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COMMENTARY

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Ethical perspectives on advances in biogerontology

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1 | INTRODUCTION

Worldwide populations are aging with economic development as a result of public health initiatives and advances in therapeutic discoveries. Since 1850, life expectancy has advanced by 1 year for every four.[1] Accompanying this change is the rapid development of anti-aging science. There are three schools of thought in the field of aging science. One perspective is the life course approach, which considers that aging is a good and natural process to be embraced as a necessary and positive aspect of life, where the aim is to improve the quality of existing lifespan and "compress" morbidity. Another view is that aging is undesirable, and that rejuvenation and indeed immortality are possible since the biological basis of aging is understood, and therefore, strategies are possible for engineering negligible senescence. Finally, a hybrid approach is that life span can be extended by anti-aging medicines but with uncertain effects on health. While these advances offer much promise, the ethical perspectives are seldom discussed in cross-disciplinary settings. This article discusses some of the key ethical issues arising from recent advances in biogerontology.

2 | ADVANCES IN GEROSCIENCE

The biological basis of aging is increasingly understood, and myriad ways of altering aging are now known. One cause of aging is the accumulation of molecular damage, such as DNA mutations and misfolded proteins. Damage can further lead to "meta-effects," such as the emergence of senescent cells or dysfunctional mitochondria, which contribute to a feedback loop of damage and dysfunction.[2] These deleterious causes of aging are offset by endogenous repair and rejuvenation pathways, many of which are linked to nutrition and metabolism. Dozens of genetic, pharmacological, and other interventions can slow aging in the laboratory, in species ranging from yeast to non-human primates. Two major classes of interventions are currently entering human clinical trials. One class activates nutrient signaling pathways to turn on endogenous repair and rejuvenation pathways. The other class targets deleterious meta-effects of aging, such as senescent cells or stem cell dysfunction. Metformin is a diabetes drug that appears to activate aging-related nutrient signaling pathways.[3] A large randomized controlled trial to test if metformin can delay age-related multimorbidity is being planned in the United States. Inhibitors of the protein-sensing TOR complex can activate protein repair pathways and extend lifespan in the laboratory,[4] and a clinical trial recently showed that TOR inhibitors can prevent respiratory infections in vulnerable elderly patients.[5] Drugs that restore the metabolic signaling molecule NAD[6] and activate NAD-dependent sirtuin enzymes are also under investigation.[7,8] Eliminating senescent cells extends healthy lifespan in the laboratory by reducing damaging inflammation,[9,10] and a number of drugs to target senescent cells are entering clinical trials.[11] Stem cells can be rejuvenated in the laboratory with factors derived from young blood,[12] or by

direct infusion of healthy stem cells. Both approaches are now being studied in clinical trials to treat physical frailty[13] and dementia.[14] In the future, direct genome editing could be used to treat aging.[15] An international consortium is working to move anti-aging therapies more rapidly into clinical trials.[16]

3 | TECHNOLOGICAL ADVANCES

If maintenance of function rather than life extension is a key desirable outcome during the aging process, then technology has an important role in achieving this goal in the presence of physical disabilities as well as cognitive function impairments.

Stroke is a commonly encountered disease that increases with age and is a major contributor to disability burden. Advances in technology-assisted rehabilitation are developing rapidly in augmenting neuroplasticity during the recovery period through the use of exoskeleton robotics. Robotics are also being used for surgical procedures to improve accuracy, and to a smaller extent, service and companion robots are being developed and adopted in care of older people with physical and cognitive impairments. Artificial intelligence is being applied to diagnosis and treatment using algorithms. Another rapidly developing field involves surveillance of older people in hospitals or residential care settings, as well as at home, to prevent adverse outcomes, such as falls, accidents, acute medical conditions for which older people may have reduced ability to call for help, and also for health maintenance (monitoring of drug compliance, vital signs, activity patterns). Older adults are not always involved in the development or deployment of these systems. For both biogerontological research and gerotechnological developments, other than addressing the scientific question, the needs of older people should also be a driver and hence older people's input is desirable.

4 | ETHICAL PERSPECTIVES

4.1 | Is aging a disease?

It is commonly assumed, in the debate on the ethics of anti-aging research, that the question of whether aging is a disease or not carries high normative significance. For instance, some people hold that if (and only if) aging is a disease, then it is an appropriate target for medical intervention; otherwise it is not. On a more pragmatic note, it seems clear that being able to label aging as a disease would facilitate access to research funding, the initiation of clinical trials, and potential coverage of future anti-aging interventions by medical insurance.

The question of whether aging is a disease or not depends on how we should understand disease and health, which is a contentious issue in the philosophy of medicine. One approach holds that disease is a departure from "normal" human functioning, and that if a condition is universal and the result of internal biological processes, it cannot be abnormal.[17] Since all humans age, this approach implies that aging itself is not abnormal, and therefore not a disease. On a different, conflicting approach, any condition that demonstrates sufficient structural similarity with paradigm examples of disease should itself be regarded as a disease, even if it is universally shared. Some authors have argued that this description applies to aging.[18]

When it comes to establishing the medical legitimacy of anti-aging interventions, it might be possible to sidestep that difficult issue by considering the fact that a medical, preventive rationale can be offered for slowing down (or, if at all possible, reversing) the aging process, regardless of its status as a disease. Indeed, a growing number of biogerontologists are suggesting that doing so might help delay, if not prevent completely, the advent of diseases like cancer, Alzheimer's, or cardiovascular disease. That being said, the existence of such a medical rationale does not automatically put an end to the ethical debate about the overall permissibility of this kind of intervention: at least in principle, it could be overridden by countervailing considerations. Neither does it show that the question of the status of aging as a disease can be avoided completely, if only because of the significant practical implications of the answer that we collectively decide to give to that question, as mentioned previously.

Still, it would seem that the preventive rationale for anti-aging medicine is not always sufficiently taken into account in the ethical debate. The onus is on those who oppose intervening in the aging process to offer an explanation as to why the putative undesirability of doing so outweighs the preventive rationale for intervention. Without prejudging whether they can succeed, one can at least note that it is important for them not to confuse the effects of *biological* and *chronological* aging. Of course, the same point applies to those who support anti-aging research: They must take care not to overestimate the potential impact of such research on the diseases of the elderly—on this, it is primarily scientific experts who can provide the needed reality check.[19]

4.2 | Life extension, justice, and equity

Modern medical science could give humans an extended lifespan, increased life expectancy at birth, and a compression of morbidity in late life. Would this be desirable? An extended life is not (yet) the immortality that has been viewed by some philosophers (e.g., Bernard Williams) as undesirable for being intolerably "boring" and as undermining the conditions of continued identity.[20]

Reasons for and against extending life may be divided into the personal and external. The latter include the increased costs of an older population. But it is not clear that this is problematic if morbidity is compressed. Moreover, longer lives increase the temporal discounting of costs, as well as the number of productive years.

It is also not evident that extended lives mean that the young would unfairly subsidize the old if we adopt a whole-life perspective and think in terms of turn-taking.

Longer lives might, of course, mean more lives and thus raise population ethics issues. Yet the evidence here is unclear. Moreover, the extensions envisaged by geroscience need not be dramatic; and the problematic pressure on global resources is a broader one than that of prolonging human lives.

It would not be ethically problematic to control reproduction and thereby balance a right to a longer life against a right to procreate.

Personal reasons to want more life are for more of what life offers. Such reasons for longer life should be clearly distinguished from impersonal reasons for longer life. Whether everyone has such reasons is doubtful. If Williams is right that longer life will be intolerably boring and undermine the conditions of continued identity, after a certain age (which might differ from person to person) they will not.

Concerns are likely to be raised about justice when considering any interventions to extend life. One source of such concerns centers on the ease with which people can access the results of biogerontological research. Where doing so is expensive, it is likely that the beneficiaries will primarily be those who are already better off—resulting in longer lives for the rich alone. But even with equal access, concerns about the justice of biogerontological research remain. This is because differences in adult life expectancy, tracking socioeconomic status, already exist in all societies. In general, the rich live longer lives, on average, than the poor—something that can largely be explained by social and environmental factors.[21,22] While work in biogerontology does not directly address those factors, it has the potential to either reduce or exacerbate their impact. In doing so it can either increase or decrease health inequality.

However, inequality is also inherently human. Some people on reaching an advanced age feel as though they have already lived life to its fullest, and do not feel the need to extend it further. It may or may not be that what life has to offer them is not something that they care to extend. The structural conditions of their lived lives may already have been patterned by social inequality at a very basic level.

For this reason, assessing the ethical acceptability of work in biogerontology requires taking account of its impact on both individuals and society. Doing so is not easy. It requires answering three questions. First, what are the overall benefits, and how will those benefits be distributed? Second, what is the likely effect on health inequality, and would alternative ways of using resources affect inequality differently? Third, how should we balance increases in well-being against increases in inequality where these occur? The first two questions are empirical. The answers will depend not only on the nature of the research. They will also depend on the social structures and makeup of each society. That is because how new treatments and interventions affect health inequality is likely to vary with existing levels of inequality, and systems of governance and welfare provision. The final question is normative and requires an assessment of how different values should be balanced where they come into conflict.[23-26] Answering these questions cannot be done in the abstract, and for each case will require a multidisciplinary approach that brings together scientists, economists, political scientists, and ethicists.[27]

4.3 | The good and the bad (misapplications)

Research and development in the field of anti-aging medicine has fueled a multi- billion dollar industry in the past decade,[28] with the largest proportion spent on integration of large omics datasets to find patterns in age-related diseases and the therapy of neurodegenerative diseases. While there are robust guidelines regulating clinical research in humans in the form of clinical research ethics committees, the regulation of unjustified and misleading claims about anti-aging products together with unethical clinical practices is problematic. Aggressive marketing and misleading claims in the pursuit of profit are not uncommonly encountered. This industry is fueled by a universal desire (albeit subconscious) to remain young, as well as the attraction of taking a product (medicines, hormones, dietary supplements) instead of changing behavior to lead healthy lifestyles, even though there is ample evidence of the health benefits of the latter. The recent case of gene editing of an implanted human embryo in a private facility illustrates how regulatory mechanisms have failed to keep pace with activities in these fields, even though there have been widespread discussions on the ethical perspectives of gene editing, where there remains uncertainty regarding long term side-effects of irreversibly altering the human germ cell line.[29]

4.4 | Issues relating to artificial intelligence and robotics

Various ethical issues need to be flagged up relating to the above developments. The use of robotic surgical techniques needs to be regularly audited to evaluate performance and complications. Similar data are needed for service and companion/social robots. Widespread use will depend on cost-benefit analyses, which may guide governments to decide on financing, and this will raise debates regarding prioritization in health care and issues of justice, as discussed above. Promising use of artificial intelligence and deep learning with big datasets from other industries is being introduced to health care with the availability of healthcare informatics and evidence-based medicine. Although this is predominantly led by commercial companies, many clinicians and data scientists are beginning to work together to determine how this may impact on clinical practice. Algorithms in diagnosis and management are determined by clinicians based on the latest evidence. The latter changes with time, and also there are many clinical scenarios for which evidence based on randomized controlled trials is not available, particularly among frail elderly populations, women, and people of various ethnicities who tend not to be included or are included in inadequate numbers to reach a definite conclusion. There are also issues with potential misuse of patient data and the legal framework if there are adverse outcomes. Nevertheless, machine learning would facilitate diagnosis and prognosis as an aid to doctors to manage increasing complexity; yet the "human" attributes of a doctor-patient relationship that distinguishes a good doctor would be difficult to replace.[30-32]

4.5 | Ethics and policies

Ethical recommendations as to what is permissible, obligatory, or impermissible are clearly distinct from proposals to make a law or to institute a policy. What is needed for proposals of this latter kind is a sense both of what is defensible and of what is feasible given existing laws, institutions, and practices, as well as public opinion.

Changes in law and policy can and should best be made by organizations that are sensitive to social and political realities, well connected to policy-makers, and able to engage in objective evaluation of issues. The Nuffield Council on Bioethics is such an organization. It is an independent body within the United Kingdom that examines and reports on ethical issues in biology and medicine. It was established by the Trustees of the Nuffield Foundation in 1991, and since 1994 it has been funded jointly by the Foundation, the Wellcome Trust, and the Medical Research Council. The Council has achieved an international reputation for advising policy-makers and stimulating debate in bioethics. It functions very much as the United Kingdom's national bioethics committee. Its terms of reference are: to identify and define ethical questions raised by recent developments in biological and medical research that concern, or are likely to concern, the public interest; to make arrangements for the independent examination of such questions with appropriate involvement of relevant stakeholders; to inform and engage in policy and media debates about those ethical questions and provide informed comment on emerging issues related to or derived from the Council's published or ongoing work; and to make policy recommendations to government or other relevant bodies and to disseminate its work through published reports, briefings, and other appropriate outputs. Many changes in law and policy within the United Kingdom—such as the legislation to permit mitochondrial replacement treatment—can be attributed to the work of the Council. Recommendations within Council reports may also be adopted by professional bodies. Its horizon-scanning activities allow it to identify those topics, arising from new developments, that might fall within this remit. It is for the Council then to decide on whether to engage in work on any particular topic. This work could take the form of a major report or only the preparation of a short briefing note that can provide policy-makers and relevant stakeholders with a clear sense of the scope of the topic and of the relevant social, ethical, and legal issues. The Council has already produced an eight-page briefing note on "The search for a treatment for aging."[33] Should circumstances or developments make it important to produce a longer report, the Council would be able to do so.

5 | CONCLUSION

Scientists, gerontologists/geriatricians, economists, engineers, bioethicists, and politicians should take a truly cross-disciplinary comprehensive approach, with formation of regulatory bodies accountable to governments, and development of mechanisms for monitoring. Current clinical research ethics committees may need to be expanded to link with government regulatory bodies. The exact requirements will likely depend on variations in development in this area in different countries; there would be an advantage to the formation of a transnational organization following the principles of the Nuffield Council.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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