IMMORTALITY: Medicine and the defeat of death

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‘Millions long for immortality who don’t know what to do with themselves on a rainy Sunday afternoon’

Susan Ertz 1894-1985

It is with a sense of inadequacy that I approach this task of delivering the Osuntokun Memorial lecture 2009. As a young schoolboy at Christ’s School, Ado-Ekiti, one of our heroes, or in today’s language, a role model was Osuntokun. He was reputed to have been the best student that an exceptional school had produced. He had achieved an aggregate of 6 at the school leaving examinations, in other words he had achieved six ‘As’. By the time that I arrived at clinical school at Ibadan he was already Professor; his stature was immense and he was the pre-eminent medical scientist of his day, at least as far as us students were concerned. I remember two close contacts with him; the first when he led us, at my graduation in June 1977, in taking the Hippocratic oath and the other when Christ’s School alumni at the Medical School held a reception for him to celebrate his award of DSc. On both occasions, he gave an account of the transition from Ibadan students going to the UK for their clinical years to staying on in Ibadan. What I learnt from his account was the need to replace a misplaced dependence on foreign experience, foreign qualifications, with greater self-belief in our own institutions and ourselves. The lesson he sought to teach is still relevant today. I hope that he would have been pleased with the implicit theme of my lecture, the need for Nigerian medical students and medical scientists to look to the future, to engage with knotty biological problems, to own science as part of our cultural heritage, and to develop a curious and courageous spirit.

My thesis is that human beings need not regard our mortality as given, that the age-old fascination with immortality can now be submitted to empirical analysis and research and that this development, this research agenda ought to be one that African scientists, in particular Nigerian scientists, engage with. At the beginning of the 20th century, flying a heavier-than-air machine, an aircraft was merely a dream, and some would have argued, a crazy notion, until the Wright brothers completed their 26-second flight in 1902. But today, it is a wholly accepted part of human life not worthy of comment. In the same way, in future, we may come to regard the discussions, at the beginning of the 21st century, about immortality as prescient.

IMMORTALITY

Immortality is defined as 'endless life or existence, exemption from death, perpetuity' (OED, 1993). The subject has fascinated human beings presumably for as long we *Homo sapiens* have been around. The world's first truly great work of literature *The epic of Gilgamesh* [1] was composed at least 4,000 years ago and survives in clay tablets dating back to 3,700 years ago. It predates Homer's [4]*Odyssey* and *The Bible*. The hero of the myth is obsessed with the avoidance of death. Perhaps this not surprising, as Death, the limiter of life, is ever present as a theme in the life of self-aware species as human beings are. The French philosopher, Derrida[2], makes this distinction between animals and human beings; for him animals *perish* whereas human beings *die*. The point he is seeking to make is that human beings have a concept of death because of their self - awareness, something that animals do not possess. We humans being aware of what death is, seek naturally to avoid it. Along with the avoidance of pain and

suffering, this may be regarded as the main task of medicine. Other great literary works deal with this same subject in varying forms. Homer's *Iliad*[3] draws a picture of a god-like Achilles whose search for immortality is by way of his achievement as an extraordinary warrior. The search for physical or symbolic immortality is the theme of literature as diverse as Oscar Wilde's *The Picture of Dorian Gray*[4] to Jose Saramago's *Death at Intervals*[5]. In *Death at Intervals*, for example, Saramago, the Portuguese Nobel prizewinner for literature deals with the possible, imaginary consequences of a temporary suspension of dying. The consequences are both absurd and telling. In this imaginary world, sick individuals remain in limbo unable to die and the obvious and overt distinction between sickness/health and living is drawn out, but so are the many cultural and economic aspects of dying. Funeral directors and doctors, lawyers and institutions such as hospitals and care homes all are caught up in the unexpected changes in their roles and positions. The novel demonstrates how far life is unalterable linked to death in human culture and society. The novel opens as follows

> 'The following day, no one died. This fact, being absolutely contrary to life's rules, provoked enormous and, in the circumstances, perfectly justifiable anxiety in people's minds, for we have only to consider that in the entire forty volumes of universal history there is no mention, not even one exemplary case, of such a phenomenon ever having occurred, for a whole day to go by, with its generous allowance of twenty-four hours, diurnal and nocturnal, matutinal and vespertine, without one death from an illness, a fatal fall, or a successful suicide, not one, not a single one' (p 1).

This quotation emphasises how remarkable it would be if death were to be abolished. In drama, our own Ola Rotimi's *Gbekude* and the TV series Star Trek's

Requiem for Methuselah all point to the signal importance of this subject in popular culture and our fascination with longevity, eternal youthfulness and immortality.

Various conceptual forms of immortality exist. Spiritual immortality flows from religious notions of the afterlife and speak to the idea of an indestructible or transmigrating soul that survives death. I will not be dealing with these ideas any further. There is the idea of abstract/hypothetical immortality. This refers to 'fame', and other metaphysical universals such as Plato's ideals. To summarise and simplify, this is the realm in which the idea of beauty or perfection or unity resides such that it exists before any of us mere mortal humans have grasped the concept or notion. These ideas are deemed incorruptible and thereby eternal. I do not intend to discuss these any further but simply to remark that the metaphysical notion of immortality by way of fame and accomplishment is a patent and powerful motivating force for human action. The striving for accomplishments that athletes, scientists, scholars and writers evince is an example of the desire for hypothetical immortality. This is a substitute for our inability to achieve physical immortality. An example of displacement activity; if we are unable to live forever, then perhaps our achievements will ensure that our name and reputation outlive us and the result of this is the accolade we pay Darwin, Einstein, Osuntokun and others like them.

Physical immortality refers to the state of life that allows a person to avoid death and yet maintain conscious thought. It can also be conceptualised as the

unending existence of a person from a physical source other than organic life such as a computer. This is the proper subject of my talk.

I want now to turn to the sources of death, the sources of the limits upon life.

CURRENT POSITION

There has been a marked increase in the population of those aged over 65 years in the developed world in the past 100 years. In the United States of America, the proportion of those aged over 65 years has increased from 3-4% in 1900 to 14% in 2000 (Figure 1). The corresponding figures for the UK are 3 – 18% and by

Figure 1 US: Proportions of persons aged 65+

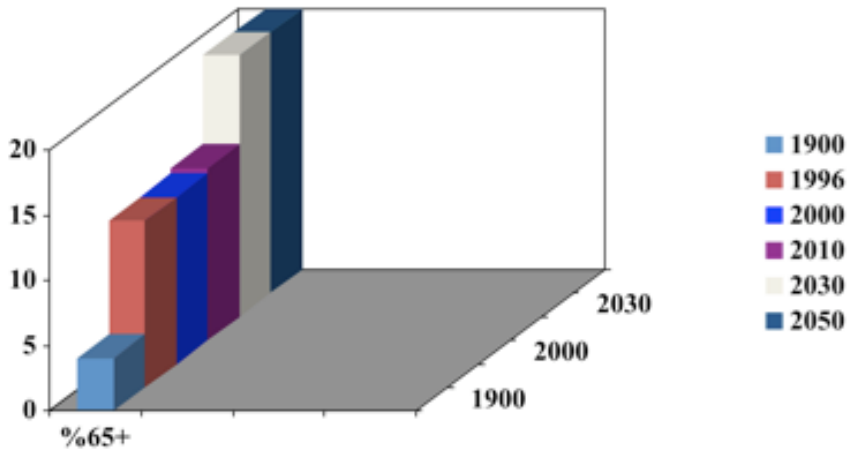


Figure 2:UK: Projections of elderly OPCS 87

60+ yrs (millions)

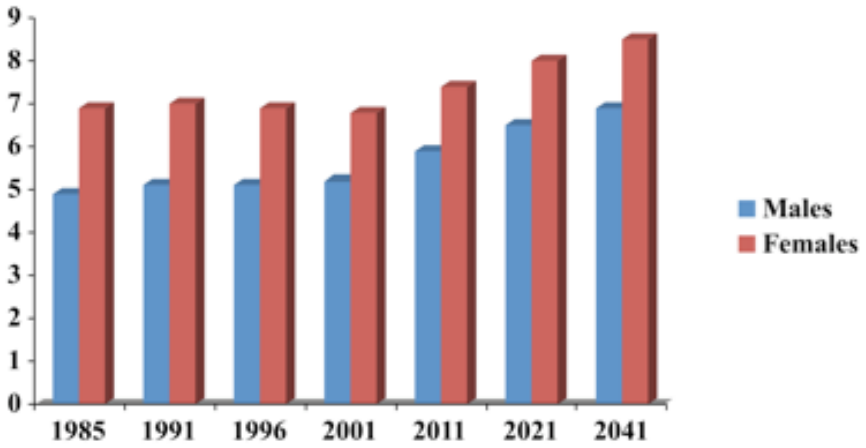


Fig 3 England & Wales 100+ years

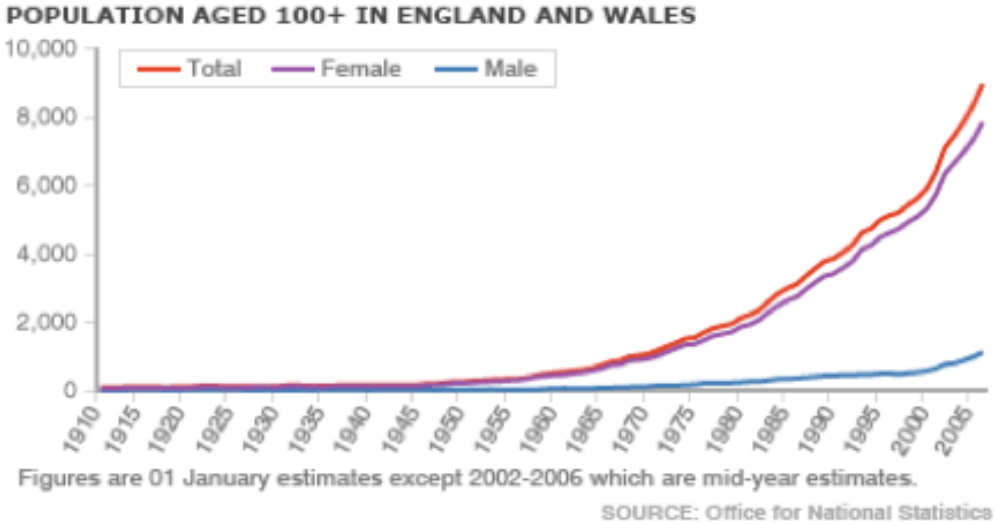


Table 1: Centenarians

Country	No centenarian (yr)	% >65	Rate/10^6
Canada	3,795 (2006)	13%	
China	17,800 (2007)	7.9%	13.4
France	20,000 (2008)		
Japan	36,276 (2008)	22.3%	284
Korea	961 (2005)		
USA	50,454 (2000)	13%	200
UK	8,370 (2007)	16%	169.8

Table 2: Supercentenarians

Name	Age
Jeanne Calment (French)	122 yrs 164 days
Sarah Knauss (US)	119 yrs 97 days
Lucy Hannah (African American)	117 yrs 248 days
M-L Meilleur (Canada)	117 yrs 230 days
Maria Capovilla (Ecuador)	116 yrs 347 days
Tane Ikai (Japan)	116 yrs 75 days
Elizabeth Bolden (African-American)	116 years 118 days

2040 this will amount to approximately 16 million people (Figure 2). It is estimated that there will be further increase to 20% in the USA by 2050 (Figure 1).

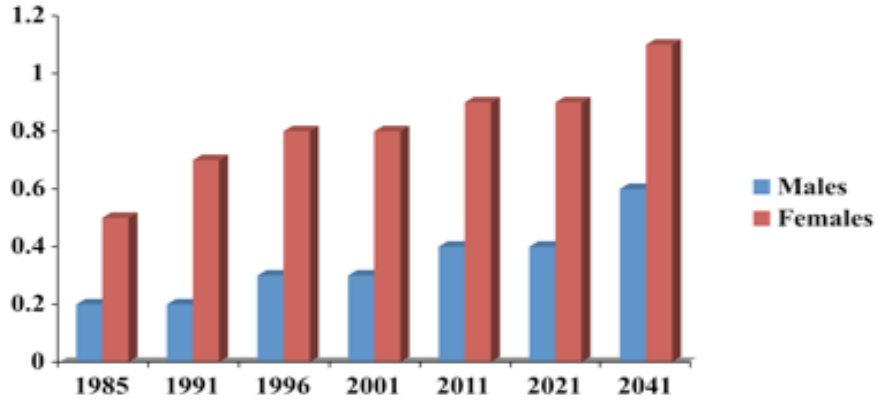
There has been a corresponding increase in the crude numbers of those aged over 100 years in developed countries, particularly Japan but also in the United Kingdom. In the UK, from very few centenarians in 1900, there are now in excess of 9,000 individuals aged over 100 years (Figure 3). This increase in centenarians is also evident in Canada, USA, France, Japan and China (Table 1).

As the proportions of centenarians has increased the crude number of supercentenarians, that is, those aged over 110 years has been increasing worldwide. It is significant that in the top seven of the most long-lived supercentenarians are two African-Americans, suggesting that the rarity of confirmed centenarians in African populations probably reflects environmental factors (Table 2)

Figure 4 UK: Projections of elderly OPCS

87

85+ yrs (millions)



In contrast the proportion of people aged over 65 years in Nigeria is estimated as 3% of the population and the number aged over 100 years are insignificant. It is estimated that by 2050, in Africa there would be over 2 million people aged over 80 years and 1.3 million in Nigeria in 2020 (Table 2). This compares with 1.5 million people aged over 85 years in the UK alone in the year 2040 (Figure 4). The figures for China are breath taking. By 2050, the population of those aged over 65 years in China is expected to treble to 24% of the general population, a staggering 322 million people. It is expected that by 2060 the average life expectancy in the developed world will pass the 100-year mark.

Table 3: Nigeria 2020: age & sex (millions)

	Total	Males	Females
65-69 yrs	6.4	3.0	3.4
70-74 yrs	4.5	2.1	2.4
75-79 yrs	2.7	1.2	1.5
80+ yrs	2.1	0.8	1.3

It is important, though, to keep in mind the brute realities of the situation in most African countries. There continues to be low life expectancy, often in the 40s and

largely contributed to by incredibly high infant mortality rates. The figure below illustrates this very by adjusting the world map for data on infant mortality it demonstrates the grossly excessive infant deaths in Africa and Asia (Figure 5) and these deaths are determined by preventable diseases (Figure 6).

Figure 5: All infant deaths 2001
www.worldmapper.org

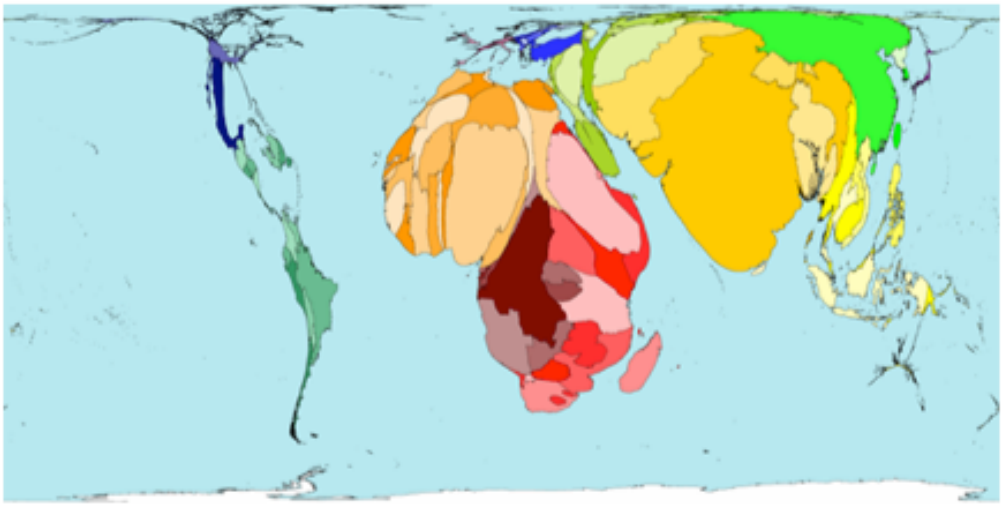
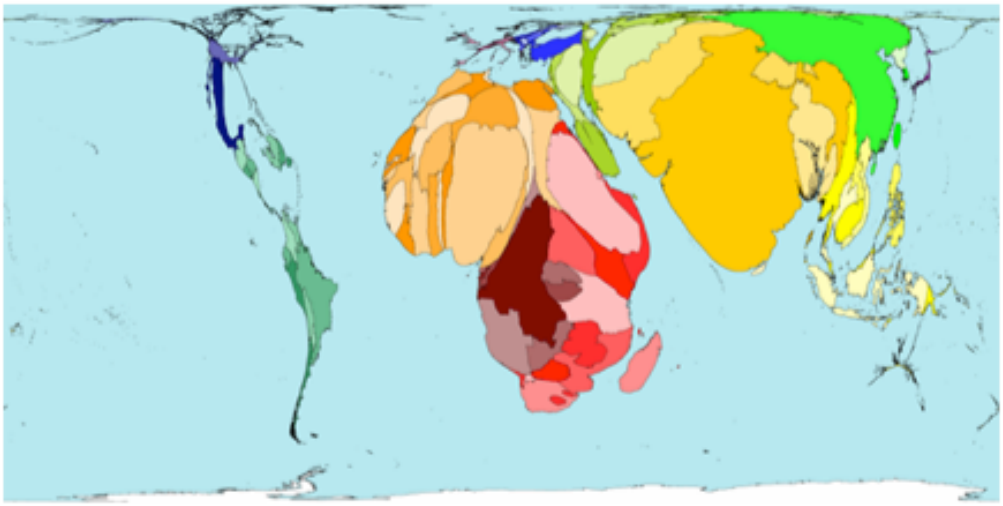


Figure 6: Preventable deaths
www.worldmapper.org



In some respects it could be argued that a lecture on immortality is foolhardy since it is in the face of facts that suggest a pessimistic and forlorn outcome. But, my thesis is that we need to look forward whilst at the same time dealing with our immediate realities. The poverty in both India and China is gross and palpable; nevertheless both countries are forging ahead into space and making strides in biotechnology research. The message is that our scientists and the intellectual elite need to grasp the moment and provide the necessary framework to make the desired changes possible.

DETERMINANTS OF MORTALITY

It has never been exactly clear why we die at all. In 1952 Peter Medawar[6] theorised that we age and die because ageing is not selected against by evolution simply because fit individuals have offspring before the mortal mutations are expressed. In other words, ageing and mortality is determined by the relationship between procreation and youthfulness. Once reproduction occurs mutations that are expressed in old age tend to accumulate since they are passed down to the progeny. More recently, Thomas Kirkwood[7] has put forward the hypothesis that the organism uses an energy conserving strategy to allocate resources for metabolism, reproduction, at the expense of bodily maintenance. It is this compromise in the allocation of energy to repair functions that results in bodily deterioration with age. The search is of course on to determine the exact mechanisms that underpin ageing and mortality. The goal is to determine what these processes or mechanisms are so that we might intervene in order to prolong life. At present there is consensus that ageing, disease and trauma are the three principal causes of mortality. I discuss ageing and disease below.

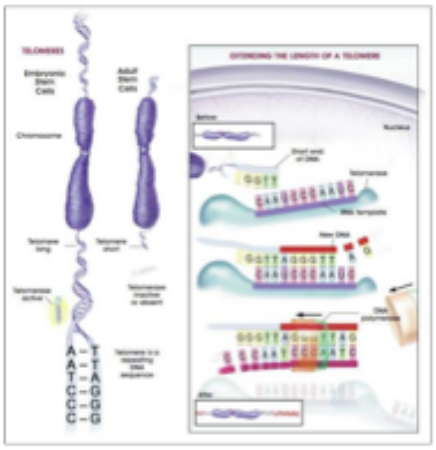
Ageing

There are a number of leading researchers in this area. One of the better-known scientists is Aubrey de Grey[8]. He defines ageing as 'a collection of cumulative changes to the molecular and cellular structure of an adult organism, which result in essential metabolic processes, but which also, once they progress far enough, increasingly disrupt metabolism, resulting in pathology and death'. The molecular processes underlying the ageing process include cell loss such as cerebral atrophy; oncogenic nuclear mutations and epimutations responsible for

cancers; cell senescence; mitochondrial mutations; lysosomal aggregates; random extracellular cross-linking; immune system decline, and endocrine changes. These processes are the subjects of investigations so that we can find a solution to these causes. One of the best studied of these processes is the role of telomeres in the ageing process and by extension the involvement of telomerase, the enzyme involved in telomere division, in this process. It is accepted that with each cellular division, the length of the telomere decreases and telomerase activity is involved in this process (See Figure 7). Simply put, telomeres function to prevent chromosomes from losing base pair sequences at their ends. Each time a cell divides, some of the telomere is lost (usually 25-200 base pairs per division). When the telomere becomes too short, the chromosome can no longer divide, and the cell dies by a process of apoptosis. Telomerase activity elongates telomeres and theoretically can induce cells to grow and divide indefinitely, thereby producing immortal cells.

Normally, telomerase is not expressed in somatic cells. The aim of research is to better understand the processes regulating the expression of telomerase activity in somatic cells. A variety of premature ageing syndromes such as ataxia telangiectasia are associated with short telomeres. But, it is notable that the length of telomeres does not directly correlate with longevity. Amongst primates, human beings have the shortest telomeres yet the longest lifespan. The problems associated with intervening in these processes are not minimal. Disruption of telomerase activity is involved in cell division in cancers, thus care must be taken in interfering with telomerase activity.

Figure 7: Telomere & telomerase



It is also the case that decreases in calorie intake is associated with decreases in cell division and telomerase activity. The work on calorie restriction and its implications for longevity has shown this association to be true in yeast, the nematode *C elegans*, Drosophilia, birds and mammals (mice, rats, and Rhesus monkeys). At present, this association is thought to be mediated by SIR2 (silent information regulator), a gene that encodes for an enzyme that removes acetyl moiety from proteins. This mechanism probably involves inhibition of apoptosis, suppression of adipogenesis and increased generation of nitrous oxide. In summary, calorie restriction probably slows down metabolism, resulting in diminution of cell replication and conservation of telomere length. The

foregoing suggests that manipulation of telomere length may result in longevity and indeed this is the case. A study was conducted using the nematode *Caenorhabditis elegans.* This study indicates that by lengthening the Telomere, longevity can be increased[9]. Thus, there is work underway to investigate how to control telomerase activity and thereby slow down the underlying ageing mechanism.

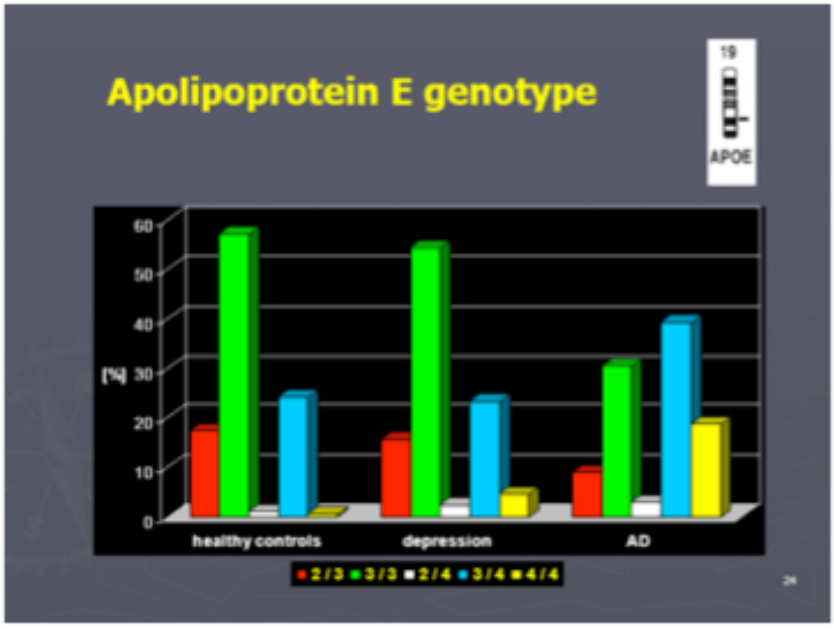
Disease

Alzheimer's disease occurs in 5% of the population aged over 65 years and in those aged 80 years occurs in 20%. Thus, this is a quintessential disease associated with ageing. Whether the underlying disturbance is in beta amyloid or in the production of tau protein is yet to be clearly delineated. However, there are already identified causal and susceptible genes for Alzheimer's dementia on chromosome 1, 14, 19 and 21.

Much of the role of apolipoprotein (ApoE) genotype in Alzheimer's disease has already been worked out (Figure 8). The risk of Alzheimer's disease is 3-fold in individuals who are heterozygote for ApoE4 and 10-fold for those homozygote for ApoE4. We now know that ApoE4 attaches itself to neuronal cell membrane and induces endocytosis of amyloid precursor protein and secretase, resulting in Beta-amyloid production and eventual cell death[10-13]. The consequence of this process is Alzheimer's disease. Work here in Ibadan, initiated and led by Professor Osuntokun, has furthered our understanding of these matters in the African popultion[10-12]. We now know that ApoE4 does not confer the same level of risk in the Nigerian population. This suggests that other factors are at play and

most probably these include environmental factors such as diet. It is notable that Alzheimer's disease, a common and disabling neurodegenerative disorder is the subject of intense and productive investigations. The hope is that this age-related disease may hold a key to our understanding of how ageing influences the development of disease. Work is also progressing into the underlying pathophysiology of Parkinson's disease and various cancers. The role of stem cell research in this context cannot be underestimated as has very recently been demonstrated in the transplantation of an engineered trachea to a live patient[14]. Here we have the potential for constructing hollow organs such as the trachea, gastrointestinal structures, bladders, etc. The day when solid organs such as the liver, spleen and

Figure 8



thyroid can be made is not too far off. The development of spare parts for surgery is no longer a mere dream! At a more manageable level of promise is the idea of using stem cells as renewable source of replacement cells and tissues to treat conditions such as Parkinson's disease, Alzheimer's disease, stroke disease, spinal cord injury, etc. Before any of these can happen, there are obstacles that need to be overcome. Stem cell proliferation must be sufficient and differentiation into the desired cell type must be guaranteed. The stem cells must integrate into the surrounding tissue, function properly and not harm the recipient. In short much still needs to be learnt about how to control the growth and function of stem cells.

Miscellaneous

There are other possibilities, which in today's terms seem far-fetched and fantastic. These include the ideas involving nanotechnology, the gradual replacement of organic bodily parts with electronic artefacts that in due course will lead to difficulties in determining what it means to be human. And, there is the far more radical idea that our consciousness including memories might be uploaded to a computer so that even if were to physically die, our consciousness may survive. In some respects there are already hints of these potential developments. None of us is surprised to see film clips and audio clips of our deceased loved ones today. These ordinary everyday experiences would have been unthinkable in the preceding 150,000 years of human experience. The implantation of chips that have the capacity to act as retinas and can assist sight in blind individuals suggests that the use of electronic technology will quickly develop certainly in the next 100 years. Finally, as we move in the direction of

creating total new life, artificially as Craig Venter[15] intends to do, the possibility of manufacturing genes and inducing these genes to make proteins of various kinds, or indeed to make organs becomes possible. The goal of synthetic biology is the creation of artificial biochemical life. Craig Venter talks about synthetic genomics and synthetic biology whilst others have talked about the distinction to be drawn between synthetic and artificial biology. This distinction can be exemplified by Craig Venter's group's announcement on 6th October 2007 that they had built a synthetic chromosome dubbed 'Synthia' and on 24th January 2008 another US team announced that they had made a laboratory copy of the DNA of *Mycoplasma genitalium*, a small parasitic bacterium that lives in primate genital and respiratory tract. There is little doubt that we are on the threshold of the human creation of new life that has never previously existed on this planet. Of course, this development has profound ethical and for the religious, utmost religious implications. Like all scientific discoveries, these developments are value-free. It is the use to which they put that determines whether they are malign or beneficent.

It is not my intention to specify how exactly and in what manner these developments will result in immortality. My aim was to suggest that work is underway to tackle some of the basic cellular biological problems, to explore different ways of extending life, and if even in the end immortality is revealed to be a mirage, we may have added further life-years to our existence. Usually at this stage of lectures of this sort the senior members of the audience who invariably are sitting at the front of the audience turn round to look at the

younger members of the audience to urge them on to do this work quickly and with urgent determination.

ETHICS AND IMMORTALITY

It is not my aim to systematically analyse the ethical dimension of our quest for immortality. Nonetheless, there is space to indicate that in a world that has yet to provide basic amenities for the vast majority of people, developing technologies to lengthen the life of a few is open at least to debate. Current estimates are that there are already 8 billion people on planet Earth. Many people think that this population size will make impossible demands on the world's physical environment. There are suggestions that the combined activities of 8 billion people are at the root of global warming and our current way of life is unsustainable. How to factor into this algorithm indefinite life, particular if that life requires considerable investment to keep it going is difficult to fathom. Put like that, the quest for immortality can easily be portrayed as an indulgence, an unrealistic or even selfish desire. None of these sentiments is likely to deter the search for medical approaches to lengthen life and indeed to make lengthened life healthier to live. So, whilst I acknowledge the problems and paradoxes of the quest for eternal life, it seems palpably true that the quest will continue whatever the difficulties envisaged by some. Even if eternal life is not achieved and probably will not be, the spin offs of the basic scientific research will be immense and beneficial in surprising and unpredictable ways.

Ortega y Gasset's, the Spanish existential philosopher, argued that life is only meaningful in the context of death, and that it is death that gives life the intensity

that we experience. In the absence of death much that we value in life may cease to be the worthy object of our admiration. It is not unusual in psychiatric practice to find that it is in extremis, in terminal illness that human relationship, love, and the importance of what is good and right assume their central position in life. This finding from clinical practice merely confirms what Ortega y Gasset had propounded. What would be the behavioural consequences of having all the time in the world? How will decisions, political and economic decisions, be affected? Given our natural difficulty in deferring gratification, our wired in impulsivity, and our inability to truly imagine the long-term future properly, would immortal subjects have the capacity to plan adequately for a future that is likely to be experienced by them but that is far into the future to be adequately imagined or modelled? It may be that decisions will take on new gravity, that they the weight given the weight that they are due. All these considerations will become part of the life of immortal beings.

It is unlikely that ethics, moral philosophy will determine whether these technical developments occur. It is more likely, as is usual with human beings, that we adapt to the radical changes as necessary and that even if the changes are revolutionary, that is sudden and like irruptions, our human capacity to adapt being immense, will see us through. Witness how we have accepted the incredible and fast-paced changes in the past 100 years, the introduction and remarkable consequences of electricity, of cars, trains, the computer, and of course of the Internet.

WHY IS THIS SUBJECT IMPORTANT IN AFRICA?

I return to my opening remarks. It is my view that there is a need for African scientists, and Nigerian scientists in particular, to engage with developments and emerging ideas. I remember as an 8-year old boy, being told that the white man, the European, had already discovered all that there was to discover. Even then I was totally astonished by this remark made by an elderly relative. It seemed even then to be a rather defeatist attitude, a sign of resignation, a passivity that smothered ambition and inspiration. I also remember as a student here in Ibadan, prefacing many statements with the expression 'they have found', an expression that definitely excluded me from the body of scientists and investigators. Within 3 months of moving to Newcastle-upon-Tyne, my language had adjusted unconsciously to the term 'we know that' indicating that I was a member of the body of practitioners who had proprietary rights to the said piece of knowledge. These subtle changes in the uses of language hint at a deeper problem, that there is a perceived intellectual distance between a student in Ibadan and much that is recognised as scientific knowledge today. In ordinary words, that there is a tendency to see an African student as a consumer of knowledge produced elsewhere. This is a problem of attitude and stance.

My aim was to draw attention to a pioneering area of human thought with the express desire to colonise the subject, that is, to render it as much Nigerian as American, so to stimulate discussion, debate and interest. It is only by the process of naturalisation that a novel idea, a pressing possibility for invention, can make itself manifest within us. Sowing an idea was my aim. I hope that it has found fertile ground.

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