

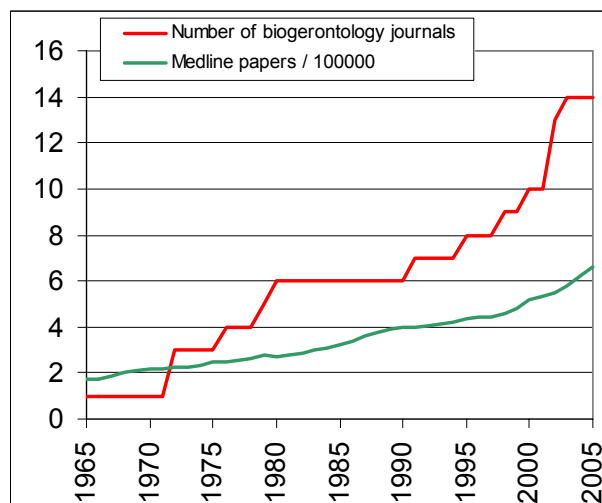
Biogerontology

Biogerontology is the study of the biological mechanisms and effects of ageing. It is distinct from 'gerontology' (which overlaps with 'biogerontology' but focuses more on the study of the causes of the problems of old people) and geriatrics (which is the study of ageing medical discipline of the treatment of the old, and specifically of diseases that only occur in old people such as senile dementia).

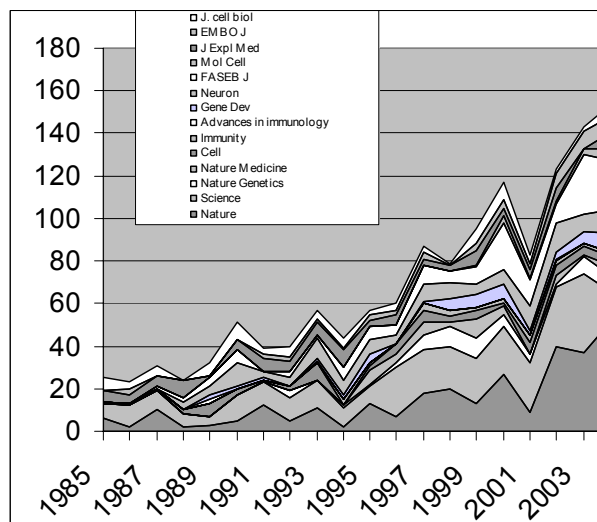
Biogerontology looks at the mechanisms of ageing at all levels: genes and genetics, proteins and their function, intracellular and intercellular signalling, metabolism, and organ and organism physiology. Over the last decade research has been dominated by gene-orientated research. Some groups, notably in Newcastle, are now focusing on the role of mitochondria in ageing, but still primarily using a gene-based approach because of the power of the technologies. The role of mitochondrial biology and reactive oxygen species, and their metabolism, has remained a part of biogerontology for over 40 years, as summarised in the PMRS technical appendix.

Rise in biogerontology

Despite the obvious importance of the ageing process to medicine, biology and society, systematic study of ageing has generally been regarded as a minor part of biology, and any study of ageing that implies ways of treating, slowing, preventing or reversing it (as any fundamental study must do) has in the past been regarded as fringe medicine. This has changed over the last two decades, and over the last 10 years in particular. Biogerontology has risen from being a fringe science in the 1970s and 1980s to being part of the mainstream of biology. The number of specialist journals in the field has grown at over twice the rate of growth of the scientific literature as a whole

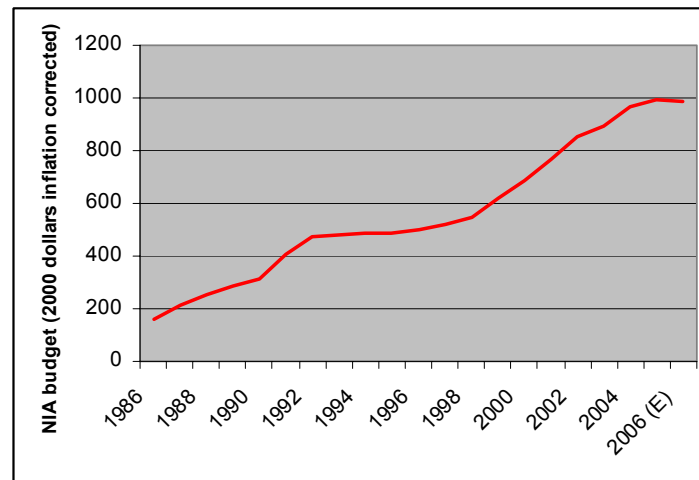


and articles on ageing itself started to appear in increasing numbers in the top scientific journals such as Nature, Science and PNAS in the 1990s



demonstrating an increasing scientific acceptance of this as a serious and important area of research.

Support for research in the field has grown substantially in real terms. The leading supporter worldwide for ageing research by budget size is the US National Institutes of Health National Institute for Ageing. The NIA budget has quadrupled in real terms in the last 20 years:



In the last decade many leading research centres have recognised this trend and created specialist research centres for biogerontology. Many Universities and medical schools have departments of gerontology, researching a variety of medical, social and psychological aspects of ageing, but in recent years three UK Centres have set up specialist research centres in biogerontology to research more basic aspects of ageing, again reflecting the increasing acceptance of this type of research in top-class academic institutions.

What has biogerontology found?

All living things 'age' – apparently ageless organisms, such as some plants, bacteria or yeast discard ageing parts to grow new, 'young' ones. For more complex or specialised organisms, such as flies or humans, we cannot do that and so the ageing process affects us. Many decades of hypothesising about how ageing happens lead to two general schools of thought:

- ageing is programmed into living things. This might be deliberate – in order to make room for our descendants and so allow the species to evolve – or might be accidental. But there is a 'clock' of ageing. Ageing is analogous to the school budget – if you do not use it by the end of the year, it vanishes so that the new year can be started with a clean balance sheet.
- ageing is a result of accident, the accumulation of damage that inevitably occurs in anything with time. Ageing is analogous to the gradual decay of a car or a piece of furniture: after a certain time, the cost of repair rises beyond that which makes it worthwhile repairing.

Due in part to the groundbreaking work of Tom Kirkwood, this second hypothesis is now accepted as being true for most aspects of ageing. Living tissue takes constant repair and maintenance, just as a car does, and for much the same reasons – to be alive is to be active, from the level of molecules to whole individuals. No process is completely accurate and efficient – a few rogue molecules slip by, some food has some minor toxin in, cosmic rays 'zap' some DNA, our own metabolism mis-fires and generates damaging chemicals. This damage takes resources to repair in the form of metabolic energy. Kirkwood coined the phrase 'disposable soma' to summarise that the body is just there to support the germ cells – sperm and ovum – and the offspring that they produce. Once that task is achieved, the body can be disposed with. So there is a balance between investing energy in keeping the body healthy and in breeding. Where that balance is depends on the reproductive strategy of the species. Humans invest a lot of time in raising a small number of children, so our body maintenance mechanisms are good. Mice spend less time raising many infants, so they live shorter lives before their investment in repairing their bodies is overwhelmed by the damage done to them by just being alive.

There are a wide range of types of damage that accumulate in living things (specifically humans) as they live, and so which are the cause of the phenomenon we call 'ageing'. All of them are a result of molecular 'accidents' that accumulate with time. Most are also believed to themselves reduce the body's ability to defend against and repair the damage that accumulates with time, which is why ageing seems to accelerate as we get older rather than happen at a uniform rate during life. They can be summarised in these six categories:

Damage rising with age	Date identified	Comment
Cell loss, cell atrophy	1955	Loss of cells causes loss of tissue mass and function. To an extent, this is an effect of other factors, but is central to the body's loss of ability to repair itself
Nuclear [epi]mutations	1959 / 1982	The main effect of changes in the genes of cells <i>other</i> than the germ cells (sperm and ova) is that they are the critical trigger for causing cancer
Mutant mitochondria	1972	Mitochondria are the 'powerhouses' of the cell, and when they fail there are a variety of consequences
Death-resistant cells	1965	This is a feature of mutation, mitochondrial mutation and (probably) other factors. This is also important for cancer, but also for the accumulation of 'useless' cells that will not go away, but do not contribute to body functions.
Extracellular crosslinks	1981	Chemical links between proteins and other molecules outside cells makes the matrix in which cells live rigid and resistant to change. A major cause of the cosmetic changes of ageing, and also arterial disease and muscle weakness
Chemical 'junk'	1907 / 1967	The body can dispose of almost anything that is thrown at it or is made inside it, but not everything. The residual 'junk' gradually accumulates with age and blocks the function of an increasing number of cells.

The specifics of how these categories of damage occur, the molecular mechanisms involved, and the biological processes they affect is the subject of research in the biogerontology field.

Note that Telomeres does not appear in the list, not 'free radicals' or 'oxidative damage'. The former is a specific example of genetic change, the latter a specific mechanism for generating several of the classes of damage above.

However biogerontology is much more than a search for the mechanisms of ageing. It also works in understanding how organisms (and particularly people) change with age at a physiological and at a whole organism level. When people's cognitive abilities decline with age – apart from the onset of specific diseases such as Alzheimer's disease – what exactly declines, and can the decline be slowed? When we loose muscle mass with age (in part due to cell loss), why is it not replaced, and what are the consequences for the people concerned? Biogerontology aims to bring rigorous science to all these types of questions, from molecules to whole people.

How can this knowledge be applied?

The growing body of knowledge about how ageing happens has started to reveal how some of the diseases associated with ageing can be better diagnosed and treated. At the moment, 'old age' is not recognised as a disease, but the changes underlying how our body gets old clearly are important for many diseases such as cancer, cardiovascular disease, neurodegenerative diseases and others. Some of the links between basic mechanisms of ageing and disease were quite unexpected, others were expected but the detailed mechanisms not known. Thus it was known that the arteries of the old are less elastic than those of the young, which results in a variety of blood pressure problems that can lead to cardiac damage and hypertension: however the chemistry of what is happening in the arterial walls (part of point 5 in the table above) is still being worked out.

Much of this can lead quite quickly to improved diagnosis, separating disease caused by different mechanisms (and hence likely to respond to different treatments), and separating disease from 'normal' ageing. However it makes sense to use the knowledge generated bio biogerontology not just to diagnose disease but also to create new treatments for it, treatments that attack the disease in quite a different way from existing treatments. Because ageing happens throughout life, this does not mean only developing treatments for diseases of the very old. All of medicine could benefit from better understanding of the biology of ageing.

What this is not about is 'curing ageing'. The molecular damage that accumulates with time and causes 'ageing' is ubiquitous, and genuinely curing ageing would require feats of molecular engineering far beyond what we can achieve, and amounting to rebuilding the entire human body. Delta G specifically does not aim to 'cure ageing'.