1 Painting a Clear Picture

Once upon a time it was fair to say that most people knew little of science. After all, scientists spent years learning their job so it's clearly tough-going and, by and large, the rest of the world could get by knowing nothing of superconductivity or the origins of the universe. But increasingly our daily lives have come to be dominated by science, and part of that revolution has been the ever-expanding reach of television and the Internet as sources of information. It's as though, unwittingly, we've all signed up to the Open University. And, it should be said, when it comes to science this has all been helped by a growing awareness among those in the trade that they have an obligation to let the world know how they while away their days.

High time too, I say – but all might not agree. Friends of mine who are general practitioners tell me that increasingly folk turn up to their surgeries fully armed with a diagnosis of their perceived condition, courtesy of the Internet. I can see that being forced to wonder why you spent years slogging through medical school could be rather dispiriting but, as I point out, setting the personal aside, you have to concede that people being willing and able to teach themselves has to be a step forwards for civilization.

That's as may be, but in science, and especially in biology, there is almost always another side to any argument. Alexander Pope, in his 1709 essay, noted that 'A little learning is a dangerous thing', and that 'shallow draughts intoxicate the brain'. Wise words, and with them in mind let's make a start on

https://doi.org/10.1017/9781009043243.003 Published online by Cambridge University Press

understanding cancer by looking at some critical questions that often cause confusion – and not just for non-scientists!

As we launch ourselves into this story, there's one thing we all might agree on: cancer is complicated. However, and you might find this surprising, what emerges from short answers to a handful of rather obvious questions is that cancer is a great paradox. On the one hand, it is indeed mind-boggling – which is why clinicians will almost never say 'This will work' with regard to treatments. But, when you cut to the heart of the matter, cancer is very simple – that is, it's easy to grasp the key points and thus to see how, in principle, to go about dealing with it. It's only then that the going gets tough as our ingenuity is tested by the immense weight of evolution that underlies the disease.

What is Cancer?

A three-word answer to this most basic of questions is 'Cells behaving badly'. More scientifically, it's a group of cells somewhere within an animal that are reproducing (i.e., making more of themselves) either faster than they should or in a place where they should not be. Put another way, these cells have lost control of their capacity to divide. The result is that the cells grow and divide to make more copies of themselves, paying no heed to normal controls. The resulting unruly mass of cells constitutes a tumour. This word comes from the Latin for 'swelling' – that is, an abnormal growth. It's used interchangeably with 'cancer' and 'neoplasm' (new growth), and all three words mean much the same. Tumours may grow relatively quickly or very slowly, but to expand significantly food and oxygen are required – just like for any other cell in the animal body. To achieve growth, tumours can release chemical signals that switch on growth in nearby blood vessels. New 'sprouts' penetrate into the tumour cell mass. The whole ensemble is now primed to take off: to expand regardless of the best interests of its host. Most ominously of all, by acquiring its own blood supply the tumour now has a conduit and cancer cells can be carried the circulatory system to any part of the body. Cells may also be carried by the lymphatic system but, whatever the means of transport. The process of tumour cells spreading to other places is called metastasis and it's critical because it results in over 90 per cent of deaths due to cancer.

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What Causes Cancer?

Perhaps the most frequently asked question about cancer. In today's world most of us can come up with a quick answer: mutations – that is, damage to our genetic material, otherwise known as DNA. The term DNA has, of course, passed into common speech as we have all learned more and more about the science of molecular biology. That's good, because it means we don't need to use its full name (deoxyribonucleic acid) when, in Chapter 4, we come back to this wondrous molecule that is the eternal language of the living cell and look at how it works and the many ways in which it can be 'damaged'. The key point for now is that what we inherit comes in the form of DNA – a gigantic chemical molecule made of four types of unit joined together. The units are bases (abbreviated as A, C, G and T), and it is their sequence that encodes genetic information.

The term 'genome' was invented in 1920 to describe the entire genetic material of an organism – thus, in humans that includes the DNA in the nucleus of our cells (almost all our DNA) and a tiny amount in mitochondria, membrane-bound units in cells often called the powerhouse of the cell. It's mitochondria, and hence mitochondrial DNA, that are passed almost exclusively from mother to offspring in the egg.

Within the length of DNA there are blocks called genes, which carry specific, functional units of heredity. The study of genes and genetic variation is called genetics. The study of the genome is called genomics. Before you ask, the Danish botanist Wilhelm Johannsen is credited with coining the word 'gene' ('gen' in Danish and German) in 1909. Because cancers arise from changes in genetic material, they are 'genetic diseases'. That doesn't make them unique: about 6,000 other genetic disorders are known. What is unique about cancers is that almost all need mutations in several genes to get them started and keep them going. Thus, the vast majority of cancers arise from the combined effects of mutated genes. We should note that about 20 per cent of cancers are initiated by infection but, ultimately, these too acquire mutations that drive tumour development.

Given that they are genetic diseases, you might suppose that cancers could be passed from one generation to another through defective genes – and indeed

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they can. As long ago as 1820, a Stourbridge doctor, William Norris, described a family in which individuals from several generations had developed the same form of cancer. This inference that some families might be predisposed to cancer was extended by the extraordinary French physician Paul Broca who, in 1866, suggested it might be possible to inherit breast cancer. He'd looked at his wife's family tree and noted that 10 out of 24 women, spread over four generations, had died from that disease and that there had been cases of other types of cancer in the family as well. We know now, of course, that a changed (mutated) form of a gene passed from generation to generation was almost certainly responsible for the suffering of this family.

One consequence of the rise of the 'media' is that breast cancer genetics has in recent times come into the spotlight, with the much-publicized saga of Angelina Jolie, the American actress. Jolie's mother and maternal grandmother had both died of ovarian cancer, and her maternal aunt from breast cancer – a family history that persuaded Jolie to opt for genetic testing that indeed revealed she was carrying a mutation in one of two genes named *BRCA1* and *BRCA2* (the acronyms come from BReast CAncer type 1 and type 2, so named because they were the first major genes to be identified, in 1990 and 1994, as associated with hereditary breast cancer). *BRCA* genes are mutated in about 10 per cent of breast cancers and 15 per cent of ovarian cancers. The National Cancer Institute estimates that 'about 12% of women in the general population will develop breast cancer sometime during their lives'. By contrast, a recent large study estimated that about 72 per cent of females who inherit a harmful *BRCA1* mutation and about 69 per cent with a harmful *BRCA2* mutation will develop breast cancer by the age of 80.

These estimates prompted Jolie to have a preventive double mastectomy, thereby reducing her risk to less than 5 per cent. The 'Angelina effect' saw a doubling in the number of women being referred for genetic testing for breast cancer mutations in the months after she revealed her story. A study in 2020 concluded that screening entire populations for *BRCA* mutations, rather than only those with a strong family history of breast or ovarian cancer, could prevent millions of breast and ovarian cancer cases

https://doi.org/10.1017/9781009043243.003 Published online by Cambridge University Press

worldwide. For the UK the estimate was that about 10,000 deaths from these cancers would be prevented.

Breast cancers are an enormously varied set of diseases, and as such they're a challenge even to classify, let alone to treat. The recent rapid progress in DNA sequencing has led to a new genome-based classification system but there is still strong reliance on the traditional prognostic and predictive factors, notably what's called hormonal status – meaning the presence on the surface of the tumour cells of protein receptors to which the hormones oestrogen and progesterone attach, together with the presence or otherwise of the human epidermal growth factor receptor 2 (HER2). One significant sub-group has no detectable levels of these proteins. These are called triple-negative breast cancers (TNBCs), and they make up 10–15 per cent of breast cancers. They are very aggressive cancers (i.e., have a poor prognosis), known for some years to disproportionally affect young women of African origin – they are about twice as common in African Americans as in European Americans. Sequencing has revealed that mutations in *BRCA1* are present in most (69 per cent) TNBCs in females of European origin. But here's a very odd thing: African American women have a low *incidence* of *BRCA1* mutations (less than 20 per cent – incidence being the number of new cancers occurring in a population per year), despite the fact that they are relatively prone to TNBC. This implies, of course, that if *BRCA1* isn't doing the driving there must be other potent drivers for TNBC in this group.

These examples clearly show that cancer can 'run in families' and the estimate is that 10–30 per cent of cancers arise from inherited genetic damage. However, the majority occur as the result of accumulated DNA damage as we pass through life. In other words, cancers are, by and large, diseases of old age. In the UK and the USA about 70 per cent of all newly diagnosed cancers occur in people aged 60 or over. Knowing the rate at which we collect mutations, it's easy to work out that if we lived to be 140 years old we'd all have a cancer of some sort. 'Thank heavens we don't have to worry about that yet' is a perfectly reasonable reaction, but there's an important point here, namely that the fact of the inevitability of cancer (if we live long enough) tells us that it's an in-built feature of life. It may be difficult to deal with, but it's not something freaky and weird. It arises because our

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DNA is not made of stone: it's mutable and hence vulnerable, as indeed it must be, for without its plasticity there would be no evolution.

Are All Cancers Equally Bad?

We've just noted that the critical event in terms of potential lethality is the acquisition of metastatic capacity: the tumour is no longer self-limiting in terms of growth, it can invade adjacent tissues and spread to distant sites. In short, it's become malignant. However, it may have occurred to you that if cancer cells have to do 'something' to become malignant, it is quite likely that many of them won't bother. Indeed, a lot of them do just that (nothing, that is) and we've known since early in the twentieth century that mini-tumours can form and then stop growing, remaining static as 'dormant tumours'. The most likely reason is that they are not able to flip the switch that turns on the growth of new blood vessels.

It has transpired from autopsies of road traffic accident victims that many, perhaps all, adults are wandering around carrying dormant tumours – clumps of about 100,000 cells – in a variety of organs and tissues. Sometimes called *in-situ* tumours, these microscopic growths would normally never be detected – it just happened that accidental deaths provided tissues for pathological analysis.

The key point here is that these micro-tumours were clearly dormant: their carriers died in accidents and had shown no signs of cancer. Knowing what we do about the time course of cancer development, we can be sure that most of them would not have gone on to produce cancer for many more years, or even decades.

Malignant versus Benign

We've now met the two ends of the cancer spectrum: dormant tumours that we can ignore and malignant tumours that we ignore at our peril. We should note in passing that malignancy is preceded by a pre-malignant phase, namely groups of cells (lesions) that are not yet cancerous but have the potential to develop into malignant cancer (i.e., become metastatic). One example would be colon polyps, growths on the lining of the colon or rectum that can progress to bowel cancer.

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There's one further group of cancers that we need to meet – not least because almost all of us have got some of these too – benign tumours. They are indeed extremely common. For example, in 9 out of 10 women it's possible to detect changes in breast tissue that are benign and not dangerous. Fibroids are another type of abnormal growth: they occur in the uterus and are also typically benign. And that's the most important thing about benign tumours: they're not malignant – that is, they can't invade surrounding tissues and therefore do not spread. Benign tumours can arise in any tissue, the most common being lumps of fat called lipomas and, in general, they are fairly harmless. They're usually surrounded by a membrane, a sort of sac that helps to prevent them from spreading. They tend to grow very slowly, but they can reach the size of a grapefruit. The only real problem comes if they press on other tissues (e.g., blood vessels or the brain). That may require surgical treatment, but the good news is that once removed they usually don't return.

One other way in which they can have harmful, indirect effects is by growing in tissues that make hormones, such as the adrenal glands or the thyroid. When this happens, the tumours are derived from cells of the tissue and you might guess that the extra growth would give rise to abnormal levels of the hormones normally made by those glands. They're often symptom-free and only detected by chance (say, from a blood test).

An obvious thought is that, if the evolution of malignant cancers is driven by picking up changes in DNA, perhaps benign growths don't arise from mutations but are just caused by, say, a local imbalance in growth factors – chemical signals that turn on cell proliferation. As ever in cancer, it's not that simple. Mutations that in some tissues are associated with malignancy also pop up in benign tumours and in normal tissue, which tells us that knowing the mutational state of genes doesn't enable you to say for sure whether a growth will become malignant. We're stuck with what, as this story unfolds, you will come to recognize as a typical cancer problem. The difference between benign and malignant tumours is critical: one of them can kill you. But even with the all-conquering power of modern molecular biology that we will come to

https://doi.org/10.1017/9781009043243.003 Published online by Cambridge University Press

shortly, we are yet to define precisely what it is that converts a relatively harmless abnormal growth into the fatal variety.

Warts and All

I suspect everyone will have noticed that human beings tend to come adorned with a variety of moles, birthmarks and warts. Try as you might, it's hard not to ask yourself sometimes whether these things, that are undoubtedly unusual growths, are some form of cancer – and if they are, what should be done about them. Relax. The answers are almost always 'no' and 'nothing'. If you want to be pedantic, as abnormal growths of skin they are indeed 'neoplasms', but the best thing is to forget about them or, if they're Angelina Jolie's mole or Mikhail Gorbachev's port-wine stain, turn them into an adornment. Sometimes these oddities will disappear of their own accord, as often happens with 'strawberry marks' usually found on the face. Otherwise, if they are a cosmetic concern, it's often possible to reduce their prominence by laser treatment.

One other abnormality you may acquire is a cyst. These are not benign tumours but are closed sacs of cells containing liquid or semi-solid material that can form almost anywhere and can be removed by surgery.

You probably spotted another reference to the enigma of cancer a few lines ago in 'almost always', and, although we'll return to this point later, we need a word about moles before we get to warts. These are birthmarks, called nevi, the most common form being a growth of melanocytes in the outer layer of the skin. These cells make melanin – a skin pigment that gives a dark colour to hair, skin and eyes. Moles are therefore benign clusters of pigmented skin cells. Normally no more than decorative, just once in a while a mole can kick off into something nasty and turn into a fully malignant tumour. No need for panic, however, for that almost always requires us to give it a helping hand – usually by lying in the sun without any protection, that is, by exposing it to ultraviolet radiation. Hence the widely publicized advice to use sun cream. Regardless of sun or creams, the essential thing is to consult a doctor if one of your moles changes appearance – gets blacker, starts growing, itching or bleeding. At that point the problem can be resolved by surgical removal of the offending

https://doi.org/10.1017/9781009043243.003 Published online by Cambridge University Press

spot. We'll return to the other scenario later, when we look at drug treatments for malignant melanoma.

The key thing that distinguishes birthmarks and moles from warts is that warts are caused by viral infection. That means we aren't born with them, but most of us get them at some point, often before we are 20 years old. More often than not they disappear of their own accord, although they may take years to do so. Usually they form on the hands or feet or in the anogenital area. Palmar warts occur on the palm of the hand; plantar warts, otherwise known as verrucas (*verruca plantaris*), on the soles of the feet. It's worth noting that warts are not the same as the irritating condition known as athlete's foot (*tinea pedis*), which is a fungal infection of the skin between the toes.

Warts are caused by infection with human papillomavirus (HPV), which means they are contagious. There are over 100 different types of HPV, giving rise to variant forms of warts in the outer layer of skin (epidermis) where the virus causes excessive amounts of a protein called keratin to be made. Once infected, you can't get rid of HPV. Nevertheless, most warts can be treated either chemically or by freezing (cryosurgery), burning (cauterization) or laser treatment.

Why Do Some Children Get Cancer?

They're very unlucky. Either they've inherited a powerful cancer-driving mutation in the DNA they received from a parent, or they acquired such a mutation in the womb. When our very young are stricken it is, of course, especially shattering, so it's worth pointing out that childhood cancers are very rare – less than 1 per cent of all cancers. In the UK the yearly incidence is about 1 child in 500 under the age of 14 – around 1,900 in total with just over 200 deaths. The corresponding US figures are just over 11,000 new cases with 1,200 deaths. The most common childhood cancer affects the blood cells (acute lymphoblastic leukaemia). For this disease the wonderful advances of the last 50 years have seen the cure rate soar to 90 per cent from about 50 per cent in the mid-1970s.

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How Many Different Cancers Are There?

There are over 100 different types of cancer that can be identified by examining cells from the tumour. Cancers are usually described by the part of the body from which they originated (liver, lung, etc.). However, as we shall see when we look at the molecular picture, that classification is beginning to be replaced by a genetic definition – that is, on the basis of specific mutations.

A further classification is based on the type of cell from which the tumour formed. The three main groups are as follows:

1. Carcinomas – cancers derived from epithelial cells. Skin is made of epithelial cells (epithelial cells are what you scrape off the inside of your cheek) but they also form the lining of all your organs – throat, intestines, blood vessels, etc. Cancers that arise in this type of epithelia are called adenocarcinomas. Carcinoma *in situ* is a pre-malignant change that happens in many cancers in which cells proliferate abnormally within their normal location: the epithelial cells show many malignant changes but have not invaded the underlying tissue. Ductal carcinoma *in situ* (DCIS) is one of the two most common forms of breast cancer, characterized by abnormal proliferation in the wall of the milk ducts. It carries a risk of developing into the invasive ductal carcinoma (IDC) form in which the cells are malignant. The majority of cancers (85 per cent) are carcinomas (e.g., breast, prostate, lung, colon).
2. Sarcomas involve connective tissue – that is, bone and soft tissues such as muscles, tendons and blood vessels. They are much rarer than carcinomas, accounting for less than 1 per cent of cancers, and are not thought to have a pre-malignant (*in situ*) phase.
3. Leukaemias (liquid cancers or blood cancers) and lymphomas are two groups of cancers arising in blood cells. Leukaemias affect bone marrow, whereas lymphomas arise in lymph node cells. The word 'leukaemia' comes from the Greek for 'white' (*leukos*) and 'blood' (*haima*). White blood cells are sometimes called leukocytes but, as that term covers all white cells, including lymphocytes, it's apt to be a bit confusing. Lymphomas are cancers of lymphocytes, the cells of the immune system that fall into the two main classes of T cells and B cells. The two major

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divisions of this cancer are Hodgkin's disease (Hodgkin's lymphoma) and non-Hodgkin's lymphoma. This is our first meeting with our immune system, but we'll return to it as one of the hottest strands of current cancer therapy.

Is There A Difference Between Men and Women?

We're talking cancer here, of course, and it's pretty even-handed in its affliction of males and females, but men come off slightly worse (global new cases in 2018 were 9.5 million men vs 8.6 million women, and male vs female deaths were 5.4 million against 4.2 million). There's a general trend towards increased numbers of cancers that is more pronounced in females. However, survival rates are slightly higher in women.

Can You Catch Cancer from Someone Else?

The answer to this oft-asked question is: 'No, you can't.' But, as so often in cancer, the true picture requires a more detailed response – Alexander Pope might have approved – even though dealing with generalizations that aren't quite absolute tends to make scientists unpopular. It's not our fault! As Einstein more or less said, 'make it as simple as possible but no simpler'.

As we have noted, some human cancers arise from infection – notably by human immunodeficiency viruses (HIV) that can cause acquired immunodeficiency syndrome (AIDS) and lead to cancer, and by HPV. We met HPVs just now and noted that, although they may have some rather unappealing effects – namely warts – most of the 100-plus HPV types are not life-threatening. However, and regrettably, 15 of them are. Of these the most important are types 16 and 18. These cause about 70 per cent of cervical cancers and a variety of other anogenital tumours, as well as some cancers of the mouth, voice box, windpipe and lung. The strains of HPV responsible for most cervical cancers are sexually transmitted – meaning that the causative agent (i.e., the *virus*) is transmitted, *not* tumour cells, and it is viral infection that can give rise to lesions that are the precursors of cervical cancer. We'll return to HPVs later, when we look at the molecular basis for their effects and

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how that has led to therapies that now offer the possibility of eliminating cervical cancer.

However, while humans cannot catch cancer from each other, there are three known examples in mammals of transmissible cancers in which tumour cells *are* spread between individuals: the facial tumours that afflict Tasmanian devils, a venereal tumour in dogs and a cancer passed between Syrian hamsters. Not to be outdone, the invertebrates have recently joined this select club and it has emerged that a variety of clams, mussels and other members of the bivalve mollusc family can transfer cancer cells between themselves. About a dozen species of these little beach-dwelling chaps have been shown to acquire a form of cancer through cells spreading from a single 'founder' throughout a population. This remarkable effect with, it is presumed, the inadvertent transport of infected molluscs on shipping vessels, has led to the spread of cancers from the Northern to the Southern Hemisphere and across the Atlantic Ocean.

Despite these rare events in the animal world, the key point to grasp is that humans cannot 'catch' cancer from each other in the way that, for example, influenza can be spread.

Do Metastases Metastasize?

Given that metastasis is the formation of secondary tumours from cells that have been shed from a primary tumour, an obvious question is 'Can cells similarly detach from a secondary and seed yet another site?' Mice at least can certainly carry out what Joan Massagué of the Memorial Sloan Kettering Cancer Center has called 'tumour self-seeding', whereby circulating tumour cells can colonize the tumours from which they originated. This can be tracked by tagging metastatic cells with a fluorescent label and inoculating them into mice, which reveals that extensive seeding by circulating tumour cells is a common occurrence.

This type of metastasis may occur in at least some human cancers and returning tumour cells may increase the aggressiveness of the tumour.

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How Does Cancer Kill?

Given that tumours are abnormal growths of cells, one might expect them to have lethal potential if they interfere with normal function, rather as we noted for benign tumours if they compress adjacent tissues. This is a particular problem with brain tumours, the vast majority of which (about 90 per cent) are secondary cancers (i.e., metastases arising when tumour cells spread from another part of the body – commonly from breast or lung cancers). These secondary growths can create pressure on surrounding brain tissue, thereby affecting function. Bowel and gastrointestinal tract tumours, and also ovarian carcinomas, can obstruct the bowel, which would be fatal without surgical intervention. Damage to blood vessels caused by tumours can result in haemorrhage, particularly in the liver. Lung tumours can block lung function and some thyroid tumours can, in effect, cause strangulation.

Some liquid cancers can produce such an excess of white cells over red cells that the blood becomes very viscous and the supply of oxygen via the circulation is drastically impaired.

Human beings are, however, astonishingly resilient to organ damage: we can manage with half a kidney, and if we lose two-thirds of our liver it will regenerate itself. It is therefore relatively rare for cancers to kill via organ failure. Death usually results from secondary effects, principally infection by bacteria, such as *Escherichia coli* (*E. coli*) that can overwhelm the host even with antibiotic treatment. Cancer patients usually become more susceptible because the efficiency of their immune system declines.

About 50 per cent of cancer deaths are ultimately from malnutrition – a general condition of starvation and debilitation called cachexia (wasting syndrome) that develops in many other chronic diseases. In cancers, loss of appetite and inadequate digestion of food can occur. Cancer cachexia is poorly understood and there are no satisfactory treatments.

Can Plants Get Cancer?

Yes, even trees, corals and fungi can get a form of cancer. In plants and trees their abnormal growths tend to arise from infection by microorganisms (fungi,

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bacteria and viruses); insect infestation can also cause 'plant cancers'. They're not as serious as animal cancers because the cells of plants and trees have rigid cell walls and are locked into a matrix so they can't migrate. Thus, uncontrolled proliferation may result in the appearance of galls or burrs (burls), but not much damage is done.

Can We Cure Cancer?

No is the answer, notwithstanding the fact that, as we shall see, an increasing number of cancers can be treated with approaching 100 per cent success in terms of survival. The problem is that cancers are a fact of life – they're an inevitable result of how living organisms work – and in an increasingly elderly population, even if we have 'cures', in patients who are frail or in whom cancers are picked up at a very late stage, these 'cures' become either intolerable or ineffective. But in this book we will look at some of the ingenious methods being developed both to treat and to detect cancers. The expectation is that within the next 30 years the major cancers will be controllable and that it will become increasingly possible to 'nip cancers in the bud', so to speak – that is, to detect their presence ever earlier and target them before they become life-threatening. But we should always bear in mind that about half of all cancers are self-inflicted in that they arise from how we treat our own bodies.

Can Cancer be Modelled?

One of the longest running challenges in science has been to replicate cancer in the laboratory, a critical first requirement being to maintain animal cells under conditions that allow them to survive, grow and reproduce themselves. This is known as cell culture *in vitro*, first achieved in 1885 when the German zoologist Wilhelm Roux kept a piece of chicken embryo alive for several days by immersing it in saline (salt) solution. The first half of the twentieth century saw the development of *in-vitro* methods to the extent that by 1948 poliovirus could be grown in both human and monkey cells, a critical step in the production of the poliovirus vaccine.

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In 1951 George and Margaret Gey derived the first human 'cell line' to be established in culture by taking cervical cancer tissue from Henrietta Lacks, a patient at Johns Hopkins Hospital in Baltimore. Named HeLa cells, these have become one of the best known and most widely used cell lines in biological research. A decade later, George Todaro and Howard Greene found that in cultures of mouse embryo cells most of the cells stopped growing after a short while, but some survived and grew rapidly. These cells could be removed when they completely covered the culture dish, then diluted and allowed to continue growing, a process that could be continued indefinitely. Todaro and Greene had shown that normal cells with a finite lifespan could give rise to 'established cell lines' that survived indefinitely.

The establishment of the basic principles for the *in-vitro* study of animal and plant cells has underpinned the acquisition of much of our knowledge of cell biology in general and of cancer biology in particular, although no *in-vitro* system has yet completely recapitulated *in-vivo* cancer. As we shall see, the twenty-first century has brought further progress in the shape of 3D cell culture technology and the capacity to do tissue engineering.

The use of mice is an important complement to *in-vitro* systems, either by studying the growth of transplanted tumour cells or by introducing predisposing mutations via genetic engineering. Although expensive and time-consuming, mice have provided considerable evidence about specific genes in cancer and are useful in testing anti-cancer agents.

The word 'model' may also refer to hypotheses or explanations – in this case as to how cancer cells originate and develop from normal cells in the process variously called carcinogenesis, oncogenesis or tumorigenesis. From this brief opening chapter it will already be evident that a basic model for cancer rests on the accumulation of mutations that ultimately perturb the normal processes of cell proliferation, cell death and control of cellular location. A vast amount of evidence supports this premise, although, as our story unfolds, it will become apparent that current knowledge is a long way from being able to explain all that happens in cancers. Inevitably, these shortcomings have led to alternative notions being put forwards – for example, that carcinogenesis arises from disruption of local tissue organization. As we shall

see, it has indeed become clear that the tumour microenvironment – made up of a variety of host cells and tissues – is critical in the development of solid cancers. However, an overwhelming weight of evidence indicates that the fundamental driving force in the genesis of cancers is the acquisition of mutations in DNA.

Admiring the Picture

I promised that a clear picture would emerge from these answers, so let's just see what we've got! Cancer is the abnormal growth of cells, either in speed, location or both. It's caused by changes in our genetic material, DNA, collectively referred to as mutations. Mutations affect the activity of the proteins encoded by genes; for this reason, the term 'cancer gene' has come into common usage. It's a very handy expression but you need to bear in mind that there's no such thing. 'Cancer gene' is just a way of referring to a gene that has a perfectly normal, often essential, role in cellular control that has been changed either in the activity of the protein encoded or the amount of protein made, so that it can now help to drive cancer. Mutations occur randomly throughout life, from the point where sperm meets egg, and some infections may give a helping hand to this accumulation, as does smoking, one of the most common causes of cancer. Because cancers arise from mutations in our own DNA, they are not contagious: you can't pass 'cancer genes' to someone else, nor do they arrive from outer space.

Most cancers are diseases of old age, but they can occur at any age – so from conception to death we are engaged in a game of genetic roulette. By examining the affected tissues we can identify a huge number of different types of cancer. However, we will shortly come to the revolution that has enabled us to identify all the changes that have occurred in the DNA of an individual cancer, and we will have to grasp the astonishing fact that not only are *all* cancers different at the molecular level, but also that within a given tumour *each cell* has unique differences in its DNA. They're horribly varied and unstable – and hence very unpredictable. This quite staggering picture of evolutionary diversity has been acquired during the lifetime of the cancer within one person. It you wish, you could call it hyper-dynamic Darwinism (Figure 1.1).

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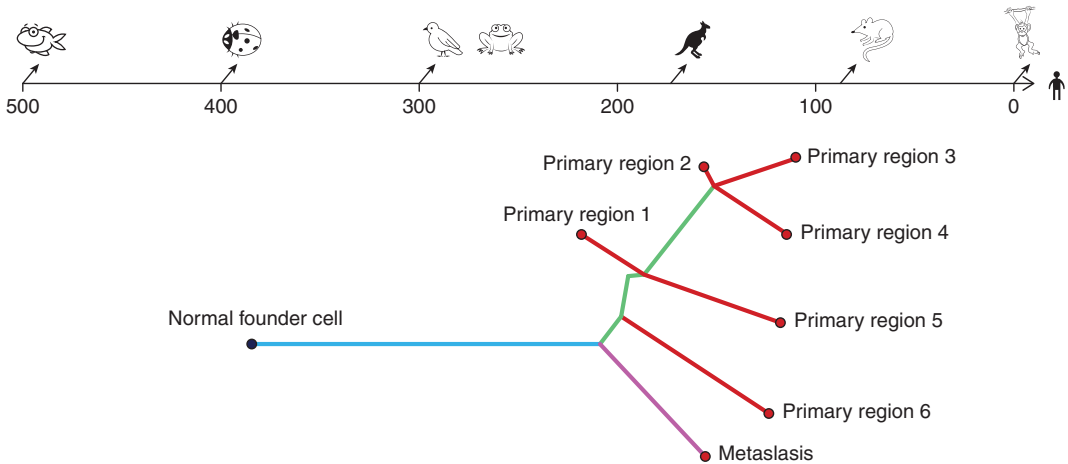

Figure 1.1 Species evolution versus cancer evolution. The top scheme is our family tree: the numbers are millions of years ago. The earth is about 4.5 billion years old, the first simple cells appeared around 3.8 billion years ago, and multicellular life started about 1,000 million years ago. The lower scheme represents the dissection of a tumour as an evolutionary tree. Six different regions of the same primary tumour and a secondary metastasis (M) are shown. The length of the lines between the branch points is proportional to the number of mutations picked up – thousands of them – on that stretch of the journey.

After that brief summary of the current position, it's timely to spend a moment (well, the next chapter) on a brief history of how we got here. In part it's an homage to all the patients, doctors and scientists who have gone before and struggled with this mightiest of problems. But it also enables us to see how mankind has applied his powers to making advances, however small or crude, and that gives an insight into how science works. That, in turn, is both useful and interesting because, like it or not, we live in a world increasingly dominated by science, and over the last 20 years cancer has become high-powered science in spades, so we need to be able to keep up!

https://doi.org/10.1017/9781009043243.003 Published online by Cambridge University Press