

## AGEING – PUTTING OFF THE EVIL DAY

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An increasing number of people are living to a greater age when biological limitations are taking their toll on health and happiness through frailty, disability and disease. This poses a challenge for current research to acquire a better understanding of the biological basis of ageing and age-related diseases and to develop new science-based and technological solutions. These are designed to help the elderly maintain their freedom of movement and independence for as long as humanly possible, both for their own sake and that of society.

Tom Kirkwood describes the outcomes of his research designed to reveal the principal drivers which give rise to human ageing. John Lever shows how bioengineers evaluate the biomechanical aspects of ageing and thereby help to design and improve therapies for the increased longevity and health of the aged. Reynold Greenlaw presents the products of current research on technological aids for those suffering from Parkinson's disease and discusses additional technological support systems designed to help the aged maintain free and independent lifestyles for as long as humanly possible.

# The Science of Ageing: New Frontiers

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Something remarkable happened yesterday: life expectancy increased by 5 hours. The same thing occurred the day before, and the day before that. In fact, on each of the more than 70,000 days of the last two centuries, life expectancy within the United Kingdom increased by a similar amount, adding up to a total of 40 years – a doubling in our average lifespan over just eight generations.

This relentless increase in life expectancy is so much a part of the fabric of our lives that one might think that we would have well established plans to accommodate it into our changing society, and that we would have invested time and effort to understand exactly why it is happening and whether and when it might end. The truth, however, is very different. Few of us properly appreciate just how fast life expectancy is changing, most of us continue to regard the societal implications of our continuing success in lengthening life with a mixture of bewilderment and concern, and we have, until very recently, largely

neglected the challenge of asking what is really going on.

The early increases in life expectancy were easy enough to understand. Improvements in sanitation, nutrition, housing and education all worked together to reduce the heavy burden of infectious disease that struck down our predecessors at startling rates, particularly at young ages. This continued with the introduction of vaccines and antibiotics. By the time we entered the second half of the 20th Century, the causes of mortality had been transformed. Deaths now occurred mainly in later life from causes linked to the degenerative conditions associated with ageing. At this point, most organisations charged with forecasting future life expectancy predicted that the increase would slow down and eventually halt, as human lifespan bumped up against the ineluctable reality of the ageing process. They were wrong.

During recent decades life expectancy has continued to increase. Furthermore, the increases are now



being driven by dramatic falls in *old-age* mortality, indicating that the ageing process is much more malleable than was previously thought. Although unexpected, this malleability of the ageing process is compatible with new scientific understanding of the ageing process. This understanding needs to inform public policy and practice to a much greater extent than has happened so far.

### What Controls the Length of Life?

To explain what is happening to human longevity we need to know what controls lifespan. In spite of a widely held belief that some kind of biological clock programmes the ageing process, we now know that this is highly unlikely. The main reason is that when we survey the animal kingdom we discover that although many species, when in protected environments, age in broadly similar ways to us, ageing is hardly ever seen in wild populations.

For most natural populations, mortality due to accidents, predation, starvation, disease, and cold is such that death occurs well before “old age”. This means that whatever functional value is assigned to a clock for ageing, for example as a means to control population growth, there is scant evidence that such value is actually realised. Also, it is extremely difficult to see how such a clock might have evolved under natural selection, if animals in the wild do not normally survive to an age when the actions of the clock become apparent.

Although we must discard the idea of a genetically programmed clock for ageing, we know that genes do influence length of human life. Research on twins has shown that genetic factors explain about 25% of the variation in human lifespan. Resolution of the conundrum that genes influence longevity, but not by programming a clock, comes in large measure from a concept known as the “disposable soma” theory.

Instead of asking why genes might cause death, we need to ask how assiduously our genes should strive to keep the body alive. In particular, how much of its energy budget should an organism be prepared to invest in the maintenance and repair of its body (soma)? The answer is simple. Maintenance, which requires significant amounts of energy, needs only to be good enough to keep the organism in sound condition for as long as it has a reasonable chance of survival in the wild. For example, more than 90% of wild mice die in their first year, and more than 99% die before their second birthday. Thus, any investment of energy by the mouse in mechanisms to keep the body strong beyond a couple of years benefits at most 1% of the population. This must be set against the advantages that might accrue from using such energy for other functions, such as reproduction.

What holds for the mouse was similar also for our human ancestors, although of course the timescales were longer. Early humans probably had no more than 30-35 years expectation of life in the “wild” conditions of our evolutionary past. From the genetic point of view, it was just too expensive to evolve survival mechanisms that

would keep the body working well indefinitely, when in reality an accident would be likely to cut us down while still in our prime.

### The Malleability of Ageing

Once we recognise that ageing happens not because we are programmed to die, but because our genes evolved to place limited priority on mechanisms for long-term survival, many features of ageing begin to fall neatly into place. We see that the primary cause of ageing is the accumulation of unrepaired cellular and molecular damage. This fits well with a very wide range of experimental observations.

As we live our lives, all kinds of faults arise within our cells. For example, each time a cell divides it must copy the billions of nucleotides that make up the genetic sequence that defines our biological identity and programmes all of our functions. The DNA copying machinery is exquisitely accurate, but a few DNA mistakes are likely to be made every time a cell divides. Gradually, the DNA sequences of our cells become corrupted. Added to these copying errors is the onslaught of damage caused by highly damaging molecules called “reactive oxygen species”, also known as “free radicals”, which are formed as accidental by-products of our cells’ dependence on oxygen to produce cellular energy. Free radicals damage DNA at a high rate, and they also damage other cellular constituents, such as proteins and the energy-forming organelles called mitochondria. Damaged proteins contribute to a range of age-related disorders, including cataract, Alzheimer’s disease, and Parkinson’s disease. Damaged mitochondria accumulate in many tissues as the body ages and probably contribute to the declines in function that are so commonly experienced during ageing.

Combating the accumulation of damage is a wide repertoire of repair and protection systems. For example, if damage to DNA contributes to ageing, the capacity for DNA repair will be an important determinant of the rate of ageing. This idea has been confirmed by several studies showing that when different species are studied, a higher level of DNA repair activity is associated with longer lifespan. There

is also some evidence that human centenarians have higher repair levels than the general population, suggesting that innate differences in repair capacity may be part of the basis for heritability of human longevity.

Once we recognise that ageing is driven by an accumulation of damage, at rates which are held in check by repair, it becomes straightforward, at least in principle, to understand the malleability of the ageing process. Factors that increase exposure to damage accelerate ageing. Factors that boost repair functions slow it down. For example, we know that nutrition affects human life span both adversely in the case of poor nutrition (diets rich in sugars, saturated fats, etc) and positively in the case of good nutrition (diets rich in fruits, vegetables, unsaturated fats, red wine, etc). Similarly, the effects of lifestyle factors (eg exercise) and environmental factors (eg poor housing) can be understood, even though a great deal more work is needed to determine the magnitudes and precise mechanisms of action of these effects.

### Conclusions

Even though we have as yet invested tiny amounts in scientific understanding of healthy ageing, we can begin to understand why lifespan is continuing to increase. The kinder conditions of modern life are helping our bodies to reach old age with less accumulated damage – a 70-year old today is indeed biologically younger than a 70-year old of a generation or two ago. But in what ways exactly? And will the trend continue, or will increasingly sedentary lifestyles and fast-food diets halt or even reverse it? What does the increase in lifespan mean for health in old age? We need urgently to take better stock of what we know and act accordingly. Even more important, we must work to fill the enormous gaps that still remain in our emerging knowledge of the human ageing process.

### Suggested Further Reading:

Kirkwood TBL *Time of Our Lives: The Science of Human Ageing*. London: Weidenfeld & Nicolson, 1999.  
Kirkwood TBL Understanding the odd science of ageing. *Cell* 2005;120:437-447.

# Biomechanical Aspects of Ageing

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## Introduction

Ageing causes all too visible changes in the external appearance of the body. The skin wrinkles and sags, the skeleton atrophies and the body stoops. These signs are the result of progressive alterations in the structure of certain bio polymers that are components of the hard and soft skeletons that support the various organs of the body. Of particular importance are the two proteins collagen and elastin. Collagen confers stiffness and strength to body tissues while elastin confers compliance. Consequently, modification of the amounts and detailed structure of these two components alters the mechanical properties of the tissues, so not only does their appearance change but also their ability to perform their normal functions. Indeed much of the diminished performance of many of the organs in the body on ageing can be attributed to adverse changes in tissue mechanics and explains why this topic is of such interest to Bioengineers. Working in an engineering faculty at Imperial with plenty of opportunities to collaborate with scientifically-thinking physicians and surgeons provides an ideal environment to explore some of these problems. This brief review will concentrate only on changes in the cardiovascular and skeletal systems,

but will be indicative of how most body tissues can be adversely affected.

## Changes in connective tissues on ageing

The production of the fibrous structural proteins in the body is determined by genetic programming, by interactions between adjacent cells and by environmental factors including the mechanical forces applied to the tissues. Collagen is constantly being replaced, and so bones, for example, are able to remodel themselves if the prevailing stresses are altered. This occurs in bed-bound patients who undergo skeletal atrophy or, conversely, in tennis players in whom the bones of the racquet arm become thicker and stronger.

Collagen consists of protein molecules which are tightly bound to each other and then further linked to form long fibres or flat sheets. It can be replaced quite rapidly, as when wounds heal, and in all normal tissues there is a balance between the expression of new protein and enzymatic degradation and mechanical damage to older molecules. As we age, this balance shifts and degradation wins out over production. Some of the fragments, matricryptins, can themselves cause additional trouble

by stimulating the production of enzymes that attack other proteins or lead to the production of cytotoxic free radicals. Collagen fibrils may more cross-linked in older than younger individuals and while this might be expected to make them stronger, such changes seem to cause diminished production. Excess cross-linking is exacerbated by elevated sugar levels, explaining in part why diabetics are more prone to connective tissue diseases.

Elastin, a protein which is coiled to confer rubber-like properties, is even more problematical since its production is almost completely switched off at puberty so that the replacement in adults is negligible. Not only is elastin progressively lost on ageing but it easily fragments, diminishing its compliance, and becomes calcified, also making it stiffer.

## Cardiovascular changes

Our large blood vessels contain very large quantities of elastin and in arteries it enables the heart pulse to be quickly transmitted around the body. As we lose elastin and its properties change, the vessels become wider and stiffer. The heart now has to pump into more rigid pipes, making it work harder, and making it more likely to fail. In arteries close to the heart,

mechano-receptors monitor blood pressure by sensing the degree of stretch of the vessel wall. As the wall stiffens, they become less able to sense changes so blood pressure rises, causing hypertension.

As collagen structure changes, blood vessel walls become unable to cope with the large pressures sometimes generated by the heart and aneurysm can occur.

The heart and veins have valves to keep blood flowing in the right direction around the body. With loss of elastin and collagen, the flaps of tissue that constitute the valves are no longer able to come together across the widened vessels and blood can leak backwards through them. The heart will, once again, have to work harder. On suddenly standing, incompetent valves in veins may allow blood to flow downwards towards the feet taking it away from the brain, leading to dizziness. Venous pressure will also rise above normal in the legs and feet, causing excess exudation of fluid, oedema.

### **Atherosclerosis**

Other changes occurring in blood vessels with increasing age are probably associated with blood flow as much as with the mechanical properties of the vascular tissue. Fluid mechanics is usually associated with other branches of engineering, aeronautics, mechanical, chemical and civil engineering. But it is also an important component of bioengineering. Unlike most engineering constructs, blood vessels are compliant structures which branch, have complex three-dimensional geometries, and carry a fluid, blood, which has highly non-ideal rheological behaviour in a pulsatile manner. Not surprisingly, blood flowing in arteries displays very complex patterns including swirling, eddies and reversal of flow direction. Any fluid flowing over a surface exerts a shearing stress. Just as normal stresses applied to bones

can change their properties, shear stresses applied to the inner surface of blood vessels may underlie the development of atherosclerosis which shows a predilection for sites where the most complex flow patterns are observed.

Once formed, the fate of an atherosclerotic plaque may be also determined by the mechanical stress that it bears. Large forces exerted by shear or changes in blood pressure may cause fracture. The exposed contents may be swept downstream blocking smaller vessels and causing an infarct which might lead to heart attack or stroke. Alternatively a thrombus may form on the damaged tissue which can either block the artery or become dislodged and cause a blockage downstream. Plaques may also weaken the underlying wall, and atherosclerosis is an underlying cause of aneurysms.

### **Skeletal changes**

Articular cartilage is present on the surfaces of adjacent bones in moveable joints and acts as a lubricant and a shock absorber. It is a stiff gel, comprising very large sponge-like molecules, proteoglycans, bound together by fibrous collagen. Mechanical and biochemical fragmentation of this collagen can allow fissuring of the articular cartilage, reducing its lubricating function. This is one of the features of osteoarthritis. Progression of the condition can lead to complete loss of the layer of cartilage causing the bones to grind together with resulting severe pain. Bones also contain very large quantities of collagen, as well as the mineral component, hydroxyapatite. Osteoporosis is a progressive reduction of bone mass in the skeleton, resulting largely from the progressive degradation of collagen. There is a thinning both of the compact surface bone and progressive attrition of the three-dimensional plates of the "spongy" bone, that comprises the inner part

of many bones. All older people have some osteoporosis and continual and usually symptom-free compression fractures in the vertebrae lead to distortion of the spine, while the neck of the femur and radius bone of the arm become susceptible to fracture on falling.

As indicated above, sustained and repeated forces applied to bone causes it to hypertrophy and herein lies a simple approach to controlling the development of osteoporosis. Increased mobility and simple exercises can have dramatic effects on bone density and limit the susceptibility to fracture.

### **Conclusion**

So, what can we do in the future? Cosmetic surgery can disguise degradation of the skin. But surgical intervention will never tackle the more critical changes that occur within internal organs which shorten life expectancy and in those that do survive, lead to severe disability, with enormous costs involved in caring for the aged.

Bioengineers can devise techniques for tracking tissue changes which will hopefully reveal problems before they become critical. For prevention of the mechanically mediated effects of ageing we have to learn, firstly, how to limit the adverse changes in our structural proteins. Body movement, including exercise, contributes to damage, but this should not be compromised, since to do so would invoke other adverse changes in the body. Secondly we have to learn how to deal with the progressively increasing amounts of mechanically compromised protein fragments while maintaining adequate stocks of healthy material. In particular, we need to understand, better, how we can overcome the switching off of elastin production at an early age. Tissue and genetic engineering may prove the answer and bring us at least to a healthier future if not immortality.

# INDIGO: A technical aid for people with Parkinson's disease

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Parkinson's disease (PD) is a common neurological disorder. Research indicates a prevalence of approximately two per thousand of the general population, with the older population being most affected. In Europe, the average age of onset is slightly below 60 years.

Untreated, the mortality of people with PD is three times higher than healthy controls; however, with the advent of modern pharmacology, the life expectancy of PD patients is tending towards the (male) average. Estimates of the number of people with PD in Europe lie between 700,000 and 1,000,000 with 72,000 new people diagnosed every year.

The cardinal symptoms of PD are tremor, rigidity and bradykinesia (slowness of movement). A shuffling walk, start hesitation (inability to start walking at will), and freezing are mobility problems that appear in the mid to late stages of PD. These mobility problems get worse with longer duration of illness and result in people with Parkinson's disease (PwPD) gradually leaving the home less and less and eventually becoming inactive even in the home. This confinement at home and restriction of activity

can lead to social isolation and have a significant adverse effect on the quality of life of PwPD. The walking-related symptoms of PD are not greatly improved by medication or surgery. Standard mobility aids such as walkers or walking sticks do not improve walking in PD.

Since the seminal observations of Purdon Martin (Martin, 1967), it has been known that provision of external stimuli such as horizontal lines marked on the floor over which the PwPD steps can substantially improve walking in PD. There is experimental support for this observation from studies using visual markers on the floor (Morris et al, 1996; Azulay et al, 1999; Lewis et al, 2000), which have been shown to improve the stride length and gait velocity of PwPD. The rationale behind the use of external stimuli to improve mobility in PwPD is the phenomenon of paradoxical kinesis. An often cited example of paradoxical kinesis is the triggering effect of emotive or dangerous external stimuli, such as an immobile PwPD being able to walk normally when triggered by unusual external situations such as during a fire. The

phenomenon of paradoxical kinesis has experimental support from functional imaging studies (Jahanshahi et al, 1995; Hanakawa et al, 1999). These have shown that external triggers for movement such as a tone or transverse lines on the floor, "normalise" blood flow in PD and are associated with use of an alternative route to action via the lateral premotor cortex-parietal-cerebellum instead of the medial premotor system which is impaired in PD (Jahanshahi et al, 1995; Hanakawa et al, 1999).

Despite the evidence for the value of external stimulation in improving mobility in PwPD and its possible physiological mechanisms, no viable commercial device of proven efficacy is available for use by PwPD as an aid to mobility. INDIGO (INDdependently I GO) has been developed from the results of an earlier EU R&D project called "PARREHA" (PARKinson REHAbilitation) (IST-1999-12552, 2000-2003) and earlier was called PARKWALKER. The company PARKAID was founded by PARREHA partners out of their own resources to further develop INDIGO. INDIGO displays moving visual

cues in the user's peripheral visual field within specially adapted glasses running MPEG video software on dedicated portable hardware. The video is generated by a mini MPEG player worn on the user's belt or placed in their pocket. Commonly an endless video of black and white stripes scrolling slowly upwards is used. The sets of visual cues have been constructed in conjunction with PwPD. Once set up, all the user needs to do is to put on the glasses and press the On button. This simplicity is essential since the device is intended as an aid to daily living by PwPD. This user group has the motor disabilities of PD and is typically over 60 years old and may not be confident with equipment that looks too "technical".

INDIGO provides the user with support during intermittent akinetic phases. Users wearing INDIGO can walk more easily and freely. A further benefit is likely to be accident avoidance and reduction of the number of falls and injuries suffered by people with PD.

Comparable devices (such as dark glasses with flashing red LEDs inside) exist in research laboratories at the University of Washington, USA, the University of Iberoamericana, Mexico and the Technion Institute in Israel. These devices are research tools and have not been subjected to controlled clinical trials or commercialised.

This year INDIGO has won the support of the UK Parkinson's Disease Society. This is the largest



PD society in Europe (30,000 members) and has agreed to fund a two year clinical trial to answer two questions crucial to the further development of these aids: firstly, what is the size and clinical profile of the PD population who would benefit from INDIGO (and similar aids) and secondly, what is the objectively measured effect on gait of INDIGO compared to lines on the floor or walking unaided with no visual cues. This trial will be conducted by Professor Jahanshahi's group at the Institute of Neurology, University College London.

If proven effective, the social contribution of the INDIGO system will be to offer PwPD increases in mobility, freedom and quality of life which no other IT application can offer. The device is entirely complementary in that it can be used alongside conventional pharmacological and medical treatments.

#### Links:

- (1) ParkAid: <http://www.parkaid.net/>
- (2) Oxford Computer Consultants Ltd.: <http://www.oxfordcc.co.uk/>

(3) Institute of Neurology, University College London: <http://www.ion.ucl.ac.uk/>

(4) The Parkinson's Disease Society: <http://www.parkinsons.org.uk/>

#### Enquires to:

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#### References:

Azulay J-P; Mesure S; Amblard B; Blin O; Sangla I; Pouget, J Visual control of locomotion in Parkinson's disease. *Brain*. 1999 Jan; 122 ( Pt 1): 111-20

Hanakawa T; Fukuyama H; Katsumi Y; Honda M; Shibasaki H Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. *Ann-Neurol*. 1999 Mar; 45(3): 329-36

Jahanshahi M; Jenkins HI; Brown RG; Marsden CD; Passingham RE; Brooks CD (1995) Self-initiated versus externally-triggered movements: I. An investigation using regional cerebral blood flow and movement-related potentials in normals and in patients with Parkinson's disease. *Brain*, 118, 913-933.

Lewis GN; Bylow WD; Walt SE Stride length regulation in PD: the use of extrinsic, visual cues. *Brain* 2000, 123, 2077-2090.

Martin JP. The basal ganglia and posture. London Pitman Medical , 1967

Morris ME; Iannsek R; Matyas TA; Summers JJ Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. *Brain*. 1996 Apr; 119 ( Pt 2): 551-68

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#### *In discussion the following points were made:*

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There is a very surprising linear increase in the age of death with time for which there is currently no explanation. The death rates of the elderly in their 80s are only half of what they were 50 years ago. There is definitively no clock that drives the ageing process and all searches for it have failed. There is no programme and there are no genes for ageing, although longevity tends to run in families and studies of identical twins show that 25% of longevity can be accounted for in this way. Variability in ageing of the human population is immense. There is however a link between diets high in antioxidants and an increase in longevity. The jury is out on the potential role of dietary supplements such as vitamin C. Early nutrition, such as in utero, is a factor in controlling the trajectory through life. Brain exercise is also important in maintaining functional capacity with age. Technology transfer of bright ideas from the laboratory is still a major problem in the UK, and has been for a long time, with inadequate financial and managerial support to pull these through to the market place