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EDUCATIONAL SECTION

The evolutionary biology of death and human malignancy

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> We must, however, acknowledge ... that man with all his noble qualities ... bears in his bodily frame the indelible stamp of his lowly origin.
>
> Charles Darwin (1871). *The Descent of Man*. London.

Introduction

Surgical oncology is the application of craft, knowledge, science and technology to the delay of death through the prevention and treatment of malignant disease. Human intervention can only postpone the inevitability of death. The dynamic of life obliges nature to discard everything that it creates. We may never resolve the meaning of life for individual men and women in secular terms, but we can resolve the meaning of death for the individual in the context of reproduction, of ageing and of cancer. It is difficult to explore a biological function for death and the role which cancer plays in it without encroaching on the metaphysical, and there is little published literature to turn to for guidance. Nevertheless, the study of evolutionary biology helps us to understand the role of death and even the contribution of cancer to the continuity of life. Biology and evolution have placed effective constraints on what is achievable in cancer treatment, but clear biological principles can help us to understand more about the nature of cancer.

Death is consequent upon life and evolution. All biology is founded upon the cell as the building block of life, which is thus defined by cell replication. The evolution of life on Earth may be considered to have passed several milestones. The first was the emergence of the stable organic chemistry of sugars, lipids, amino acids and nucleic acids in the early planetary environment. The second, and most extraordinary milestone, was the emergence of self-sufficient, replicating cells, a process which is yet to be understood or duplicated under laboratory conditions.[1] The fossil record shows that prokaryotic cells existed some 3000 million years ago. By this time, the key elements of DNA replication, cell proliferation, and structural organization must have all been mature. These durable molecular systems gave form, function and continuity to cells, and have withstood all of the vagaries of the planetary environment. They have been conserved to an extraordinary degree across the natural world. They provided the building blocks for all subsequent biological processes and evolutionary maturation. The first durable, perpetually self-replicating protobacterial cell line thus defined the probability of evolutionary biology, the perpetual expansion in numbers creating competition for space, resources, the search for new environmental niches and, inevitably, selection and death.

The third achievement, or consequence, of evolution, with the durability of cell biology and reproduction established, was the production and replication of the independent multicellular organism, with all its extraordinary complexity. This required the development of molecular controls to embryogenesis, differentiation, tissue and organ formation, and cell signalling, for example. Once a multicellular organism could display all of the functions necessary for independent existence, the fourth great achievement, or consequence, of evolution was possible. Speciation, from the earliest eukaryote, through the Cambrian explosion of some 500 M years ago, to the emergence of the vertebrates and man,[2] was a continual reorganization and augmentation of the gene pool under competitive pressures, using the same tried and tested molecular building blocks. Multicellular organisms replicated and modified continuously to occupy all available environmental niches and to respond to geological catastrophes, from the local to planetary extinction-level events such as at the end of the Palaeozoic era some 250 M years ago, and the disappearance of the dinosaurs 65 M years ago.

Evolution, death and the reproductive lifespan of species

Darwin and his contemporaries showed us the fundamental principles of evolutionary biology and speciation, wherein all organisms adapt to their environments through natural selection, the survival of the fittest, and selective advantage through endless competition.[3,W1,W2] All cells, tissues and

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individuals are biologically advantaged or disadvantaged through their position in time and space relative to other individuals, whether in competition for the essentials of life in their ecological niche, or for reproductive partners.

We may ask why nature discards the extraordinarily intricate machines represented by the physical and intellectual being of all individuals when it does. There must be powerful reasons to do so within the logic of evolutionary competition. Dawkins' concept of the selfish gene[4] helps to explain the apparent wastage. If we place the continuity of the germ line rather than the existence of the individual organism at the centre of biological strategy, then we see how the individual body becomes disposable once continuity of the germ line through the offspring has been secured. Dawkins has also introduced the engineering concept of 'the utility function' to the disposal of living organisms.[5,6] Any characteristic which does not add specifically to the security of the germ line, such as post-reproductive ageing, is not selected by evolutionary competition. We may thus identify features of life and biology in species and individuals which are specifically selected as Darwinian adaptations, from those which are, in effect, by-products. The latter persist by virtue of their irrelevance to the reproductive strategy of the organism, such as, perhaps, the various forms of degenerative diseases of old age.[7,8]

The reproductive stem cell may thus be considered the biological soul of every organism, and the body is simply a vehicle for the reproductive strategies of the germ line. It replaces individual organisms in a continued procession of diversity, speciation and a search for evolutionary security. The DNA stemline is continuous, while the individual organisms which carry and nurture it all have finite lives. Thus, each and every organism on Earth expresses and preserves the absolute continuity of DNA from its evolutionary origins and is its own biological archaeological record. There is clearly huge utility in reproductive replenishment and supercession, because this is evolution's favoured, or perhaps inevitable, mechanism. The drive to continuity of the germline through cell reproduction and gamete exchange creates the inevitability of biological and evolutionary competition. Otherwise, nature would have evolved life processes tending to the immortality of individual organisms. Individual death must thus be absolutely advantageous to the overall survival and procession of the gene pool on planetary, astronomic, geological and evolutionary timescales.

Logic dictates that the age of death is thus a function of the reproductive lifespan and reproductive strategy of the species, including that time needed to nurture offspring to reproductive maturity. Male germline cells possess the property of reproduction over many generations. Conversely, the female germline contingent of ova are laid down *in utero* and do not replicate thereafter. The longevity of these cells thus appears to determine the safe reproductive span, and consequently the life-expectancy, of the female. The menopause may mark the evolutionary watershed in female mammals.[9]

The reproductive clock for each species, and in man in particular, is set by female biology, as male fertility extends much later through life. There is a set limit on the reproductive period of between 20 and 30 years in women. Fertility is set by the number of viable ova in the ovary, but there is no obvious reason why this should be fixed as it is, other than that nature has found this the optimum arrangement for reasons which may not now be apparent. Male spermatogenesis, in comparison, continues unimpeded up to the ninth decade. The difference in reproductive longevity and germline function between males and females is a curious observation. We may ask why men die, when the male germline is effectively immortalized compared with the female ova. We can conceive of powerful selection pressures in favour of longevity in men compared with women, and yet the male life expectancy is generally shorter than in women.

Once the security of offspring is achieved, there is no biological, evolutionary or competitive pressure at work to prolong the median or maximum life expectancy of the species. There has been no added evolutionary or reproductive benefit in investing nature's resources in longevity once offspring have been nurtured to reproductive maturity. The view propounded by Medawar,[10,W3] Williams[8] and Dawkins is that deleterious genes of all kinds escape more natural selection pressures the later in life they express their effects, thus making death inevitable by evolutionary neglect. The maximum life span of individuals of any species is relatively constant for that species and inevitable over a defined life span. Nature and Darwinian selection can create and select from many choices, so as to optimize the durability of individuals within each species. Trees live for many hundreds of years; butterflies may live for a few fleeting hours; men and women may now count themselves lucky with a median of 75 years of active life. In past generations, infectious disease tended to limit life expectancy to four decades, so there was no evolutionary pressure to reverse the processes of degenerative disease beyond the phase of parenthood. There can have been no evolutionary pressure to select directly for disorders of degeneration, such as endocrine collapse at menopause, decay in the skeletal structure, atherosclerosis and the arthritides. Nevertheless, we might expect a proportion of individuals to linger on for many decades later. And yet none live to 150, 200 or 250 years. This suggests that it is in the interests of species for the diseases of degeneration to accelerate later in life, and that nature is specifically intolerant of old age. These views have been developed in detail by Nesse and Williams.[8]

We can conceive of a biology founded upon a slower turnover of dominant organisms. In competition, the young have a competitive advantage over the old, notwithstanding the greater experience, be it immunological or neurological, of the older individuals. Nature has found it more advantageous to allow the aged to wither than to invest resources in prolonging the actual and reproductive lives of individuals. Death from old age is a luxury which has not been afforded many in the animal kingdom. Man's modern life expectancy in the developed world appears to be a significant prolongation of our own evolutionary norms, and this may be the key to the weakening of effective defence mechanisms later in life. Nature helps to eliminate the post-reproductive individual through imposing, permitting or accelerating the diseases of age and degeneration. Some of the greatest gains in longevity seem to be attainable in the remote regions of Central Asia, where life expectancy

frequently exceeds 100 years. However, even in these individuals, marked physical degeneratation and frailty with the passage of time is the norm. Immortality is otherwise as elusive a goal today as it has ever been.

The genomic consequences of ageing

Longevity might be a greater asset and attract greater selection pressures were it not for the cumulative risk to the static genome with time. Cumulative genomic damage to both germline and somaticline cells occurs through a number of mechanisms. The most important environmental factor on the evolutionary timescale is probably radiation of astronomical and terrestrial origin.

Damage may also be in consequence of the sheer complexity of chromosomal organization and the frequency of replication errors, which are estimated to occur at a rate of 50,000 per cell per hour, in the replicating fraction of the 10×10^{10} or more cells in the human body. The cumulative risk of genomic damage is thus immense. That cells and tissues are remarkably resilient over many generations is due to the function of the various DNA damage resistance mechanisms. The majority of cell lines studied *in vivo* appear to have a life expectancy of 40 generations or so, with telomere shortening acting as a brake on further cycles of replication of DNA. There is evidence that the life span of some cell lines can be extended by molecular mechanisms for many generations, a process known as immortalization. The telomere shortening which confers senescence is circumvented by the telomerase mechanism, thus securing their reproductive fidelity from generation to generation. The properties of male germline cells are believed to be due in part to the expression of telomerases, which thus confers reproductive longevity to the male. Immortalization may also be found in tumour stem cells.[11-15] Thus, cells have a capacity for longevity which appears to be underexploited by nature.

The natural tendency of all proliferating tissues may be towards uncontrolled growth and neoplastic features. These are effectively suppressed to the end of the reproductive years in most individuals by the various molecular mechanisms of repair and regeneration within individual cells. We do not know whether all proliferative tissues will eventually develop the malignant genotype as a statistical inevitability if other diseases do not intervene to kill the patient, or whether there is a peak age incidence for the aggressive malignant phenotype.

Evolution and cancer

Cancer is an active process of abnormal growth, proliferation and behaviour of tissues in a body where the exquisite control of differentiation and steady-state tissue dynamics is disturbed.[16] In general terms malignant change is due to degenerative change in the genome, whether through mutation, translocation, allelic loss or aneuploidy. Cancer cells continue to display most of the complex and intricate functions of normal cells, including the ability to proliferate, apoptose and differentiate. It thus seems probable that the early malignant phenotype follows from subtle, minor disorder with catastrophic consequences, rather than gross initial genetic disorder. We recognize that the genotype of cancers can continue to change over the time-frame to death, manifested, for example, by progressive aneuploidy.

Cancer is now a major cause of death in the developed world, although it figures rarely in the historical record and in the developmental biology of mankind until the past few hundred years. Its emergence appears to be in consequence of longer life expectancy and the changed environmental circumstances of modern populations, which have escaped the natural selection pressures of earlier times, because it is largely a phenomenon of the post-reproductive years. Cancer has thus come to prominence in consequence of the unnatural median increase in human life expectancy in the past two centuries and by virtue of improved public health and economic circumstances. This longevity increases the physical and biological risk to the individual genome and to the population. For example, 20 years' additional life expectancy in a population of 50 million people produces an additional 1000 million individual exposure-years. Such damage may be accelerated by environmental carcinogens, such as tobacco smoke, and in individuals with a genetic and hereditary predisposition to cancer.

We may thus seek in evolutionary biology an explanation for the modern problem of cancer from a range of options. Firstly, the body defences may be neutral to the malignant genotype, because there has been no evolutionary pressure for these to evolve. Thus, there are no specific cancer defence mechanisms, and malignant change is immunologically neutral.

A second possibility is that the body does possess effective extracellular anti-cancer mechanisms within the immune and lymphatic system which destroy cells displaying the malignant phenotype. It remains immunologically competent to a substantial degree during the reproductive years, but the defences weaken or can be outmanoeuvred by specific combinations of mutations. Immunological competence against cancer would imply the existence of cancer-specific antigens, and this possibility is being exploited in the search for effective cancer vaccines.[17]

Thirdly, it is possible that nature deliberately imposes malignancy upon the ageing organism as an evolutionary ploy to accelerate post-reproductive death. This might include the evolution of molecular mechanisms to activate the malignant genotype and to disable normal cell regulatory controls. This alternative, and perhaps more sinister view implies that any disease process which eliminates post-reproductive individuals from any species might in biological terms be considered advantageous and attract positive selection pressures by virtue of improving the survival prospects of the offspring. Indeed, to follow the harsh logic of the Darwinian natural world, cancer may simply be one of the cruel degenerative processes which destroys individuals after their reproductive years to ensure the genetic diversity of man, of other species, and of the genome itself. Thus, the falling of the autumn leaves helps to preserve the vitality of the tree of life.

The emergence of such a proactive function for cancer seems unlikely on evolutionary grounds, if only because

infectious diseases and other vigorous competitive pressures have performed this task effectively during the reproductive years. Such distinctive, pre-selected destructive mechanisms might also be expected to confer upon the cancer cell distinctive molecular features, targets for therapy, and immunogenicity. Moreover, cancer is still notable for its relative rarity and for its diversity of type and aggressiveness in individual bodies. There is no single pattern which would evidence a specifically evolved killer mechanism.

Evolution and cancer genetics

We recognize at least three classes of genes which are associated with the cancer phenotype. We must reconcile the existence of these genes with the lack of evolutionary pressures to produce cancer-specific genes, and can infer that each of these genes has a normal regulatory function in the non-mutated state.

Oncogenes are those which have gained malignant function through mutation or chromosomal defect, or in the case of some cancers in animal models, through viral acquisition into the genome. Examples of human oncogenes include *ras*, *c-myc*, *bcl-2* and *EGF-R*. *Tumour-suppressor genes* are those which promote neoplasia in consequence of loss of normal regulation, by mutation or allelic loss. Examples include the *RB1*, *p53*, *p16* and *APC* genes. *DNA repair genes* are evolutionarily conserved, nuclear DNA associated enzymes which undertake DNA housekeeping operations, such as the repair of strand breaks and the facilitation of chromosome cleavage and segregation, disruption of which may produce mutation, translocation or aneuploidy.[18-21] They include the topoisomerases,[22] and the *BRCA 1* and *BRCA 2* genes.[23,24] Other genes having such functions are known as *gatekeepers* and *caretakers*.[25]

There is considerable evidence that it is the mutation and dysfunction of normal, regulatory genes which have a role in key processes such as proliferation, apoptosis, growth regulation and differentiation, rather than the production of entirely new, cancer-specific genes, which lead to cancer.[26-28] The majority of mutations are probably neutral in their effect on genes. Haber and Fearon point to rare mutations, or rate-limiting mutations, the acquisition of which substantially increases the likelihood of malignant change. One example is the *APC* gene in colorectal cancer.[29,30]

Another interesting concept is that of synergy of genotypes and disease susceptibility, such that a gene predisposing to one disease may protect against another. Such an association has been suggested between cystic fibrosis and typhoid fever.[31] We have no evidence to show that the tumour-susceptible genotype confers resistance to other disease processes, but we might consider this as a possibility.

The biological rarity of cancer

Despite the emergence of cancer as a fatal spectrum of diseases for some 20% of the population in developed countries, and the attention drawn to it by our huge research effort, malignant transformation in cells is in reality an extraordinarily rare event. Most tumours are believed to emerge from one clonal stem cell, and most individuals only develop one malignant tumour in their lifetime. Given the number of stem cells in proliferative tissues in the human body, and the number of generations which they traverse, the odds of effective malignant change in a viable stem cell are much greater than 10^{14}:1. This testifies to the enormous security in cell reproduction and genomic damage limitation. It is a tribute to the DNA-repair capacity of the cell that cancer is not immediate and overwhelming early in life, and that serious malignant change is so infrequent. Where effective mutations arise, they must confer growth and survival over many more generations, and resistance to elimination by intrinsic and extrinsic defence mechanisms, including physical removal such as by exfoliation from the gut lumen. In other words, the malignant cells will be as nearly normal as possible in all functional respects, while declaring the cancer phenotype.

The apoptotic mechanism is another potent intrinsic defence against defective cells,[32-35] where minimal rate change in a virtually normal process can have profound consequences for the accumulation of abnormal cells. Dysfunctional apoptosis is of particular interest in the aetiology of cancer. Apoptosis plays a key role in the modelling of tissues during embryogenesis, maturation and steady-state tissue kinetics. Any cell which is not proliferating normally is programmed to self-destruct. However, later in life, through cumulative dysfunction in the apoptotic and repair pathways leading to genetic neglect, the probability of survival of defective cells, the cancer tendency, increases.

Conclusions

It thus seems likely on the grounds of evolutionary logic that cancer is an expression of late, intrinsic biological dysfunction rather than a disease imposed from without upon innocent tissues. We should thus not expect to find a simple cure, as only the most subtle and elusive changes will produce established malignancy. As such, we must identify and modify the various forms of genetic damage and regulatory disorder, such as in apoptosis. This view converges with the new biological model of cancer propounded by Schipper *et al.*[37] Here, the classical model of a clonal tumour with exploitable tumour–host differences is replaced by a model of clonal evolution (within the lifetime of the individual tumour) of virtually normal cancer cells with the most subtle regulatory imbalance which require the most sophisticated therapeutic exploitation.

These subtle regulatory changes are likely to account for the limited therapeutic index which is the reality of most conventional adjuvant therapies for cancer. Indeed, it may be that we will never eliminate cancer, whether by vaccination[17] or any other strategy, because cumulative malignant change with time is inseparable from the processes of life and is as inevitable as ageing and ultimately death itself. We may at best aim to postpone or alleviate cancer, until other degenerative processes cause death.

What message is there for cancer surgeons? The evolutionary and biological sophistication of malignant change seems likely to provide a continued role for surgical extirpation of cancer until molecular biology delivers on its many upheld promises. The subtlety of the biology of aggressive cancer often confers great resistance to the relatively crude forms of radiotherapy and chemotherapy at our disposal. Even where candidate molecular mechanisms are identified, the more sophisticated strategies of molecular therapy have yet to prove their worth in delivery of therapy to the tumour environment.

Such a reading of the degenerative biology of malignant change in the natural order should not diminish our search for new treatment strategies. Human life has a dimension of intellect and community which transcends the brutality of Darwinian competition and the manipulations of the selfish genome, and which underpins the battle for a longer life expectancy. While the additional gains in life expectancy diminish with an ageing population, there are still billions of life-years to be gained worldwide from economic, public health and political maturity. We also have the particular challenge of younger patients with cancer, for whom successful therapy brings much greater rewards.

Evolution may take a random path over the surface of one small sphere on a fixed trajectory in one solar system, but we may discern direction and purpose in human existence and activity which bucks the trend in the struggle to harness and redirect natural biological forces and to expand the limits of the human intellectual universe. Individual death ensures the vitality and renewal of life and the continuity of the genome, but we may make a worthy goal the bending of the laws of nature to afford all human beings the median luxury of death at three-score years and ten.

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W1. www.talkoriginal.org/origins (accessed 30 May 1998)
This site contains a large number of well written essays on aspects of evolutionary biology, and access to the full text on-line of Darwin's works.
W2. gopher://gopher.vt.edu:10010/02/89/1
The complete edition of *The Descent of Man* by Charles Darwin (1872) online (1.6Mb data set).
W3. www.physics.wisc.edu/~shalizi/Medawar/
The collected works of Sir Peter Medawar online.