look at resilience. In the last iteration of the BLSA, we started to implement new measurements across the four main domains of aging — changing body composition, energetics, homeostatic mechanisms, and neurophysiology and neurodegeneration — by challenging individuals through physical, mental and physiological tests, looking at the robustness of their responses, and measuring how quickly and effectively they return to a state of equilibrium after such perturbations. For example, we know that many metabolites change in the blood during a treadmill test and then usually return rapidly to baseline values. Does a mental challenge — for example, two consecutive hours of cognitive testing — have the same effects? We believe that information on resilience will be strongly related to outcomes, even in individuals who are seemingly healthy. So, I think that the BLSA remains up to date. It does have limitations: this is a study of healthy volunteers. To join, individuals must be of optimum health, they must agree to take part in the study for the remainder of their lives and many of them agree to an autopsy. It is not a true population-based epidemiological study in the sense that it is not representative of the general population, so it’s not very good for looking at incidence and prevalence of diseases. There are other studies that are much better for analysing prevalence and incidence, but they are not as helpful for studying mechanisms.

■ **For the last few years, the NIA has been ramping up its spending on Alzheimer's disease (AD) and AD-related dementias. Such spending has represented more than half of the institute's appropriations in recent years. Can you tell us why the NIA has placed such a strong emphasis on brain health in aging and dementia, and if this going to be a lasting trend?**

Starting in 2012, the United States Congress decided that AD was a central issue that needed to be studied, and we were lucky that they identified the NIA as the institute that was required to make progress towards the discovery of prevention and treatment. Why they decided this was important is simple: as the population ages and the burden of cardiovascular mortality is reduced, there are more and more people surviving into old age, and we know that the rate of dementia increases dramatically with age. There are many more people living with dementia, and this poses an important problem for our society and for the families of these patients. Patient groups have also pushed to address this not only from the perspective of understanding the disease, but also to organize care and reduce the stress of caregiving, and this represents an important part of how we can reduce the burden of dementia on society. When I was a geriatrician, I always said to people with dementia that we didn't have any drugs. There were drugs, but the drugs didn't and still don't really work. But I could do a lot by talking to the families, teaching them how to help the patients in order to reduce the burden of care and how to behave in the most critical situations, and I think that this 'treatment' was incredibly effective. But science had to grow, and that's why the NIA got involved. AD is a very difficult nut to crack. I think the amyloid hypothesis is kind of fading and people are struggling to find other hypotheses, but I'm confident that we will find solutions, although it will take some time.

This gives me the opportunity to talk to you about the Center for Alzheimer's and Related Dementias (CARD; <https://bit.ly/33hirHR>). As extra funds were granted to the NIA, the NIA leadership felt that we needed to do something different. More and more resources were dedicated to AD using traditional funding mechanisms. It was time to break this cycle and experiment with something different. The idea of CARD is to create an intramural entity located on the NIH campus that is strongly focused on finding a cure for dementia; we want to see progress towards a cure. We will provide considerable funding, enough for people to try new things, more risky things,

to steer the field in new directions. Some projects will likely fail, but if you don't take risks, you're more likely to miss important discoveries. There will be opportunities for young people who have bright and innovative ideas; we will provide them with opportunities for early independence. So instead of being postdocs under somebody, if they show initiative, they will be given the means to fulfill their research dreams. Another idea is that we will try to connect the intramural and extramural programs with industry and advocacy groups and foundations. I know that this is a really difficult thing to do, but it will be one of the missions of CARD. We are recruiting a Director, and we have excellent candidates that we are currently interviewing. The Director will be given a lot of flexibility to implement his or her own vision. We won't be dictating what they're going to do, but, of course, we will maintain strong general oversight to make sure that the appropriate steps are taken, and we will also oversee the connections with external communities. We are trying to do something different here. As I always say to Richard Hodes, the NIA Director, this is an experiment. Sometimes pilot studies bring new knowledge, sometimes they don't work, but I hope that this one will work. It's certainly worth trying something new.

■ **The year of 2020 has seen the issue of systemic racism brought to the forefront of public interest worldwide, and several movements and initiatives have emerged to address racial inequalities in the STEM fields. How does the NIH in general, and the NIA in particular, support diversity, inclusion and equity in research, including among research participants?**

Diversity at the NIH is becoming a theme of central importance. We are trying to increase diversity in our working environment, and there is a strong push to grow a cadre of young investigators from diverse backgrounds, including different racial and socioeconomic backgrounds. I am confident that this action will enrich the NIH and make it a more effective and productive scientific environment, as well as a more welcoming workplace. There are many opportunities and many initiatives along these lines. Just a couple of examples are the Diversity in Aging Research Pipeline Program, or DARPP (<https://bit.ly/3fxE4Zu>), which provides development opportunities within the NIA for fellows from underrepresented minorities, socioeconomically disadvantaged backgrounds or with a strong commitment to promoting diversity and inclusion; a further example, at the NIH

level, is the Scientific Workforce Diversity Office (<https://diversity.nih.gov/>), which leads the NIH's effort to diversify the national scientific workforce (<https://www.diversityprogramconsortium.org/pages/>) and expand recruitment and retention of emerging diverse scientists across different disciplines (<https://commonfund.nih.gov/first>).

There is also a strong commitment to include diverse populations in clinical trials and in epidemiological studies. The COVID-19 pandemic further highlighted that race, socioeconomic status and access to health care are barriers to equal health for all. In collaboration with other NIH institutes, the NIA recently co-funded the Rapid Diagnostic Accelerator for Underrepresented Populations (<https://bit.ly/3fxGTty>) funding opportunity announcements (RADx-UP), which are focused on underserved and other COVID-19-vulnerable populations. It is also a general policy at the NIH that women and members of minority groups must be included in all NIH-funded clinical research (<https://bit.ly/2JcxFqo>), and this policy should be considered in all NIH-funded research. In spite of the difficult period the United States is in, I think the NIH is a place where creating an enthusiastic and productive diverse workforce is possible. This really is an important issue that we want to address, and I'm fully in agreement. I'm totally in support. My lab is highly representative of different racial backgrounds. I think that diversity makes life inside the lab more interesting and rich.

■ **My final question is about COVID-19. It would not be a complete interview without me asking a question on something that has greatly affected all of us this year, and which is, of course, of primary importance in aging research given the demographics of the disease. What is the impact of the pandemic on running a large scientific institution like the NIA, and how do you think the pandemic will affect future funding levels and opportunities in aging and geriatric research?**

As you can imagine, this is on my mind every time I go to bed and try to sleep. Depending on the day, I'm either pessimistic or optimistic, and I'll have different views. On the days that I'm optimistic, I think that the public and Congress realize that we need science more than ever.

COVID-19 is the first pandemic in a long time, and many years ago I used to tell people "this is not a problem of 'whether', this is a problem of 'when' this is going to happen." We knew this would happen,

and we cannot exclude the possibility that this will happen again. I hope that people realize that having strong scientific institutions where threats such as this virus can be studied quickly and proficiently is an asset for the United States. As a result, I think that ultimately the NIH and other related institutions could grow and become stronger. But on more pessimistic days, I feel that there is also the possibility of a catastrophe, that people will say, “well, we have the country that is on the verge of collapse; yes, we’d like to have the NIH, but that’s something that we don’t absolutely need to have”, and they could decide to cut the budget by 20 or 30%, or more. This would be a tragic mistake, but we will deal with whatever situation we are confronted with. The NIH would certainly try to do more with less and continue its mission in spite of the difficulties. Curtailing science would be a mistake, because COVID-19 has shown that a strong scientific enterprise, encompassing the public and the private sector, can act as a shield against unexpected events that challenge the health of the United States and other nations. A weakened science would also put into question the primacy of the United States in the business of science.

In the end, this will be a political decision. It will depend on who is the next President of the United States. But this is also true elsewhere in the world. Some governments will say that they will be protecting science, academia and education, and others will say “no, this is really of no value; we don’t really want to invest in this”. I don’t have a crystal ball, but I will say that there are more days where I’m optimistic than pessimistic.

“Curtailing science would be a mistake, because COVID-19 has shown that a strong scientific enterprise, encompassing the public and the private sector, can act as a shield against unexpected events that challenge the health of the US and other nations”

COVID-19 has been a horrible experience for all of us, but it’s also an incredible natural experiment. Going back

to my definition of aging as the competition between damage accumulation and resilience mechanisms, when you are an older person and are exposed to an insult, your body’s ability to respond to that stress is reduced. This is absolutely consistent with the fact that a disease like COVID-19 is more likely to be fatal in older people, and particularly older people with multimorbidity, because these populations are less resilient and have accumulated more damage. One great question that at some point we will need to address is what’s going to happen to those who have developed COVID-19 but have overcome the disease. Has the disease affected their compensatory capacity? Does this put them at risk of accelerated aging in the future? And think about the children who have contracted and overcome the disease. Did the disease create an epigenetic memory that will last for their lifetime? I think these are questions that those who study aging will really need to address.

Interviewed by Sebastien Thuault

Published online: 14 January 2021
<https://doi.org/10.1038/s43587-020-00009-z>