Chapter 17
Unlike the Stochastic Events That Determine Ageing, Sex Determines Longevity

Leonard Hayflick

Abstract Contrary to popular belief, very little research is done on the fundamental etiology of biological ageing. Most research is done on longevity determinants or on age associated diseases, neither of which will provide insights into the fundamental cause of ageing. Although my research did not intend to answer questions in biogerontology the accidental discoveries that we made did. The phenomenological finding we made in 1961 that normal human cells have a finite replicative capacity torpedoed a dogma held since the invention of cell culture technology in 1907. The belief since then that cultured cells were immortal, mislead researchers to believe that ageing was caused by extracellular phenomena. Our findings focused attention on intracellular events as the origin of ageing. Twenty years later the discovery of telomere attrition and the enzyme telomerase explained the molecular basis for our findings and in 2009 their discoverers were awarded a Nobel Prize in Medicine or Physiology. The most likely cause of ageing in both animate and inanimate objects is based on the 2nd Law of Thermodynamics which underlies all other theories of ageing. For decades the failure to define key words and fundamental concepts in the field of biogerontology has thwarted progress in understanding the basic cause of ageing and this failure shows little sign of change.

Keywords Ageing • Longevity determinants • Age associated diseases • 2nd law of thermodynamics • Etiology of ageing • Intellectual property rights • Telomeres • Telomerase

17.1 Introduction

As in past centuries, most research on ageing today is predominantly descriptive at all levels of complexity. Studies on causation are a trivial part of what is called research on ageing. Efforts to slow, stop, or reverse the ageing process concerns a

L. Hayflick (✉)
Department of Anatomy, School of Medicine, University of California, The Sea Ranch, San Francisco, P.O. Box 89, CA 95497, USA
e-mail: lenh38@aol.com

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few biogerontologists but it is mostly the provenance of the huge lunatic fringe that, at least in the United States, has historically bedeviled the field. For centuries this fringe has exploited the ignorance of the general public by offering nostrums and life style changes that claimed, without evidence, to modify human ageing. These efforts are further confounded by the lack of biological markers to indicate the rate of aging. Birthdays are useless.

Even in today's era of scientific enlightenment main stream biogerontologists have collectively endorsed the fact that we know of no intervention that will perturb the fundamental process of ageing (Olshansky et al. 2002). The huge industries that market products to cover up the clinical manifestations of ageing depend on the differences in how much we value young people more than we value old people. These industries are a major economic force in many nations.

It has been argued that there are as many theories of the cause of ageing as there are biogerontologists but this cynical observation is now fading with the increasing understanding that, like all matter, – both animate and inanimate, the etiology can be found at the molecular level or even below. I will return to this notion later.

My experimental results in which we found that normal human cells have a finite capacity to replicate (Hayflick and Moorhead 1961) led us to three general conclusions, one of the most important of which was that the limited replicative capacity of normal human cells might be telling us something about ageing and the determinants of longevity. Second, that there are two classes of cultured cells, – mortal cell strains and immortal cell lines. I realized that having discovered that normal cells are mortal it was now possible for me to observe that only cancer cells were immortal (Hayflick 1965). These properties are also found in vivo where most cancer cells can be shown to be immortal and, of course, our normal cells are mortal. Later others have found senescent cells in vivo where considerable research is now ongoing (Jeyapalan and Sedivy 2008; Muller 2009; van Deursen 2014).

The third conclusion that my work revealed was that normal human cells were exquisitely sensitive to replicate virtually all of the then known human viruses, and were free of contaminating viruses. Consequently, I suggested that they would make an excellent alternative to the use of virus contaminated primary monkey kidney cells that were then used in the manufacture of the Sabin and Salk poliomyelitis vaccines and in other human virus vaccines (Hayflick and Moorhead 1961; Hayflick 1965). This will be discussed below.

17.2 Thanks for the Memories

Other discoveries followed. After a few months of frozen storage I was stunned to discover that, upon thawing, the cells had a memory. When they were thawed months after freezing and cultured they remembered at what doubling level they were frozen and then underwent only that number of doublings remaining from the total of 50 that were possible. Clearly, the cells had a system for counting the number of times that they could divide. One of the normal human fetal cell strains

that I developed, called WI-38, has been stored frozen for 53 years and the memory of the cells is as good today as it was in 1962. This is the longest time that normal human cells have ever been frozen in the living state.

17.3 The Importance of Being Normal

I realized that it was essential to prove that my cell strains were normal in order to make the novel claim that immortal cultured cell lines differed by having abnormal or cancer cell properties. For example, at this time the HeLa cancer cell line had been cultured continuously since 1952 (Gey et al. 1952) and after a decade of continuous culturing could be considered to be immortal. A few other immortal cancer cell lines also existed at this time. All were chromosomally abnormal, replicated when inoculated into laboratory animals, and were abnormal in other ways. The fact that my cultured cells were chromosomally normal, did not replicate in laboratory animals and were normal in all other respects demonstrated the critical insight that cell immortality is a property only of abnormal cancer cells (Hayflick 1965).

My additional finding in 1965 that the normal cells from adults replicated fewer times than those from fetuses seemed to support our earlier suggestion that my discovery might bear directly upon problems of ageing, or more precisely, "senescence" (Hayflick and Moorhead 1961). These observations compelled me to abandon my cancer virus research plans and motivated me to make an excursion into the question of why normal human cells stopped dividing after a specific number of population doublings.

What I thought would be a brief expedition lasted for more than 40 years. I never did return to the cancer virus project.

17.4 How Cultured Normal Human Cells Benefitted Billions

In the 1960s one of the major research areas at the Wistar Institute was the development of human virus vaccines. Many scientists, including the director, were engaged in these studies so I was immersed in knowing about this work because of the usual interactions with colleagues who worked in this area. This resulted in my efforts to determine whether my normal human cell strains would grow human viruses. I found that they grew all of the major human viruses then known (Hayflick and Moorhead 1961).

Of equal importance was my finding that the normal human cell strain WI-38, on which I decided to focus, did not contain any contaminating viruses. This was contrary to the many new and dangerous viruses found in primary monkey kidney cells then used for the manufacture of the widely used Salk and Sabin poliomyelitis vaccines.

WI-38 soon became a standard cell culture in virus diagnostic laboratories worldwide for the detection of viruses from human clinical specimens. We also isolated a new common cold virus using these cells (Tyrrell et al. 1962). This resulted in our suggestion that normal human cells would be a better and safer substrate for human virus vaccine preparation than the then existing and dangerous primary monkey kidney cells (Hayflick and Moorhead 1961). Two years later we reported that a safe and efficacious poliomyelitis vaccine had been produced in these cells (Hayflick et al. 1962).

After a 10-year struggle over objections made by the Division of Biologics Standards (DBS, NIH), now a part of the FDA, WI-38 became the first subcultivated culture and the first normal human cell strain to be used for human virus vaccine production (Hayflick 1989, 2001). Today, more than one billion people have received virus vaccines produced in WI-38 or similar normal human cell strains developed later by others. These include vaccines against poliomyelitis, adenovirus types 4 and 7, rubella, measles, varicella, mumps, cytomegalovirus, hepatitis A and rabies (Fletcher et al. 1998; Olshansky and Hayflick in preparation).

There is no other cell substrate, including the HeLa cell line that has benefited so many people. These benefits occurred without any of the putative dangerous side effects predicted for the use of these cells that had been feared by early detractors from both within and without of the U.S. Control Authority. These baseless fears caused a 10-year delay in the use of WI-38 as a human virus vaccine substrate in the United States until, in 1972, Pfizer Laboratories received U.S. approval for their Sabin poliomyelitis vaccine grown in WI-38. During the preceding decade WI-38 was widely used for vaccine manufacture in many other countries including Yugoslavia, the USSR, Poland, Germany, the UK, and France. In the same decade several people in the U.S. and elsewhere either died or became permanently comatose from working with virus contaminated primary monkey kidney cells. Also, prior to 1972, millions of people received poliomyelitis vaccines grown in primary monkey kidney cells and later found to be contaminated with the S.V.40 virus. This virus can transform normal human cultured cells into cancer cells (Koprowski et al. 1962; Shein and Enders 1962) and has been suspected to be associated with some human cancers (Hayflick 1984, 1989, 2001; Bookchin and Schumacher 2004).

17.5 Is It Ageing?

Our suggestion that we found ageing to have its origins within the cell was revolutionary because the central dogma claimed that all cultured cells were potentially immortal, so that those researchers on ageing, who preceded us, logically concluded that the ultimate cause of ageing did not have an intracellular origin. This was clear to them because if cultured normal human cells are immortal in the absence of the body's normal control mechanisms, then ageing could not be the result of intracellular events. It was for this reason that the focus of attention on

what little fundamental work was done in biogerontology during the 60 years prior to our work, was directed to extra-cellular causes of age changes like radiation, changes in the extra-cellular matrix, stress, and many other putative non intracellular causes.

Of the tens of thousands of papers published in this field in the last 42 years (which I subsequently named "cyto-gerontology", none have disproved our suggestion. In fact, most independent studies made during these years have added significant weight to our suggestion that the cessation of normal cell replication is telling us something about one or both aspects of the finitude of life. That is, ageing and longevity determination, each of which will be discussed subsequently.

The dogma that we thought we had overturned was so well entrenched that our manuscript was rejected in 1960 by *The Journal of Experimental Medicine* chosen because it had previously published most of the work by Alexis Carrel who reported that his chick cell culture grew continuously for 40 years until it was voluntarily terminated. We showed that his conclusion was erroneous (Hayflick and Moorhead 1961). In later years this journal published several articles by authors who had worked with cultured human cells but did not realize that their cells were mortal (Marcus et al. 1956).

The letter of rejection from *The Journal of Experimental Medicine* read, in part, "The inference that death of the cells . . . is due to 'senescence at the cellular level' seems notably rash. The largest fact to have come out from tissue culture in the last 50 years is that cells inherently capable of multiplying will do so indefinitely if supplied with the right milieu in vitro." The letter was signed by Peyton Rous, discoverer of the Rous sarcoma virus, the use of trypsin in cell culture, and soon to be awarded a Nobel Prize in Medicine or Physiology.

Paul Moorhead and I were crushed because we both thought that our 3 years of work was a significant contribution. The paper was then sent to Experimental Cell Research and within 2 months it was accepted for publication without change (Hayflick and Moorhead 1961). The paper has been cited more than 6,000 times (Hayflick 1978; Garfield 1980) and was one of the 200 most cited papers in the world for the 21-year period from 1961 to 1982 when the total number of citations reached 1,560 (Garfield 1984). Its sister paper, published in 1965, has been cited more than 4,000 times (Hayflick 1990). Only 0.4 % of all scientific papers receive more than 100 citations (Pendlebury 1999, Institute for scientific information, personal communication). Today, citations to the articles number above 10,000 (www.researchGate.net).

Despite the mounting citations to our publications and confirmation by others of our work, overturning the dogma took a decade or more. Full acceptance of my phenomenological finding did not occur until the molecular mechanism was discovered 20 years later.

It is a well-known phenomenon in science that the length of time necessary to accept a new discovery is directly proportional to how much that discovery is thought to defy received knowledge.

17.6 The Telomere Replicometer

Two observations led me to the notion that normal, mortal, human cells must contain a replication counting mechanism. First, was the reproducibility of our finding that normal human fibroblasts from different embryonic donors underwent a finite number of population doublings that spanned a narrow range between 40 and 60. Second, cells frozen at any population doubling level from 1 to 50 retained "memory" of that level until reconstitution so that the total number of population doublings traversed, both before and after freezing, totaled 50 (Hayflick and Moorhead 1961; Hayflick 1965).

The replication counting mechanism should not be called a clock or chronometer because time is not measured but cell doublings, or more precisely DNA replications, are. I named the unknown mechanism that I predicted a "replicometer" because it counts replication events.

In 1975 we made the first effort to determine the location of the putative replication counter. By employing enucleation and fusion techniques in which nuclei removed from old and young cultured cells were fused to opposite aged enucleated cytoplasts, we concluded that the counter was located in the nucleus (Wright and Hayflick 1975; Muggleton-Harris and Hayflick 1976).

17.7 The Coming of Age of Ageing Research

It is only within the past 40 years or so that the field of research on the biology of ageing has emerged as a legitimate area for scientific inquiry. Today, the science of biogerontology flourishes but it still has far to go before it escapes completely from what is analogous to alchemy in the middle-ages. The popular belief that the goal of most biogerontologists is to stop or reverse the ageing process or to make us all immortal is equivalent to the belief that the goal of modern chemistry is to turn base metals into gold.

Adding to the stigmatization of the field is the belief by a gullible public, at least in the United States, that some nostrum or life style will soon be found to slow or stop the ageing process in humans. The fact is that we know of no intervention that has been proven to alter the ageing process in humans nor is one likely to be found (Hayflick 1996, 2000; Olshansky et al. 2002). The goal of biogerontology research is not different from the goals of research in, for example, embryology and childhood development. That is, to understand the processes with no intention of reversing, slowing or stopping them. Curiosity itself is a legitimate goal in scientific research.

17.8 Old Things Considered

There are several impediments to our understanding of the ageing process, the most important of which is the belief that our present understanding of fundamental biological mechanisms is sufficient to understand its cause and to interfere in the

process. This same belief, which has been held during many previous decades, also did not result in an understanding. Research on the etiology of ageing in the nineteenth century or later, and prior to our understanding of the structure of complex biomolecules and pathways failed, although researchers had the chutzpah to believe that the state of knowledge at those times was sufficient to succeed. Those who pursue the etiology of ageing today are likely to fall into the same trap again because we have no biomarkers of ageing and still fail to understand that many major discoveries bearing on the biology of ageing have yet to be made. Worse, is the present lack of support to conduct research on the fundamental biology of ageing.

A second impediment to understanding the ageing process is the failure to distinguish ageing from the determinants of longevity and from age-associated diseases.

Finally, the terminology used in this field has resulted in the misdirection of most of the funds that could be available for research on the etiology of ageing into other fields. This aspect of research on biological ageing will be discussed later.

There are four aspects of the finitude of life, – ageing, longevity determinants, age-associated diseases and death. All but the latter will be discussed here.

17.9 Ageing and the Determinants of Longevity

Biological ageing can be defined at many levels of organization from population ageing to ageing at the molecular level or below.

Age changes can occur in only two fundamental ways, – either by a purposeful program driven by genes or by stochastic or random events.

It is a cornerstone of modern biology that a purposeful genetic program drives all biological processes that occur from conception to reproductive maturation. But, once reproductive maturation is reached, thought is divided in respect to whether the ageing process results from a continuation of the genetic program or whether it occurs by the accumulation of dysfunctional molecules. Yet, there is no direct evidence that genes drive age changes – a claim made because of the failure to distinguish age changes from longevity determinants.

The ageing phenotype is expressed after reproductive maturation and is driven by random events in animals that reach a fixed size in adulthood. No gene that codes for a universal biomarker of ageing has been found. Analogously, inanimate objects also require no instructions to age. Evidence for the belief that ageing is a random or stochastic process is that, (1) everything in the universe changes or ages in space-time without being driven by a purposeful program, (2) there is no direct evidence that age changes are governed by a genetic program and, (3) there is a huge body of knowledge indicating that all age changes are characterized by the expression and accumulation of dysfunctional molecules.

The common denominator that underlies all causes of ageing is change in molecular structure and hence, in function. It is caused by the intrinsic thermo-

dynamic instability of complex biomolecules, or the manifestations of the Second Law of Thermodynamics. Entropy increase in non-equilibrium systems was, until recently, dismissed as a cause of biological ageing because biological systems are open systems. The recent re-interpretation of the Second Law applies to biological systems and states that:

> Entropy is the tendency for concentrated energy to disperse when unhindered regardless of whether the system is open or closed. The 'hindrance' is the relative strength of chemical bonds. (See www.secondlawcom/six.html and www.entropysimple.com)

The prevention of chemical bond breakage until reproductive maturation is the *sine qua non* for the maintenance of life and species continuity. This is the role of longevity determinants or maintenance, repair and synthesis systems. All ultimately suffer the same effects of the Second Law as do their substrate molecules.

Thus, biological ageing can be defined as the random, systemic accumulation of dysfunctional molecules that exceeds repair or replacement capacity. This occurs throughout life, but in youth the balance favors the bodies' enormous capacity for repair, turnover and synthesis, – otherwise individuals would not live long enough to reproduce and the species would vanish. After reproductive maturation the balance shifts to slowly favor the accumulation of irreparable, dysfunctional molecules, including those that compose the maintenance and disposal systems themselves. Natural selection causes the balance to shift because in animals that reach a fixed size in adulthood favoring life to be extended beyond reproductive maturation is unnecessary for species survival. The repair shops also age. Then the myriad decrements that produce the ageing phenotype become slowly revealed. Most significantly, the accumulation of dysfunctional molecules increases vulnerability to age-associated diseases.

Blueprints contain no information to instruct a car, or other inanimate object, how to age. Yet, in the absence of blueprints, molecules composing these objects also obey the 2nd Law as their molecules dissipate energy (increasing entropy) and incur structural and functional losses over lengths of time that vary from picoseconds to light years. Analogously, the genome also does not contain instructions that determine age changes because, like the car and everything else in the universe, instructions are unnecessary to drive a spontaneous process.

17.10 Genes Do Not Govern Ageing

Because ageing is not a programmed process it is not governed directly by genes. On the contrary, ageing is a stochastic process. The many studies in recent years where invertebrates have been used have led to the view that genes are involved in ageing. Yet, none of these experiments has shown a reversal or arrest of the inexorable expression of molecular dysfunction that is the hallmark of ageing. These studies are more accurately interpreted to have increased our understanding of longevity determination (discussed below). Most of the experimental results

using invertebrates, and allegedly thought to modify age changes, alter physiological capacity well before the ageing process begins. Furthermore, most experiments with invertebrates use an "all-cause mortality" end point that is falsely interpreted to be exclusively caused by ageing. It erroneously excludes possible causes of death attributable to disease, pathology, predation, toxicity, accidents, etc. Finally, because there are no generally accepted biomarkers for ageing in these, or any other animals, the effects of experimental manipulations on their fundamental ageing process can only be speculated upon.

Another argument against the direct role of genes in programming the ageing process is that animals do not age at the same rate nor are the patterns of age changes identical. This results in the great variations found in the location and timing of the acquisition of pathology and the subsequent differences in the chronological age of death. When these random events, which characterize the ageing process, are compared with the orderly, virtually lock-step, changes that occur during genetically driven embryogenesis and development, that orderliness and precision stands out in stark contrast to the quantitative and qualitative disorder of age changes. The variability in the manifestations of ageing differs greatly from animal to animal but the variability in normal developmental changes from animal to animal differs trivially. Humans from conception to adulthood are virtually identical in respect to the stages and timing of biological development but from about age 20 on, age changes make humans much more heterogeneous.

That heterogeneity is often mollified by the reduction in pathological processes and causes of death that have occurred in recent decades in developed countries. This phenomenon is typical of the causes of loss in function that occurs in inanimate objects like automobiles. There is a striking similarity in the loss of function in identical systems in the same make, model and year of automobiles. Yet to argue that these are programmed similarities is indefensible. A weakest link always occurs in inanimate mechanical or electronic objects.

17.11 The Determinants of Longevity

The second aspect of the finitude of life is longevity determination – a completely different process from ageing.

Longevity is determined by the length of time that the synthesis, turnover, disposal and repair processes can maintain the biologically active state of molecules. These processes are governed by the genome.

Unlike the stochastic process that characterizes ageing, longevity determination is not a random process. It is governed by the enormous excess of physiological reserve produced prior to, and during, the time of reproductive maturation and evolved through natural selection to better guarantee survival to that age.

Life does not end immediately after reproductive maturation in most species because it does not benefit species survival. Also, the energy necessary to produce a mechanism that would cause death immediately after reproductive maturation in

higher animals is too costly. Exceptions are semelparous "big bang animals" like the Pacific salmon, and some insects. But, it is rare in vertebrates other than some bony fish.

Thus, the determination of longevity is incidental to the main function of the genome, which is to reach reproductive maturity.

After reproductive success feral animals soon die as the result of predation, disease or accidents. But humans have learned how to substantially eliminate or slow many of these causes of death allowing us and the animals we choose to protect to experience increased life expectancy. Ageing in its extreme manifestations is unique to humans and our protected animals.

Longevity determination is an entirely different process from ageing and is independent of it. One might think of longevity determination as the energy state of molecules before they incur age changes. This energy state is part of the answer to the question: "Why do we live as long as we do?"

One might think of ageing as the state of molecules after they have incurred irreparable damage that leads to the ageing phenotype. This condition answers the question: "Why do things eventually change or go wrong?"

Ageing is a catabolic (destructive) process that is chance driven. Longevity determination is an anabolic (constructive) process that, indirectly, is genome driven. They are opposing forces.

The genome directs events until reproductive maturation after which the ageing process dominates. Thus, the genome only indirectly determines potential longevity by governing the levels of excess physiological capacity, repair, synthesis, waste disposal and turnover. No specific genes determine longevity but, collectively, they all govern aspects of biological processes that increase the likelihood of survival to reproductive maturity. The quantitative variation in physiological capacity, repair, and turnover, accounts for the differences in longevity both within and between species.

Because longevity is indirectly governed by the genome it is sexually determined. Because ageing is a stochastic process it is not.

17.12 Age-Associated Diseases

Absent any discussion of death, the third and last of the four aspects of the finitude of life to be discussed are age-associated diseases. The distinction between the ageing process and age-associated disease is critical and it is rooted in several practical observations:

Unlike any disease, age changes: (1) occur in every animal that reaches a fixed size in adulthood; (2) cross virtually all species barriers; (3) occur in all members of a species only after the age of reproductive maturation; (4) occur in all animals protected by humans even when that species probably has not experienced ageing for thousands or even millions of years; (5) occur in most animate and all inanimate objects; and (6) have the same universal molecular etiology, that is, thermodynamic instability or increase in entropy.

There is no disease or pathology that has all of these properties.

Age-associated disease is the research and care provenance of geriatric medicine. The fundamental biology of ageing is the research provenance of biogerontology.

17.13 The Alzheimerization of Ageing

Since the establishment of the National Institute on Ageing in the USA in 1974, support for research on Alzheimer's disease has increased dramatically. One consequence of this has been the phenomenon in which, at almost every meeting or conference on ageing that has been held in the last 40 years, a session on Alzheimer's disease has been virtually mandatory. The phenomenon has been called "The Alzheimerization of Ageing" (Adelman 1998).

The resolution of Alzheimer's disease as a cause of death would add about 20 months onto human life expectancy (Arias et al. 2013). In the last 5 years $200,000,000 has been added to the Alzheimer's disease research budget. The budget for research on the biology of ageing has remained static at orders of magnitude less.

It is remarkable that this pathology has become so inseparable from research on ageing that its importance has eclipsed that of the major causes of death, – cardiovascular disease, stroke and cancer. These rarely appear as a separate part of conferences on the biology of ageing. Yet, these causes of death require as much attention, or more, from care givers, physicians and from researchers as does Alzheimer's disease.

17.14 What Would Life Expectancy Be if All Causes of Death Were Resolved?

In 2001 life expectancy at birth was 77 years (Arias et al. 2013). If cardiovascular diseases would be resolved life expectancy would increase by about 5.48 years, stroke 0.65 years and cancer 3.2 years. If all of the causes of death legally allowed on death certificates (ICD-10 or International Classification of Disease Version 10) were resolved, average human life expectancy could not increase more than about 12 years. Or, age 89 years would be the maximum life expectancy for humans if all of the present causes of death would be resolved (Olshansky et al. 1990; Hayflick 2003; Arias et al. 2013). Curiously, and contrary to what frequently appears in the media, it is illegal for anyone to die from either "natural causes" or "old age" in the United States or in other developed countries who have adopted the ICD-10.

For age associated diseases the fundamental question is: "Why are old cells or those near the end of a lineage more vulnerable to pathology than are young cells?" Regrettably, little research is, or has been, done in an effort to answer this important question.

17.15 Discovery of Telomere Attrition and the Enzyme Telomerase

In 1989, Calvin Harley, who had worked for several years with my system of senescent human cells, had a fortuitous discussion with Carol Greider that resulted in a collaborative experiment in which it was found that chromosome ends (telomeres) decreased in length at each round of normal human cell division (Harley et al 1990).

The remaining critical question was: "How does that class of cells that we identified as immortal avoid telomere shortening that, if it occurs, would lead to their loss of replicative capacity?"

In 1985 Greider and Blackburn discovered the enzyme "telomerase" that, in cancer cells, adds the missing molecules onto the telomeres at each division. Thus, the telomeres of cancer cells do not shorten to some critical length and therefore provide them with the property of immortality that I conjectured they had (Hayflick 1965). The Nobel Prize in Medicine or Physiology was awarded to Blackburn, Greider and Szostak in 2009 for their discovery that telomeres protected chromosome ends and for discovering the existence of telomerase (Gilson and Ségal-Bendirdjian 2010). This had the effect of eliminating all of the doubt about my phenomenological discoveries which were now explicable by their findings at the molecular level. It also provided enormous interest in my interpretation in 1961 that these findings might be associated with ageing when the Nobel Committee announcements associated the prize with my original suggestion that the phenomenon illuminated our knowledge of the biology of ageing.

17.16 Telomeres as Longevity Determinators

The suggestion that telomere attrition in cultured normal human cells is associated with biological ageing was a conclusion quickly reached by many. However, that conclusion is spurious because biological ageing as described above is a stochastic process that is not governed by the genome. The attrition of telomeres and the subsequent downstream chromosomal events that trigger the cessation of cell division is more likely to be associated with longevity determination than it is with the stochastic process of ageing.

17.17 Biologists Have Intellectual Property Rights

Other interesting events in the history of my discovery of the replicative limit of normal cells includes the confiscation of WI-38 from my Stanford University laboratory by NIH, FDA and DHEW zealots in 1975 (Hayflick 1984, 1990, 1998)

who believed that the government was the sole owner of the cells. Their belief was held despite the fact that the government did not support my discovery of the cell strains or of my discovery of the limited replicative capacity of cultured normal human cells. Overhead funds supported my laboratory which was a central supplier of cultures to other institute members. I used surplus materials from the cultures I prepared for others that would have ordinarily been discarded. I sued the NIH, FDA and DHEW in which I maintained that there were three other stakeholders that included the institute where the work was done, the estate of the donor and the scientists who gave value to the cells.

During the 6 years of litigation several significant events occurred that forced the government to ask me for an out-of-court settlement. First, amicus briefs were offered by the nascent biotechnology industry founded on the use of materials directly supported by government grants made to academic laboratories. Second, the Supreme Court ruled that living cells could be patented. Third, a presidential executive order declared that federally supported research resulting in cells or microorganisms with new features could be commercially exploited. Finally, the passage of the Bayh-Dole Act made the executive order law (35 USC 200-212). Critically, the settlement of my lawsuit established for the first time that biologists have intellectual property rights.

Eighty three scientists published a letter in Science in support of my position (Hayflick 1978, 1998; Strehler et al. 1975; Wadman 2013).

The history of WI-38 also includes the actions of the anti-choice people who picketed Cape Kennedy in an unsuccessful effort to thwart NASA's launch of Skylab 2 which contained an elaborate experiment designed to determine whether the normal WI-38 human chromosomes would be affected by zero G. WI-38 was chosen because it was the most well characterized human cell strain in the world. Objectors to orbiting WI-38 believed that it was wrong to undertake an experiment on cells obtained from an aborted fetus. This objection was held despite the fact that the abortion was a choice made by the mother and the fact that it would have otherwise been incinerated. However, after the launch director spoke with me and learned that the legal voluntary abortion occurred in Sweden, the protesters ultimately dispersed and the launch was successful (Montgomery et al. 1978).

17.18 The Present Status of Research on Ageing

Fifty or 60 years ago a review of the status of research on the etiology of biological ageing could have been done in a few pages because most work was descriptive. I do not intend to review the present state of what is commonly called "Research on Ageing" because the misleading use of this undefined and vague term has seriously compromised the field for the last half century.

Research on ageing is rarely defined to mean the study of the biology of the fundamental cause of ageing. Many would assume that the rubric "Research on Ageing" would be defined this way. It is not. And, it has resulted in a "One Billion Dollar Misunderstanding" (Hayflick 2003).

Research on ageing does not apply to geriatric medicine because that is the provenance of research on, or treatment of, age-associated pathologies and the decrements of old age in humans.

One example of the abuse of the term is how the word "ageing" is used in the titles of institutes, centers, departments and similar organizations. Rarely do any members of these organizations conduct research on the etiology of ageing. Research is either focused on the geriatric aspects of ageing or descriptive events that occur during the ageing process. When questioned, most organization leaders will reply that appeals for funding research on the fundamental biology of ageing rarely produces results. But, an appeal for the support of research on age-associated diseases is significantly more productive because most decision makers have had direct, or indirect, experience with at least one of these pathologies. The importance of the highly probable link between the biology of old cells, which increases vulnerability to all of these pathologies, goes unappreciated.

The rubric "Research on Ageing" could involve research on virtually any aspect of human, animal, microbial or plant life. It could also reasonably include the ageing of inanimate objects. These enormous areas would also be increased if we incorporate research from the molecular level up to the whole animal, object, and groups of each.

This universal embrace is one of the most serious past and present problems in the field called "Research on Ageing." It is also one of the least understood or appreciated problems. Yet, the impact that this language failure has had on the field, and will continue to have, is extraordinary.

17.19 The Tyranny of Words

Decision makers who direct and or fund "Research on Ageing" usually have little understanding of the imprecision of terms used in the field. In respect to biology, the term usually means research on longevity determinants or age-associated diseases. It rarely means research on understanding the cause of biological ageing which should be its only meaning. Biologists have attempted to distinguish themselves from geriatricians and non-biologists in the field of "Research on Ageing" by characterizing themselves as biogerontologist or cyto-gerontologists. But, these labels are not universally used. Calling those who do research on the non-biological aspects of ageing as "Researchers on Ageing" is misleading because it includes everything from economics, sociology, psychology and architecture to geriatric medicine and anything old.

Research funds that may be appropriated under the rubric "Research on Ageing" are largely expended for research on longevity determinants because of the failure to understand that increasing the longevity of animals by manipulating constructive, synthesizing or anabolic processes will tell us little about the dysfunctional molecules that characterize the destructive or catabolic process of ageing.

Further evidence for this misunderstanding is that the availability of funds for research on age-associated diseases is several orders of magnitude greater than what is available for research on the fundamental biology of ageing. What is far more meaningful is that most decision makers believe that the resolution of age-associated diseases will tell us something about the fundamental biology of ageing. It will not.

This spurious belief is comparable to the notion that resolving childhood diseases will enlighten us about the fundamental biology of embryogenesis or childhood development. The resolution of childhood diseases, like poliomyelitis, Wilms' tumors and iron deficiency anemia, added nothing to our fund of knowledge about embryogenesis or the biology of human development. Likewise, the resolution of age-associated diseases has not in the past, nor will it in the future, add to our understanding of the fundamental biology of ageing. A century ago, the leading cause of death in old age was pneumonia, often called "the old man's friend" (with its sexist overtones). Pneumonia is no longer one of the leading causes of death in old age but its resolution did not advance our knowledge of the biology of ageing. Nor will the resolution of any other age-associated cause of death or pathology. If the goal of research on ageing is to understand the fundamental process at the molecular level little, if any, progress has been made in the last 50 years.

The irony of these observations is that the common mantra uttered and published by most geriatricians, and also by some biogerontologists, is that "The greatest risk factor for cancer, Alzheimer's disease, cardiovascular disease, or stroke is ageing."

It does not take a great leap of intellect to conclude: "Then why are we not doing research on the fundamental biology of ageing."

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