Article

The Genetics of Mortality and Immortality

Alfred Cuschieri
Department of Anatomy, University of Malta, Msida, Malta.

Introduction

In Man's perpetual concern about life and death, the topic of mortality and immortality is undoubtedly an attractive and intriguing topic, especially if combined with the even more attractive and intriguing subject of genetics. From a strictly scientific and genetic point of view, the meaning of mortality and immortality is, perhaps, somewhat different from what immediately comes to mind when one is talking about these topics. The main concept underlying mortality and immortality is not concerned with death and dying but is centred on life, and this paper will consider the subject of mortality from the point of view of life.

This paper will not attempt to give a metaphysical discussion on life after death. From a strictly scientific viewpoint, this is a contradiction in terms. There are many different aspects of mortality and immortality. This paper will define the meanings of mortality and immortality in the context of the present discussion and will attempt to explain the genetic aspects of mortality and immortality and how these two contrasting concepts can be reconciled in scientific terms.

Death is a Part of Life

Paradoxically mortality is a feature of living organisms. We cannot speak of mortality in relation to inanimate objects. Death can only ensue where there is life and we generally consider death to be the termination of an individual's life. We may think of death as being caused by severe disease or injury which may occur at any age of one's life. We may also think of death as the ultimate stage that follows senescence in the life of an individual's physical existence. Although one may be fortunate enough to escape fatal disease or injury, no one can escape the ravages of time and ultimately everyone will meet with death. From the epidemiological viewpoint mortality is largely concerned with the ages at which people die. In the last century there have been social changes and medical advances, which have radically altered the pattern of mortality. Up to about 60 years ago infections were the main killers. Babies died of enteritis, children died of diphtheria and other infectious diseases and adults died in the prime of life of tuberculosis. People of all ages died of epidemics of plague and cholera. All these diseases have now been almost entirely relegated to the past. Now more and more people are living to a ripe old age because they are not dying younger, although they are increasingly subject to chronic diseases such as diabetes, hypertension and cancer. These diseases too are gradually finding more effective cures. Changes in the way of life, education, and social improvements, scientific discoveries and medical progress have all contributed to alter drastically the life expectancy of individuals over the last century.

Maximum Life Span

However, none of these advances have altered at all the maximum life span of people. There are plenty of recorded instances from time immemorial of people living to over 100 years, but nowhere can one find reliable evidence of people living to be more than about 125 years. The person who is considered to hold the record of longevity is the late Madame Jeanne Calment who died in France in 1997 at the age of 122 years and 164 days (Robine and Allard, 1998). The previous record holder was a Japanese person who also died at the age of 122 years, but was a few days younger than Madame Calment. This can be considered to be close to the maximum life span of humans, the limit of longevity. It is thought that the maximum life span of humans has not been affected at all by the changes that have promoted the dramatic increase in life expectancy over the last century. Today, centenarians are becoming commoner than they used to, but there is no evidence that people are exceeding the limit of the maximum life span. This maximum limit ensures that all people die.

It is believed that the maximum life span is fixed for every animal species and cannot be altered. Mice, for example, have a maximum life span of 4 years. No matter how well a mouse is cared for, it cannot live for 20 years. Every animal has an innate, genetically determined maximum life span.

Maximum Life Span is Part of the Programme of Life

The maximum life span may be considered to be part of the programme of life of animals. Taking human beings as an example, the programme of life begins at conception and passes though innumerable series of perfectly timed and co-ordinated developmental stages. The subject of human development is very vast and has many aspects. I will only mention a few notable landmarks just to set the scene of the programme of life. Embryonic life is the period of differentiation, which transforms one cell into a variety of tissues and organs. Foetal life is the period of growth and shaping of organs. Birth heralds the beginning of an independent existence; childhood is the great period of learning, which opens the way to a creative life. Puberty marks the beginning of reproductive life and the transition to the fully-grown and mature adult. Finally, the post-reproductive stage is characterised by a marked and progressive physiological decline, ultimately leading to inevitable death. All these stages are controlled by a genetic programme of life and accurately timed by a biological time clock. For example, the heart is formed and begins to pump at 4

weeks; birth occurs after 40 weeks of gestation; we begin to walk at the age of 12 months; puberty occurs at the age of about 12 years; the menopause occurs at 45 to 50 years. Life takes us through a series of developmental milestones at appropriate time intervals. If these times are not adhered to within rather narrow limits, there will almost certainly be a problem. As the clock ticks away we approach closer and closer to the ultimate notable landmark, the maximum permitted limit of life.

Genetics Regulates the Programme of Life

This biological programme is all encoded in the genome. Genetics is the basis of all life. In the genetic molecules of DNA are encoded the messages which regulate all biological processes. They regulate all embryological and post-natal events, which, in a precisely regulated manner, gradually unfold the development of the biochemistry, anatomy, and physiology and of the body. The genetic messages regulate with molecular precision the differentiation of cells, tissues and organs from the time of conception to full maturation of the individual. They also regulate the functioning of all body systems throughout life.

The saga of development includes the processes of cell proliferation and cell differentiation. As the cells multiply, the pluri-potent cells of the early embryo differentiate and undergo morphological and functional changes leading to the formation of specialised tissues of the brain, kidney, liver, heart, limbs and so on. Development also includes the co-ordination of these events so that the differentiated tissues organise themselves to form organs in precisely determined positions, and communicating with one another to function in perfect harmony as faithful members of one individual body. Development includes modelling of the body and its individual components to form a precise and remarkably constant anatomy.

The remarkable paradox is that cell death is also an integral part of this developmental process of sprouting life. Programmed cell death, which also goes by the euphemistic term "apoptosis", is a genetically determined and pre-programmed cell death, which is essential for normal development. Some developmental defects are precisely the direct results of failure of cell death to occur at the right place and the right time. Some cells, having outlived their pre-determined functions at a particular stage of development, need to make way for other specialised cells with different functions to take their place. Programmed cell death is an integral part of life.

The Conflict of Life and Death

It appears that the programme of life includes an in-built mechanism whereby it is ensured that all individuals die. But does it make sense that self-sustaining life in all its variety and beauty should programme itself to ensure that all individuals die? That life terminates at the time when people are finding their fulfilment of life? As Oscar Wilde remarked in: A Woman of No Importance, "The soul is born old, but grows young. That is the comedy of life. And the body is born young and grows old. This is life's tragedy."

However, there is more to life than the comedy and the tragedy, the emotions created by this conflict. There is also the beauty of life in which we might find some explanation for this paradox. The beauty of life lies in its variation. Not only is there the almost infinite variety of plants and animals and other living organisms to capture our admiration but even more impressively there is the individual variation which makes us all different from one another physically, psychologically and emotionally, which makes each one of us unique.

Genetics is the sum and substance of life, that which makes life self-perpetuating and self-regulating; genetics is the basis of variation; genetics is the driving force behind evolution. Evolution is survival. To appreciate the significance of evolution we must look at organisms in the wild. Evolution is the mechanism of natural adaptation to ensure survival in the face of new, adverse or hostile environments brought about by factors such as physical isolation, availability of food, the threat of predators and other life-threatening situations. Genetic mutations are nature's experiments to produce variation. Among these variants, a few would have a distinct survival advantage in the prevailing circumstances, and so continue to propagate themselves from one generation to the next by natural selection. This variation necessarily appears in new individuals and for these to be evolutionarily useful they must replace others. Death of the individual, therefore, is an integral part of the evolutionary process that ensures survival of the species.

This is the genetic justification of mortality! In the mind of Homo sapiens, however, death presents the harsh reality of an end to the beauty of life, an end to our physical sensation of life. Death is therefore interpreted by the conscious mind as void and darkness. But there is also a dim vision that death has a purpose, which, however, cannot be interpreted in terms of natural experience but is projected in terms of the supernatural.

In this light it, would be absurd to suggest that the justification for death is evolution and the preservation of the species. Man is situated at the apex of the evolutionary pyramid, at a point beyond which there appears to be nothing but an infinity of space and time. The evolutionary forces that have culminated in Man have produced a being that does not need to rely on chance events and natural selection to survive adverse and new environments. Instead, he has achieved an intellectual capacity of such a degree that he is capable of adjusting almost any environment to suit his needs. This enables man to live in extremes of climatic conditions or even in outer space and to survive where no other organism can survive. Man has intellectual capacity to understand and control life itself. He can now create genetic mutations almost instantly to suit his needs and whims. He can create new species and clones. Potentially he can do in a few days what evolution would do in thousands of years. Is it possible that man will come to understand life to such a degree that he might even learn how to exert a genetic control over the maximum life span? Before discussing this issue I would like to have a brief look at the biological aspect of immortality.

Immortality of Unicellular Organisms

The pattern of life as presented does not apply to all living organisms. A programmed time clock is not present among primitive organisms, particularly the unicellular ones such as amoeba or bacteria. Take bacteria as an example - they can easily be grown and studied in cultures in the laboratory. Each bacterium divides to produce two organisms, which then divide again and again and can continue to do so indefinitely producing an infinite number of generations. There is no limit to the number of proliferation times and the number of generations and so we can call such cells "immortal". The individual organisms do not die between generations. If any of the individual organisms die it is because of accidental circumstances such as toxic substances or lack of nutrients. Colonies of bacteria may die at a particular location where a hostile environment prevails but others will continue to proliferate.

In adverse environments, which are harmful but not quite lethal, the organisms may gradually undergo genetic mutations, which make them capable of surviving the adverse conditions. A familiar example is when bacteria become resistant to antibiotics, thus creating new strains. These mutations provide the mechanism to ensure survival of the species and continuity of life. Potentially the organisms can live indefinitely. Death of individual organisms is an incidental chance occurrence. The concept of mortality here is not that death is an inevitable and inescapable occurrence, but that living organisms require certain conditions beyond which they cannot survive. Within those limits, life is self-perpetuating and self-adjusting. Within those limits, life is immortal.

The Concept of the "Individual" in Higher Organisms

Does this concept of immortality apply only to primitive organisms, or can it be extended to all life, even human life? Here some clarification is required about the meaning of an "individual". Among higher organisms the concept of an individual is different from that among primitive organisms. Although in both cases the unit of life is the cell, the complex body that constitutes an individual in higher organisms is much more than its component cells. In higher organisms the multiplicity and variety of the component cells of the body contrast with the unity in the genetic composition of the body and its uniqueness. The genes contained in all the cells of the body are identical, no matter how diverse their functions may be. The genome belongs to the individual as a whole, and its component cells are all regulated by this singular genome. Each cell contains a copy of the individual's genome. Furthermore the genome of each individual is unique. The genome of each individual is different from that of other individuals of the same species. By contrast, the individuals in unicellular organisms are clones, all of which are genetically and structurally identical to one another and to the individuals from which they were derived.

The Mortal Soma and the Immortal Germ Line

In higher animals the propagation of life from one individual to another is restricted to only one particular cell line, the germ cell line, which produces spermatozoa and ova. The germ cell line is responsible for the continuity of the species in perpetuity. There is no limit to the number of generations that can be produced, and in this sense we can speak of an "immortal" germ cell line. This perpetuity, however, does not affect the rest of the body, the soma, which is in fact genetically programmed to die within the specified maximal life span. In higher organisms, including man, we can speak of the mortal soma and the immortal germ line!

Mortality in Individual Cells

The inherent, in-built programmed mortality mentioned earlier, refered to the mortality of the body as a whole. However, death of the body is not the same as death of the component cells, although the two may be interdependent. An in-built, genetically programmed mortality is also to be found in the component somatic cells. If somatic cells, such as fibroblasts, are isolated from the body and nurtured in cell culture, providing all the nutrients and environmental conditions necessary to support growth, they will proliferate repeatedly. In this respect they are rather like unicellular organisms and bacteria. However, they differ from these organisms in one crucial factor - they will not proliferate indefinitely. They have a limited maximal life span, characteristic for the organism from which they were taken. The life span of human cells is different from that of similar cells derived from mice, sheep or other animals. And when they approach their maximum limit, they become unhealthy and aged, lose their ability to divide further and die.

Interestingly, the maximal life span of cultured cells is not measured in chronological time but in the number of cell divisions, or the number of times the cell population doubles itself. In fact, it is quite independent of time. Under optimal conditions the limited number of divisions may be exhausted within several weeks. The process may be slowed down under certain conditions but the number of permitted doubling times remains the same. The process may even be interrupted by putting the cells in a deep freeze for a prolonged period of time. When the cells are again placed in culture, even after several years, they resume proliferation, retaining a memory for the number of their previous divisions, and continue to proliferate until they reach their limit. The component cells of the body, therefore, and not only the body as a whole, have in-built life-limiting biological clocks.

Telomeres and Telomerase

While the somatic cells are mortal and have a limited time span, the germ cells are not similarly programmed. What is it that creates this dichotomy? What genetic mechanism ensures that somatic cells die while germ cells continue to propagate life and proliferate indefinitely through the generations? Cell biology has provided a likely answer to this question. The thin strands of DNA, which carry along their lengths the genetic messages encoding the programme of life, are coiled in a complex manner to form the chromosomes. The ends of each of these strands are called telomeres. They contain repeated coded signals. With each cell division the telomeres shorten slightly so that the number of repeat signals decreases slightly until, eventually, they are completely exhausted. This, it is thought, is the

genetic time clock that determines cell longevity. Germ cells are, however protected from this shortening and life-limiting mechanism by the enzyme telomerase. This enzyme actually promotes the telomeres to be re-built. Telomerase prevents cells from the life-limiting mechanism of mortality (Bodnar 1998). It enables cells to become immortal. Like all enzymes and all other proteins in cells, the gene for telomerase is encoded within the genome of the organism. The genome, therefore, has simultaneously incorporated into it both the genetic mechanisms, which ensure mortality of somatic cells and immortality of the germ line for propagation of the species.

Can Somatic Cells be Immortalised?

The logical reasoning is that, if the same mechanism were to be applied to somatic cells, they too would become immortal. An interesting and very illustrative story emerging from experiments with cultured cells illustrates this point. Somatic cells were growing in culture for some time so that they had exhausted most but not all of their telomeres. These cells were infected purposely with a certain type of virus, such as the Rous Sarcoma virus. As expected, the virus invaded the cells, monopolised the genetic mechanism of the infected cells and used it to propagate itself, producing millions of viruses, which occupied the cells. The viruses caused havoc and the cells died. In this scenario of devastation, destruction and death there were a few lonely cells which survived this terrible ordeal. They began to recover and once again began to proliferate. They continued to proliferate over and over again and continued to do so. They had become transformed into immortal cells. They had been genetically altered by the virus, which, among other things, had activated their telomerase and so were liberated from the life-limiting telomere shortening.

A similar mechanism also operates in most cancer cells. These too are genetically altered cells, which have been liberated from the normal mechanisms regulating cell proliferation. They proliferate without restraint. Since then they have been grown in laboratories world-wide and are acknowledged as immortal cells which will continue to proliferate as long people continue to culture them.

Genes for longevity

The mechanisms controlling cell mortality and immortality that have been referred to are not the same as those imposing mortality on the body as a whole. In fact, the two are quite distinct, although they are related. The aged body does not die because its component cells have reached their maximum limit of longevity. So why does the aged body die?

Over the years there has been a shift of thought in this regard. The original idea that people died of old age has long been discarded. In 1819 Sir Anthony Carlisle commented: "It seems little more than a vulgar error, to consider the termination of advanced life as the inevitable consequence of time, when the immediate cause of death in old persons is generally known to be some well-marked disease". People do not die of old age but, people die in old age because of a cardiac infarct, a stroke, gangrene, cancer or some other condition. So can we dismiss the notion that there is a maximum limit of longevity?

The actual life span of an individual is determined by a multitude of factors including lifestyle, diet, socio-economic status, environmental conditions and genetic inheritance. Most of these factors are alterable, and influence the mean life span of individuals. They have been instrumental in altering the life expectancy in communities.

Many inherited genes are known to limit longevity in individuals, such as the genes for hypercholesterolaemia, and for diabetes and familial genes predisposing to cancer. These genes affect mortality indirectly, and death results from the disease condition rather than the direct effect of the gene itself. The disease-causing genes responsible for such conditions are mutated genes and their normal counterparts, found in normal individuals, do not influence longevity. We now know that even in the absence of these specific inherited disease-causing genes, there are other genes which undergo mutation in occasional cells (somatic mutations); these are the underling causes of non-inherited cancer, auto-immune diseases and other age-related diseases. While it is now generally accepted that people, even in extreme old age, always die of illness or accident and not of the passage of time per se, are we to believe that all these illnesses occur purely as chance occurrences. One of the theories of ageing postulates that the chance of getting a serious and eventually fatal disease or injury increases with time so that fewer and fewer people will be fortunate enough to survive to extreme old age. If we were to rely on chance alone, however, we would expect that a small, perhaps very small number of individuals would escape fatal disease and survive to two, three or even four hundred years. This would not be different from the increasing chance of destruction of artefacts with the passage of time. We still find artefacts dating back to thousands of years, which have escaped chance destruction, but we never find people who live to exceed the specified age limit.

The programmed time clock that mentioned earlier does not refer to a sort of alarm clock that, at the pre-set time, suddenly activates a genetic switch. It is a gradual process, evidenced in the gradual physiological decline that is invariably noticed in ageing individuals. The genetic time clock is a sort of in-built obsolescence, which causes organs to age and to decline in function in spite of the very effective and remarkable repair mechanisms with which our body is endowed.

So now scientists are asking the question: "Are there longevity genes that directly determine how long an individual is permitted to live? Which genes determine the maximal life span?" We can expect that if such genes exist, they can be mutated so that their life-limiting effect would be modified, extending the maximum limit of longevity.

Over the past decade in several laboratories, the life span of at least two multicellular animal species has been significantly altered by genetic manipulation - one in

Drosophila and the other in Cyaenorhabditis elegans. In Drosophila (Jaswinski, 1996), mutations induced in the SOD1 gene, which controls free-radical metabolism, increased the animals' life span to about twice the normal span. SOD (superoxide dismutase), which is the product of this gene is essential for removing harmful free radicals, which are thought to be an important factor in ageing. In Cyaenorhabditis elegans (Ewbank, 1997), the situation is much more impressive. Here, two gene mutations were induced resulting in a sixfold increase in the maximal life span of this species. This is no mean achievement.

In more complex organisms, the problem is not as simple as this because we would expect that there would be several genes interacting with one another in complex fashions. This makes investigation of possible longevity genes very difficult. At present, there is still no concrete evidence that it is possible to induce life-lengthening mutations in higher animals and humans. However, there has certainly been a shift in our belief that the maximal life span is immutable. The possibility of extending the maximum life span in humans has now gone from legend to laboratory. It is being taken very seriously.

Is Man immortal?

In a discussion about mortality and immortality, it is inevitable that the question, " Is Man immortal?" should crop up. My first reaction was to keep well away from this question and not even to mention it. It is not possible to discuss the topic of immortality, which is entirely spiritual, in terms of genetics, which is entirely materialistic. The concept of Man's immortality, which dates back to the earliest cultures, is based on belief rather than on visible and tangible facts. Therefore, I will not try to answer the question "Is man immortal?" Instead I will take as my starting point my personal belief in Man's spiritual immortality. The question that I asked myself became "What is immortal in man if the body dies?" I tried to answer this question for my own personal satisfaction.

We speak in a rather "matter of fact" way, that man and all living things are made up of living matter and of the molecules of life. Is there such a thing as living matter? The genetic material and all that constitutes living cell and organisms are made up of atoms, just like all other matter. These are the same atoms that participate in all of nature's re-cycling of carbon, hydrogen, oxygen, nitrogen and so on. No particular molecule or substance in the cells is living. The body as a whole and its constituent, intact cells are living. If we think of the moment just after death, a person is made up of exactly the same matter as that immediately before death. So what has happened to the matter when an individual dies?

When we speak of "living matter" we are really referring to matter that has been animated by life. Life is the moving force that enables the matter to function in a perfectly harmonised way. Life becomes an integral part of the matter it animates. However, life does not originate of its own accord. Life is transmitted from one generation to the next through two germ cells, which fuse to form a small mass of matter, the zygote.

Here life assumes a new identity, a new individuality and a new character. And as the zygote develops into the human body, this life becomes one with the body with its personality and uniqueness. The individual, component cells share of the same life, the singular genome. When the body dies we are left with inanimate, lifeless matter. There comes a stage when for one reason or another the body is so deranged as a consequence of damage or disease that it can no longer support the life that animated it and dies. That life which had assumed the identity, the individuality, the personality and the character of a person lives on and is truly immortal.

References

Robine JM and Allard M (1998). Science, **279**, 1834-1835.

Wilde, O. A Woman of No Importance, Act 1.

Bodnar AG et al (1998). Science, **279**, 349-352.

Carlisle A (1819) *An Essay on the Disorders of Old Age and on the Means for Prolonging Life.*

Jazwinski SM (1996). Science, **273**, 54-59.

Ewbank JJ, Barnes JM, et al (1997). Science, **275**, 980-983.

Errata

The Application of Multivariate Analytical Techniques to the Study of Marine Benthic Assemblages: A Review with Special Reference to the Maltese Islands.

Rene' M. Micallef and Patrick J. Schembri
Department of Biology, University of Malta, Msida MSD 06, Malta

In the Contents page, the first author's name was incorrect. It should have read *Rene' M. Micallef.*
Also, in Figure 1 (page 10) *Manhatten* was misspelt. It should have read *Manhattan.*