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The Fallacy of the Longevity Elixir: Negligible Senescence May be Achieved, but Not by Using Something Physical

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Abstract: The process of aging is a continuum of degeneration which eventually leads to loss of function and clinically manifest disease. Yet, in the purely therapeutic sense, there is a distinct clinical and practical separation between age-related degenerative diseases and the background process of aging itself. It is quite possible that biomedical technologies will prove invaluable in treating or alleviating the impact of distinct age-related degenerative diseases such as cardiovascular disease, arthritis or dementia. However, when it comes to addressing the fundamental, background stochastic nature of aging, it is unlikely that regenerative biotechnologies will have any appreciable impact in continually counteracting the process. In this paper we discuss some essential conceptual obstacles, both functional and translational, which will prove overwhelming and which preclude the notion that aging can be eliminated by using physical therapies. Our reasoning is two-fold: 1. Disruptive regenerative biotechnologies interfere with the complex, dynamic topological architecture of the human organism, in a manner that will render them unsuitable for clinical use against all age-related degeneration. 2. Even if some regenerative biotechnological treatments are developed in the laboratory, the translational issues will be insurmountable, and the treatments will thus be practically unusable by the general public at large. Predictions about the near or mid-term development of rejuvenating biotechnologies are not sufficiently grounded, and do not provide a framework for effective practical achievement of negligible senescence. Instead, the answer must lie in more global and abstract methods which align well with evolutionary mechanisms based on techno-cultural societal necessities. These are likely to operate in a way which ultimately may downgrade the importance of human aging and make it an evolutionarily unnecessary process.

Keywords: Biotechnologies, cellular networks, clinical medicine, complexity, rejuvenation, translational medicine.

INTRODUCTION

It must be emphasised at the outset that in this paper we will discuss the shortcomings of therapeutic interventions directed at the basic biological process of aging. The discussion is not applicable to individual clinical age-related degenerative diseases, but to the evolutionary cause of this degeneration. It is quite possible that we will devise effective therapies based on biotechnology aiming to temporarily postpone certain age-related degenerative diseases. Considerable progress has been made in targeting individual diseases, and research appears promising. However, it would be almost impossible to radically extend lifespan and achieve a state of Negligible Senescence, where the rate of human mortality by reasons of age is negligible, solely by using these 'repair-only' biotechnological methodologies [1, 2].

The rationale of the 'repair-only' worldview is to repair time-related damage when this damage is of sufficient magnitude to cause clinical or pre-clinical manifestations [3]. This line of thinking is flawed on many fronts [4], as it depends on a number of assumptions which have not been addressed in sufficient depth. In this discussion, we will concentrate on two such broad assumptions:

1. That the human organism is defined by mechanistic characteristics, and
2. That rejuvenation biotechnologies will be usable by the general public at large.

Our intention is to show that both of these assumptions are false.

PART 1. THE MECHANISTIC NATURE OF HUMANS

Although some scholars compare the human organism to a machine [5] which can be repaired merely by replacing damaged or worn out parts [6], this is a fallacious view routed in reductionist and even naïve thinking. The human body is not a machine. It is not even a very complicated machine. It is something immensely greater and this greatness can be measured [7]. It is a complex adaptive system with emergent characteristics which are more than the total sum of its constituents [8]. Although there are structural modular characteristics to the way a human body is organised, new properties emerge at higher levels which are external to the dynamics of individual constituents. These upper level properties can influence the behaviour of the individual constituents without necessarily being influenced by them [9].

Several authors have challenged the traditional view of the mechanistic and reductionist nature of human biology [10, 11]. The determination of biological organisation is a

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complex phenomenon depending on more comprehensive and abstract factors [12]. While it is true that complexity science does not eliminate the need for reductionism, nor does it invalidate all reductionist philosophy, it nevertheless helps us comprehend, and deal with, many natural phenomena. The issue here is that if the human body cannot, for therapeutic purposes, be compared to a machine but it is treated as such, then the results of this treatment are bound to be ineffective [13].

Talbot [10] states:

> *"When scientists talk about…genes that are components comparable to the cogwheels of a mechanical (device), this ought to be scandalous. As a strange aberration of thought, the biologists' intransigence in likening organisms or their parts to machines…is extraordinary in the history of science and perhaps notable even by the standards of a pre-scientific age!" (exclamation ours).*

For instance, the behaviour of signalling pathways is not mechanically straightforward with a clear input and a clear output. Signalling pathways use collaborative 'cross-talking', transferring information back and forth, and continually evaluating the response from other signalling pathways (for example [14, 15]). Tabulation of this cross-talk between just four such pathways has led to a 'horror graph' where it seemed that 'everything was doing everything to everything' [16, 17], although others have claimed that many of these signalling activities may be non-functional and thus easier to predict [18].

Many studies show that body components can adopt 'unexpected' functions depending on their environment. One example is the tissue transglutaminase (TG2) gene which has been called a 'molecular Swiss Army knife' due to the constant discovery of new functions for it [19]. Another example is adrenaline, which functions either as a hormone or a neurotransmitter depending on the situation being studied.

A single signalling receptor may have up to 2 billion different possible configurations depending on the interactions of the activator molecule with other molecules, and this activated receptor is not a mechanical clockwork device, but it has been described more like a 'pleiomorphic ensemble' or a probability cloud [20].

Furthermore, the DNA is not a mere sequence-specific molecule, a linear arrangement of bases exhibiting 'Read Only Memory', but it is a dynamic, plastic nucleoprotein complex which is constantly changing, interacting with its environment and achieving polymorphic states [21, 22] and its expressive communication characteristics are different depending on the tissue type, the stage of the organisms' development and its state of health [10].

This begs the question: if a widespread 'repair-only' rejuvenating biotechnological therapy is developed, how would its actions align with the above notions? In the above arguments, there is no place for simplistic approaches which aim to merely delete a deleterious gene or enzyme and replace it with a new one. Replacing a damaged gene or enzyme with another would also need to question its ability to be re-integrated and establish itself within the entire network, and take active part in the existing 'cross-talking' [23], otherwise the procedure may result in further malfunction.

For instance, according to the view that the function of a gene is not solely dependent upon the molecular sequence of the gene alone [24] an attempt to repair a faulty gene may, even if successful, not provide lasting effect, as this will not take into account the multiple other (non-gene) factors which participate in the totality of the gene's environment, such as degeneracy, epigenetic influences, or disturbances in the cell-to-cell, gene-to-gene, or receptor-to-membrane interactions.

In addition, the effects of antagonistic pleiotropy need to be taken into account. If a gene codes for a beneficial protein early in life and for an adverse one late in life, then an attempt to repair this specific gene needs to determine which configuration of the gene needs repairing, and what would the consequences of this intervention be on other neighbouring genes or molecules. Designing a genetic therapy aimed at silencing a particular gene early in life, may have completely unintentional adverse effects later on [25].

TOPOLOGY OF CELLULAR AND GENE NETWORKS - INTERFERENCE WITH NETWORK INTEGRITY

Cellular networks are not homogeneously cross-reacting with other cells but are integrated according to different configurations. It is known for example, that there exist weak links between some cells, and strong links between others [26]. Aging results in decreased attractiveness (fewer cells are attracted into a hub of strong links), increased isolation between cells, and loss of integration [27]. In humans, cellular networks are 'small worlds' which means that information can reach any given cell within the network by passing through only a small number of other cells [28] (Fig. **1**). This assists in the global propagation of information within the network. Our networks have a scale-free distribution with hubs of cells having a large number of neighbours forming hierarchical (structured, of increasing functional complexity) communities [29]. This helps protect the constituents of the network against insults and stresses.

Age-related damage is both due to deletion of links between cells and permanent damage of the network elements themselves (*i.e.* the cells), leading to deterioration of emergent properties of the network [30]. This results in poor spread of information across the network and thus eventual dysfunction. Repair-only approaches aim to repair some cellular elements of the network but ignore the damaged links, therefore network remodelling remains disorganised and inefficient. When we consider therapeutic replacement of cells (such as in the case of stem cells) the final effect will depend on whether the cell is able to assume a function within the network with either weak or strong links with other (either existing or transplanted) cells. This makes the result difficult or impossible to predict because some elements of the network carry less importance than others. Restoration (through repair) of a large number of weakly-connected cells will lead to a different functional result than the restoration of a small number of strongly-connected cells. In addition, it is not just the individual cells that matter but also molecules such as chaperones which may, largely inde-

pendently of the cell, improve or alter the links between cells [31] (Fig. **1**).

With respect to genes, it has been proposed that certain elements of the aging network are less important than others, and many longevity-related genes (just as in the case of cells, discussed above) can be found in hubs [32]. Therefore, it must be determined which hubs need repairing, hubs that are more likely to result in improvement in function, compared to a blind repair aimed at all affected genes.

CONCLUSION OF PART 1

In order to make progress in eliminating aging, we may need to move away from First and Second Phase science methodologies and embrace the Third Phase science worldview [33]. Currently, science treats humans as objects and empirically assumes that they can be treated with minimal mistakes. Patients are considered as 'non-constructed objects'—as problems, whose needs can be diagnosed and assessed without any degree of self-construction. This approach is quite unsuitable for dealing with the complex phenomenon of aging. Third Phase science on the other hand, is concerned with the nature of our interactions with the outside world (also based on information technologies), where the observer must also behave as a participating actor, aggressively contributing to the process and developing new activities and innovations. This is contrary to the view that humans are machines which depend on individual component replacement in order to achieve and maintain health. Instead, it inspires us to adopt more complex and sophisticated methodologies which take into account the fact that we (the observers and therapists, as well as the patients) also play a part in the repair process itself [34].

PART 2. APPLIED CLINICAL CONCERNS: TRANSLATING BIOTECHNOLOGY INTO CLINICAL PRACTICE

Even if we assume, for the sake of argument, that some rejuvenation therapies will be developed, substantial clinical concerns remain [4, 35]. In this section we will highlight certain crucial problems. The clinical applicability of these putative treatment suites is quite confusing and vague. For instance, de Grey suggests that we need to target age-related damage before this becomes manifestly pathogenic, to everybody from the age of 40 and up [36]. However, a practical concern is that there are people who have no clinically manifest pathological age-related illness, even at the age of 70 or 80 years. Therefore, each patient will have to be individually assessed before initiating the therapies, as it would not be a matter of a universal chronological age cut-off point. In addition, questions such as "which organ to concentrate on?", and "what happens when a new disease appears in someone who is already on treatment for something else?", still remain and need to be individually evaluated. Rejuvenation therapies with stem cells aimed at specific clinical diseases (such as those, for example, against heart disease) can eventually be successful. However, the process of aging will continue to operate long after the treatment has been applied, and so the damage will continue to be an issue. Therefore, the putative treatment will need to be repeated in perpetuity in order to be effective.

A. PROBLEMS WITH STEM CELL THERAPIES

One methodology of delivery of biotechnology rejuvenation therapies (such as stem cell therapy) is through bone marrow transplant [37]. This is a complex, clinically risky,

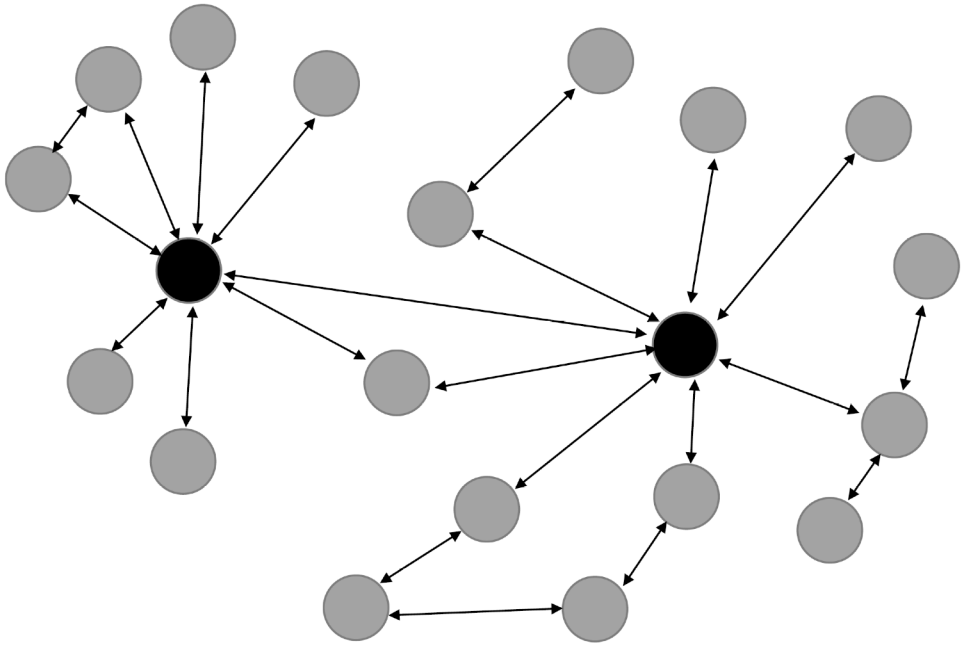

Fig. (1). 'Small-world', scale-free cellular networks.
Schematic representation of transmission of information between individual cells which are connected with other cells. Most cells in this network interact with only one or two other cells (weakly-connected cells) whereas two (black) are connected with many other cells simultaneously (strongly-connected cells, forming hubs). In this example, these strongly-connected cells can communicate directly with 75% of other cells, whereas weakly-connected cells interact with just 10% of others. Random damage (or repair of damage) in some weakly-connected cells is not likely to cause significant disruption (or benefit) to the network, whereas damage to, or repair of strongly-connected cells is going to affect huge parts of the network.

and administratively complicated procedure. It is well beyond the relatively simple technical issue of artificially manipulating and repairing cells in the laboratory. Treatment protocols with stem cells need to be devised, having in mind the specific needs of each and every patient, and these must be modified to take into account each patient's precise condition as it develops. The approach needs to be tissue-specific, time-specific, and patient-specific.

We will now consider an example of the clinical intricacies of autologous cell harvest and subsequent bone marrow transplant. This is a protracted and complicated procedure, involving several clinical assessments, administration of a Colony-Stimulating Factor [38], chemotherapy, insertion of an indwelling central venous access line, followed by intravenous (or intra-bone marrow) injection of primed stem cells and a hospital stay for up to three months. The follow-up period can be one or two years in some cases, and there is a need for specialist nutritional input, home care, occupational therapy, medical follow-ups and regular clinic appointments. The injected stem cells need to develop cross-talking pathways with existing mesenchymal and endothelia cells, as discussed above [39], which involves a precise, co-ordinated, dynamic and hierarchical expression of genes and proteins, many of which are based upon stochastic elements, which are impossible to predict [40]. This may influence the lifespan of the injected stem cells and require an earlier-than-planned retreatment. For specific organs, such as for example, the lungs, the procedure may involve endobronchial infusion of stem cells, repeated once a month for three months [41]. It would be necessary to devise evidence-based standards which would encompass and address issues such as cost-effectiveness, and must be clinically practical and acceptable by the regulating authorities of each and every country [42]. We are, of course, acknowledging the possibility of the development of softer methods such as harvesting stem cells from the skin, but these are unlikely to totally eliminate all the translational problems.

B. PROBLEMS WITH VACCINATION

One possible way for augmenting the rate of elimination of extracellular abnormal material could be by stimulating the immune system *via* a vaccine [3]. The technical obstacles in developing this would be formidable, however its introduction into the clinical domain would pose additional, although non-insurmountable problems. For example, it is well known that many people are reluctant to be vaccinated: vaccines such as those against pneumonia, or hepatitis [43], have low adherence levels and the non-compliance rate for hepatitis B vaccination in the US is around 28% [44]. In addition, only 30% of physicians may agree to vaccinate the patients if they are not clear on the guidelines or its benefits [45]. Therefore, it is not only a matter of persuading and educating the patient to use the vaccine, but also a matter of persuading and educating the physician.

C. PROBLEMS WITH TISSUE ENGINEERING

A proposed biotechnological therapy against a feature of aging, such as abnormal tissue function due to cell loss, is based upon tissue engineering [46]. Although the technology necessary for developing large amounts of viable engineered tissue such as bone, skin or even heart can be achieved, a major problem is the transplantation of this engineered tissue to the appropriate organ in humans. Autologous cells must be harvested from the patient, either surgically or through a bone marrow procedure as discussed above, and then, following appropriate engineering interventions, transplanted surgically in the patient. The clinical sequences of the procedure, particularly those involving more advanced techniques such as *in situ* and *in vivo* tissue engineering [47] currently take a year from beginning to end [48]. Therapies involving allogenic tissues will require lifelong immunosuppression [49]. This would be a therapy for one type of tissue, and therefore the entire procedure would need to be repeated for other types of tissue, until all tissues affected by age-related damage would have been repaired. Questions about the number of qualified surgeons needed in order to carry out these procedures *en masse* would need to be addressed. Post-procedure assessments, risk of infection or thromboembolism, and other intrinsic consequences of surgery would add to the existing difficulties.

D. PROBLEMS WITH GENETIC THERAPIES

As a concept, gene therapy appears ideal in treating age-related degeneration. However, this is an oversimplification fraught with clinical obstacles. There are several hundred genes that can modulate the aging process. In mice alone there are over 100 [50]. Issues with pre-existing immunity to the vector, choice of vector, costs, dose, and many others need to be addressed. Non-viral vectors such as liposomes or methods based on nanotechnology need to be administered to the patient *via* an intravenous route with all the problems discussed above. The new gene may not be inserted correctly on the DNA, or it may be overexpressed, causing more problems than it resolves. The risk of introducing infection or inducing a cancerous change remains.

For these and other reasons, the progress with gene therapy has not been as vigorous as expected [51]. New techniques such as CRISPR cannot easily be applied in clinical situations involving humans. The current administration technique involves a hydrodynamic injection method which in mice has been proven effective in some experiments, but, at present, remains unusable in humans.

E. PROBLEMS WITH NANOMEDICINE

It is almost certain that future rejuvenation biotechnological therapies will depend to some extent upon nanomedicine. However, the state of nanomedicine in the present and near-term future remains problematic. There is little information about these new materials and virtually no useful data on their bioaccumulation or toxicity. Environmental impact remains unknown [52]. The use of nanomaterials in bioengineering is being hampered by a host of unknown variables [53], for instance, unwanted neutrophil activation [54], vascular toxicity [55], inflammation ([56], and lipid peroxidation [57].

DISCUSSION

These methods of administration are likely to remain the same (with minor, irrelevant to this argument, technical

modifications) in the near-term (10-15 years) and perhaps in the medium-term (20-50 years) future. Bone marrow transplant is currently an appropriate method for patients who have one specific disease [58], but its applicability must be questioned when it is intended for people who have many co-existing age-related sub-clinical conditions. Our medical systems can tolerate this treatment if it is directed at a few patients having one condition each [58]. But a single stem cell intervention will not have an effect on multiple conditions or organs, therefore if we consider that there are many organs needing treatment against degeneration, then this becomes a clinical and administrative nightmare. However, it becomes an impossibility when, in addition to the above, we aim to treat large numbers of people.

Worldwide, there are approximately 60,000 bone marrow transplants performed each year [58]. If we assume that an arbitrary minimum 1% of all humans could possibly be treated with marrow transplant-dependent rejuvenation biotechnologies each year, then there will be a need to provide 70, 000, 000 such transplants a year. Assuming a reasonable, and perhaps generous, yearly 20% increase in our clinical capability to deliver rejuvenation biotechnologies, it will still take us 10 years to reach a mere 1 000 000 target patients - and at that point, the procedures would need to be repeated, in order to maintain the *status quo* [37]. In this hypothetical scenario we would only be able to treat a total maximum of 0.015% of humans, ever. Even if we consider more generous scenarios, it remains unlikely that the numbers will be improved significantly in practical terms.

In addition, patients would need to undertake other rejuvenation procedures such as vaccinations, cytotoxic and other drugs [3] or oral compounds [37], multiple crosslink breakers (drugs or enzymes), intravenous immunotherapy, apoptotic-modulators, and other treatment modalities [3]. And this has to be repeated until all organs or tissues where there is accumulation of age-related pathology have been treated. But this is not the end, as all of these procedures will need to be repeated on the same patient in perpetuity, in order to ensure a continual absence of age-related pathology for an indefinite time [3].

Let us look at the matter in a different way: One cycle of treating one group of sub-clinical damages *via* disruptive biotechnologies can take two or three months. The same patient will need to undergo the procedure again in order to address different organs for several other types of damage such as neurodegeneration, pancreatic degeneration, or visual age-related damage. If each such cycle takes on average three months, then there will not be enough months in the year for each patient in order to have the full treatment for each and every organ or tissue. The quality of life of the recipient will be reduced to a minimum, and it will be a miserable and endless cycle of hospital and clinic visits, treatments and follow-up appointments repeated into perpetuity in a dystopian, dehumanised society. The above discussion refers to the difficulties encountered during a scenario where we aim to treat just 10% of humanity spread over a 10 year period. If we now consider the difficulties associated with treating the other 90%, then it must be obvious even to the most ardent advocate of rejuvenation biotechnologies that this method of globally addressing the aging problem becomes a fanciful delusion. The hope that, perhaps, new technologies will be developed that can make our views obsolete, remains just that: a hope, which is not grounded in anything concrete or pragmatic.

We should also acknowledge the possibility that, although some therapies could be developed, these may not by themselves result in any appreciable benefit for the patient until other therapies have also been developed and deployed [59]. For instance, if a therapy is devised against atherosclerosis but not against cancer, the patient will perish from cancer-related damage, even if their arteries are healthy. So all of the above interventions need to be developed at an appropriately advanced clinical stage.

Pharmacological [4] and funding issues remain difficult, and if we can learn from the example of cancer, 300 billion dollars [60] have been spent in research during the past 40 years, while the cure rates are not significantly better [61]. This indicates the difficulty of translating research into clinically efficient treatments for large numbers of patients.

The dynamics of the therapy applied to any specific individual are likely to be disrupted in a way we cannot predict [62] in the presence of any pre-existing illness involving the liver, kidney or any other organ. In an individual affected by age-related degeneration, organs may not behave optimally and any intended treatment may result in unpredictable side effects, particularly if such treatment is complicated [4]. Issues of non-compliance to the treatment are real and relevant. We can compare rejuvenation biotechnologies to those aimed at treating cancer involving life-saving chemotherapy, where there is a significant 37% noncompliance rate in certain instances [63] rising to over 80% in those whose treatment was optional due to age or clinical condition. That is to say that up to eight out of ten older patients may decide not to have the treatment [64]. These are just some general indications of what we could expect with compliance to rejuvenation biotechnologies (Table **1**).

Each biomedical technology is associated with significant translational problems. The totality of these problems creates immense problems with respect to practical clinical applications. This is balanced by the possibility of new developments and achievement of 'proof-of-principle' methodologies.

At this point it may be worth reiterating that we fully recognise the value of biomedical rejuvenation technologies but only insofar as these are applied to specific and isolated diseases, and not to the biological process of aging itself. We are not arguing against the entire concept of biomedical technologies and we are not claiming that this field is entirely wasteful and clinically useless. It is important to emphasise our view: Rejuvenation biotechnologies will not be of any value for the great majority of people who are aiming to avoid all aging conditions and live a life without any clinically-relevant chronic degeneration.

FUTURE PROSPECTS

Within a wider framework [65] and based on the concepts of Third Phase science discussed above [66], it may be possible to explore ways where the process of aging may become redundant, or at least, significantly downgraded [67]. This may happen as a result of a change in the direction of human evolution [68], a transition from conventional evo-

Table 1. Problems and promises of biomedical technologies.

Proposed technologies	Expected clinical problems	Possible sources of optimism
Stem Cell Therapies	Harvesting, delivery	New methods of stem cell harvesting such as from the oral mucosa, modulators of stem cell generation, potential cost reduction
Vaccination	Compliance, provider reluctance	High mortality and disability risks without vaccination
Tissue Engineering	Harvesting, transplantation surgery	Proofs of principle for both intra-corporeal and extra-corporeal tissue engineering, at continuously reducing costs
Genetic Therapies	Delivery methodologies, integration	Developments in gene therapy against otherwise incurable metabolic conditions
Nanomedicine	Side effects, unknown results	Continual research and increasing experience in clinical settings
Pharmacological therapies	Non-compliance, polypharmacy	Past successes in treating both infectious and non-communicable diseases, strong role in extending life expectancy in the recent period

lution by natural selection to a state of 'co-evolution' (or intentional evolution [69]), whereby heritable adaptations to our environment which facilitate our survival can also influence the evolution of our environment itself. These adaptations are based on epigenetic modifications which act in relatively short periods of time. Our continuous integration within a techno-cultural environment [70] may enable certain, hitherto speculative, mechanisms [71] to operate in a way that shifts the allocation of repair resources from the germ-line to the soma, and thus promote a more effective somatic repair activity leading to a reduction of the rate of mortality due to chronic age-related degeneration [72]. The rationale is that, those humans who are embedded and well-integrated within a wider global meta-entity [73, 74] may be able to survive longer because their functional usefulness to the network is more important than their demise, according to the Law of Requisite Usefulness [75]. The term 'usefulness' refers to the value of an agent in facilitating the evolution of the entire network, rather than to individual utility. Here we are not referring to any conscious power that determines the length of human life. We are suggesting that natural mechanisms may exhibit a tendency to retain a 'useful' agent within a network if it is more economical, in energy terms, to continue repairing this well-embedded and active agent (mature human), rather than allow it to die and then spend additional resources in order to facilitate the re-integration of a new agent (baby) with the existing human network.

This concept can be tested in a variety of ways, for example conceptually [76] and experimentally (by comparing the telomeres of people who are meaningfully connected on line, to those who are not connected, perhaps living in a totally agricultural setting). Or, it can be tested practically by comparing survival statistics of people who use technology, plotted against life expectancy [75] (Fig. **1**). Mathematical ways of validating this are also being developed.

CONCLUSION

In this paper we argue against the perception that the global elimination of age-related degeneration will be based on any physical therapies. One reason is the adoption of inappropriate therapeutic approaches which do not take into account the complex nature of humans [77]. Human aging is an immensely complicated process, originating from profound evolutionary principles. Therefore, if our aim is to totally eliminate age-related degeneration and achieve negligible senescence (where there is no measurable functional decline with aging), we need to abandon simple mechanistic methods and, instead, adopt more sophisticated approaches based on more abstract principles which explore our evolving relationship with a technological environment.

In our view, the role of biotechnology in this respect is to help maintain function in clinical terms, even when starting at an early age [78] while background processes of aging are addressed by more fundamental evolutionary means. In this way it may be possible to have full integration of the two approaches within a holistic context which does not depend on whether aging may be viewed as programmed or not-programmed [79-81].

CONFLICTS OF INTEREST:

The authors confirm that this article content has no conflict of interest.

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Declared None.

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