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The microevolution of cancer

"One general law, leading to the advancement of all organic beings, namely, multiply, vary, let the strongest live and the weakest die." Charles Darwin

In this chapter, we describe the development of **cancer as the microevolution of damaged cells.** According to this model, **cells that divide rapidly and do not breed true will eventually become cancerous**.
Many existing hypotheses can be related to this microevolutionary model. Subsequently, we will integrate these different ideas, to provide a more comprehensive explanation.

Evolutionary theory applies to any population of living cells that are subject to selection pressure. **According to the microevolutionary model, cancer has no single cause: each individual case evolves along its own unique pathway. Cancers use varied mechanisms to achieve growth**.1
However, there are common features, which arise because of growing cells' shared requirements for evolutionary success.

The model explains the limitations of conventional therapies, such as radiation and cytotoxic chemotherapy, and points the way to consistent methods of treatment. In later chapters, we describe why current therapies often fail, before going on to develop a potentially more productive approach to treatment.

Cancer: an inevitable result of microevolution

The characteristics of cancer cells include **uncontrolled growth, failure to breed true and longevity**. A more complete list is given below. These features arise in many ways, including some that are not yet fully understood. Nature is more capable than any human of devising ways for life forms to evolve. **Microevolutionary principles lead us to expect**

variation in the biochemistry of cancer cells, even those from the same tumour.94
Thus, cancer cells might evolve several different biochemical ways to achieve the properties required to become malignant. For example, one cancer might grow rapidly because it has a defect in the gene that inhibits growth, whereas another may over-respond to signals that stimulate cell division.

According to the microevolutionary model, a pre-cancerous cell will generate a varied population of damaged but dividing cells. The

requirements for malignancy are similar to those for evolutionary success in a population of single-celled organisms. In the race to leave most offspring, the winning cells will have the properties of rapid division, extended life and high invasiveness.

Single-celled organisms have inhabited the earth far longer than multicellular creatures. **Long ago, when individual cells began to group together to form multicellular life forms, they retained the core biochemistry of single-celled organisms**. Many such features, important to the success of single-celled organisms, are also used in the development of complex animals.

However, in order to enable cooperation between cells, multicellular organisms added layers of communication, signalling and control mechanisms, on top of the primitive, single-celled biochemistry. Since these controls developed later in the evolutionary process, they have had less time to become robust and resistant to injury. Damage to the relatively recent control mechanisms is likely to occur more frequently than to the older features that multicellular animals share with their single-celled ancestors.

Characteristics of cancer

Throughout the different classes of cancer, malignant tumour cells have a consistent set of properties. These are considered to be:

• Growth, in the absence of “go” signals

• Growth, despite the presence of “stop” signals

• Evasion of cell suicide (apoptosis)

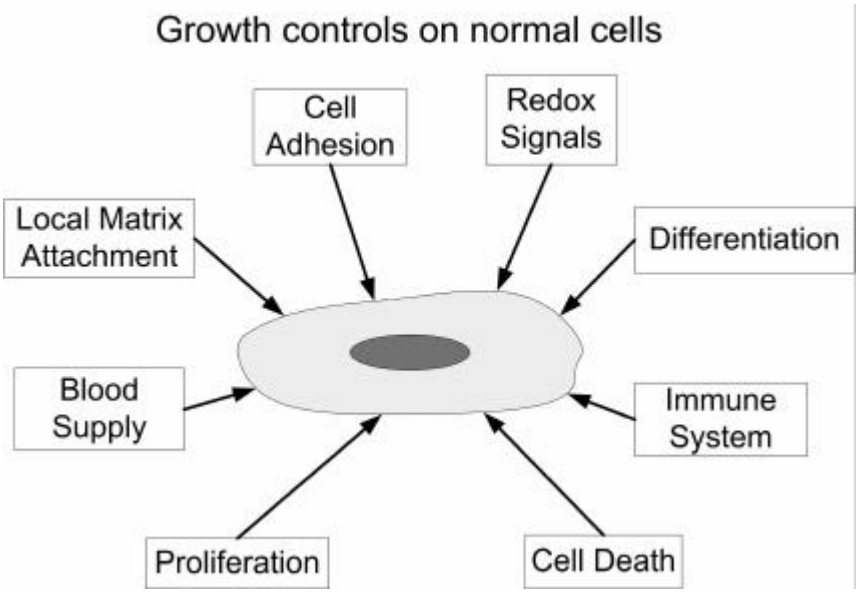
• Ability to promote local blood vessel growth, known as angiogenesis

• The potential for an unlimited lifespan, called immortalisation

• Ability to invade nearby tissues, and to travel and create distant tumours, known as metastases

• An abnormal number of damaged chromosomes

The most visible characteristic of cancer is the uncontrolled multiplication of cells in the body. Cells divide by a process called mitosis, when each cell splits into two daughter cells. In the healthy body, cell division is tightly controlled, so our tissues stay a consistent size and shape. **Cells have a natural cycle of growth and cell division**. Normal cells
act constantly on signals to inhibit this cycle, thus maintaining the current tissue structure, whereas cancer cells keep on dividing. This suggests that the regulation of cell division, essential to multicellular organisms, has failed. **Cancer cells have lost their ability to cooperate with the body, instead they evolve and grow like single-celled organisms**.95,96,97,98



Another characteristic of cancer is that the cells do not breed true.178 Daughter cells often differ from the parent. The process of cell

division involves duplicating the cell's contents. However, errors can occur at any stage of the process: when the DNA is copied, for example, or when the duplicated chromosomes are transported into the daughter cell body.

Cancer cells live a long time and may be immortal. In contrast, normal cells die after a given time or number of cell divisions. Cells from a given species will divide only a specified number of times; this number helps determine aging and longevity. **In cancer cells, the cell mortality mechanism is faulty.** Indeed, one reason for the mortality of human cells

is to prevent them from dividing uncontrollably and producing cancer. A healthy cell that breaks free of the controls on its growth will divide only so many times, before it dies.

Speciation

The term species, despite being a fundamental criterion of biological diversity, is poorly defined. Biologists find this lack of a precise definition useful for describing the large and varied organisation of living things. In sexual creatures, such as many animals and plants, species can be defined as groups that do not interbreed under natural conditions. For asexual creatures, the position is more difficult. When organisms do not engage in any form of sexual activity, species may be inferred from genetic, physiological or structural differences.

The generation of a cancer cell can be compared to development of a new species, which has the properties of a single-celled organism. The characteristics of malignancy are similar to those of bacteria, which are likewise imposed by evolutionary pressure. Although derived from body cells, cancer cells have a different genetic makeup. In particular, malignant cancer cells have an altered number of chromosomes. Such a genetic difference between organisms in a population will generally lead to evolutionary competition. While we do not suggest that a cancerous cell is a new species under the biological definition of the word, the cell is sufficiently different from healthy cells for the description to be apt.

When a cell becomes cancerous, it changes from its original, cooperating multicellular form and starts to act for the replication of its

own genome, which has become markedly different from that of the host. A cell with these characteristics competes with its neighbours. We use the analogy of a new species to describe this behaviour; some might prefer the concept of a “selfish cell”, analogous to the idea of a “selfish gene.” a

Cancer cells do not normally acquire the properties described above all at once. The most important feature of cancer is faulty cell division, which is followed by natural selection.b If a cell with a faulty

a Evolution acts on the whole organism (phenotype) at the population level, rather than the level of individual genes. However, it is easier to analyse the process mathematically at the gene level.
b By faulty cell division we mean any process that can lead to the daughter cells having a different genetic makeup to the parent. This could be a mutation, chromosome duplication or some other abnormality.

division process produces daughter cells, they will differ from the parent cell. Some of the daughter cells will be less able to survive; such cells may grow slowly, or die. Other cells may be viable enough to survive and occasionally divide: these will continue to produce a population of increasingly varied, abnormal cells. Occasionally, some of the errors will produce cells that, under current conditions, are hardy and divide rapidly. These robust cells will produce more offspring and will be favoured by natural selection.

Healthy human cells generally contain identical genetic information, with a few notable exceptions. In contrast, the genes in cancer cells differ substantially from those in normal cells. Abnormal numbers of chromosomes are a clear sign of potential malignancy. This means the cells will tend to evolve separately, looking after their own genetic makeup, rather than that of the host. With minor genetic variations, the effect will be small. However, large-scale chromosome duplication and deletions are massive alterations, consistent with speciation and competition.

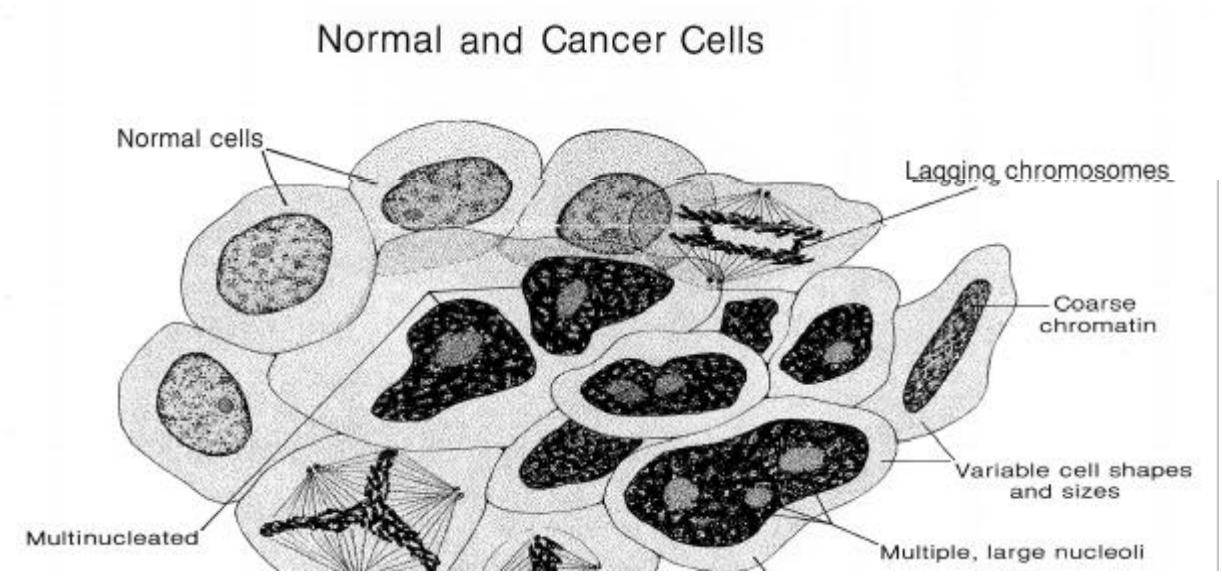
Inheritance

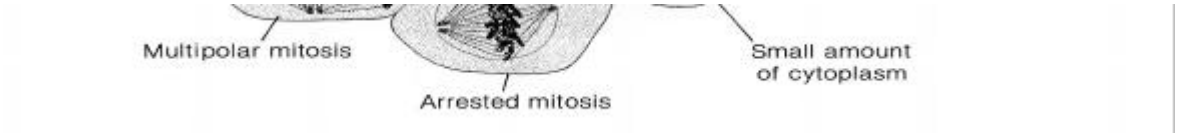
The salient feature of the errors in cancer cells is that the cellular changes pass on to descendent cells: they are inherited. According to the conventional view of cancer, inheritance is assumed to mean that changes result from mutations in the DNA. However, this view is unnecessarily restrictive. Changes in chromosome numbers, or in the machinery that separates chromosomes during cell division, could have a similar effect, as could any inherited structural changes to the cell. A physician reading

this latter statement may reject it, because it appears to suggest Lamarckian inheritance, the passing on of acquired characteristics. This is not the case. Most biologists are aware of special cases that do not depend on the genes or DNA. As an example of this, we will describe a strange phenomenon in the single-celled organism, paramecium. Paramecia are covered in a series of small hairs, or cilia, that beat together to provide directional movement. Most paramecia have an ordered arrangement of such cilia. However, the surface of the cell can be damaged, to produce a small patch in which the direction of the cilia is reversed. Biologists have discovered that such rearrangements can pass to daughter cells, during division, for several generations. This effect was demonstrated in 1965, in a series of experiments by Janine Beisson and Tracy Sonneborn.99 One explanation for this surprising finding is based on physics or bioengineering. This suggests that the orientation of new

cilia is determined locally by the existing structure, in a process called structural guidance.

Another example of structural inheritance occurs when treatment with streptomycin destroys the chloroplasts in euglena, a small, green, single-celled organism, found in fresh water. Chloroplasts are disk-like structures within cells; they contain chlorophyll and are the site of photosynthesis, the process by which plants convert sunlight to chemical energy. The treated cells no longer contain chloroplasts and neither do their descendants.100





This diagram illustrates aberrant mitotic cell division in cancer cells. This cell division produces cells with abnormal number of chromosomes and varying amounts of DNA, in unusual nuclei. Also evident are cancer cells with multiple nuclei and others with nuclei so enlarged they almost fill the cells.

Cell division in cancer cells can involve a change in the number of chromosomes, which suggests that structural mechanisms could influence the future inheritance of the cell. When a cell divides by mitosis, protein molecules pull the chromosomes into separate daughter cells. Structural alterations to the arrangement of these proteins could result in one daughter cell getting more of the separating chromosomes.

If viable, the resulting daughters would have different numbers of chromosomes from the parent cell, as would their descendants. Despite cases such as these, genetic mechanisms dominate inheritance and, as far as we are aware, no important structural guidance mechanism has been demonstrated in either healthy or cancerous human cells.

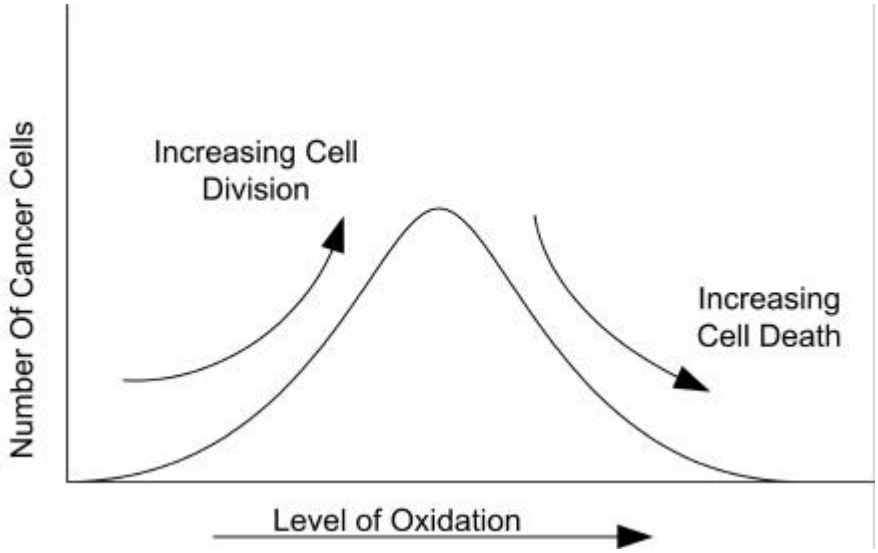
Oxidation and antioxidants

Oxidants cause biological effects, which depend on their concentration. A simple rule of thumb is that the environment of healthy cells is reducing, rather than oxidising. Cells use free radicals and oxidants, such as hydrogen peroxide (H2O2), as signalling and control molecules. Reactive oxygen species, such as hydrogen peroxide, superoxide (•œO2**-**) and the vicious hydroxyl radical (•œOH) are widely generated in biological systems.c If left unchecked, these could damage the cells. Consequently, cells have evolved complex antioxidant defences, which limit the production of reactive molecules and reduce them to low levels.101 An important reason for this is to prevent cancer.102
Cell division mechanisms depend on redox control and signalling.103,104 Even small changes in the redox state can be important to regulation of cell growth and differentiation, indicating that oxidation lies at the core of cell signalling mechanisms.105 A moderate increase in the level of oxidants can promote cell growth and division. Growth factors act through oxidants and, in particular, by increasing hydrogen peroxide.106,107,108,109 Hydrogen peroxide blocks the primary signalling

mechanism that inhibits growth in the cell.110,111,639 Cancer-causing genes,called oncogenes, can act by increasing the level of oxidants.112 Thus, cells that are in the process of becoming cancerous generate a more oxidising state, which facilitates cell division.

c The dot in the chemical formula, eg •œOH, indicates an unpaired electron, a characteristic of a free radical.

Effect of oxidation on a population of cancer cells



The level of oxidants in a cell has numerous effects. Oxidants influence the cell's ability to divide, can signal the cell to commit suicide, and are intimately involved in the progression of the cell to a malignant condition.116,113 Although a moderate increase in cellular oxidants signals a command to divide, a further increase could be damaging and cause the cell to die.114 Intracellular production of higher levels of active oxygen species, such as hydrogen peroxide, is associated with prevention of cell proliferation.101 Initially, as the hydrogen peroxide increases, the cells grow. Then, as the level becomes too high, they die.

Cancer cells divide and grow, even under crowded conditions, which is unusual. When healthy cells are grown in culture, they increase in number while they are dispersed. However, as the density of cells increases, the growth rate falls and they stop dividing. This is known as density-dependent growth inhibition. When cells crowd together and touch, as often occurs within body tissues, they stop growing because of contact inhibition: the cells sense the crowding and cease dividing. Contact inhibition is associated with a decrease in the

concentration of oxidants within the cells.115 Removing oxidants from the culture medium produces a reducing environment, which can mimic the effects of the contact inhibition signals. As a result, the cells stop dividing. Control of contact inhibition may depend on the cells' internal

redox state, which is directly influenced by the sum of *grow* and *stop growing* signals received.115 Unlike healthy cells, malignant cells ignore contact inhibition signals and continue to divide.

Oxidation and cancer

Cancer cells generally have an oxidising internal environment, with higher concentrations of free radicals and lower levels of antioxidant enzymes.101,645 Compared to healthy cells, their antioxidant defences are deficient.116,117,118,119,120,121,122 Although a few cancers show increased levels of certain antioxidant enzymes, none has a full complement of defences against free radical attack. As far as we know, all but one type of cancer is deficient in two important antioxidant enzymes,d called catalase and glutathione peroxidase.645 The lack of these enzymes is a weakness in cancer cells, offering a potential way to attack the cells with new treatments.

Cancer cells increase their internal oxidation levels as a redox control mechanism, to maximise growth. This method appears to be ubiquitous in cancer cells. While the cancer is growing, the body's levels of oxidants and inflammatory markers increase.123 Later, we will see that cancer's dependence on redox changes suggests mechanisms for its selective eradication.

The action of antioxidants on cancer cells is far from simple: it may depend upon the cells' redox state and the stage of the cancer. Some cancers may find an external supply of antioxidants beneficial. For example, in healthy mouse cells, the antioxidant supplement, NAC,e can decrease growth, by lowering the oxidant level.124 However, in cancer cells, another antioxidant, the enzyme thioredoxin, stimulates growth and prevents cell suicide.125 This apparent paradox may be explained if we consider that the levels of oxidants in some malignant cells are so high as to be almost fatal to the cell. Thioredoxin may lower these levels enough to restore the cell to relative health and stimulate growth. Increased levels of thioredoxin occur in many human cancers and are a sign of resistance to therapy.

d The granular cell variant of human renal adenocarcinoma apparently does not have low catalase and glutathione peroxidase levels, but may have a modified redox biochemistry.
e The normal cells were from a mouse embryonic fibroblast culture and N-acetylcysteine (NAC) is a sulphur-containing antioxidant supplement, which increases the amount of glutathione within cells.

Oxidation and reduction are central to our microevolutionary model. We have stressed that healthy cells maintain themselves in a reducing state.15 They use oxidants and free radicals as signals to initiate cell division,126 responding to external and internal chemical signals to grow and divide. Hydrogen peroxide, nitric oxide (NO) and superoxide (•œO2-) are all used as signals for a cell to divide. These reactive molecules were once thought to be wholly damaging to the cell, because they cause free radical damage. However, at low levels, these chemicals, especially hydrogen peroxide, are vital for cell signalling.127 The effects of such signalling reveal a fundamental role for the redox balance in the cell. Given the parsimony of nature, this may be no accident, as it also provides a mechanism to prevent cancer.

This is how the mechanism could work. Moderate increases in oxidation levels stimulate cell division. However, if the level of oxidation in normal cells increases too much, the cell initiates a suicide program. This curbs the possibilities for uncontrolled growth, which might otherwise lead to cancer.

Cancer cells are generally under oxidative stress,128,129,130 which may be an essential feature of cancer growth.131,132,133 Natural selection favours cancer cells with a high level of oxidants, because they divide more rapidly. Cellular oxidation therefore occurs early in cancer development,134 and tissue oxidation is associated with development of cancer.135,136 Cancer cells can flourish when they have developed an increased response to redox growth signalling and an oxidative internal environment, which favours multiplication.137,138

The body uses redox signalling for both cell division and cell suicide.139,140 If the oxidant levels rise greatly, the signal causes it to destroy itself, rather than divide.141 The body needs to protect itself against the possibility of rogue cells going haywire and causing cancer. By using different levels of the same signal to initiate both cell division and cell suicide, the body has a mechanism to catch and kill cells that have lost their antioxidant controls and are dividing abnormally rapidly.
We have seen that cancers start with error-prone cell division, producing a variety of daughter cells. Some of these precancerous cells

might happen to have fewer of the antioxidant enzymes or other controls that normally suppress oxidation and the generation of free radicals. This could result in cancer cells with a more oxidising redox state, which stimulates division and growth, without being so oxidising that it causes a high proportion to commit suicide by apoptosis.

The story does not stop there. One immediate side effect of losing antioxidant controls is that the cell and its DNA will be damaged by free radicals. Thus, by becoming more oxidising, the cell has achieved the two basic features required to break free as a malignant cancer: it divides rapidly, and its daughter cells have modified DNA, together with other oxidation-induced errors.

From this description, it is obvious that any factors that make the healthy cell and its environment more oxidising will increase the risk of cancer. Since almost any insult to a tissue results in oxidation, inflammation or both, the confusing variety of factors that increase cancer risk begin to make sense.

Redox cycling

Redox cycling is an important mechanism, by which cancer cells can be destroyed. Some molecules can be reversibly oxidised and reduced. For example, Vitamin C, as ascorbate, is oxidised by losing two electrons to form dehydroascorbate. Dehydroascorbate can then gain two electrons from the cellular metabolism, to reduce it back to ascorbate. This process of oxidation and reduction can go round and round, forming a redox cycle.142

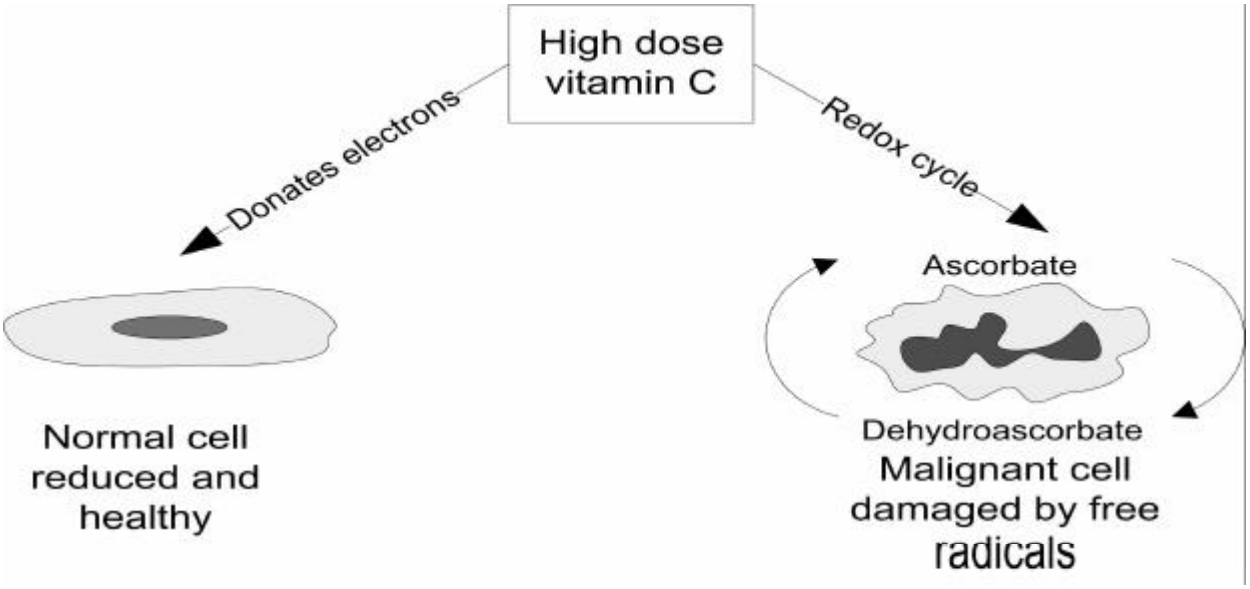
In healthy cells, this cycle is used to regenerate ascorbate from dehydroascorbate, so it can continue to act as an antioxidant. Since ascorbate's antioxidant action requires it to donate electrons, it needs to replace the donated electrons before it can continue to prevent oxidation.f The ascorbate-dehydroascorbate cycle is used to maintain a healthy reducing environment in normal cells.

In cancer cells, however, the mechanism fails, causing oxidants to be generated. One mechanism that can cause this production of oxidants is the presence of free iron within the cell. Ascorbate reacts with iron, producing hydrogen peroxide and ascorbyl radicals.143,144 The hydrogen peroxide then reacts with the iron, releasing highly reactive and damaging hydroxyl radicals. The iron is then available to react with another molecule of ascorbate.g Given a supply of vitamin C, this reaction can

cycle round, producing large amounts of hydrogen peroxide and hydroxyl ions, which eventually kill the cancer cell.

f In dynamic flow, with frequent large doses, vitamin C can donate its electrons and be excreted. Therefore, the reducing electrons are available without using cellular energy.
g The reactions are Fe(III) + ascorbate • ¨ Fe(II) + ascorbate • œ and Fe(II) + H2O2 • ¨ Fe(III) + •œOH + OH-

The selective effects of vitamin C



Other dietary antioxidants can also take part in redox cycles. In particular, several forms of vitamin K can react with transition metals, such as iron and copper, to generate oxidants. The antioxidant supplement, alpha-lipoic acid,h can act to prevent such oxidant production by vitamin K.145 However, in cancer cells, alpha-lipoic acid also participates in a free radical generating redox cycle. Alpha-lipoic acid can be reduced to dihydrolipoic acid, which acts as a powerful antioxidant within cells. Dihydrolipoic acid is then oxidised to alphalipoic acid. In cancer cells, this redox cycling of alpha-lipoic acid can generate free radicals, particularly in the presence of large amounts of vitamin C. The oxidising redox cycles of these and other dietary supplements occur in cancer cells, but not in normal cells. Therefore, such cycles provide a potential mechanism for selective eradication of the disease.

Immortal cells

Cells that are both damaged and dividing would usually have a reduced life expectancy. Many injured cells would be unable to compete

or survive. In some cases, the damage itself would be terminal, providing a form of selection, since cells with damage that shortens their lifespan

h References to alpha-lipoic acid should be taken to be r(+)-alpha-lipoic acid unless otherwise indicated.

will leave fewer offspring. However, if the damage resulted in an extended lifespan, the cell would be expected to produce a larger number of offspring. Thus, selection pressure will favour the longer-lived cells in the colony. Given enough time and cell divisions, errors will be selected that result in an extended, and possibly immortal, cell line.
Single-celled organisms, such as bacteria, provide a model for this process: they have evolved an effectively immortal lifespan. Human cells have the biological machinery required for immortality. For example, the germ cells that form sperm and ovum cells are immortal. However, normal body cells have mechanisms to prevent an indefinite lifespan. Once again, we see that a feature of cancer cells is a consequence of cellular microevolution. However to be immortal is not enough; in order for the cancer to grow, it needs to produce offspring.

Limiting cell division

Multicellular animals, such as humans, prevent the growth of cancers by setting a limit to the number of times that cells can divide. One consequence of preventing cancer in this way is that animals age and die. A cell from a given species can divide a maximum number of times, which is called the Hayflick limit, after Leonard Hayflick, who described the phenomenon in the 1960s.146 Almost a century earlier, in 1881, a German biologist called August Weismann suggested that,

*"death takes place because a worn-out tissue cannot forever renew itself, and because a capacity for increase by means of cell division is not everlasting but finite".*147

The maximum age attainable by an animal species is related to the Hayflick limit. Human fibroblasts - cells that make connective tissue, such as cartilage - will divide for about 60 cell divisions. The maximum age for man is about 120 years. Mice live up to three and a half years, and their fibroblasts divide about 20 times. Chickens, which live up to 30 years, have fibroblasts that divide 30-40 times. The Galapagos tortoise can live for about 175 years, or more, and has fibroblasts that will go through 125 cell divisions.

The mechanism underlying the Hayflick limit is related to the shortening of telomeres. A telomere is a region of highly repetitive DNA, at the end of a chromosome. Each time a cell divides, the telomere is shortened and, unless it is repaired, the chromosome eventually becomes damaged and unstable. The presence of telomeres had been known since 1938, when they were described in a lecture by Hermann Muller. Barbara McClintock confirmed the finding in 1941.147

A Russian biologist, Alexey Olovnikov, provided an explanation for Hayflick's limit on cell division. He was thinking about the limit, when a train he was travelling on entered a Moscow subway station. He realised that the engine of a train must cover some of the railway track at the end of the line, so the passenger cars can never reach the true end of the line. By analogy, he realised that a protein (the train) copying DNA (the track) would not reach the telomeres at the end of the molecule.148 It was later found, as predicted, that telomeres in human fibroblasts shorten as cells divide.149

Limiting the number of cell cycles helps to prevent cancer but shortens lifespan. Disturbed cells, which enter a phase of rapid cell division, are unable to grow indefinitely. With each cell division, the telomeres are shortened and the resulting cell line dies. This can be viewed as one of our primary defence mechanisms against cancer and other forms of abnormal cell growth.

As mentioned, certain germ cells are immortal. Such cells use an enzyme, telomerase, to restore telomeres to their full length. Telomerase is sometimes called the cellular immortalizing enzyme. While typical body cells contain the gene for telomerase, it is inactive, preventing unlimited cell division. The use of telomerase by normal cells is highly restricted during early development.

Unfortunately, the cell cycle control provided by the Hayflick limit appears to be inactivated in cancer cells. Like germ cells, cancer cells contain telomerase, which repairs the telomeres and may be a necessary factor for repeated cell division in cancer.150 Cancer cells have increased levels of telomerase, although they do not reach the levels found in germ cells.1 When cells become cancerous, telomeres may get shorter, but those below a minimum length are replaced. Telomerase repairs the telomeres, prolonging the life of the cell. Most malignant tumours have active telomerase. Activating the telomerase gene is a mechanism by which cancer can subvert the cell cycle limit and achieve unlimited growth potential.

Anaerobic selection

When a new colony of cancer cells starts growing, it soon reaches a volume that is large, relative to the diffusion of oxygen into the tissue. Such cells experience a reduced supply of oxygen and other nutrients: they are suffocating. An everyday analogy is building a town in a green field site. Simply adding new houses will work for a short time but, unless

roads and services are adequate, people will not be able to gain access and the town will not prosper.

As a tumour grows, pre-malignant cells come under selection pressure to develop an anaerobic metabolism, so they can manage with less oxygen. This means changing the controls on the cellular metabolism.151 The method they use is glycolysis, which is the anaerobic conversion of glucose to lactic acid, for energy.152 Normal cells also use glycolysis, for example, muscle cells use it when sprinters require a sudden burst of energy.

Even when oxygen is plentiful, cancer cells generally rely on glycolysis to generate energy. The cell does not have to develop new genes to switch to anaerobic metabolism: instead, those damaged cells that over-express existing glycolysis genes have a selective advantage in the environment of the growing tumour. However, this form of metabolism is inefficient, so the colony experiences growth restriction.

New blood vessels

As the tumour grows, its oxygen supply becomes inadequate. A second solution to this problem is for the tumour to grow more blood vessels. Potential cancer cells that can stimulate the development of blood vessels in the tumour have a greater ability to grow. Given time, a colony of dividing cells, which generates damaged offspring, will result in some cells with a mechanism to stimulate blood vessel growth. Once again, the cells already have the genes to stimulate or inhibit blood vessel growth, as this is a function of normal physiology. They do not need to find a new method, just to activate a gene that promotes blood vessel growth, or inactivate a gene that suppresses this growth. Eventually, given sufficient cell divisions, combined with errors and selection pressure, such cells will arise.

Local invasion

Since cells in the tumour are competing for resources, a cell that can migrate a short distance has an advantage. It can find a new habitat,

where growth is free from the constraints of competition with other cancer cells. Given time, microevolution will generate cells that can move and invade the surrounding tissue. The genes for this behaviour already exist within the cells, but are inactive. A cancer cell that expresses these genes gains the opportunity to prosper in a new environment, so is favoured by natural selection.

Spreading to new sites

A single tumour with a reasonable blood supply can grow to a large size. However, as it consists of a number of genetically different cell types, competition is intense. A biological model for this is the evolution of species on an isolated island. The spread of tumours to distant sites is, in some ways, analogous to the dispersion of species between islands. Such dispersion of animals has been studied intensively. Knowledge about biological diversity can be used as a model for the metastatic spread of cancer.153

Population dynamics on islands was described, in 1967, by ecologists Edward O. Wilson and Robert McArthur, who proposed an "equilibrium theory of island biogeography."16 Species move from the source area, which is the nearest mainland or another island, at the immigration rate. This rate is dependent on the distance between the source area and the sink island. The immigration rate is balanced by the sink island's extinction rate. To maintain a species, the sink island needs to have a suitable habitat for the invading animal.

As the area of the island increases, the number of species it can support also increases. If an island has ten times the area of a second similar island, it will contain about twice as many species. If a species can escape the confines of its island, it may find another where it can start a new colony, free from the constraints of competition. A recent investigation of the diversity of beetles and spiders on roundabouts and traffic islands, in the town of Bracknell, England, found that larger areas contained more species.154

Most organisms that leave a source site are lost during travel, or do not find a site for a new colony. The conditions in the new colony need to provide a suitable habitat. When they do, a new colony is formed and rapid growth may be possible. A cancer cell forming a tumour at a suitable new site has a similar growth advantage, although most cells that break away from the original tumour site will be lost. The metastatic spread of cancer is a predictable result of microevolution and is a special case of geographic spread and species diversity.i

As a tumour grows, not only does it get bigger but also, we predict, its cells will become more diverse. The spread of metastases results in i One difference is that cancer spread within the body is more three imensional thanthe spread of most island species, involving volumes of tissue rather than areas of habitat.

geographical isolation of cells at the new site, and a correspondingly rapid increase in variation. The diversity helps the cancer to withstand treatment, as it improves the chances of at least some cells being resistant to the therapy. This might explain why larger cancers and those with more metastases are harder to eradicate.

Microevolution

The microevolutionary model can be summarised as a sequence of phases. These phases are analogous to the generation of a new species and its spread. In the case of cancer, redox processes underlie each phase.

Phase One
Damage involving redox mechanisms increases cell division. The cells enter a more oxidising state to facilitate growth. The dividing cell does not breed true because of increased error generation.

Phase Two
Multiple cell divisions occur, with selection pressure for survival and growth. Growth is limited by the supply of nutrients and an anaerobic metabolism is favoured. Cells are under selection pressure to become immortal and resist apoptosis. At some point, the cell becomes “selfish” and reverts to unicellular behaviour, a process associated with alterations in chromosome number.

Phase Three
The disturbed cells come under selection pressure to generate a blood supply, invade other tissues and migrate to other sites. This phase is associated with an increase in cellular diversity and, hence, greater resistance to extinction caused by therapy or other factors.

Consistency
We have described a model of cancer in terms of microevolution. The theory is internally consistent and has the ability to explain core phenomena associated with the disease. Furthermore, it places cancer research in a broad biological context. However, just because an idea is logically reliable, it is not necessarily scientifically correct. We need to

show that this approach is consistent with conventional ideas and that it has predictive value. In particular, can this model provide a key to effective treatment?

A malignant cell

This scanning electron micrograph of a malignant cell shows the cell extending “arms” or pseudopodia to assist its movement through tissues. It illustrates the independent nature of a “selfish” cancer cell.

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