Ageing and Ageing-related Disease

(Linda Partridge)

Contents

“If I'd known I was gonna live this long, I'd have taken better care of myself." - Eubie Blake (1883-1983), ragtime composer and pianist, on his 100th birthday, five days before his death.

1. At a glance

- Ageing is a complex process of accumulation of damage, and it is the major risk factor for the predominant killer diseases in developed societies.
- A major recent breakthrough has come from the discovery that mutations in single genes can produce a broad-spectrum improvement in health during ageing in laboratory animals and combat ageing-related disease.
- These findings are pointing to a new, broad-spectrum, preventative medicine for the diseases of ageing.

2. Definition of Topic

Ageing occurs by accumulation of damage to molecules, cells and tissues, resulting in loss of function and increased risk of death. Ageing is the major risk factor for the predominant killer diseases of developed countries, including dementia, cardiovascular disease and cancer. The major burden of ill health in is now falling on the older section of the population, and we therefore need to understand the mechanisms underlying the ageing process and the ways in which it increases vulnerability to disease.

Research is thus directed to understanding mechanisms of ageing in order to intervene in the process to improve health and reduce risk of disease in the older section of the population (*1*). A powerful approach to understanding ageing is to identify

interventions, genetic and environmental, that can slow the process and ameliorate ageing-related loss of function and disease in laboratory animals (*2-4*). Genetic manipulation of candidate mechanisms either for generation of damage or protection against it, such as mitochondrial function (*5*) or stem cell activity (*6*), has also provided major insights. Increasingly, research is examining the interactions between lifespan-extending interventions and specific models of ageing-related disease, to understand how ageing acts as a risk factor (*7, 8*). Much research into ageing-related disease is disease-specific, focussing, for instance, on Alzheimer's Disease, cardiovascular disease, sarcopenia or cancer. Increasingly the commonalities in the etiology of these diseases is likely to be recognised and understood.

Research into ageing is frequently conducted with laboratory model organisms, particularly budding yeast, the nematode worm, the fruit fly and the mouse (*9, 10*). Tissue culture systems and work with isolated tissues and with stem cells are also important. Comparative work on the evolutionary diversity the rate of ageing in different organisms, especially those with exceptional longevity, has also proved informative. Population-genetic association studies of longevity and health during ageing in humans are starting to make their appearance (*11*). Some experimental work with humans has looked, for instance, at the effects of dietary and exercise interventions (*12*). Demographic work with humans provides an interface with the social sciences, and often examines the whole life course as well as the ageing process itself (*13*). Clinical work on ageing *per se* is less common. Work on ageing-related disease also uses laboratory model organisms, as well as tissue cultures and tissue isolates. Work on human population genetic associations has been particularly successful in identifying genes, and hence processes, that are important in particular types of ageing-related diseases. The Alzheimer's precursor protein (*14*) and the proteins that process it, together with a group of genes associated with Parkinson's Disease (*15*), are already classic examples for neurodegeneratioin. The interface with clinical activity is much more firmly established for ageing-related disease than for ageing itself, a situation that should change over the next decade.

3. Status of the field

Research into ageing has moved forward extremely rapidly in recent years, and the field is changing and developing at an increasing pace. The main engine for change has been the discovery of single-gene mutations that extend healthy lifespan in laboratory animals. Furthermore, some of the processes involved, such as activity of nutrient sensing pathways, play a role in ageing in evolutionarily diverse organisms such as yeast, worms, flies and mammals (*16*). Simpler and shorter-lived organisms can thus be used to understand many aspects of human ageing. Increasing effort world-wide is directed to understanding exactly how these interventions that extend lifespan exert their effects.

One of the main messages coming out of work on the basic biology of ageing is that ageing is THE major risk factor for ageing-related disease. Interventions, such as single gene mutations and dietary restriction, that extend lifespan in laboratory model organisms by protecting against the effects of the ageing process itself, also delay or reduce the impact of diverse, ageing-related loss of function and disease (*17-19*). Thoughts in this field are therefore rapidly turning to the idea that there might in the

future be a broad-spectrum, preventative medicine for the diseases of ageing. This contrasts sharply with current medical practice, which tackles each disease separately at the level of research and clinical practice, and also tackles ageing-related disease separately from geriatrics, which is a largely non-research based clinical speciality. Unlike a scientific investigation, identification of possible drug targets does not require that we know everything about the system. One of the major, probably tractable, challenges in the near future is to identify and validate potential drug targets in animals that might be therapeutic in humans. This will require an understanding of just how deep the evolutionary conservation of the pathways involved penetrates. For instance, a key player here is insulin/Igf and TOR signalling. Reducing activity of these pathways in mice can extend healthy lifespan, but can also cause diabetes and apoptosis. It may be possible to narrow down to the benefit side of the disruption by homing in on the transcription factors somewhat downstream in this signalling cascade, depending upon how deep into the pathway the evolutionary conservation extends.

Research into ageing-related faces major challenges, with there still being essentially no preventative or palliative treatments for, for instance, Alzheimer's or Parkinson's Diseases. On the other hand, the research field is more mature than is the ageing field, with a substantial international community of researchers working in the area and many large international meetings devoted to the topic. A major new opportunity exists, none the less, to tackle these diseases through the contribution of the ageing process to them, and already work in animal models of these diseases has provided some promising results, for instance with lithium, rapamycin (*20*) and mutants in the insulin/Igf signalling pathways ameliorating neurodegenerative disease aetiology (*8, 21*).

Research on ageing frequently has to draw on expertise from other fields. For instance, molecular chaperones and their role in prevention of proteotoxicity are of great relevance both to ageing-related damage and to neurodegeneration (*22*). Epigenetic mechanisms are proving to be of importance in ageing, including trans-generational effects (*23*). Stem cells, tissue regeneration and biomaterials research are all coming to play a prominent role. Bioinformatics is of vital importance and, to a lesser extent, systems biology is starting to make its appearance in some areas of ageing research.

4. Key scientific questions and opportunities

There is general agreement that ageing is caused by damage, but there is much weaker understanding of the nature of the damage, the identity of the processes that generate it, and the systems that can protect against it. Many aspects of organismal state change during ageing, and a major challenge is to design and execute the crucial experiments to differentiate between the changes that are causal in ageing as opposed to bystander effects. A clear way in to these issues has been provided by the startling discovery of interventions that improve health during ageing and extend lifespan. Already these have called into question the leading importance of oxidative damage as a cause of ageing (*24, 25*), and have pointed instead to the importance of other processes such as endo- and xenobiotics and cellular detoxification and proteotoxicity. Understanding how lifespan-extending interventions achieve their effects will both throw further light on the nature of the normal ageing process and on the ways in which it can be ameliorated. Another major

challenge will be to understand the nature of the connections between the ageing process and the etiology of ageing-related disease. This will require work that combines manipulations of the ageing process with models of the diseases, to understand the interactions between them. For the findings of the work to be translated into humans, co-operation with clinicians will be essential. Research in teams with complementary expertise is therefore particularly likely to be successful.

5. Research opportunities, needs and challenges

Understanding a problem as complex as ageing provides research opportunities in many areas of the life sciences in which the Max Planck Society has strengths. Ageing occurs at many levels of organization, including modifications and damage to macromolecules, changes in gene expression, alterations in cellular biochemistry and the metabolome, damage to tissues and the systemic environment and alterations to the behaviour of the whole system. These changes lead to emergence of diverse ageing-related diseases. The relevant expertise to understand the ageing process is present in several Max Planck Institutes, spanning biomedical, social and physical sciences. Co-ordination of the effort in ageing would produce considerable synergies. The core expertise in MPG in instrumentation and technology will also be of key importance. Work on the model organisms, on cells in culture and on non-standard organisms with delayed ageing will be important, as will understanding of the causes of evolutionary diversity in the rate of ageing. Genetics, genomics in its broadest sense, imaging, bioinformatics, chemical biology and, eventually, systems biology will all be crucial for identifying drug targets and drugs for intervening in the ageing process.

Other challenges are practical and economic. Ageing research with mammals is unusually expensive – a long-lived mouse can live for over 4 years, and large numbers of animals are sometimes required for demographic analysis. Major animal facilities are therefore required to house and care for ageing cohorts. In addition, the research undertaken in at least part of the research portfolio should ultimately be translatable into clinical trials. However, a broad-spectrum, preventative medicine, for the diseases of ageing is a major promise, but also a major challenge for the drug pipeline. First, any drug would have to be put into clinical trails for years and would have to given to people who were not yet ill. This is unlikely to be practicable in the foreseeable future, and it will be necessary to home in on some more specific effects in an at-risk group, eg ApoE 4 and AD. In addition, the resulting drugs or other interventions need to be of a kind that will be considered by health care providers to be effective in terms of health economics. Industrial partnerships could be useful in, and chemical biology is likely to be an important in-house skill to be competitive in this area.

6. Expected outcome and benefit

Ageing is not only a cause of decline in function and quality of life but it is also the process that underlies diverse ageing-related diseases. Basic research in this has already identified many single gene mutations and environmental interventions that increase healthy life span, and has identified the signalling mechanisms at work. Research is now directed to refining understanding of mechanisms and identifying the changes that are

required for these effects, and will in turn lead to the identification of drugs that can be used to improve human health and protect against diverse ageing-related diseases. The impact of this research on human health will therefore be profound, and will lead to a revolution in the way in which clinicians think about and treat ageing-related diseases. Rather than a piecemeal set of interventions into specific conditions, we can instead look forward to a broad-spectrum, preventative medicine for the diseases of ageing.

7. International activities

Research on ageing-related disease is firmly established internationally, with well structured funding from public bodies and charities. Research in this area would be expected to be represented in any large, research-based, biomedical community.

The importance of more general health during ageing to national economies, given the increasing number and proportion of older people in developed countries, has been recognised with a policy shift towards funding of research into ageing. In the US, public funding is channelled mainly through the NIA (http://www.nia.nih.gov/), a branch of the NIH. Several charities are devoted to funding ageing research in the US, such as the Ellison (http://www.ellisonfoundation.org/index.jsp) and Glenn (http://glennfoundation.org/) Foundations and AFAR (http://www.afar.org/). Increasingly, large research groupings and whole institutes are dedicated to ageing research, such as the various Nathan Shock centres (http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BiologyOfAging/NathanShockCenters.htm), the Barshop Centre (http://www.barshop.uthscsa.edu/) and The Buck Institute (http://www.buckinstitute.org/) in the US.

Support and activity in Europe has been patchier. For instance, in the UK no dedicated charities for research into ageing exist, and public funding for the area has been sporadic and disorganised. Part of the reason is that most prominent diseases are ageing-related, and funding of disease-specific research predominates. EU funding has also been relatively low given the age-structure of many European countries. Examples of European foci of research into ageing include the UCL Institute of Healthy Ageing (http://www.ucl.ac.uk/iha/), The Newcastle Institute of Ageing and Health (http://www.ncl.ac.uk/iah/) and the Max Planck Institute for Biology of Ageing (http://www.mpg.de/english/institutesProjectsFacilities/instituteChoice/biologie_des_alterns/index.html).

Increasingly, international meetings are devoted to ageing research, including a Gordon Conference, the biennial Cold Spring Harbor meeting on Molecular Biology of Aging and Keystone meetings.

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